Determination of minimal important difference and patient acceptable symptom state of patient reported outcome measures in immunologically mediated oral mucosal diseases

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DECLARATION

This thesis describes research conducted in the UCL Eastman Dental Institute and Eastman Dental Hospital between 2015 and 2020 under the supervision of Professor Stefano Fedele, Professor Stephen Porter and Dr. Rícheal Ní Ríordáin. I, Paswach Wiriyakijja, certify that the research described is original and that I have written all the text herein and have clearly indicated by suitable citation any part of this thesis that has already appeared in publication. This thesis has not previously been submitted, in part or in full, for a degree or diploma of this or any other university or examination board.

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20 September 2020 ..... Date

ABSTRACT

Immunologically mediated oral mucosal diseases are a group of chronic conditions that give rise to varying degrees of painful oral symptoms, leading to impairment of normal functions of the mouth and quality of life (QoL) of affected individuals. Patient reported outcome measures (PROMs) provide standardized methods of capturing important outcomes directly from the patients, which have practical implications for monitoring the impact of the disease on patients as well as assessing the effectiveness of interventions in clinical trials of immunologically mediated oral mucosal diseases. However, little is known regarding the suitability of using PROMs as well as translation of PROM data into clinically meaningful terms in immunologically mediated oral mucosal diseases.

The aims of the present thesis were therefore to provide comprehensive overview of the application and quality properties of PROMs used in immunologically mediated oral mucosal diseases, to investigate measurement properties of frequently used PROMs specific to this patient population, and to enhance practical utility of these PROMs by developing a brief version of PROM (if needed), and determining clinically relevant thresholds for PROM scores.

Overall, the vast majority of existing PROMs have limited evidence supporting their measurement properties and no documentation of interpretability for use in immunologically mediated oral mucosal diseases. While the Chronic Oral Mucosal Disease Questionnaire (COMDQ) was the most psychometrically assessed PROM, the adoption of this instrument in clinical practice and research in immunologically mediated oral mucosal diseases appeared to be low. A prospective two-visit study was then conducted to investigate measurement properties and interpretability of a variety of frequently used PROMs as well as providing cross-sectional studies on psychological status and QoL in a relatively large cohort of patients with immunologically mediated oral mucosal diseases in a tertiary Oral Medicine clinic in the

UK. Secondary analysis of data was performed to develop a short version of the COMDQ to improve clinical feasibility and utility of this instrument.

For the assessment of psychological outcomes, the present results provided some evidence of validity and reliability of two psychological PROMs including the Hospital Anxiety and Depression Scale (HADS) and the 10-item Perceived Stress Scale (PSS-10) for use in patients with oral lichen planus (OLP) and recurrent aphthous stomatitis (RAS). Regarding QoL-PROMs, a short version of the COMDQ (COMDQ-15) was successfully developed and rigorously validated, using data of 520 patients with immunologically mediated oral mucosal diseases. The present findings showed that COMDQ-15 performed better than the 14-item Oral Health Impact Profile (OHIP-14) at capturing patient's QoL in patients with OLP and RAS as shown by its greater association with symptoms and disease activity in both patient groups.

As for the interpretation of PROM outcomes, cut-off scores for meaningful improvement thresholds including minimal important change (MIC) and minimal important difference (MID) of common measures of pain and QoL were determined to facilitate meaningful interpretation of improvement in PROM scores. Apart from PROM change scores, thresholds for patient acceptable symptom state (PASS) were estimated to provide clinically relevant cut-points for PROM individual scores.

Overall, the results of the present study provide some evidence supporting quality properties of commonly used PROMs for the application in immunologically mediated oral mucosal diseases. The established estimates of meaningful improvement thresholds and patient acceptable symptom state thresholds will allow researchers and clinicians to adopt these as standard for clinically meaningful interpretation of scores of pain and QoL outcomes in immunologically mediated oral mucosal diseases.

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IMPACT STATEMENT

The past two decades have witnessed an increasing emphasis on measuring disease and treatment outcomes from the patient's perspective, leading to a steady rise in the development of patient-reported outcome measures (PROMs) as validated instruments to capture important outcomes directly from a patient. A wide spectrum of PROMs are available for individuals with immunologically mediated oral mucosal diseases, a group of chronic inflammatory or ulcerative conditions that can cause painful oral symptoms. However, the majority of these PROMs have not been examined for their measurement properties and suitability for use in this patient population. Thus, the present findings regarding validation evidence of some frequently used PROMs in immunologically mediated oral mucosal diseases are not only a significant contribution to the literature, but also provide clinicians and researchers with the information to guide selection of appropriate PROMs for clinical management and future research of patients with immunologically mediated oral mucosal diseases.

A 15-item Chronic Oral Disease Questionnaire (COMDQ-15), successfully developed and rigorously validated in the present thesis, is a brief, easy-to-use, valid and reliable instrument that provides an overview of the impact of the diseases and associated treatment on the quality of life of patients with immunologically mediated oral mucosal diseases. Routine use of the COMDQ-15 could complement clinical data in quantifying current disease state, monitoring changes in patient's condition in response to treatment and formulating an optimal management plan tailored for each patients.

To effectively improve treatment outcomes for patients, it is important to understand the level of changes or improvement that are in fact meaningful to patients as well as the acceptable level of the symptoms and quality of life in patients suffering from immunologically mediated oral mucosal diseases. The established thresholds of minimal important change (MIC), minimal important difference (MID) and patient acceptable symptom state (PASS) arising from

the present work could improve interpretability of the outcomes generated by PROMs in immunologically mediated oral mucosal diseases by providing cut-points of PROM numerical scores that are clinically relevant and easy for clinicians and researchers to understand. The knowledge of these cut-points will provide a more meaningful way to interpret patient-reported outcomes, which ultimately have the potential to inform clinical decision-making with respect to therapy and long-term management of the conditions as well as assisting the design and interpretation of the outcomes in clinical research of immunologically mediated oral mucosal diseases in the future.

A series of comprehensive reviews, instrument development study, validation studies and interpretability studies in the present thesis have already been published in a number of international peer-reviewed journals, with further studies of the present findings are planned following thesis submission.

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LIST OF ABBREVIATIONS

α	Cronbach's alpha coefficient
ω	McDonald's omega coefficient
ω-h	Coefficient omega hierarchical
χ^2	Chi-square
AAOMP	American Academy of Oral and Maxillofacial Pathology
ABQOL	Autoimmune Bullous Disease Quality of Life
ACEI	Angiotensin-converting enzyme inhibitors
aGVHD	Acute Graft-versus-host disease
Allo-HCT	Allogeneic haematopoietic cell transplantation
AOR	Adjusted odd ratio
APCs	Antigen-presenting cells
AUC	Area under the curve
BD	Behcet's disease
BDI	Beck Depression Inventory
BM	Basement membrane
BPAg1	Bullous pemphigoid antigen 1
BPAg2	Bullous pemphigoid antigen 2
C3	Complement component 3
CFA	Confirmatory factor analysis
CFI	Comparative fit index
cGVHD	Chronic graft-versus-host disease
CI	Confidence interval
COMDQ	Chronic Oral Mucosal Disease Questionnaire
COMDQ-15	15-item Chronic Oral Mucosal Disease Questionnaire
COMDQ-26	26-item Chronic Oral Mucosal Disease Questionnaire
COS	Core outcome set
COSMIN	Consensus-based standards for the selection of health status measurement instruments
CSS	Change in Symptoms Scale
DG	Desquamative gingivitis
DIF	Direct immunofluorescence

DLQI	Dermatology Life Quality Index
Dsg 1	Desmoglein 1
Dsg 3	Desmoglein 3
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
EAOM	European Association of Oral Medicine
EFA	Exploratory factor analysis
ELISA	Enzyme-linked immunosorbent assay
FA	Factor analysis
GAD-7	7-item Generalised Anxiety Disorder Scale
GCPS	Graded Chronic Pain Scale
GRC	Patient's Global Rating of Change
GVHD	Graft-versus-host disease
HADS	Hospital Anxiety and Depression Scale
HADS-A	Anxiety subscale of Hospital Anxiety and Depression Scale
HADS-D	Depression subscale of Hospital Anxiety and Depression Scale
HADS-T	Total score of Hospital Anxiety and Depression Scale
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human Leukocyte antigen
HRQoL	Health related quality of life
HU	Herpetiform ulceration
ICC	Intraclass correlation coefficient
ICD	International Classification of Diseases
IFN- γ	Interferon-γ
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IIF	Indirect immunofluorescence
IL-1	Interleukin-1
IL-2	Interleukin-2
IL-6	Interleukin-6
IL-10	Interleukin-10

IL-12	Interleukin-12
IL-17	Interleukin-17
IQR	Interquartile range
IVIg	Intravenous immunoglobulin therapy
LP	Lichen planus
MaRAS	Major recurrent aphthous stomatitis
MHC	Major histocompatibility complex
MIC	Minimal important change
MID	Minimal important difference
MiRAS	Minor recurrent aphthous stomatitis
MMP	Mucous membrane pemphigoid
MMPs	Matrix metalloproteinases
MOMI	Modified Oral Mucositis Index
MTR	Malignant transformation rate
NICE	National Institute for Clinical Excellence
NK cells	Natural killer cells
NQF	National Quality Forum
NRS	Numerical Rating Scale
NSAIDs	Non-steroidal anti-inflammatory drugs
ODSS	Oral Disease Severity Score
OHIP-14	14-item Oral Health Impact Profile
OHIP-49	49-item Oral Health Impact Profile
OH-QoL	Oral health related quality of life
OHQOL-UK	Oral Health related Quality of Life Questionnaire-UK
OLCL	Oral lichenoid contact lesions
OLDR	Oral lichenoid drug reactions
OLL	Oral lichenoid lesions
OLL-cGVHD	Oral lichenoid lesions of chronic graft-versus-host disease
OLP	Oral lichen planus
OLP-SSM	Oral Lichen Planus Symptom Severity Measure
OPMDs	Oral potentially malignant disorders
OPMDQoL	Oral Potentially Malignant Disorder Quality of Life Questionnaire

OR	Odd ratio
PAMPs	Pathogen-associated molecular patterns
PASS	Patient acceptable symptom state
PDT	Photodynamic therapy
PFAPA	Periodic Fever, Aphthous Stomatitis, Pharyngitis, Cervical Adenitis
PHQ-9	Patient Health Questionnaire-9
POMS	Profile of Mood State
PROMs	Patient reported outcome measures
PRO-PMs	Patient-reported outcome performance measures
PSS-10	10-item Perceived Stress Scale
PV	Pemphigus vulgaris
QoL	Quality of life
RANTES	Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted
r_s	Spearman's rho correlation coefficient
RAS	Recurrent aphthous stomatitis
RCTs	Randomized placebo-controlled trials
RMSEA	Root mean square of error approximation
ROC	Receiver-operator characteristic
SD	Standard deviation
SEM	Standard error of measurement
SF-12	Medical Outcome Study Short Form 12 Health Survey
SF-36	Medical Outcome Study Short Form 36 Health Survey
SF-MPQ	Short-form McGill Pain Questionnaire
SLS	Sodium lauryl sulfate
SRMR	Standardized root mean squared residual
STAI	State-Trait Anxiety Inventory
STx	Systemic treatment
TABQOL	Treatment of Autoimmune Bullous Disease Quality of Life
Tanes	Topical anesthetic agents
TCS	Topical corticosteroids
Th cells	T helper cells
TLI	Tucker-Lewis index

TLRs	Toll-like receptors
TMD	Temporomandibular disorders
TN	True-negative rate
TNF-α	Tumour necrosis factor-α
TP	True-positive rate
TTx	Topical treatment
Tx	Treatment
USS	Ulcer Severity Score
UW-QOL	University of Washington Quality of Life Questionnaire
VAS	Visual analogue Scale
WHO	World Health Organization
WLSMV	Mean- and Variance-adjusted Weighted Least Square
WWOMVI	Sixth World Workshop in Oral Medicine

CHAPTER 1 GENERAL INTRODUCTION

Over the past decades, there has been a growing appreciation of the patient's perspective on their health conditions, leading to an increasing interest in the development, measurement property testing and application of PROMs, which are standardized instruments (usually questionnaires) used to capture important outcomes directly from the patients (Black and Jenkinson, 2009, Devlin et al., 2010). PROMs quantify various subjective outcomes including patient's symptoms and the quality of life on a numerical scale, and the differences in PROM scores can therefore be used to help inform clinical decision-making and evaluate the effectiveness of treatment both in clinical practice and research (Weldring and Smith, 2013, Chen et al., 2013).

From the perspective of clinical research, a vital step in the design of clinical trial is to select a PROM with appropriate psychometric properties to ensure that the instrument is suitable for its proposed application, valid (measure what it is intended to measure), reliable (produce consistent results on repeated measurement under identical conditions) and responsive (able to detect change over time) in a specific group of patients (Mokkink et al., 2010). Further to the psychometric properties, it is necessary that scores or outcomes generated by the PROMs are interpretable or clinically meaningful (Mokkink et al., 2010).

Little is known regarding evidence of measurement properties and application of PROMs in immunologically mediated oral mucosal diseases, a group of conditions that give rise to a wide range of oral mucosal manifestations. Some of these diseases are common (such as recurrent aphthous stomatitis and oral lichen planus) whereas others including mucous membrane pemphigoid and pemphigus vulgaris are less prevalent. The diagnosis of these immunologically mediated oral mucosal diseases can be challenging as they may share similar clinical manifestations such as ulceration and desquamative gingivitis. Also, these

diseases can be symptomatic and are usually long-standing and/or recurrent in nature, which can impair oral and psychosocial functioning as well as quality of life of affected individuals.

The overall aim of the present work is to review the application of PROMs that have been used in research of immunologically mediated oral mucosal diseases, to provide evidence supporting measurement properties of commonly used PROMs in this patient population, and to enhance clinical utility of these PROMs by developing a short version of the Chronic Oral Mucosal Disease Questionnaire as well as determining clinically important thresholds for PROM scores to facilitate meaningful interpretation of outcomes derived from these instruments.

Chapter 2 provides a brief overview of four significant immunologically mediated oral mucosal diseases including oral lichen planus (OLP), recurrent aphthous stomatitis (RAS), pemphigus vulgaris (PV) and mucous membrane pemphigoid (MMP). While these four conditions are diseases of interest in Chapter 3 and 5 of the present thesis, special attention is paid to two most commonly encountered diseases, namely OLP and RAS, on the remaining Chapters.

Chapter 3 first outlines crucial background information on PROMs including terminology, measurement property testing and application of a PROM, and then provides a series of comprehensive review on the range of PROMs measuring symptoms, psychological profiles and quality of life used in immunologically mediated oral mucosal diseases. Finally, all identified PROMs are assessed for the evidence of measurement properties supporting their usage in order to identify appropriately validated PROMs as well as PROMs requiring further examination on measurement properties in these patient populations.

Chapter 4 focuses on testing validity and reliability of two common PROMs measuring psychological status – the Hospital Anxiety and Depression Scale (HADS) and the 10-item

Perceived Stress Scale (PSS-10) – on a relatively large cohort of patients with OLP and RAS in a tertiary Oral Medicine clinic in the UK. Following their validation, the HADS and PSS-10 are then used to assess the prevalence of self-reported symptoms of anxiety, depression, emotional distress and perceived stress in patients with OLP and RAS. In addition, the association of these psychological comorbidities with demographic and clinical factors in these patient populations are investigated.

The purpose of Chapter 5 is to develop a brief version of the Chronic Oral Mucosal Disease Questionnaire (COMDQ), a PROM measuring quality of life specific to chronic oral mucosal conditions, and examine validity and reliability of this newly developed short-form COMDQ in a large cohort of patients with four immunologically mediated oral mucosal diseases. The development of this instrument could improve clinical feasibility and widespread adoption of this questionnaire into clinical practice.

Chapter 6 begins with investigation of quality of life using the short version of COMDQ (from Chapter 5) and the 14-item Oral Health Impact Profile (OHIP-14), a measure of general oral health related quality of life) in a cohort of patients with OLP and RAS. Then the strength of associations between scores of these two quality of life measures and disease activity and symptoms of OLP and RAS are compared. Finally, independent predictors of worse quality of life in patients with OLP and RAS are identified.

Both Chapter 7 and 8 provide evidence for interpretability of scores derived from PROMs measuring symptoms and quality of life in patients with OLP and RAS. Chapter 7 focuses on clinical meaningfulness of change PROM scores by first investigating responsiveness or sensitivity to change of studied PROMs and then determining two meaningful improvement thresholds including minimal important change (MIC) and minimal important difference (MID) for use in clinical and research settings of OLP and RAS. In contrast, Chapter 8 emphasizes

on clinical relevance of individual PROM score by providing explanation on concept of acceptable symptom state and determining thresholds of patient acceptable symptom state (PASS) on scores of common measures of symptoms and quality of life in a cohort of patients with OLP and RAS. Associated predictors of achieving PASS in OLP and RAS are examined.

Chapter 9 provides general discussion on the findings of the present thesis, and overall strength and limitation as well as suggestions for future research.

Chapter 10 provides future potential research or research topics following the present thesis

CHAPTER 2 IMMUNOLOGICALLY MEDIATED ORAL MUCOSAL DISEASES

2.1 ORAL LICHEN PLANUS

Oral lichen planus (OLP) is a common chronic immune-mediated inflammatory condition affecting the oral mucosa. OLP affects approximately 0.5-2.2% of population worldwide, and predominantly manifests in middle-aged women (Al-Hashimi et al., 2007). Pathogenesis of the disease is driven by inflammatory infiltrates of dysregulated immune cells particularly T-lymphocytes beneath oral epithelium (Eisen et al., 2005). OLP has a wide range of clinical appearance from asymptomatic white lesions (reticular, papular, plaque-like types) to symptomatic erythematous-dominating lesions (erosive, ulcerative types) and uncommon bullous lesions (Ingafou et al., 2006). Patients with symptomatic OLP may suffer from burning sensation, pain and/or discomfort arising from affected area, which can have significant negative impact on daily oral activities including eating, speaking and tooth cleaning (Lopez-Jornet and Camacho-Alonso, 2010). Patients with OLP may also experience changes in their psychological well-being due to the chronicity and unpredictable clinical behaviour of the disease, as well as the increased risk of oral cancer development (Warnakulasuriya et al., 2007, Ni Riordain et al., 2011a).

2.1.1 Epidemiology

The prevalence of OLP varies widely depending upon studied population (ethnicity/ adult or children/ clinical-based or population-based) and case definition (clinical or histopathological diagnosis/ criteria used) (McCartan and Healy, 2008). According to the data from epidemiological population-based studies, reported prevalence figures of OLP in adults range from 0.38% (Malaysia), 0.5% (Japan), 1.9% (Sweden) to 2.6% (India) (Murti et al., 1986, Axell and Rundquist, 1987, Ikeda et al., 1991, Zain et al., 1997). Although rarely found, OLP can affect children and adolescents, with reported population-based prevalence of 0.03% in one Dutch study (Laeijendecker et al., 2005).

OLP seems to occur most commonly in the 4th to 6th decades of life, with the average age at the time of diagnosis of OLP in the range from 50 to 60 years of age (Al-Hashimi et al., 2007). Among referred patients, there is a slight predominance in women (Scully and Carrozzo, 2008), with a female-to-male ratio being reported varying between 1.4:1 (Sugerman and Savage, 2002) and 2:1 (Eisen, 2002).

2.1.2 Clinical features

2.1.2.1 Clinical signs, symptoms and behaviour

OLP can affect any oral mucosal surface; however, typical intraoral sites include buccal mucosa (60-70% of the cases), dorso-lateral surface of the tongue and the gingivae (Mustafa et al., 2015). Unlike plaque-induced gingival disease, gingival lesions of OLP can arise on both the free and attached gingivae (Mignogna et al., 2005, Camacho-Alonso et al., 2007). Up to 10% of OLP patients have the disease confined only to the gingiva (Scully and Carrozzo, 2008). OLP with single oral site involvement other than the gingiva is not common and those with isolated lesions appear to develop widespread disease later (Schlosser, 2010). Unilateral lesions of OLP or lesions on the palate, the floor of the mouth and lips are atypical and rarely occur (Eisen et al., 2005, Alrashdan et al., 2016).

Six distinctive clinical presentations of OLP have been described ranging from the more common keratotic-dominant type (reticular, papular and plaque-like type), through erythematous-dominant type (erosive) to ulcerative and finally the uncommon bullous type (Table 2.1) (Scully and Carrozzo, 2008). These clinical subtypes can be seen individually or in combination within the same patient (Ingafou et al., 2006, Crincoli et al., 2011). With all clinical variants, some post-inflammatory black or brown hyper-pigmented areas may occur, particularly in dark-skinned individuals (Schlosser, 2010, Mergoni et al., 2011).

Symptoms of OLP vary greatly among patients, ranging from mild roughness of affected mucosa to significant oral discomfort and burning sensation (Alrashdan et al., 2016). Some patients may report mucosal sensitivity to certain food types (e.g. acidic, spicy, hot, abrasive), beverages (e.g. carbonated, alcohol) and toothpaste. OLP is a chronic, possibly life-long disease and affected patients frequently report intermittent episodes of exacerbation and remission (Alrashdan et al., 2016). The disease is often aggravated by stress and illnesses (Alrashdan et al., 2016).

Table 2.1 Clinical subtypes of OLP

Clinical variants	Characteristic features	Comments
Reticular	Fine, slightly elevated homogeneous white striae overlapping to form a lace-like pattern (Wickham's striae); often on posterior buccal mucosa, muco-buccal fold, tongue and gingiva; usually asymptomatic	Most common variant Bilateral, not always symmetrical lesions with white reticular striae is classic appearance of OLP Usually an incidental finding by dentists
Papular	Multiple raised white papules of a few millimetres in diameters; usually asymptomatic	Papules may subsequently coalesce to form reticular or plaque-like type
Plaque-like	Slightly raised homogeneous white patches that cannot be rubbed off; often on the tongue; usually asymptomatic	Mimic oral leukoplakia More common in cigarette smokers
Erosive	Erythematous mucosa with or without peripheral Wickham's striae; tongue lesions often show depapillation; often associated with discomfort or burning sensation	Gingival involvement of erosive and ulcerative OLP often calls *'desquamative gingivitis'* (DG) DG without Wickham's striae is indistinguishable to other immunobullous diseases such as MMP and PV
Ulcerative	Irregular ulcerated area on the erythematous base with or without pseudomembrane; usually associated with considerable pain and discomfort	Most disabling variant
Bullous	Fluid-filled vesicles or bullae	Lesions easily rupture, leaving painful erosive surface Rare variant

Abbreviation: MMP = mucous membrane pemphigoid, PV = Pemphigus vulgaris

2.1.2.2 Extra-oral lichen planus

Apart from the oral cavity, lichen planus (LP) can involve skin and other mucosal surfaces, with the most common extra-oral sites of involvement being the genitalia and skin. The involvement of LP in other mucocutaneous areas including the scalp, nails, esophagus, conjunctiva, nose, larynx, and anus can sometimes occur (Bidarra et al., 2008, Mustafa et al., 2015).

In approximately 15% of patients with OLP, cutaneous lesions may occur simultaneously or develop several months after oral lesions appear (Eisen et al., 2005, Scully and Carrozzo, 2008). Cutaneous LP typically manifests as polygonal, violaceous, flat-topped scaly papules and plaques and usually displays Wickham's striae on the surface of lesions, with propensity for the flexural wrist, dorsal feet and pretibial area (Schlosser, 2010). Cutaneous LP lesions are often pruritic, and scratching the affected skin can induce the development of new lesions (Koebner's phenomenon) (Lukacs et al., 2015). Unlike its oral counterpart, cutaneous LP usually heals spontaneously without any therapy often from 1 to 2 years (Le Cleach and Chosidow, 2012).

About 20% of women presenting with OLP may have genital involvement (Rogers and Eisen, 2003, Setterfield et al., 2006). Affected patients usually present with erosive vulvo-vaginal mucosa, which may be associated with burning, itching, pain, discharge, and dyspareunia (Le Cleach and Chosidow, 2012). A triad comprising LP erosive lesions of the vulva, vagina and gingiva has been suggested to be coined as vulvovaginal-gingival syndrome (Rogers and Eisen, 2003, Setterfield et al., 2006). However, there appears to be no association of the degree of disease severity between the oral and genital sites.

2.1.2.3 Oral lichenoid lesions

Oral lesions with similar clinical and histopathological features as 'idiopathic' OLP but associated with known identifiable aetiology are collectively referred to as "oral lichenoid lesions" (OLL) (Al-Hashimi et al., 2007). A detailed discussion of all OLL entities falls outside the scope of the present section; however, three major categories of OLL including oral lichenoid drug reactions (OLDR), oral lichenoid contact lesions (OLCL) and Oral lichenoid lesions of chronic graft versus host disease (OLL-cGVHD) are outlined briefly below.

Oral lichenoid drug reactions (OLDR) have a direct temporal relationship to the administration of certain medications (Carrozzo et al., 2019). A spectrum of putative drugs have been reported to induce OLDR such as non-steroidal anti-inflammatory drugs (NSAIDs), sulphonylureas, beta blockers, angiotensin-converting enzyme inhibitors (ACEIs), thiazide diuretics, gold, methyldopa, penicillamine and hydroxychloroquine (Khudhur et al., 2014, Mustafa et al., 2015). The time interval between the exposure to a drug and onset of OLDR varies from weeks to several months but OLDR occasionally arise more than one year after commencing causative medication (Schlosser, 2010). OLDR lesions may be unilateral or manifest as a single lesion but this is not always the case (Eisen et al., 2005, Schlosser, 2010). Discontinuation of the putative medication and substitution with other drug classes may be effective, although cross-sensitivity with other drugs is frequently observed, and OLDR lesions may persist (Khudhur et al., 2014, Alrashdan et al., 2016).

Oral lichenoid contact lesions (OLCL) are thought to be a result of cell-mediated delayed hypersensitivity reactions to substances in dental restorative materials particularly mercury in amalgam although materials such as gold, composite resins and cobalt as well as some flavoring agents including cinnamon have (infrequently) been implicated (Scully and Carrozzo, 2008, McParland and Warnakulasuriya, 2012). Clinically, lesions of OLCL are difficult to distinguish with those of OLP but they may present unilaterally in close topographical contact

with a likely causative dental materials, with buccal mucosa and lateral aspects of the tongue being the most likely sites for amalgam-associated OLCL (Al-Hashimi et al., 2007, Mustafa et al., 2015). It is suggested that the majority of amalgam-associated OLCL resolve spontaneously within several months following the replacement of amalgam with other materials (McParland and Warnakulasuriya, 2012).

Graft-versus-host disease (GVHD) is one of the potential complication affecting recipients of allogeneic haematopoietic cell transplantation (allo-HCT) (Imanguli et al., 2008). While acute GVHD (aGVHD) reflects a strong inflammatory reaction involving maculopapular rash, gastrointestinal symptoms and hepatitic dysfunction, chronic GVHD (cGVHD) gives rise to a more autoimmune and fibrotic picture (Filipovich, 2008, Blazar et al., 2012). Oral involvement of cGVHD, which develop in more than 70% of patients with cGVHD, is mainly categorized into 3 groups: (1) *oral lichenoid lesions of cGVHD (OLL-cGVHD)*, (2) salivary gland disease with signs and symptoms mimicking Sjögren's syndrome and recurrent superficial mucoceles on the palatal mucosa, and (3) sclerotic disease causing fibrosis and restricted mouth opening mimicking scleroderma (Kuten-Shorrer et al., 2014). Lichenoid changes in cGVHD are clinically and histologically indistinguishable from OLP lesions, and the buccal mucosa and the tongue are the most frequently affected sites (Treister et al., 2008). Diagnosis of OLL-cGVHD is largely based upon clinical presentation and history of allo-HCT (Khudhur et al., 2014).

2.1.3 Aetiopathogenesis

2.1.3.1 Aetiology

OLP reflects cell-mediated immune process causing change in stratified squamous epithelium of the oral mucosa (Payeras et al., 2013). Although precise aetiology driving this process remains unknown, certain predisposing factors have been reported to potentially play a role in OLP pathogenesis.

Up until now four independent meta-analyses have confirmed a positive association between OLP and Hepatitis C virus (HCV) infection, with the stronger association being observed among Southern European, Middle Eastern and Asian countries (Shengyuan et al., 2009, Lodi et al., 2010, Petti et al., 2011, Alaizari et al., 2016). The geographical heterogeneity in the prevalence of OLP patients with HCV seropositive might be partly attributed to the presence of particular HLA alleles in a cohort of patient group (such as HLA-DR6 in Italian patients with HCV-related OLP), environmental factors and HCV genotypes (Carrozzo et al., 2001). However, there remains no comprehensive explanation of exact mechanism of HCV in aetiopathogenesis of OLP (Alaizari et al., 2016).

Genetic polymorphisms in cytokine genes including interferon-γ (IFN- γ) and tumour necrosis factor-α (TNF-α) may govern clinical presentation of LP, whether the lesions appear in the mouth only (IFN- γ-associated) or additionally on the skin (TNF-α-associated) (Carrozzo et al., 2004). Localised physical trauma in the oral cavity from sharp cusps, ill-fitting dentures and accumulation of plaque and calculus deposits may precipitate the formation of new OLP lesions (Koebner phenomenon) (Eisen et al., 2005). Despite relatively high prevalence of common psychological symptoms including anxiety and depression among patients with OLP, there is currently no robust evidence confirming whether these psychological symptoms are pre-existent to OLP diagnosis or a consequence of having OLP (Alrashdan et al., 2016).

2.1.3.2 Pathogenesis

Substantial evidence suggests that pathogenesis of OLP appears to largely reflect cell mediated immune dysfunction with the presence of dense T-cell infiltrate (predominantly CD8+ T lymphocytes) along the epithelial-connective tissue junction, resulting in damage of epithelial lining of the oral mucosa (Kurago, 2016). The activation of antigen-presenting cells (APCs) including resident myeloid dendritic cells (Langerhans cell, stromal dendritic cells) by certain

antigens is the key early event of OLP pathogenesis (Kurago, 2016). However, the antigen or initiating factor, which could be of endogenous or exogenous origin, remains unknown (Roopashree et al., 2010, Payeras et al., 2013).

Following antigenic challenge, APCs release cytokines to upregulate several endothelial cell adhesion molecules, leading to adhesion and migration of circulating T lymphocytes to the developing OLP lesions (Kurago, 2016). Apart from antigen-associated immune response, non-specific mechanisms including degranulation of regional mast cells, certain chemokines (RANTES), and matrix metalloproteinases (MMPs) play a critical role in pathogenesis of OLP particularly in the recruitment of additional T cells, natural killer cells (NK cells) and plasmacytoid dendritic cells to the lesions (Roopashree et al., 2010, Kurago, 2016).

Induced by pro-inflammatory mediators, T lymphocytes and NK cells secrete cytokines including TNF-α and IFN-γ. The latter cytokine stimulates the expression of MHC class II on basal keratinocytes, which facilitates activation of CD4+ T helper (Th) cells. Subsequently, CD8+ cytotoxic T cells are activated by (1) antigen presenting on MHC class I on lesional keratinocytes and (2) secretion of Th1 cytokines including interleukin-2 (IL-2) and IFN-γ by activated CD4+ T cells. Activated CD8+ T cells appear to mediate apoptotic cascade of basal keratinocytes via possible three mechanisms: direct cytotoxicity through perforin and granzyme, secretion of TNF-α, and CD95-CD95L (death receptor/ligand)-mediated apoptosis (Sugerman et al., 2002, Roopashree et al., 2010, Kurago, 2016).

Destruction of basal keratinocytes results in loss of self-renewal capacity of oral epithelium, making it become thinner. In addition, apoptotic basal keratinocytes compromise the production and integrity of basement membrane (BM). Disrupted BM in turn could not convey cell survival signal to the basal keratinocytes, and this cyclical mechanism is postulated to be related to chronicity of OLP (Sugerman et al., 2002, Payeras et al., 2013). The pathogenic

mechanism behind marked parakeratin production in clinically white OLP lesions (reticular or plaque-like OLP) remains unclear, but a recent study found that erosive OLP might be associated with the production of interleukin-17 (IL-17) by Th17 CD4+ T cells (Xie et al., 2012).

2.1.4 Diagnosis

In cases presenting with the 'classic' bilateral white reticular lesions, diagnosis of OLP can be made based solely upon clinical manifestation with a supporting patient history (Carrozzo and Thorpe, 2009). However, an oral biopsy for histopathological confirmation is recommended to establish definitive diagnosis and to exclude oral dysplasia and malignancy (van der Waal, 2009a). The World Health Organization (WHO) first proposed the diagnostic criteria for OLP in 1978, and a set of modified criteria were subsequently proposed to the WHO criteria in 2003 to improve correlations between clinical and histological diagnosis (Kramer et al., 1978, van der Meij and van der Waal, 2003, Rad et al., 2009). Later, the American Academy of Oral and Maxillofacial Pathology (AAOMP) published a position paper to make further modifications to this diagnostic criteria (Cheng et al., 2016). An overview of diagnostic criteria of OLP is shown in Table 2.2.

The histopathological features of OLP generally comprise hyperkeratosis, acanthosis, liquefactive degeneration of basal cell layer and band-like chronic inflammatory cell infiltrate (mainly lymphocytes) beneath the basement membrane (Eisen et al., 2005, Ismail et al., 2007). These features are prominent on Wickham's striae and less distinct in erosive or ulcerative lesions (Schlosser, 2010). Civatte bodies, which represent apoptotic keratinocytes and appear as homogeneous eosinophilic globules, may be evident in the lower half of epithelial layer (Schlosser, 2010, De Rossi and Ciarrocca, 2014). Direct immunofluorescence (DIF) can be employed as diagnostic adjunct to help distinguish OLP from other immunobullous diseases, particularly in cases with desquamative gingivitis alone. DIF in OLP

may demonstrate a shaggy or globular pattern of fibrinogen with or without Immunoglobulin M (IgM) along basement membrane zone (Buajeeb et al., 2015).

Histopathological features in OLL may be indistinguishable from those in OLP; hence, clinico-pathological correlation is important for the diagnosis of OLL. It has however been suggested that OLL has a mixed subepithelial inflammatory infiltrate of lymphocytes and eosinophils, which tends to be more diffuse and extend more deeper into the connective tissue when compared to OLP (van der Waal, 2009).

Table 2.2 An overview of diagnostic criteria for OLP

WHO diagnostic criteria of OLP (1978) (WHO Collaborating Centre For Oral Precancerous Lesions, 1978)
Clinical criteria
Presence of white papule, reticular, annular, plaque-type lesions, gray-white lines radiating from the papules
Presence of a lace-like network of slightly raised gray-white lines (reticular pattern)
Presence of atrophic lesions with or without erosion, may also bullae
Histopathologic criteria
Presence of thickened ortho or parakeratinized layer in sites with normally keratinized, and if site normally non-keratinized this layer may be very thin
Presence of Civatte bodies in basal layer, epithelium and superficial part of the connective tissue
Presence of a well-defined bandlike zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes
Signs of 'liquefaction degeneration' in the basal cell layer
Modified WHO diagnostic criteria of OLP and OLL (2003) (van der Meij and van der Waal, 2003)
Clinical criteria
Presence of bilateral, more or less symmetrical lesions
Presence of a lace-like network of slightly raised gray-white lines (reticular pattern)
Erosive, atrophic, bulbous and plaque-type lesions are only accepted as a subtype in the presence of reticular lesions elsewhere in the oral mucosa
In all other lesions that resemble OLP but do not complete the aforementioned criteria, the term 'clinically compatible with' should be used
Histopathologic criteria
Presence of a well-defined band-like zone of cellular infiltration that is confined to the superficial part of the connective tissue, consisting mainly of lymphocytes
Signs of 'liquefaction degeneration' in the basal cell layer
Absence of epithelial dysplasia
When the histopathologic features are less obvious, the term 'histopathologically compatible with' should be used
Final diagnosis OLP or OLL
To achieve a final diagnosis clinical as well as histopathologic criteria should be included
OLP A diagnosis of OLP requires fulfillment of both clinical and histopathologic criteria
OLL The term OLL will be used under the following conditions:
1. Clinically typical of OLP but histopathologically only 'compatible with' OLP
2. Histopathologically typical of OLP but clinically only 'compatible with' OLP
3. Clinically 'compatible with' OLP and histopathologically 'compatible with' OLP
American Academy of Oral and Maxillofacial Pathology criteria of OLP (2016) (Cheng et al., 2016)
Clinical criteria
Multifocal symmetric distribution
White and red lesions exhibiting one or more of the following forms: reticular/papular, atrophic (erythematous), erosive (ulcerative), plaque, bullous
Lesions are not localized exclusively to the sites of smokeless tobacco placement
Lesions are not localized exclusively adjacent to and in contact with dental restorations
Lesion onset does not correlate with the start of a medication
Lesion onset does not correlate with the use of cinnamon-containing products
Histopathologic criteria
Band-like or patchy, predominately lymphocytic infiltrate in the lamina propria confined to the epithelium-lamina propria interface
Basal cell liquefactive (hydropic) degeneration
Lymphocytic exocytosis
Absence of epithelial dysplasia
Absence of verrucous epithelial architectural change

2.1.5 Management

As there are presently no available curative treatment modalities for OLP, current management should aim at minimizing pain and inflammation associated with the disease together with improving patient's quality of life (Al-Hashimi et al., 2007). Since OLP has a chronic nature with fluctuating disease course as well as possible development of oral cancer, regular long-term follow-up is necessary (Scully and Carrozzo, 2008). Elimination of precipitating or provoking factors along with maintaining meticulous oral hygiene are also vital for the management of OLP (Eisen et al., 2005). Asymptomatic cases with reticular lesions do not require treatment while the first-line therapy for symptomatic patients is potent topical corticosteroids (Thongprasom et al., 2011).

Topical corticosteroids have abilities to modulate immune responses including decrease production of inflammatory cytokines and reduction of number and function of immune cells, thus lessening OLP-related inflammation (Thongprasom and Dhanuthai, 2008). The extent and severity of the lesions are factors determining appropriate choice of topical corticosteroids, which are available in different preparations and potencies. Adhesive ointments are more suitable for localized easy-to-access lesions whereas mouthwashes are appropriate in more widespread or difficult-to-reach lesions. A successful response to treatment with potent topical corticosteroids have been reported in 30-100% of treated cases (Alrashdan et al., 2016). The most common adverse side effects of topical corticosteroids is the development of secondary oral candidosis, which was reported in about one-third of treated cases (Thongprasom and Dhanuthai, 2008). However, this superficial fungal infection can be easily managed or prevented by the use of antifungals (Gonzalez-Moles and Scully, 2005, Mustafa et al., 2015).

For persistent painful erosive-ulcerative lesions of OLP, intralesional injection of corticosteroids such as triamcinolone acetonide or hydrocortisone may be beneficial but the injections can be painful and not always effective (Xia et al., 2006, Lee et al., 2013). In topical

steroid-resistant cases, topical calcineurin inhibitors including tacrolimus and pimecrolimus may be used as an alternative. However, transient burning sensation and high rates of relapse are frequently reported following their application (Al Johani et al., 2009). Long-term topical use of calcineurin inhibitors needs to be cautious since there was a case report suggesting the possibility of oral squamous cell carcinoma arising on the OLP lesions treated with topical tacrolimus (Mattsson et al., 2010). Therefore, topical calcineurin inhibitors should be used intermittently with the lowest dose possible and for only a short period of time in recalcitrant cases.

Systemic therapy should only be reserved for uncontrollable cases after maximising the effectiveness of topical treatment or those with severe acute flares (Thongprasom et al., 2011). High dose systemic prednisolone (e.g. 30-60 mg daily for 2-3 weeks) may be of clinical benefit but should be only used in the short course at the possible lowest dose with close monitoring (Silverman et al., 1991). Long-term use of systemic corticosteroids should be discouraged owing to numerous possible complications such as hypertension, hyperglycaemia, glaucoma, mood alteration, osteoporosis as well as systemic infection particularly among elderly people (Thongprasom and Dhanuthai, 2008). In some severe refractory cases, long-term use of non-steroidal systemic therapies such as azathioprine and mycophenolate mofetil may be required for achieving optimal disease control (Mustafa et al., 2015). The effectiveness of other medical treatment including retinoids, Aloe vera and curcuminoids and non-medical interventions such as photodynamic therapy (PDT), conventional surgery and laser ablation have been reported in the literature (Scardina et al., 2006, Ali and Wahbi, 2017, Akram et al., 2018a, Akram et al., 2018b, White et al., 2019). However, owing to the lack of well-designed controlled clinical trials, there appears to be no convincing evidence supporting the superiority of any specific treatment over topical corticosteroids.

2.1.6 Malignant transformation

The main concern of OLP aside from its chronic nature is its associated increased risk of oral cancer development. Since the first case report of malignant transformation in OLP published in 1910, a great number of studies have attempted to address malignant potential of this oral condition (Mattsson et al., 2002, Roosaar et al., 2006, van der Meij et al., 2007). OLP is currently considered as one of oral potential malignant disorders (OPMDs) (van der Waal, 2009b). Determining malignant transformation rate (MTR) of OLP is challenging due to the lack of uniform standard criteria for the diagnosis of OLP (including the exclusion of epithelial dysplasia), the differentiation between OLP and OLLs, and the inadequate follow-up periods (Fitzpatrick et al., 2014, Giuliani et al., 2019)

A recent systematic review by González-Moles and colleagues (2019) calculated combined MTR of 1.14% for OLP and a slightly higher rate of 1.88% for OLLs. The higher figures for MTRs were reported in studies when the presence of dysplasia was not an exclusion criterion. A higher incidence of malignant transformation was observed among smokers, alcohol drinkers and HCV-seropositive patients. Regarding clinical factors, tongue lesions and atrophic-erosive lesions of OLP were found to carry significantly higher risk of developing oral cancer in comparison to lesions at other oral sites and reticular lesions, respectively (Gonzalez-Moles et al., 2019).

2.2 RECURRENT APHTHOUS STOMATITIS

Recurrent aphthous stomatitis (RAS; aphthae; canker sores) is a very common ulcerative condition of the oral mucosa characterised by recurrent eruptions of painful single or multiple small well-delineated round or ovoid ulcers with a yellowish or greyish centre and peripheral halo of erythema (Jurge et al., 2006). Affected patients are otherwise well. The first episode of RAS typically commences during the childhood or adolescence in otherwise healthy individuals (Jurge et al., 2006, Akintoye and Greenberg, 2014). The aetiopathogenesis of RAS

has yet to be well-understood with several disease predisposing and modulating factors having been proposed (Slebioda et al., 2014). The oral manifestations of certain systemic diseases including Behcet's disease, gastrointestinal diseases and HIV infection may mimic RAS thus it is important to distinguish RAS from these conditions. The management of RAS is upon the extent, frequency and severity of the lesions. Current therapy is primarily directed towards lessening associated painful symptoms rather than reducing or stopping outbreaks of ulceration (Jurge et al., 2006).

2.2.1 Epidemiology

Approximately 20% of the population worldwide may have RAS (Akintoye and Greenberg, 2014). The documented prevalence of RAS varies considerably in the range between 5% and 66% depending upon the study populations along with the methodology and diagnostic criteria of each study (Rogers, 1997, Jurge et al., 2006). The age range of between 10 and 19 years is considered to be a peak age of RAS onset, with the prevalence, frequency of the episodes and severity suggested to decrease in middle to late life (Ship et al., 2000). Individuals with one or both parents with RAS may have a higher risk of developing RAS than those with RAS-negative parents (90% vs 20% respectively) (Ship, 1972). In the US RAS was three times more common in whites than in African Americans (Kleinman et al., 1994). Children of higher socio-economic class may have greater likelihood to develop RAS (Crivelli et al., 1988).

2.2.2 Clinical features

RAS occurs in those who are otherwise healthy and comprises recurrent episodes of painful single or multiple small well-delineated round or ovoid ulcers that can heal spontaneously at intervals of a few weeks to a few months (Jurge et al., 2006). Patients may experience prodromal symptoms such as tingling or burning sensation, lasting from 2 hours to 2 days before the eruption of macular or papular lesion, which subsequently becomes ulcerated (Akintoye and Greenberg, 2014, Cui et al., 2016).

2.2.2.1 Types of RAS

Clinically, RAS can be classified into 3 main variants: minor RAS, major RAS and herpetiform ulceration.

Minor RAS

Minor RAS (MiRAS; Mikulicz's aphthae) is the most commonly observed pattern affecting approximately 85% of RAS patients. MiRAS manifests as superficial, well-circumscribed, round or oval ulcers that are less than 10 mm in diameter, covered with yellowish or greyish pseudomembrane and surrounded by erythematous haloes. This type of RAS are usually confined to non-keratinized oral mucosa especially labial and buccal mucosa, ventro-lateral surfaces of the tongue as well as the floor of the mouth. Individuals with MiRAS generally have up to 5 oral ulcers at one time with few recurring episodes in one year. The ulcers usually resolve spontaneously in 10 to 14 days without scarring (Jurge et al., 2006, Akintoye and Greenberg, 2014).

Major RAS

Major RAS (MaRAS; Sutton's aphthae; periadenitis mucosa necrotica recurrens) lesions resemble MiRAS but are larger in diameter (exceed 10 mm), may extend deeper, and have more inflamed surrounding mucosa. This RAS variant is observed in about 10% of all RAS cases and has been suggested to occur after puberty. MaRAS has a predilection for the lips, soft palate and oropharynx. They are of longer duration than MiRAS, usually persisting for weeks to a few months before healing which occasionally leave substantial scars. MaRAS can contribute to significant pain, interfering with speech, eating and swallowing (Jurge et al., 2006, Akintoye and Greenberg, 2014).

Herpetiform ulceration

Herpetiform ulceration (HU) is the rarest pattern of RAS, accounting for at most 5 to 10% of all RAS disease. HU presents with widespread crops of small shallow ulcers, which may be

found up to 100 ulcers at one time. The ulcers are small (1-2 mm in diameter) but can coalesce into larger ulcers with irregular margins. They can affect both non-keratinized and keratinized mucosa. The age of onset of HU is later than other types of RAS, usually starting in the third decade of life. This type of RAS may have a female predilection (Scully and Porter, 1989). The lesions of HU often heal in 1 to 2 weeks without scar formation (Jurge et al., 2006, Akintoye and Greenberg, 2014).

2.2.2.2 Systemic conditions with RAS-like oral ulceration

Several systemic conditions may manifest with recurrent episodes of RAS-like oral ulcers (Jurge et al., 2006), but these do not point toward to a common aetiological factor that may indicate the cause of RAS.

Behcet's disease (BD) is an uncommon chronic immune-mediated condition with multi-organ involvement due to its inflammatory effects on arteries and veins of all sizes (Nair and Moots, 2017). The hallmarks of the disease is recurrent RAS-like oral and genital ulcerations. BD may also affect many other organs including eyes (usually anterior and posterior uveitis) and skin (erythema nodosum and papulopustular lesions) as well as giving rise to a variety of musculoskeletal, neurological, vascular, renal, cardiac and gastrointestinal abnormalities (Nair and Moots, 2017). Oral ulceration in BD tends to resemble major RAS or herpetiform ulceration but may be more severe, with recurrence occuring at least 3 times during a 12-month period (Keogan, 2009). MAGIC syndrome is considered as another variant of BD consisting of major aphthae and genital ulceration with generalized inflamed cartilage (relapsing polychondritis) (Imai et al., 1997).

Sweet's syndrome or acute febrile neutrophilic dermatosis is an uncommon cutaneous condition characterized by well-defined plum-coloured papules or plaques on affected skin with sudden onset fever and leukocytosis. Patients with Sweet's syndrome may have

superficial oral ulceration resembling RAS. Unlike RAS, this syndrome usually affects middle-aged women. Notably, some malignant conditions including acute myeloid leukemia can be observed in approximately half of affected individuals (Femiano et al., 2003).

Periodic Fever, Aphthous Stomatitis, Pharyngitis, Cervical Adenitis (PFAPA) or Marshall's syndrome is a periodic febrile disorder mostly occuring in young children presenting with periodic fevers, aphthous-like oral ulceration, pharyngitis and cervical adenitis. This syndrome has a spontaneous resolution but the use of some medications such as cimetidine and prednisolone as well as tonsillectomy may be beneficial in inducing clinical resolution (Vigo and Zulian, 2012).

Cyclic neutropenia is another rare disorder characterized by cyclic reduction of circulating neutrophils about every 3 weeks. During the period of severely depressed neutrophil count, patients may develop RAS-like oral ulceration, fever, skin infection (abscesses) and upper respiratory tract infection. Patients may also have severe gingivitis and aggressive periodontitis in the oral cavity (Rodenas et al., 1992, Jurge et al., 2006).

Patients with inflammatory bowel diseases such as Crohn's disease and ulcerative colitis may be affected by RAS-like oral lesions, which may be a consequence of haematinic deficiency secondary to malabsorption. In addition, Crohn's lesions tend to appear with indurated borders due to the granulomatous nature of the disease. Oral ulceration is observed in about 10% of individuals with Crohn's disease and oral lesions may appear before the onset of intestinal abnormalities (Greenberg and Pinto, 2003). Also, individuals with undiagnosed or poorly controlled gluten sensitive enteropathy may sometimes have oral ulceration following gluten intake (Akintoye and Greenberg, 2014).

RAS-like oral ulceration has been described as late finding in patients with HIV disease when CD4+ lymphocytes count are lower than 100 cells/mm^3. Patients with HIV disease can have recurrent major aphthous-like ulcers with more frequent outbreaks, longer lasting and more painful than healthy individuals (Akintoye and Greenberg, 2014).

2.2.3 Aetiopathogenesis

2.2.3.1 Aetiology

The aetiology of RAS appears to be multifactorial and a number of potential predisposing factors have been proposed. Genetic predisposition might increase susceptibility of RAS development as about 40% of individuals with RAS reported a positive family history of RAS (Jurge et al., 2006). Certain human leukocyte antigen (HLA) haplotypes as well as genetic polymorphisms of certain inflammatory cytokines, serotonin transporter gene, endothelial nitric oxide synthase gene and cell adhesion molecule genes have been suggested to be of aetiological relevance (Albanidou-Farmaki et al., 2008, Karasneh et al., 2011, Alkhateeb et al., 2013, Najafi et al., 2018, Wu et al., 2018). However, these genetic factors might be associated with other confounding factors including ethnic groups.

Local trauma including mechanical injury may predispose to the development of RAS ulcers in susceptible individuals (Stone, 1991). On the other hands, habitual smokers or smokeless tobacco users appear to have lower incidence of having RAS compared to non-smokers. This might be explained by increased keratinisation of the oral mucosa in response of smoking, making it less prone to local trauma. Nicotine and its metabolites can also reduce the level of pro-inflammatory cytokines (IL-1, IL-6 and TNF-α) and/or increase the level of anti-inflammatory cytokines (IL-10) (Subramanyam, 2011, Slebioda et al., 2014). It was postulated that sodium lauryl sulfate (SLS), a synthetic detergent found in most toothpastes, can denature oral mucin layer, the protective barrier of the oral mucosa, and may therefore potentiate RAS.

However, there is limited convincing evidence supporting the benefit of SLS-free toothpastes in the outbreaks of RAS, and further well-designed trials are required (Cheng, 2019).

The association of RAS and deficiencies in haematinics (iron, folate and vitamin B12) and other nutrients (vitamin B1, B2, B6 and C) have been reported (Akintoye and Greenberg, 2014, Chen et al., 2015, Haisraeli-Shalish et al., 1996). However, evidence supporting the role of these micronutrients in pathogenesis of RAS is scarce as only a small proportion of patients receiving supplementation showed clinical improvement of RAS (Nolan et al., 1991, Porter et al., 1992). Hypersensitivity to foodstuff ingredients (e.g. gluten, cow's milk, chocolate, nuts, preservatives, flavouring agents and colouring agents) has been attributed to the onset of RAS in some patients (Natah et al., 2004). However, elimination of the possible triggering foods was found to be beneficial in only a small subset of patients (Hay and Reade, 1984).

Small number of patients have been reported to have an aggravation of RAS during the luteal phase of the menstrual cycle or menopause while others have had remission or improvement of the condition during pregnancy and with oral contraceptives (Natah et al., 2004). This might be explained by an alteration in epithelial turnover driven by changes in the level of progesterone, but a comprehensive review suggested that there is no notable correlation between RAS and altered sex hormone levels (Jurge et al., 2006). While previous studies reported some association between psychological stress and disease activity of RAS (Gallo Cde et al., 2009), it remains difficult to draw a valid causal-relationship whether stress precedes the onset of RAS or is a consequence of having RAS.

2.2.3.2 Pathogenesis

RAS is considered as immune-mediated condition and there are likely several possible mechanisms that drive the pathogenesis of this disease. There is evidence of alteration in cell-mediated immunity in RAS patients from previous studies that those with RAS may have

increased circulating CD8+ and/or reduced CD4+ T lymphocytes compared to healthy individuals (Bachtiar et al., 1998, Sistig et al., 2001). In addition to peripheral blood, previous immunohistochemical studies demonstrated that there is a variation in the proportion of CD4+ and CD8+ T lymphocytic infiltration in the different stage of RAS lesions. While accumulation of CD4+ T lymphocytes was found more in pre- and post-ulcerative phase of RAS, CD8+ T lymphocytes appeared to be more numerous during the presentation of ulcers (Bachtiar et al., 1998, Sun et al., 2000). These finding indicated the important role of cell-mediated immune responses in the development and course of RAS.

Current literature also suggests that the immunological response in RAS may be also a consequence of abnormal cytokine cascade in the oral mucosa (Challacombe et al., 2015). Significantly increased production of Th1 cytokines such as IL-2, IL-12, TNF-α and IFN-γ and decreased secretion of Th2 cytokines such as IL-10 have been observed both in peripheral blood and lesional area of patients with RAS (Buno et al., 1998, Albanidou-Farmaki et al., 2007).

Recently, some researchers hypothesized that RAS is a condition mediated by the activation of Toll-like receptors (TLRs) (Gallo et al., 2012, Hietanen et al., 2012). TLRs are membrane receptors that have abilities to recognize pathogen-associated molecular patterns (PAMPs) or molecules derived from different pathogens such as bacteria, fungi and viruses. The activation of TLRs is associated with imbalance of Th1 and Th2 immune responses as well as changes in permeability of epithelial barrier. Although some studies found the evidence on the change in the expression levels of TLRs in some cohorts of RAS patients, further studies are still required for better understanding of their roles in the pathogenesis of RAS (Gallo et al., 2012, Hietanen et al., 2012, Akintoye and Greenberg, 2014, Challacombe et al., 2015).

2.2.4 Diagnosis

A definitive diagnosis of RAS is mainly dependent on patient history along with clinical examination. A history of recurrent episodes of ulcers since childhood in healthy individuals together with the presence of characteristic round or ovoid ulcers with a yellowish-center and surrounded erythematous haloes usually point towards the diagnosis of RAS. Importantly, recurrent episodes of RAS-like oral ulcers can be a manifestation of several systemic conditions (Jurge et al., 2006). Therefore, careful medical history and physical examination are necessary to exclude any possible underlying causes particularly in atypical cases with the presence of recurrent ulcers after adolescent or those who have coexistent extra-oral symptoms and signs.

The presence of genital ulceration in addition to oral ulcers should raise the suspicion of Behcet's disease. Concurrent gastrointestinal complaint such as diarrhoea or abdominal pain may suggest inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. Those with weight loss and other signs of malabsorption may indicate malabsorption syndrome or gluten sensitive enteropathy. Those with recurrent oral ulcers following the episodes of fever and recurrent infections may have an underlying cyclic neutropaenia. In some patients with coexistence of joint pain or swelling or urethritis, reactive arthritis or Reiter's syndrome should be suspected (Scully, 2006). Patient's drug history in the past two years should be reviewed since there have been reports of medication-induced oral ulcerations. Several drug classes such as NSAIDs, beta-blockers, cytotoxic agents and alendronate as well as antianginal drug like nicorandil have been implicated to cause RAS-like oral ulcers in some patients (Boulinguez et al., 2003).

Full blood count and haematinic screening may be performed in those with signs and symptoms suggestive of nutritional deficiency or haematological disorders. Referral to other specialists for further investigation is required in case of individuals with extraoral

manifestations. Biopsy is not recommended since histopathological features of RAS are not pathognomonic and non-specific but it is indicated in those with persistent oral ulcers for more than 3 weeks to rule out any malignancy or other mucocutaneous conditions (Scully, 2006, Messadi and Younai, 2010).

2.2.5 Management

Treatment strategies for RAS are generally determined by the severity and frequency of the outbreaks. Since there is no curative approach for RAS, the primary therapeutic goal is to control pain, accelerate the healing process and reduce frequency of recurrence (Challacombe et al., 2015). Avoidance of trauma, hard or acidic food and beverages, or any exacerbating factors such as some food ingredients or stress, correction of precipitating factors such as haematinic deficiency together with appropriate oral hygiene care are advocated (Altenburg et al., 2014).

Appropriate topical treatment is generally effective for the majority of patients with RAS (Akintoye and Greenberg, 2014). In cases with infrequent minor RAS, over-the-counter products including topical anaesthetics such as Benzydamine hydrochloride 0.15% spray and lidocaine 2% gel can be applied to individual lesions for temporary symptomatic relief (Matthews et al., 1987). Mucoprotective products such as Gelclair, Orabase or sucralfate suspension can be used to promote ulcer healing (Campisi et al., 1997). Amlexanox paste, a topical agent with anti-inflammatory and anti-allergic properties, has been shown to facilitate healing process of minor aphthous ulceration (Khandwala et al., 1997).

Patients with more frequent and severe episodes of RAS may benefit from the use of topical corticosteroids, which is considered to be mainstay for RAS therapy. Various types and preparations of topical corticosteroids have been reported to be effective in reducing RAS symptoms and healing time particularly when applied in the early stage of the ulcers (Liu et

al., 2012, Akintoye and Greenberg, 2014). However, they neither reduce the rate nor prevent the recurrence of the ulcers. In cases of long-standing major RAS, intralesional injection of corticosteroids may be helpful in shortening healing time (Akintoye and Greenberg, 2014). Topical antimicrobials including tetracycline mouthrinse and minocycline mouthwashes have been advocated to be used for the treatment of herpetiform ulceration as this type of RAS appears to be largely resistant to topical corticosteroids (Challacombe et al., 2015).

Patients with severe episodes of RAS or those unresponsive to topical treatment may be beneficial from the use of systemic medication. Short course of prednisolone with or without steroids-sparing agents such as azathioprine is usually useful in controlling severe episodes of RAS. However, systemic corticosteroids should be discouraged for long-term use or in those with systemic conditions from their numerous side effects (Jurge et al., 2006). Some systemic immunomodulatory medications have been reported to reduce the formation of new RAS lesions, including pentoxifylline (Thornhill et al., 2007), colchicine (Ruah et al., 1988), dapsone (Handfield-Jones et al., 1985) and thalidomide (Hello et al., 2010). Some of these medications, however, have serious adverse side effects and should therefore be reserved for severe cases with close monitoring. Other treatments for RAS documented in the literature include chemical cauterization, herbal therapies (aloe vera, berberine, Yunnan Baiyao, Myrtys communis), levamisole and CO_2 laser (Challacombe et al., 2015).

2.3 PEMPHIGUS VULGARIS

Pemphigus vulgaris (PV) is a rare and potentially life-threatening chronic autoimmune blistering disease predominantly affecting the skin and oral mucosa. The disease is characterized by the formation of intraepithelial blisters as a result of the loss of cell-cell adhesion between epithelial cells (acantholysis) (Schmidt et al., 2019). Immunopathologically, this is caused by the production of IgG autoantibodies against desmoglein (Dsg) 3 and 1, which are structural components maintaining intercellular adhesion of keratinocytes within the

epithelial layer (Black et al., 2005, Mihai and Sitaru, 2007). In the vast majority of patients with PV, the disease presents with oral mucosal blisters and ulcerative lesions (Kneisel and Hertl, 2011). Oral lesions of PV can persist for months before the involvement of the skin and other mucosal sites (McMillan et al., 2015). While mortality associated with PV has dropped dramatically with the use of systemic corticosteroids, morbidity in this patient group remains relatively high (Hsu et al., 2016). Oral manifestations of PV are often associated with debilitating pain and discomfort, leading to difficulties in performing activities such as eating, swallowing, speaking and oral hygiene care. Furthermore, the adverse effects of therapy also represent significant comorbidities and can have a detrimental impact on psychosocial status as well as quality of life of affected individuals (Ni Riordain et al., 2011a).

2.3.1 Epidemiology

The incidence of PV is approximately 1 to 6 per million population per year, with higher rate being observed in those of Mediterranean and Jewish descent (Ashkenazi Jews in particular) (McMillan et al., 2015, Kridin et al., 2016). PV appears to have a slight female predilection (Baum et al., 2016, Kridin et al., 2016) and can affect individuals of any age with the peak disease onset during the fourth and sixth decades of life (Kneisel and Hertl, 2011). Prior to the availability of systemic corticosteroid therapy in the 1950s, the mortality was approximately 90%. In more recent literature, incidence of PV mortality fluctuates from 5 to 30% depending on study population and length of follow-up (Huang et al., 2012).

2.3.2 Clinical features

PV can involve any skin and mucosal surface lined with stratified squamous epithelium. Oral cavity is the most frequently affected mucosal site, and oral sites subjected to frictional trauma including buccal mucosa, palate, lips and gingiva are particularly involved (Mustafa et al., 2015). Cutaneous lesions occur in almost every case; however, lesions of PV classically originate in the oral cavity and can present for months before other mucocutaneous

manifestations (Kasperkiewicz et al., 2017). Other mucosal sites including conjunctival, laryngeal, nasal and anogenital mucosa might also be affected (Venugopal and Murrell, 2012).

Oral lesions of PV usually appear as thin-walled bullae, which can rapidly rupture leaving well-demarcated superficial erythematous erosions usually with whitish ragged edges. The lesions of oral PV continue to enlarge as the epithelium detaches from the periphery, resulting in widespread painful lesions. These erosions can bleed easily and may be covered by yellowish slough when infection supervenes (Mustafa et al., 2015). The lesions of oral PV can persist for weeks or months and may heal slowly without scar formation (Scully et al., 1999b). Symptoms of oral PV range from mild discomfort particularly when chewing hard food to debilitating pain, which together with scarring from oropharynx and esophagus, can interfere with food intake resulting in rapid weight loss (Schmidt et al., 2019).

Cutaneous lesions of PV are characterized by flaccid blisters, erosions and crusts on normal-appearing or erythematous skin. Predilection sites for skin lesions include scalp, neck, axilla, groin and upper trunk although any sites can be affected (Kasperkiewicz et al., 2017). Gentle pressure or mechanical friction onto clinically unaffected area may produce stripping of epithelium, inducing the formation of new lesion, the so-called Nikolsky sign (Schmidt et al., 2019). This phenomenon is a characteristic of PV but is not disease-defining feature as positive Nikolsky sign may also occur in other immunobullous conditions.

2.3.3 Aetiopathogenesis

PV is a classical type II autoimmune condition in which circulating autoantibodies directed against two desmosomal adhesion glycoproteins – desmoglein 1 and 3 (also referred as Dsg1 and Dsg3) – on cell surface of keratinocytes. The binding of autoantibody to Dsg molecules results in the loss of intercellular adhesion within stratified squamous epithelium, resulting in intraepithelial blistering. As tissue distribution of Dsg1 and Dsg3 are different between skin

and oral epithelium, the underlying autoantibody profile plays a significant role in determining clinical phenotypes of PV (Kasperkiewicz et al., 2017). While keratinocytes in oral epithelium express primarily Dsg3, the skin expresses Dsg1 as well as Dsg3. The presence of anti-Dsg3 antibodies alone is therefore associated with mucosal-dominant PV as skin integrity is maintained by Dsg1. In contrast, if both anti-Dsg1 and anti-Dsg3 antibodies are detected, patients may develop more severe mucocutaneous type of PV (Schmidt et al., 2019). The titres of circulating anti-Dsg antibodies are generally proportionate with clinical severity of the disease (Amagai, 2008).

The triggering stimulus inducing the generation of autoantibodies in PV remains unclear although some predisposing factors have been postulated. It was observed that certain HLA class II genes including HLA DRB1*04:02 in Ashkenazi Jews and HLA DQB1*05:03 in other ethnicity were strongly associated with disease severity in patients with PV (Svecova et al., 2015). In genetically predisposed individuals, some exogenous stimuli might play a role in pathogenesis of PV, and they include medications (penicillamine and angiotensin-converting enzyme inhibitors), diet and viral infections (Mustafa et al., 2015). Some autoimmune diseases including myasthenia gravis, ulcerative colitis, rheumatoid arthritis, lupus erythematosus and vitiligo have been reported coexisting in patients with PV (Mohan and Ramesh, 2003, Grandhe et al., 2005).

2.3.4 Diagnosis

Diagnosis of PV is based upon a combination of clinical presentation, perilesional biopsy with histopathology and direct immunofluorescence (DIF) study, and serology (McMillan et al., 2015). Histopathological findings show characteristic acantholysis, or intraepithelial splitting superficial to basal cell layer due to loss of intercellular adherence between keratinocytes in prickle cell layer. The progressive acantholysis then results in the formation of intraepithelial

blister. The floor of the blister may reveal retention of a single layer of basal keratinocytes along the basement membrane zone (Tombstone effect) (Kasperkiewicz et al., 2017).

DIF microscopy of PV demonstrates distinct net-like immune deposits (IgG autoantibodies and occasionally C3, IgM and IgA) along intercellular junctions (McMillan et al., 2015). Apart from tissue biopsy, indirect immunofluorescence (IIF) using monkey esophagus or human skin as substrates can be used to determine level of circulating serum autoantibodies (Ng et al., 2005, Mihai and Sitaru, 2007, Schmidt et al., 2015). The titre of autoantibody has been shown to correlate well with clinical disease activity of oral PV and IIF can therefore be useful as clinical follow-up monitoring tools to guide prognosis and appropriate therapy (Harman et al., 2001). An enzyme-linked immunosorbent assay (ELISA) can specifically detect anti-Dsg1 and anti-Dsg3 autoantibodies and can thus provide higher sensitivity and specificity in distinguishing PV from other intraepithelial immunobullous diseases such as pemphigus foliaceus (Koopai et al., 2018).

2.3.5 Management

The primary goal of management of PV is to induce remission and prevent relapses after achieving remission (Harman et al., 2017). Management of PV should be tailored according to several factors including disease activity and rate of disease progression. Disease activity of PV can be quantified by both clinical disease activity assessment (e.g. the use of validated scoring system) and quantitative measure of autoantibody titre using IIF or ELISA (Harman et al., 2017). Initiation of treatment at early phase of PV is of importance as more severe and extensive disease including mucocutaneous phenotype can be indicative of poorer prognosis (Herbst and Bystryn, 2000). Oral lesions of PV appear to be slower responsive to treatment and less likely to achieve remission off-treatment than solely cutaneous disease (Kavusi et al., 2008).

Systemic administration of corticosteroids remains the cornerstone of initial treatment to gain control of clinical disease activity, which includes new lesions ceasing to form and established lesions beginning to heal (Kasperkiewicz et al., 2017, Harman et al., 2017). Corticosteroids such as prednisolone (0.5-1.5 mg per kg per day) can rapidly suppress disease activity and are effective in all stages of disease particularly remission induction. However, due to potential serious complications from prolonged use of corticosteroids, adjuvant steroid-sparing immunosuppressive agents such as azathioprine, mycophenolate mofetil and cyclophosphamide are initiated to allow reducing cumulative corticosteroid dosage over the course of treatment while maintaining therapeutic benefit from immunosuppression (Cholera and Chainani-Wu, 2016). Once remission is achieved, the dosage of prednisolone is gradually tapered to the lowest possible level (usually 10 mg per day or less) for remission maintenance (Harman et al., 2017).

Good oral hygiene is of utmost importance in cases with oral PV and topical agents may be sometimes helpful for palliative treatment of localised oral lesions (Santoro et al., 2013). Refractory cases may benefit from other treatment alternatives including intravenous immunoglobulin therapy (IVIg) and rituximab (a monoclonal anti-$CD20^{+}$ B cell antibody) to lessen autoantibody production as well as extracorporeal plasmapheresis (plasma exchange) or immunoadsorption to reduce autoantibody load (McMillan et al., 2015).

2.4 MUCOUS MEMBRANE PEMPHIGOID

Mucous membrane pemphigoid (MMP), previously known as cicatricial pemphigoid, comprises a group of chronic subepithelial immunobullous disorders, which predominantly affect the mucous membrane (Chan, 2012). The disease is mediated by immune deposits particularly IgG and sometimes IgA class antibodies to several specific antigens of the epithelial-basement membrane structure components (Di Zenzo et al., 2014). The clinical features of MMP vary greatly in terms of location and severity of the disease. Low-risk sites

such as oral mucosa usually present with localized blisters and ulcerations, the latter of which can be persistent over several months but have a tendency to heal without scarring (Lodi et al., 2010). In contrast, MMP lesions on high-risk sites including conjunctiva, larynx and anogenital region can lead to significant morbidity since subsequent scarring from the lesions can compromise normal functions of these areas, which may culminating in blindness (conjunctiva), airway stenosis (larynx), dysuria and sexual dysfunction (anogenital site) (Chan et al., 2002).

2.4.1 Epidemiology

The precise prevalence of MMP is not known. Previous studies reported an estimated annual incidence of 1.3 and 2.0 cases per million population in French and German dermatologic studies, respectively (Bernard et al., 1995, Bertram et al., 2009). However, oral and ophthalmologic cohorts appear to have a higher incidence (Scully et al., 1999a). MMP certainly tends to arise in middle to late life, being most commonly observed in those in the sixth to eighth decades of life with an average age of onset in range of 60 to 65 years (Schmidt and Zillikens, 2013, Taylor et al., 2015). Childhood onset MMP is rare (Kharfi et al., 2010). A slight female preponderance was observed with an estimated female to male ratio of approximately 2:1 (Xu et al., 2013). There is no ethnic or geographic predilection being observed.

2.4.2 Clinical features

MMP usually clinically manifests initially on recurring blisters on affected sites, which eventually burst and leave painful erosions or ulcers. These erosions and ulcers can sometimes scar and hence interfere with local function (Xu et al., 2013).

Over 85% of MMP patients have oral lesions which can represent the initial and sole manifestation of the condition. Intraorally, MMP frequently affects the gingivae, buccal mucosa, hard and soft palates, tongue and rarely lower lip. Typically, tense fluid-filled bullae

develop before progressing quickly to painful irregular erosive or ulcerative area covered with or without yellowish pseudomembranes (Scully and Lo Muzio, 2008). The most common oral presentation of MMP is desquamative gingivitis (DG), which appears as patchy or generalized gingival desquamation with the area of erosions or ulcers (Xu et al., 2013). MMP was found to be the second most common cause of DG after OLP, accounting for over 25% of the patients in one studied cohort (Suresh and Neiders, 2012).

The eyes are the second most frequent sites of involvement (in 65% of MMP patients) but ocular morbidity from MMP is critical and can substantial affect the quality of life of patients (Xu et al., 2013). Ocular lesions have a wide spectrum of manifestation ranging from mild conjunctival injection, excessive tearing, a local burning sensation or ocular dryness, to erosions, with subsequent scarring leading to symblepharon (fusion between the bulbar and palpebral conjunctiva), ankyloblepharon (adhesion of the eyelids), entropion (inversion of the eyelids), trichiasis (eyelashes rubbing on the eyeballs) and possible blindness (Xu et al., 2013).

MMP can affect mucous membranes other than those of the mouth and eyes. Nasopharyngeal involvement can give rise to nasal discharge or excessive crusting of the nasal mucosae, epistaxis and/or nasal obstruction (Ojha et al., 2007). Laryngeal involvement may cause dysphonia, and progressive scarring of the laryngeal mucosa will cause stridor and very rarely sudden asphyxation due to airway stenosis. Oesophageal involvement can manifest with odynophagia and dysphagia while anogenital disease can cause dysuria and sexual dysfunction (e.g. via vaginal scarring). Cutaneous involvement seems to be uncommon but can manifest with tense blisters of the skin of the scalp and upper body (Xu et al., 2013, Taylor et al., 2015).

MMP usually has a gradual onset and slower progression than other immunobullous diseases such as PV and bullous pemphigoid, with course of intermittent episodes of active and inactive disease. Localized disease can often (but not always) progress into extensive disease with multiple site involvement. Patients with disease restricted only to the oral cavity and/or skin with a minimal tendency of scarring are classified as having “low-risk” MMP whereas “high-risk” MMP refer to disease that cause scarring of ocular, laryngeal, esophageal or anogenital regions. The high risk of MMP to scar in the aforementioned sites related to a poor response to medical or surgical therapies (Chan et al., 2002, Kourosh and Yancey, 2011).

2.4.3 Aetiopathogenesis

MMP is a subepithelial autoimmune blistering disease mediated by the generation of autoantibodies against several components of hemidesmosome and structural proteins in the epithelial-basement membrane zone (Xu et al., 2013). At least six self different antigenic targets have been characterised molecularly including the bullous pemphigoid antigen 2 (BPAg2/ BP 180/a 180-kDa protein/collagen type XVII), the bullous pemphigoid antigen 1 (BPAg1/ BP230/ a 230-kDa protein), laminin 332 (formerly known as laminin 5 and epiligrin), α6 and β4 subunits of integrin and collagen type VII (Schmidt and Zillikens, 2013). The interactions between autoantibodies and these self-antigens trigger a cascade of complement-induced immunologic events resulting in the separation of epithelium from the underlying basement membrane zone and connective tissue (Xu et al., 2013).

Autoantibodies to α6 and β4 integrin subunits appear to be responsible for the MMP patients with exclusive oral and ocular involvement, respectively (Rashid et al., 2006). Anti-BP180 mucosal pemphigoid manifests with concomitant oral and skin lesions, with or without the involvement of other mucous membranes whereas anti-laminin-332 MMP is characterized by oral and ocular mucosal involvement (Mustafa et al., 2015). Notably, some studies suggested the increased risk of developing solid cancers including adenocarcinomas and non-Hodgkin’s

lymphoma during the course of anti-laminin-332 MMP, with the presentation of solid cancers in one third of patients with this disease entity being observed in one study (Sadler et al., 2007, Young et al., 2011).

Present evidence suggests that genetic and environmental factors may influence susceptibility to MMP. MMP may be associated with MHC class II HLA-DQB1*03:01 allele in all clinical phenotypes and HLA-DR4 allele in ocular MMP (Taylor et al., 2015). Severe mucosal injury such as burns or Steven-Johnson syndrome may potentially increase susceptibility of epithelial basement membrane zone antigens for immune processing and hence later development of MMP (Taylor et al., 2015). A number of different drugs have been reported to induce the onset of MMP including methyldopa, D-penicillamine and clonidine (Xu et al., 2013).

2.4.4 Diagnosis

The diagnosis of MMP is reliant upon the recording of an accurate clinical examination and establishment of the histopathological and immunohistochemical features (Taylor et al., 2015). Two specimens from perilesional biopsy should be submitted for histology and DIF studies. Microscopically, MMP shows subepithelial splitting with a mixed inflammatory cell infiltrate of lymphocytes, neutrophils and eosinophils. However, these findings are non-specific and cannot distinguish MMP from other subepithelial blistering diseases such as linear IgA disease and the uncommon epidermolysis bullosa acquisita hence the need for immunohistochemistry to demonstrate appropriate immune deposits (Xu et al., 2013).

DIF study of MMP perilesional tissue gives rise to a continuous, linear band of immunoreactants of IgG (97%), C3 (8%) and/or IgA (27%) along the basement membrane zone (BMZ) (Xu et al., 2013). The striking deposition of IgG4 subclass has also been observed, particularly in the anti-laminin-332 form (Mustafa et al., 2015). Standard IIF usually

fails to detect autoantibodies in serum of patients with MMP due to its low serum reactivity (Schmidt and Zillikens, 2013). When target antigens need to be identified in particularly complex cases, the use of ELISA, immunoblotting and immunoprecipitation techniques may be helpful (Bernard et al., 2013) – but there are not routine diagnostic investigation for MMP.

2.4.5 Management

Management of MMP depends largely on disease activity and site of involvement of patients, and multidisciplinary approach should be adopted to stratify and treat patients according to their risk (low-risk and high-risk cases). In low-risk patients, topical therapies including topical corticosteroids may suffice in those with mild to moderate disease (Di Zenzo et al., 2014). In cases with DG, application of gel-based high-potency topical corticosteroids via the use of prefabricated custom-made trays may facilitate optimal contact time of the drugs on gingival lesions thus perhaps enhancing their efficacy (Gonzalez-Moles et al., 2003, Xu et al., 2013).

In high-risk patients or low-risk patients with moderate to severe disease or acute exacerbation, high-dose short course of systemic corticosteroids such as prednisolone may be employed for controlling the symptoms (Chan et al., 2002). Once high-dose prednisolone (e.g. 0.5-1.5 mg/kg daily) halt new blister formation and disease control is achieved, a careful slow tapering of the drug is advocated. The concomitant use of corticosteroid-sparing immunosuppressive drugs such as azathioprine or mycophenolate mofetil may be helpful in reducing the duration of steroids use to minimize significant adverse effects from long-term steroid use (Chan et al., 2002). For high-risk cases such as ocular MMP with severe refractory disease and rapid progression, cyclophosphamide plus prednisolone, high-dose IVIG infusions and the anti-CD20 antibody rituximab have been employed successfully (Schmidt and Zillikens, 2013).

CHAPTER 3 PATIENT REPORTED OUTCOME MEASURES IN IMMUNOLOGICALLY MEDIATED ORAL MUCOSAL DISEASES: A COMPREHENSIVE REVIEW

3.1 PATIENT REPORTED OUTCOME MEASURES

The past two decades have witnessed a noticeable shift in emphasis on how health and disease are best measured particularly when studying chronic conditions (Devlin et al., 2010). Traditional clinician-reported health outcomes, which may include survival rate, improvement of clinical signs or reduction of laboratory markers, appear to be insufficient in reflecting the actual impact of the disease and associated treatment on each particular patient in comparison to subjective outcomes perceived and reported by the patients (Krabbe, 2017). This realization has led to a substantial increase in the development of patient reported outcome measure or PROM, a validated instrument to capture important outcomes directly from a patient (Devlin et al., 2010).

3.1.1 Definition

The patient-reported outcome measure (PROM) is an instrument (usually a questionnaire) for patients to directly evaluate any aspect of their health without external interpretation of patient's response (U.S. Department of Health and Human Services Food and Drug Administration, 2009). The aim of PROM is to quantify, evaluate and monitor the subjective perception of the impact of the disease from patient's perspective in a standardized way and to incorporate the patient's voice regarding the perception of their health condition and related treatment into clinical practice and research (Sloan et al., 2007, Devlin et al., 2010). The measuring construct of interest can be either unidimensional such as the state of discrete symptoms (e.g. pain intensity) or multidimensional (e.g. health-related quality of life; HRQoL) (Fayers and Machin, 2016b). There are various response formats of PROM items (i.e. questions), which can be either continuous scales (e.g. visual analog scale) or categorical options (e.g. a 0-4 (0, 1, 2, 3, 4) Likert-type scale) (Farnik and Pierzchala, 2012).

3.1.2 Generic versus specific PROMs

PROMs can be broadly categorized into generic and specific instruments. Generic PROMs are designed to measure a wide range of domains of health status or HRQoL and hence have a broad applicability across various groups of patients irrespective of their underlying conditions or illnesses (El Achhab et al., 2008). Generic PROMs can capture salient changes to health and have a potential to detect unexpected effects of an intervention. In comparison to generic PROMs, some PROMs are developed specifically to address the most relevant concerns associated with a target population (Kyte et al., 2015). These specific PROMs appear to be more responsive than generic PROMs in providing relevant details and detecting subtle but significant changes of health associated with a particular condition or a population group. However, they appear to have restricted focus and are not allowed for comparisons across a variety of conditions or populations. Apart from that, they cannot detect additional or unanticipated effects of treatment beyond the scope of instruments (Devlin et al., 2010).

3.1.3 Measurement properties of a PROM

From the perspective of clinical research, a critical step in the clinical trial design is to select a well-designed PROM with sufficient evidence of its fundamental quality properties including the three measurement or psychometric properties (validity, reliability and responsiveness) and interpretability to ensure that the instrument is appropriate and useful for a specific patient population (Mokkink et al., 2010). A psychometrically sound PROM is an instrument that is valid (able to measure what it is intended to measure), reliable (able to produce consistent scores in different occasions) and responsive (able to detect change over time if change does exists). Apart from psychometric performance of an instrument, scores or outcomes of PROMs should also be interpretable or have clinical meanings that are easily understood by both patients and clinicians (Mokkink et al., 2010).

It is imperative that all the measurement properties of a PROM have been rigorously evaluated and considered adequate during its development and validation process. This is to ensure the appropriateness and quality of a PROM in measuring subjective and non-observable concepts of interest in a specific population. As recommended by the consensus-based standards for the selection of health status measurement instruments (COSMIN) guideline, key measurement properties of a PROM are outlined below.

3.1.3.1 Validity

Validity is the degree to which a PROM measures what it is intended to measure (Mokkink et al., 2010). In general, three major types of validity have been described: content validity, criterion validity and construct validity.

Content validity

Content validity is defined as the extent to which the content of a PROM is representative of the conceptual construct it is intended to measure (Mokkink et al., 2010). In other words, it concerns how well does a PROM capture all of the important aspects of the measuring concept from the patient's perspective (Cappelleri, 2016). Content validity can be considered the most important measurement property of a PROM and lack of content validity can affect all other measurement properties (Terwee et al., 2018). The examination of content validity should involve a meticulous judgement of relevance, comprehensiveness and comprehensibility of the items of the PROM (Terwee et al., 2018). Not only all items within a PROM should be relevant for the concept measured (within a specific target population and context of use), all aspects of the measuring concept should be comprehensively covered in a PROM with a clear and easily understood description (Streiner et al., 2015).

Empirical evidence of content validity can be established from documentation of PROM development, which should report concept elicitation and analysis from target patients through

interviews and focus groups together with a comprehensive review of the current literature by experts in the field to warrant relevance and comprehensiveness of an instrument (Patrick et al., 2011a). Apart from that, cognitive interviews that address patient understanding of PROM items should be explicitly documented to ensure scale comprehensibility (Patrick et al., 2011b). In addition to the qualitative assessment, some preliminary quantitative methods using exploratory descriptive analysis, Rasch analyses or item response theory analyses may be supportive in assessing how well response options of the items address the entire continuum of target concept of interest, indirectly reflecting scale comprehensiveness (Cappelleri, 2016).

Criterion validity

Criterion validity demonstrates the extent to which the scores of a PROM adequately relate to another 'criterion' instrument that is regarded as a more accurate or superior measure (Mokkink et al., 2010). Therefore, criterion validity is only applicable to evaluate in situations when a criterion (e.g. a gold standard) is available (de Vet et al., 2015). However, rarely does a gold standard exist in the field of patient-reported outcome measurement with an exception when an instrument is reduced in length from its original version. In this case, the original PROM can be employed as a gold standard instrument (Ware et al., 1995, Mokkink et al., 2010).

Criterion validity is subdivided into concurrent and predictive validity. Concurrent validity assesses the association between the scores of a criterion measure and studied PROM at the same time while predictive validity involves an assessment of how well a target PROM predicts the gold standard in the future (de Vet et al., 2015). The statistical parameters for analyzing criterion validity depends upon the types of instrument outcome scores. For the continuous outcomes, intraclass correlation coefficients can be calculated while the area under the curve,

sensitivity and specificity should be used for the measurement instrument with dichotomous outcome (de Vet et al., 2015, Mokkink et al., 2018).

Construct validity

Construct validity is the extent to which a PROM validly measures the 'construct' or the theoretical concept that it purports to measure (Fayers and Machin, 2016b). The assessment of construct validity involves constructing and evaluating postulated associations of the scores of a PROM with respect to internal relationships within a scale, relationships with scores of other scales or differences between relevant groups (Mokkink et al., 2010, Cappelleri, 2016). While construct validity is often considered less robust than criterion validity, ongoing iterative construct validation can establish substantial evidence supporting validity of a PROM (Cappelleri, 2016). According to the COSMIN consensus, construct validity comprises structural validity, hypotheses testing, and cross-cultural validity (Mokkink et al., 2010).

Structural validity is 'the degree to which the scores of a measurement instrument are an adequate reflection of the dimensionality of the construct to be measured' (Mokkink et al., 2010). Structural validity analyzes internal structure of a PROM and appraises whether items on a subscale of a PROM are homogeneous in measuring the same latent construct, and to what extent do items from one subscale correlate with items from other subscales (Cappelleri, 2016). The assessment of structural validity involves confirmatory factor analysis to examine a priori hypotheses regarding the underlying dimensions of a PROM based upon the theoretical conceptual framework. Goodness-of-fit parameters are used to test whether the data fit the hypothesized factor structure (de Vet et al., 2015).

Empirical evidence for construct validity can be gathered by testing a priori hypotheses regarding expected correlations or differences of the scores between a PROM and other instruments, clinical variables, or other groups of patients (Mokkink et al., 2010). Based on

various designs of the test, hypotheses testing encompasses the test of convergent, discriminant and known group validity (Mokkink et al., 2010). While convergent validity addresses the degree to which the scores of a PROM correlate with other measures that are expected to be related, discriminant validity refers to the extent to which the PROM scores do not correlate or have a weak correlation with other dissimilar measures that they should not theoretically correlate with (Farnik and Pierzchala, 2012). Known group validity concerns the ability of a PROM to distinguish between two clinically distinct groups, and the scores of a PROM are expected to show differences, in a predicted direction, between these groups (Cappelleri, 2016).

In addition to the aspects of structural validity and hypotheses testing, cross-cultural validity is also a significant aspect to consider in case the original instrument is translated into another language or used in a different population. This type of validity concerns whether the performance of the translated or adapted version of the instrument adequately reflect the performance of the original one (Mokkink et al., 2010).

3.1.3.2 Reliability

Reliability is defined as "the extent to which scores for patients who have not changed are the same for repeated measurement under several conditions: for example, using different sets of items from the same PROM (internal consistency), overtime (test-retest), by different persons on the same occasion (interrater) or by the same persons (i.e., raters or responders) on different occasions (intrarater)" (Mokkink et al., 2010). Reliability determines the extent to whether a PROM yields consistent and reproducible results. Evaluation of reliability is broadly divided into two aspects including internal consistency reliability and repeatability reliability (Fayers and Machin, 2016b).

Internal consistency reliability

Internal consistency reliability is defined as “the degree of the interrelatedness among the items” (Mokkink et al., 2010). This aspect of reliability evaluate consistency of responses to items in measuring the same construct, reflecting homogeneity of a scale (Terwee et al., 2007). Prior to the test of internal consistency reliability, the scale requires to be proven unidimensional, and this can be done by performing e.g. factor analysis (Fayers and Machin, 2016b). The most extensively used method for assessing internal consistency reliability is Cronbach’s alpha (α) coefficient (Cappelleri, 2016). Cronbach’s α coefficient is based upon the average item-to-item correlation as well as the number of items and its value varies from 0 to 1, with 0 representing that the items are completely uncorrelated and 1 indicating perfect correlation (Farnik and Pierzchala, 2012). It has been suggested that a well-accepted value of Cronbach’s α coefficient should lie between 0.70 and 0.90 (Nunnally and Bernstein, 2010).

Repeatability reliability

Repeatability reliability or reliability concerns the degree to which whether a PROM, regardless of a single-item or multi-item scale, yields reproducible and repeatable scores from repeated measurement on the same patient if patient’s condition is stable (Fayers and Machin, 2016b). One method of determining reliability of the instrument is to examine test-retest reliability, which concerns stability of a PROM in providing similar results when the measurement are repeated over time. In order to examine test-retest reliability, subjects are asked to complete the same PROM on different time points and the level of agreement between the PROM scores at different occasions indicates the reliability of the PROM. The level of agreement of the test-retest study can be estimated by intraclass correlation coefficient (ICC) for continuous outcomes, and kappa (or weighted kappa) for categorical outcomes (Mokkink et al., 2018).

3.1.3.3 Responsiveness

Responsiveness is defined by the COSMIN as the ability of a PROM to detect change over time in the construct measured (Mokkink et al., 2010). Not only should the scores of a PROM

be valid and reliable when the status of a patient is stable, but these scores should also be responsive to detect relevant changes of patient's status if these alterations of the patient's status do in fact exist (Fayers and Machin, 2016b). Responsiveness can be considered as a measure of longitudinal validity (Terwee et al., 2007). The COSMIN consensus agreed that the only difference between the cross-sectional (construct and criterion) validity and responsiveness is that the former relates to the validity of a single score, the latter refers to the validity of a change score (Mokkink et al., 2010). Analogous to construct and criterion validity, the assessment of responsiveness can be done by testing a priori hypotheses but this hypotheses should focus on the expected correlations between a change score or expected differences in changes between known groups rather than concerning with a single score (Mokkink et al., 2010). The correlation between the change scores of a PROM and those from other instruments that reflects anticipated changes can be regarded as empirical evidence for responsiveness.

3.1.3.4 Interpretability

Interpretability concerns clinical meaningfulness of the scores generated by a PROM. Interpretability is not considered to be a psychometric property of a PROM as it does not concern the quality of an instrument itself (like validity, reliability and responsiveness); however, it refers to what the scores or change scores produced by an instrument mean in clinical context (Mokkink et al., 2010). The numerical scores derived from a PROM should be easily translated into clinically meaningful information that is relevant to patients, clinicians and researchers. The COSMIN consensus highlighted the importance of interpretability by including this characteristic of PROM in the COSMIN taxonomy and remarked that a proper interpretation of a score is considered to be a prerequisite for the well-considered application of a PROM in both clinical setting and research (Mokkink et al., 2010, de Vet et al., 2015).

There are two complementary concepts developed for facilitating the interpretation of PROM outcome scores including minimal important difference and patient acceptable symptom state (Tubach et al., 2005). Minimal important difference (MID) refers to "the smallest difference in score in the domain of interest that patients perceive as important, either beneficial or harmful, and which would lead the clinician to consider a change in the patient's management" (Guyatt et al., 2002). The patient acceptable symptom state or PASS threshold is defined as the highest level or score of the PROM outcome beyond which patients consider their disease or symptoms acceptable (Tubach et al., 2007, Maksymowych et al., 2010). While the MID can be described as a journey that results in the patient "feeling better" or "feeling worse", the PASS equates to an acceptable destination or "feeling well" following treatment (Tubach et al., 2006). Further discussion on the concept of MID and PASS is further provided in the chapter 7 and 8 of the present thesis.

3.1.4 Application of PROMs

PROMs can be applied in different settings and for a variety of reasons. It is increasingly recognized that PROMs should be incorporated in clinical trials (Fitzpatrick et al., 1998, Calvert et al., 2013). In clinical research, PROMs can be used as study endpoints to complement clinical measures as improvement of clinical or laboratory parameters may not always correspond to improvements on how the patient feels or functions (Cappelleri, 2016). PROM instruments can be used to provide supporting evidence for the approval of new drugs that are targeted to reduce symptoms of the conditions, facilitate functioning or improve patient's QofL rather than aiming for the cure of the diseases (U.S. Department of Health and Human Services Food and Drug Administration, 2009). Beyond label claims, PROM information can be useful as evidence for patients, clinicians and other stakeholders such as commissioners to evaluate value-for-money of the medication (Devlin et al., 2010).

PROM data can also be incorporated in clinical practice for monitoring patient's symptoms, conditions and impacts of treatment administered to patients in order to promote patient-centered care and facilitate shared decision-making process between clinician and patient as well as advanced treatment planning (Santana and Feeny, 2014). A recent systematic review suggested that the systematic use of information from PROMs leads to enhanced patient-clinician communication and partnership as well as patient satisfaction with care (Valderas et al., 2008, Chen et al., 2013). Besides, patients with the active role in their healthcare appear to have better compliance and treatment outcomes (Brook et al., 2017). Also, PROM can provide a baseline evaluation of patients' health status, HRQoL or satisfaction to care of specific population and this information can help screening and identifying unmet needs that will lead to the delivery of specific, effective care in these groups of patients (Greenhalgh and Meadows, 1999).

The PROM data can aid in discriminating eligible patients who require supportive treatment by assessing whether the condition of patient is out of the range of patient-acceptable symptom state (PASS) or not from patient's perspective (further discussion on chapter 8). In addition to this, the PROM data can also help identifying patients with special need of advanced drug management. For instance, according to current National Institute for Clinical Excellence (NICE) guidance, psoriasis patients in the UK are eligible for the use of biologics if their responses to a Dermatology Life Quality Index (DLQI) that is one of the dermatology-specific PROM are greater than 10 (Ni Riordain et al., 2015).

Routine use of PROMs offers great potential to improve the quality and results of healthcare by reflecting validated evidence of health outcomes from the perspective of the patient (Black, 2013, Chen et al., 2013). Very recently, the National Quality Forum (NQF) has coined the term 'patient-reported outcome performance measure (PRO-PM)', which refers to a performance measure, which is based upon the aggregation of PROM data for an accountable health care

entity (Basch et al., 2013). The NQF also generated a report summarizing a pathway to the endorsement of PRO-PMs and developed recommendations for assessing PRO-PM from a series of multidisciplinary stakeholder workshops that included clinicians, patients as well as experts in PROM and performance assessment.

3.2 KNOWLEDGE GAP

The aim for the management of immunologically mediated oral mucosal diseases is not for curative intent but mainly for minimizing patients' symptoms and improving patients' oral, psychosocial functioning and quality of life (Mustafa et al., 2015). Therefore, measurement of patient reported outcomes by the use of PROMs in patients with these conditions is of particular importance. There are numerous available PROMs that can be employed to assess these outcomes in patients with immunologically mediated oral mucosal diseases; however, selection of well-designed, appropriate instruments with good evidence of measurement properties and interpretability in these conditions can be challenging. Two reviews have previously investigated the use of PROMs in patients with oral mucosal diseases (Ni Riordain and McCreary, 2010, Ni Riordain et al., 2015), but there remains no comprehensive assessment of the instruments used specifically in studies of patients with OLP, RAS, PV and MMP. In addition, little is known regarding the evidence for psychometric properties as well as interpretability of PROMs assessing oral symptoms, psychosocial status and quality of life in patients with immunologically mediated oral mucosal diseases (OLP, RAS, PV and MMP).

3.3 AIMS

The aims of this chapter were:

1. To review the range of PROMs used for the assessment of oral symptoms, psychosocial status, and quality of life in patients with immunologically mediated oral mucosal diseases (OLP, RAS, PV, MMP)

2. To assess their psychometric properties and interpretability of all identified PROMs in each studied disease
3. To identify PROMs which have been appropriately validated in each studied disease

3.4 METHODS

A series of comprehensive reviews of English language articles in the literature were conducted to explore the development, evidence for psychometric testing and interpretability, and application of PROMs used for the assessment of oral symptoms, psychosocial status and quality of life in patients with immunologically mediated oral mucosal diseases.

3.4.1 Search strategies

A series of structured literature searches were performed on three medical databases, namely the MEDLINE (through PubMed), EMBASE and Web of Science Citation Index to retrieve all relevant clinical studies related to the development, validation and/or use of PROMs in patients with OLP, RAS, PV and MMP. The terms for the search strategies were composed a range of keywords for each disease combined with AND to keywords for each domain of concept.

The following search terms were applied for each disease.

1. OLP: 'oral lichen planus'

2. RAS: 'recurrent aphthous stomatitis' OR 'recurrent oral ulcers'

3. PV: 'pemphigus vulgaris' AND 'oral'

4. MMP: 'mucous membrane pemphigoid' AND 'oral'

The following search terms were applied for each domain of concept.

1. oral symptoms: 'pain' OR 'burning sensation' OR 'symptom*' for OLP

'pain' OR 'discomfort' OR 'symptom*' for RAS

'pain' OR 'symptom*' for MMP and PV

2. psychosocial status: 'psych*' OR 'anxiety' OR 'depress*' OR 'stress' OR

'mood' OR 'emotion*' OR 'social'

3. quality of life: 'quality of life' OR 'oral health related quality of life'

Searches in each domain of oncept were limited to the literature from 1990 until 2016 based on substantial rise in the development and validation of PROMs since 1990 (Garratt et al., 2002). However, due to the large number of articles related to the use of PROMs assessing symptoms, the scope of time frame was then refined to a period of 10 years (2007-2016 inclusive).

3.4.2 Selection criteria

English language, peer-reviewed original articles involving the development, testing of psychometric properties (validity, reliability and responsiveness), documentation of interpretability and/or use of at least one validated PROM for the measurement of oral symptoms, psychosocial status and quality of life in participants with OLP, RAS, PV and MMP were included. Clinical studies using PROMs as a screening instrument rather than for measuring outcomes, clinical studies using ad hoc instrument (instrument developed without psychometric testing), review articles, letters, commentaries, editorials or abstracts were excluded.

3.4.3 Data extraction

All identified PROMs were categorized based upon their underlying concepts into oral symptom-PROMs, psychosocial-PROMs and QoL-PROMs. The number of items, subscales or domains, rating scales and score types and ranges of each identified PROM were then

reviewed and summarized. These PROMs were subsequently evaluated for their evidence for quality properties including measurement properties and interpretability for the application in patients with OLP, RAS, PV and MMP (detailed in Table 3.1).

Quality properties	Definition
Validity	The degree to which a PROM measures the construct(s) it purports to measure
Content validity	The degree to which the content of a PROM adequately reflects the proposed construct to be measured
Construct validity	The degree to which a PROM validly measures the 'construct' or the theoretical concept that it purports to measure
Criterion validity	The degree to which the scores of a PROM adequately relate to another 'criterion' measure that is considered to be a 'gold standard' in the field of study
Reliability	The degree to which the measurement is free from measurement error
Test-retest reliability	The degree to which the same results are obtained on repeated measurement of the same PROM when no change in patient's status has occurred
Internal consistency reliability	The degree of inter-relatedness between the items
Responsiveness	The ability of a PROM to detect change over time in the construct measured
Interpretability	The degree to which one can assign qualitative meaning to a PROM's quantitative scores or change in scores

Table 3.1 Definition of quality properties of an instrument assessed (Mokkink et al., 2010)

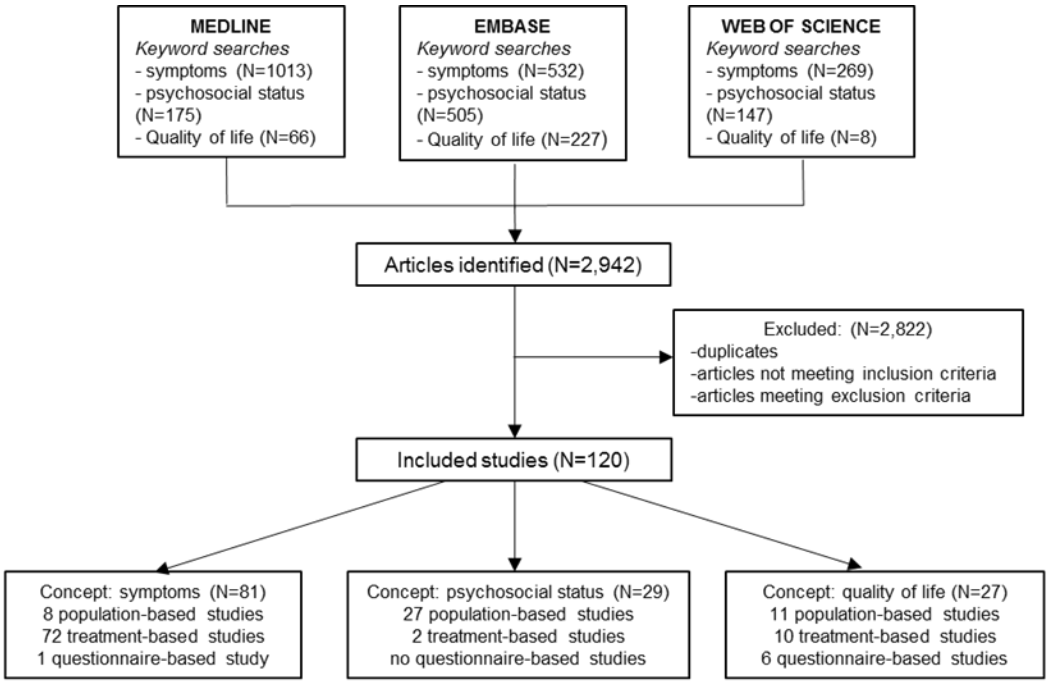
3.5 RESULTS

3.5.1 The use of PROMs in clinical studies of patients with OLP

3.5.1.1 Search results

The initial literature search yielded a total of 2942 citations. After removing duplicates and spurious references, and following a review of the titles and abstracts, 120 articles were considered to meet the inclusion criteria (Figure 3.1).

Figure 3.1 Flow chart showing database search results and number and types of included studies of OLP patients



Note: questionnaire-based study related to the development and/or psychometric testing of PROMs for the use in OLP patients

A total of 41 PROMs were identified from 120 clinical studies of patients with OLP. There were 3 PROMs of oral symptoms, 30 PROMs of psychosocial status and 8 PROMs of quality of life. None of these PROMs were OLP-specific instruments. The name, acronyms and frequency of use of all identified PROMs categorized by concepts measured in the OLP studies are shown in Table 3.2.

Table 3.2 Types (by concepts measured), acronyms and frequency of use of PROMs in clinical studies of patients with OLP

Instrument type and name	frequency of use
PROMs assessing oral symptoms	
Symptoms	
Visual Analog Scale (VAS)	75
Numerical Rating Scale (NRS)	7
Change in Symptoms Scale (CSS)	2
PROMs assessing psychological status	
Anxiety (only)	
State-Trait Anxiety Inventory (STAI)	9
Beck Anxiety Inventory (BAI)	1
Depression (only)	
Beck Depression Inventory (BDI)	7
Centre for Epidemiologic Studies Depression Scales (CES-D)	1
Stress (only)	
Perceived Stress Questionnaire (PSQ)	2
Perceived Stress Scale (PSS)	2
Lipp's Inventory of Stress Symptoms of Adults (LISS)	1
Social Readjustment Rating Scale (SRRS)	1
Test of Recent Experience (TRE)	1
Anxiety and depression	
Hospital Anxiety and Depression Scale (HADS)	7
Anxiety, depression and stress	
Depression, Anxiety and Stress Scale (DASS-42)	3
Anxiety, depression and vulnerability	
Hassanyeh Rating of Anxiety-Depression-Vulnerability (Hassanyeh RADV)	1
Distress/psychological symptoms	
Brief Symptom Inventory (BSI)	1
General Health Questionnaire-12 (GHQ-12)	1
General Health Questionnaire-28 (GHQ-28)	1
Self Reporting Questionnaire (SRQ)	1
Symptom Checklist (SCL-90)	1
Coping	
Coping Orientation to Problems Experienced Inventory (COPE)	1
Freiburg Questionnaire on Coping with Illness-short form (FKV-LIS)	1
Ways of Coping Questionnaire (WCQ)	1
Hardiness	
Hardiness Scale	1
Health locus of control	
Health/Illness Locus of Control Questionnaire (KKG)	1

Table 3.2 Types (by concepts measured), acronyms and frequency of use of PROMs in clinical studies of patients with OLP (cont)

Instrument type and name	frequency of use
PROMs assessing psychological status (cont)	
Psychological well-being	
Psychological General Well-being Index-short form (PGWBI-S)	1
Spirituality	
Systems of Belief Inventory (SBI-14-R-D)	1
PROMs assessing emotional impacts	
Mood	
Mood Adjective Check List (MACL)	1
Profile of Mood States Questionnaire (POMS)	1
Anger	
State-Trait Anger Expression Inventory (STAXI-2)	1
Emotion regulation	
Multidimentional Negative Emotions Self-Regulatory Efficacy Scale (MNESRES)	1
Loneliness	
UCLA Loneliness Scale	1
PROMs assessing social impacts	
Social support	
Social Support Questionnaire-short form (F-SozU-K22)	1
PROMs assessing quality of life	
Oral health related quality of life	
Oral Health Impact Profile-14 (OHIP-14)	12
Oral Health Impact Profile-49 (OHIP-49)	6
Oral Health-Related Quality of Life-UK (OHQOL-UK)	2
Oral Health Impact Profile-German version (OHIP-G)	1
Oral health related quality of life specific to chronic oral mucosal diseases	
Chronic Oral Mucosal Disease Questionnaire (COMDQ)	2
Health related quality of life specific to head and neck cancer	
University of Washington Quality of Life Questionnaire-version 4 (UWQOL V4)	1
General health related quality of life	
Medical Outcome Study Short Form 36 Health Survey (SF-36)	3
Medical Outcome Study Short Form 12 Health Survey (SF-12)	1

3.5.1.2 PROMs assessing oral symptoms of OLP

Three generic PROMs were identified from 81 studies: the visual analog scale (VAS), the numerical rating scale (NRS) and the change in symptoms scale (CSS). The majority of studies (75/81, 92.59%) used the VAS while the NRS and CSS were used in seven (8.64%) and two studies (2.47%), respectively. However, there was a lack in the uniformity in the use of verbal descriptor for the VAS among OLP studies. For instance, “pain” was used in 49 times (in 65.33% of studies using the VAS), followed by “pain and/or burning sensation” (used 12 times; in 16% of studies using the VAS), “burning sensation”, “symptoms”, “pain and/or discomfort” and many others (Table 3.3).

Table 3.3 Word descriptors used in the VAS in the studies assessing oral symptoms of OLP

Word descriptors	**frequency**
pain	49
pain and/or burning sensation	12
burning sensation	5
oral symptoms	4
pain and/or discomfort	3
taste function/disorder	2
breath odor	1
discomfort	1
dry mouth	1
loss of appetite	1
oral freshness	1
pain at rest	1
pain at meal time	1
postoperative pain	1
spontaneous pain	1

Out of the seventy-five OLP studies using the VAS, less than 50% (33/75, 44%) provided clear and accurate information, in the relevant material and methods section, regarding the use of the instrument and the measurement of results; twenty-five articles (33.3%) reported incorrect or unclear information while seventeen articles (22.67%) did not provide any information.

3.5.1.3 PROMs assessing psychosocial status of OLP

A total of 30 PROMs assessing psychosocial status in OLP patients were identified from 29 studies. All of them were generic instruments (Table 3.4), which measure a range of psychosocial concepts including anxiety (20 studies), depression (19 studies), stress (11 studies) and many others. The most frequently used PROMs were the State-Trait Anxiety Inventory (STAI; 9 studies), followed by the Beck Depression Inventory (BDI; 7 studies) and the Hospital Anxiety and Depression Scale (HADS; 7 studies).

3.5.1.4 PROMs assessing quality of life of OLP

A total of 8 PROMs focusing upon quality of life (QoL) in patients with OLP were identified from 27 studies. Six of these PROMs were oral health-related quality of life (OH-QoL) instruments while the other two measured general aspects of QoL (SF-36 and SF-12). Out of the six OH-QoL instruments, two were developed for specific group of patients: individuals with head and neck cancer (UW-QOL) and with chronic oral mucosal diseases (COMDQ). Table 3.5 provides characteristics of these instruments. The most frequently used QoL-PROMs in the OLP population was the Oral Health Impact Profile-14 (OHIP-14; 11 studies), followed by the Oral Health Impact Profile-49 (OHIP-49; 6 studies) and the Medical Outcome Study Short Form 36 Health Survey (SF-36; 3 studies).

Table 3.4 Characteristics of PROMs assessing psychosocial status in clinical studies of patients with OLP

Name	Items (N)	Concept	Subscale (Nitems)	Rating scale	Score types and range		
					Subscales	Total	Others
BAI	21	Anxiety	Anxiety (21)	4-point scale (0-1-2-3)		0-63	
BDI, BDI-II	21	Depression	Depression (21)	4-point scale (0-1-2-3)		0-63	
BSI	53	Psychological symptoms	Somatisation (SOM); Obsessive-compulsive behavior (O-C); Interpersonal sensitivity (I-S); Depression (DEP); Anxiety (ANX); Hostility (HOS); Phobic anxiety (PHOB); Paranoid ideation (PAR); Psychoticism (PSY)	5-point scale (0-1-2-3-4)	✓		GSI* PST* PSDI*
CES-D	20	Depression	Depressive affect (7); Positive affect (4); Somatic and retarded activity (7); Interpersonal (2)	4-point scale (0-1-2-3)		0-60	
COPE	60	Coping	Positive reinterpretation and grow th (4); Mental disengagement (4); Focus on and venting of emotions (4); Use of instrumental social support (4); Active coping (4); Denial (4); Religious coping (4); Humor (4); Behavioural disengagement (4); Restraint (4); Use of emotional social support (4); Substance use (4); Acceptance (4); Suppression of competing activities (4); Planning (4)	4-point scale (0-1-2-3)	4-16		
DASS-42	42	Anxiety, depression, stress	Anxiety (14); Depression (14); Stress (14)	4-point scale (0-1-2-3)	0-42		
FKV-LIS	35	Coping	Depressive coping; Active problem-oriented coping; Distraction and self-motivation; spirituality; Minimisation and w ishful thinking	5-point scale (1-2-3-4-5)	mean of all subscale items		
F-SozU-K22	22	Social support	Emotional support; Practical support; Social integration	5-point scale (1-2-3-4-5)	mean of all subscale items	22-110	
GHQ-12	12	Distress	Distress (12)	4-point scale (0-0-1-1 or 0-1-2-3)		0-12 0-36	
GHQ-28	28	Distress	Somatic symptoms (7); Anxiety and insomnia (7); Social dysfunction (7); Severe depression (7)	4-point scale (0-0-1-1 or 0-1-2-3)	0-7 0-21	0-28 0-84	
HADS	14	Anxiety, depression	Anxiety (HADS-A) (7); Depression (HADS-D) (7)	4-point scale (0-1-2-3)	0-21		
Hardiness Scale	45	Hardiness	Control (15); Commitment (15); Challenge (15)	4-point scale (0-1-2-3)	0-45	0-135	
Hassanyeh RADV	68	Anxiety, depression, vulnerability	Anxiety (AN) (17); Global depression (GD) (47); Vulnerability or Personality Predisposition (PD) (16)	2-point scale (0-1)	N/A		
KKG	21	Health locus of control	Internality (7); Pow erful other externality (7); Chance externality (7)	6-point scale (1-2-3-4-5-6)	mean of all subscale items		
LISS	56	Stress	Phase: Alert (Q1) (16); Resistance amd Near-exhaustion (Q2) (16); Exhaustion (Q3) (24)	2-point scale (0-1)	0-15 (Q1, 2) 0-23 (Q3)		
MACL	72	Mood	Pleasantness/unpleasantness; Activation/deactivation; Extraversion/introversion; Calmness/tension; Positive/negative social orientation; Control/lack of control	4-point scale (0-1-2-3)	N/A		

Table 3.4 Characteristics of PROMs assessing psychosocial status in clinical studies of patients with OLP (cont)

Name	Items (N)	Concept	Subscale (Nitems)	Rating scale	Score types and range		
					Subscales	Total	Others
MNESRES	15	Emotion regulation	Perceived self-efficacy in dealing with negative emotions: Anger/irritation (3); Despondency/sadness (3); Fear (3); Shame/embarrassment (3); Guilt (3)	5-point scale (1-2-3-4-5)	3-15		
PGWBI-S	6	Psychological well-being	Anxiety (1); Vitality (2); Depressed mood (1); Self-control (1); Positive well-being (1)	6-point scale (0-1-2-3-4-5)	✓	0-30	
POMS	65	Mood	Tension (T) (9); Depression (D) (15); Anger (A) (12); Fatigue (F) (7); Confusion (C) (7); Vigour (V) (8)	5-point scale (0-1-2-3-4)	✓		TMD*
PSQ	20	Stress	Worries (5); Tension (5); Joy (5); Demands (5)	4-point scale (1-2-3-4)		20-80	
PSS	10	Stress	Perceived stress (10)	5-point scale (0-1-2-3-4)		0-40	
SBI-15-R-D	15	Spirituality	Belief and practice (10); Social support (5)	4-point scale (0-1-2-3)		0-45	
SCL-90	90	Psychological symptoms	Somatisation (SOM); Obsessive-compulsive behavior (O-C); Interpersonal sensitivity (I-S); Depression (DEP); Anxiety (ANX); Hostility (HOS); Phobic anxiety (PHOB); Paranoid ideation (PAR); Psychoticism (PSY)	5-point scale (0-1-2-3-4)	✓		GSI* PST* PSDI*
SRQ-20	20	Psychological symptoms	Mental health (20)	2-point scale (0-1)		0-20	
SRRS	43	Stress	Stressful life events (43)	2-point scale (0-life change units)		✓ (total life change units)	No of events
STAI	40	Anxiety	State anxiety (STAI-S) (20); Trait anxiety (STAI-T) (20)	4-point scale (1-2-3-4)	20-80		
STAXI-2	57	Anger	State anger (S-Anger) (15) (Feeling angry, S-Ang/F; Feel like expressing anger verbally, S-Ang/V; Feel like expressing anger physically, S-Ang/P); Trait anger (T-Anger) (10) (Angry temperament, T-Ang/T; Angry reaction, T-Ang/R); Anger expression-out (AX/Out) (8); Anger expression-in (AX/In) (8); Anger control-out (AX/Con-Out) (8); Anger control-in (AX/Con-In) (8); Anger expression index (AX index) (32)	4-point scale (1-2-3-4)	✓		AX index* (0-96)
TRE	42	Stress	Vital events (42)	2-point scale (0-life change units)		0-600	
UCLA Loneliness Scale	20	Loneliness	Loneliness (20)	4-point scale (1-2-3-4)		20-80	
WCQ	66	Coping	Confrontive coping (6); Distancing (6); Self-controlling (7); Seeking social support (6); Accepting responsibility (4); Escape-Avoidance (8); Planful problem solving (6); Positive reappraisal (7)	4-point scale (0-1-2-3)	✓		

**Abbreviation: AX index* = AX/Out + AX/In – (AX/Con-Out + AX/Con-In) + 48; GSI = Global Severity Index (mean of all subscale scores); PST = Positive Symptom Total (number of items with score > 0); PSDI = Positive Symptom Distress Index (the sum of all item values divided by PST); TMD = Total Mood Disturbance ([Tension + Depression + Anger + Fatigue + Confusion] - Vigour)*

Table 3.5 Characteristics of PROMs assessing quality of life in clinical studies of patients with OLP

Name	Items (N)	Concept	Subscale (N items)	Rating scale	Score types and range		
					Subscales	Total	Others
COMDQ	26	OH-QOL specific to COMD	Pain & function limitation (PF) (9); Medication & treatment (MT) (6); Social & emotional (SE) (7); Patient support (PS) (4)	5-point scale (0-1-2-3-4)	0-36 for PF 0-24 for MT 0-28 for SE 0-16 for PS	0-104	
OHIP-14	14	OH-QOL	Functional limitation (FL) (2); Physical pain (PhyP) (2); Psychological discomfort (PsyD) (2); Physical disability (PhyDis) (2); Psychological disability (PsyDis) (2); Social disability (SDis) (2); Handicap (H) (2)	5-point scale (0-1-2-3-4)		0-56 (Severity)	Extent*
OHIP-49	49	OH-QOL	Functional limitation (FL) (9); Physical pain (PhyP) (9); Psychological discomfort (PsyD) (5); Physical disability (PhyDis) (9); Psychological disability (PsyDis) (6); Social disability (SDis) (5); Handicap (H) (6)	5-point scale (0-1-2-3-4)	0-36 for FL, PhyP, PhyDis 0-24 for PsyDis, H 0-20 for PsyD, SDis	0-196	
OHIP-G	53	OH-QOL	Functional limitation (FL) (9); Physical pain (PhyP) (9); Psychological discomfort (PsyD) (5); Physical disability (PhyDis) (9); Psychological disability (PsyDis) (6); Social disability (SDis) (5); Handicap (H) (6); Additional German Items (AGI) (4)	5-point scale (0-1-2-3-4)	0-36 for FL, PhyP, PhyDis 0-24 for PsyDis, H 0-20 for PsyD, Sdis 0-16 for AGI	0-212	
OHQOL-UK	16	OH-QOL	Physical effects/impacts (Phy-E/I) (6); Social effects/impacts (S-E/I) (5); Psychological effects/impacts (Psy-E/I) (5)	5-point scale (1-2-3-4-5 for effects and 0-1-2-3-4 for impacts)	6-54 for Phy-E/I 5-45 for S-E/I, Psy-E/I	16-144	
SF-12	12	GH-QOL	Physical functioning (PF) (2); Role physical (RP) (2); Bodily pain (BP) (1); General health (GH) (1); Vitality (VT) (1); Social functioning (SF) (1); Role emotional (RE) (2); Mental health (MH) (2)	2- to 6-point scale			PCS-12 MCS-12
SF-36	36	GH-QOL	Physical functioning (PF) (10); Role physical (RP) (4); Bodily pain (BP) (2); General health (GH) (5); Vitality (VT) (5); Social functioning (SF) (2); Role emotional (RE) (3); Mental health (MH) (5); Health transition (HT) (1)	2- to 6-point scale	0-100 (transformed from raw score)	0-100 (transformed from raw score)	PCS* MCS*
UWQOL-V4	16	H-QofL specific to H&N cancer	Domain: Pain (1); Appearance(1); Activity (1); Recreation (1); Swallowing (1); Chewing (1); Speech (1); Shoulder (1); Taste (1); Saliva (1); Mood (1); Anxiety (1) Importance rating (1) Global score: HRQofL compared to mouth before had cancer (1); HRQofL during the past 7 days (1); Overall QofL during the past 7 days (1)	3- to 6-point scale	0-100		Physical subscale score* Social-Emotional subscale score*

*Note: Extent = N of items reported fairly often (3)/very often (4); GH-QOL = general health related quality of life; H-QOL = health related quality of life; OH-QOL = oral health related quality of life; PCS = Physical Component Summary; MSC = Mental Component Summary; Physical subscale score = Chewing+Swallowing+Speech+Taste+Saliva+Appearance; Social-Emotional subscale score = Anxiety+Mood+Pain+Activity+Recreation+Shoulder function)

3.5.1.5 Evidence for psychometric properties and interpretability of identified PROMs for the use in patients with OLP

Of all identified PROMs, only 6 instruments including 3 PROMs of oral symptoms (VAS, NRS, CSS) and 3 OH-QoL-PROMs (OHIP-14, OHQOL-UK and COMDQ) have been investigated for their psychometric properties in patients with OLP. All three identified oral symptom-PROMs have been demonstrated to have moderate to high correlation with other PROMs measuring oral symptoms, reflecting good construct validity in the OLP population. The NRS was found to have stronger correlation with intensity of erythema and ulceration than the VAS in a cohort of American patients with OLP (Chainani-Wu et al., 2008). Regarding OH-QoL-PROMs, the OHIP-14, OHQOL-UK and COMDQ have been shown to have good evidence of validity (including convergent and discriminant validity), internal consistency reliability and responsiveness to change in OLP patients in the UK (all three PROMs) and Ireland (the COMDQ only). Summary of psychometric testing of all identified PROMs is provided in Table 3.6. Importantly, none of any PROMs used in clinical studies of OLP have evidence for the interpretability of their results in this patient population.

Table 3.6 Summary of psychometric properties of identified PROMs in clinical studies of patients with OLP

Authors	PROMs	Questionnaire language/country	Main Methods of Evaluation	No of patients	Major reported outcomes
(Hegarty et al., 2002)	OHIP-14	English/UK	Convergent validity (correlation with VAS for pain), Discriminant validity between patients with symptomatic and asymptomatic lesions, Internal consistency	48	Correlation with VAS for pain: $r = 0.44$, $p < 0.01$; Significant difference in OHIP-14 scores between patients with symptomatic and asymptomatic lesions; Cronbach's $\alpha = 0.90$
	OHQOL-UK	English/UK	Convergent validity (correlation with VAS for pain), Discriminant validity between patients with symptomatic and asymptomatic lesions, Internal consistency	48	Correlation with VAS for pain: $r = 0.43$, $p < 0.01$; Significant difference in OHIP-14 scores between patients with symptomatic and asymptomatic lesions; Cronbach's $\alpha = 0.93$
(McGrath et al., 2003)	OHIP-14	English/UK	Responsiveness to change	48	Significant postintervention change in OHIP scores ($P = 0.036$)
	OHQOL-UK	English/UK	Responsiveness to change	48	Significant postintervention change in OHIP scores ($P = 0.003$)
(Chainani-Wu et al., 2008)	VAS for symptoms	English/USA	Concurrent validity (correlation with other PROMs measuring symptoms), Construct validity (with clinical sign scores)	33	Strong correlation between VAS and NRS scores ($r > 0.9$, $P < 0.001$) at each visit; Good correlation between difference in VAS scores from previous visit and CSS; mild to moderate correlation with MOMI scores
	NRS for symptoms	English/USA	Concurrent validity (correlation with other PROMs measuring symptoms), Construct validity (with clinical sign scores)	33	Strong correlation between VAS and NRS scores ($r > 0.9$, $P < 0.001$) at each visit; Good correlation between difference in VAS scores from previous visit and CSS; mild to moderate correlation with MOMI scores (stronger than VAS for symptoms)
	CSS	English/USA	Concurrent validity (correlation with other PROMs measuring symptoms), Construct validity (with clinical sign scores)	33	Good correlation between CSS scores and difference in VAS/NRS from previous visit; Low to high correlation with change in MOMI scores
(Ni Riordain and McCreary, 2011)	COMDQ	English/Ireland	Convergent validity (correlation with VAS for pain and OHIP-14), Discriminant validity between patients with and without COMD, Internal consistency	109	Good convergent validity with VAS for pain ($r = 0.883$) and OHIP-14 ($r = 0.819$); Significant difference in COMDQ scores between patients with and without COMD; Cronbach's $\alpha = 0.929$
(Ni Riordain and McCreary, 2012)	COMDQ	English/Ireland	Test-retest reliability, Responsiveness to change	76	Good test-retest reliability (ICC = 0.81); COMDQ is responsive to changes in the patient's overall conditions
(Li and He, 2013)	COMDQ	Chinese/China	Structural validity; Internal consistency; Test-retest reliability	72	EFA extracted four factors (consistent with original english version) and all items demonstrated adequate factor loadings; Cronbach's $\alpha = 0.894$; ICC of total COMDQ scores = 0.83
(Ni Riordain et al., 2016)	COMDQ	English/UK	Convergent validity (correlation with VAS and OHIP-14), Internal consistency	100	Moderate to good convergent validity with VAS and OHIP-14; Cronbach's $\alpha = 0.93$

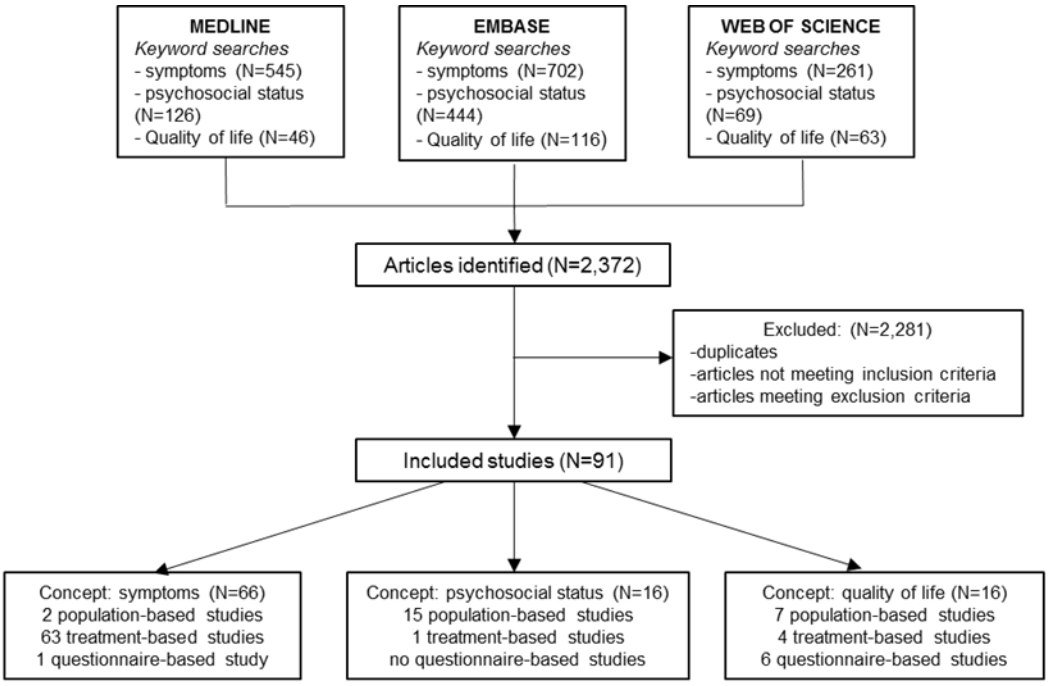
Abbreviation: COMD = chronic oral mucosal disease; EFA = Exploratory factor analysis; ICC = Intraclass correlation coefficient; MOMI = Modified Oral Mucositis Index

3.5.2 The use of PROMs in clinical studies of patients with RAS

3.5.2.1 Search results

Database searches identified 2,372 potentially relevant citations, which included duplicates and spurious references. When assessed against the selection criteria, a total of 91 articles were included in this review (Figure 3.2).

Figure 3.2 Flow chart showing database search results and number and types of included studies of RAS patients



Note: questionnaire-based study related to the development and/or psychometric testing of PROMs for the use in RAS patients

Overall, a total of 25 PROMs used for the assessment of patient reported outcomes in patients with RAS were identified from 91 publications. There were 4 PROMs of oral symptoms, 13 PROMs of psychosocial status and 8 QOL-PROMs. The name, acronyms and frequency of use of all identified PROMs categorized by concepts measured in clinical studies of RAS are shown in Table 3.7.

Table 3.7 Types (by concepts measured), acronyms and frequency of use of PROMs in clinical studies of patients with RAS

Instrument type and name	frequency of use
PROMs assessing oral symptoms	
Symptoms	
Visual Analog Scale (VAS)	58
Numerical Rating Scale (NRS)	6
Graded Chronic Pain Scale (GCPS)	1
Pain, functional status and oral ulcer activity	
Mumcu's composite index (CI)	1
PROMs assessing psychosocial status	
Anxiety (only)	
State-Trait Anxiety Inventory (STAI)	3
Self-Rating Anxiety Scale (SAS)	1
Depression (only)	
Beck Depression Inventory (BDI)	2
Quick Inventory of Depressive Symptomatology (QIDS-SR16)	1
Stress (only)	
Recent Life Change Questionnaire (RLCQ)	1
Symptoms of Stress List (SSL)	1
Test of Recent Experience (TRE)	1
Anxiety and depression	
Hospital Anxiety and Depression Scale (HADS)	5
Anxiety and anger	
State-Trait Personality Inventory (STPI)	1
Distress/psychological symptoms	
General Health Questionnaire-12 (GHQ-12)	1
General Health Questionnaire-28 (GHQ-28)	1
Symptom Checklist (SCL-90)	1
Coping	
Ways of Coping Questionnaire (WCQ)	1
PROMs assessing quality of life	
Oral health related quality of life	
Oral Health Impact Profile-14 (OHIP-14)	8
Oral Health-Related Quality of Life-UK (OHQOL-UK)	3
Oral Health Impact Profile-49 (OHIP-49)	1
Oral Impacts on Daily Performances (OIDP)	1
Oral health related quality of life specific to chronic oral mucosal diseases	
Chronic Oral Mucosal Disease Questionnaire (COMDQ)	1
Oral health related quality of life specific to children	
Child Oral Impacts on Daily Performances (Child-OIDP)	1
General health related quality of life	
Medical Outcome Study Short Form 36 Health Survey (SF-36)	3
Medical Outcome Study Short Form 12 Health Survey (SF-12)	1

3.5.2.2 PROMs assessing oral symptoms of RAS

A total of 4 PROMs were identified from 66 studies. There were 3 generic PROMs utilized for the assessment of oral symptoms of RAS in 65 studies: the VAS, the NRS and the graded chronic pain scale (GCPS). The majority of studies (58/65, 89.23%) used the VAS while the NRS were used in six studies (9.23%) and only one study (Sherman et al, 2007) used GCPS. Word descriptors in VAS differed considerably among included studies. The most common word descriptor used in the VAS was “pain” (48 times, used in 76.19% of the VAS in RAS studies), followed by “pain and/or burning sensation” (4 times, used in 6.35% of the VAS in RAS studies) and many others (Table 3.8).

Table 3.8 Word descriptions used in VAS in the studies assessing oral symptoms of RAS

Word descriptors	**frequency**
pain	48
pain and/or burning sensation	4
burning sensation	1
contact pain	1
discomfort during brushing	1
discomfort during eating	1
discomfort during speaking	1
idiopathic pain	1
irritation	1
pain and discomfort	1
pain and irritation	1
pain and tingling	1
soreness	1

Out of the fifty-eight RAS studies using the VAS, only twenty-four studies (41.38%) provided clear and accurate information, in the relevant material and methods section, regarding the use of the instrument and the measurement of results; twenty articles (34.48%) reported incorrect or unclear information while fourteen articles (24.14%) did not provide any information.

Apart from generic PROMs, there was one disease-specific instrument identified for the assessment of RAS-related pain and other different constructs: Mumcu's composite index (composite index: instrument generating single combined score of two or more individual components). It was developed by Mumcu et al (2009) for determining the impact of oral ulcer activity in RAS and Behcet's disease, with the input from 7 patients with RAS and 18 patients with BD. This composite index consists of 3 scales assessing three different constructs including oral ulcer activity (as reflected by the presence or absence of oral ulcers in the previous month; 0 - 1 point), pain (measured by the VAS; 0 – 5 points) and functional status (assessed the impacts of oral ulcers on taste, speaking, and eating/chewing/swallowing on a 5-point Likert-type scale; 0 - 4 points), with total score of 10. However, this composite index was validated for use only in Turkish population, without any evidence of translation or cross-cultural validation for other countries/languages.

3.5.2.3 PROMs assessing psychosocial status of RAS

A total of 13 PROMs have been used for the evaluation of psychosocial status in patients with RAS from 16 clinical studies. All of the included PROMs are generic instruments (Table 3.9), which measure different psychological and emotional constructs including anxiety (10 studies), depression (7 studies), stress (4 studies), distress/psychological symptoms (3 studies), coping (1 study) and anger (1 study). The most commonly used PROMs were the HADS (5 studies), followed by the STAI (3 studies).

3.5.2.4 PROMs assessing quality of life of RAS

A total of 8 QOL-PROMs were identified from 16 studies. Six of these PROMs assessed oral health-related quality of life while two (SF-36 and SF-12) examined general aspects of quality of life. Of six OH-QoL-PROMs, one instrument was developed for the use in children aged 11-12 years old. Table 3.10 provides characteristics of these instruments. The most frequently used QoL-PROMs in RAS population was the OHIP-14 (8 studies), followed by the OHQOL-UK (3 studies) and SF-36 (2 studies).

Table 3.9 Characteristics of PROMs assessing psychosocial status in clinical studies of patients with RAS

Name	Items (N)	Concept	Subscale (Nitems)	Rating scale	Score types and range		
					Subscales	Total	Others
BDI, BDI-II	21	Depression	Depression (21)	4-point scale (0-1-2-3)		0-63	
GHQ-12	12	Distress	Distress (12)	4-point scale (0-0-1-1 or 0-1-2-3)		0-12 0-36	
GHQ-28	28	Distress	Somatic symptoms (7); Anxiety and insomnia (7); Social dysfunction (7); Severe depression (7)	4-point scale (0-0-1-1 or 0-1-2-3)	0-7 0-21	0-28 0-84	
HADS	14	Anxiety, depression	Anxiety (HADS-A) (7); Depression (HADS-D) (7)	4-point scale (0-1-2-3)	0-21		
QIDS-SR16	16	Depression	Depression (16)	4-point scale (0-1-2-3)		0-27	
RLCQ	68	Stress	Stressful life events (91)	2-point scale (0-life change units)		✓ (total life change units)	No of events
SAS	20	Anxiety	Anxiety (20)	4-point scale (1-2-3-4)		20-80	
SCL-90	90	Psychological symptoms	Somatisation (SOM); Obsessive-compulsive behavior (O-C); Interpersonal sensitivity (I-S); Depression (DEP); Anxiety (ANX); Hostility (HOS); Phobic anxiety (PHOB); Paranoid ideation (PAR); Psychoticism (PSY)	5-point scale (0-1-2-3-4)	✓		GSI* PST* PSDI*
SSL	59	Stress	Stress (59)	4-point scale (0-1-2-3)		0-177	
STAI	40	Anxiety	State anxiety (STAI-S) (20); Trait anxiety (STAI-T) (20)	4-point scale (1-2-3-4)	20-80		
STPI	80	Anxiety, anger	State anxiety (10); Trait anxiety (10); State anger (10); Trait anger (10); State curiosity (10); Trait curiosity (10); State depression (10); Trait depression (10)	4-point scale (1-2-3-4)	10-40		
TRE	42	Stress	Vital events (42)	2-point scale (0-life change units)		0-600	
WCQ	66	Coping	Confrontive coping (6); Distancing (6); Self-controlling (7); Seeking social support (6); Accepting responsibility (4); Escape-Avoidance (8); Planful problem solving (6); Positive reappraisal (7)	4-point scale (0-1-2-3)	✓		

**Abbreviation:* GSI = Global Severity Index (mean of all subscale scores); PST = Positive Symptom Total (number of items with score > 0); PSDI = Positive Symptom Distress Index (the sum of all item values divided by PST)

Table 3.10 Characteristics of PROMs assessing quality of life in clinical studies of patients with RAS

Name	Items (N)	Concept	Subscale (N items)	Rating scale	Score types and range		
					Subscales	Total	Others
Child-OIDP	8	OHQOL specific to children	Eating (1); Speaking (1); Cleaning teeth (1); Smiling (1); Emotional stability (1); Relaxing (1); Doing schoolwork (1); Social contact (1)	4-point scale on frequency and severity (0-1-2-3)		Total (0-100) (each item score: frequency x severity x 100/72)	
COMDQ	26	OH-QOL specific to COMD	Pain & function limitation (PF) (9); Medication & treatment (MT) (6); Social & emotional (SE) (7); Patient support (PS) (4)	5-point scale (0-1-2-3-4)	0-36 for PF 0-24 for MT 0-28 for SE 0-16 for PS	0-104	
OHIP-14	14	OH-QOL	Functional limitation (FL) (2); Physical pain (PhyP) (2); Psychological discomfort (PsyD) (2); Physical disability (PhyDis) (2); Psychological disability (PsyDis) (2); Social disability (SDis) (2); Handicap (H) (2)	5-point scale (0-1-2-3-4)		0-56 (Severity)	Extent*
OHIP-49	49	OH-QOL	Functional limitation (FL) (9); Physical pain (PhyP) (9); Psychological discomfort (PsyD) (5); Physical disability (PhyDis) (9); Psychological disability (PsyDis) (6); Social disability (SDis) (5); Handicap (H) (6)	5-point scale (0-1-2-3-4)	0-36 for FL, PhyP, PhyDis 0-24 for PsyDis, H 0-20 for PsyD, SDis	0-196	
OHQOL-UK	16	OH-QOL	Physical effects/impacts (Phy-E/I) (6); Social effects/impacts (S-E/I) (5); Psychological effects/impacts (Psy-E/I) (5)	5-point scale (1-2-3-4-5 for effects and 0-1-2-3-4 for impacts)	6-54 for Phy-E/I 5-45 for S-E/I, Psy-E/I	16-144	
OIDP	8	OH-QOL	Eating (1); Speaking and pronouncing clearly (1); Cleaning teeth (1); Sleeping and relaxing (1); Smiling without embarrassment (1); Maintaining emotional state (1); Enjoying contact with other people (1); Carrying out major school work (1)	6-point scale on frequency and severity (0-1-2-3-4-5)		Total (0-100) (each item score: frequency x severity x 100/150)	
SF-12	12	GH-QOL	Physical functioning (PF) (2); Role physical (RP) (2); Bodily pain (BP) (1); General health (GH) (1); Vitality (VT) (1); Social functioning (SF) (1); Role emotional (RE) (2); Mental health (MH) (2)	2- to 6-point scale			PCS-12 MCS-12
SF-36	36	GH-QOL	Physical functioning (PF) (10); Role physical (RP) (4); Bodily pain (BP) (2); General health (GH) (5); Vitality (VT) (5); Social functioning (SF) (2); Role emotional (RE) (3); Mental health (MH) (5); Health transition (HT) (1)	2- to 6-point scale	0-100 (transformed from raw score)	0-100 (transformed from raw score)	PCS* MCS*

*Note: Extent = N of items reported fairly often (3)/very often (4); GH-QOL = general health related quality of life; OH-QOL = oral health related quality of life; PCS = Physical Component Summary; MSC = Mental Component Summar

3.5.2.5 Evidence for psychometric properties and interpretability of identified PROMs for the use in patients with RAS

Of all identified PROMs, 5 PROMs including 4 QoL-PROMs (SF-36, OHIP-14, OHQOL-UK and COMDQ) and the Mumcu's composite index have been investigated for their psychometric properties in RAS patients. Of five PROMs with psychometric properties tested, only the COMDQ was found to have good psychometric evidence on all major measurement properties including validity, reliability and responsiveness in patients with RAS, while Mumcu's composite index have been examined for its validity and reliability in patients with RAS in Turkey (Mumcu et al, 2009). Three other QoL-PROMs including the SF-36, OHIP-14 and OHQOL-UK were investigated only for their internal consistency reliability in Turkish patients with RAS (Mumcu et al, 2006), with results showing high Cronbach's α coefficient ($\geq$ 0.92) in all instruments. However, other measurement properties including validity and responsiveness in these QoL-PROMs have yet been examined in RAS population. Table 3.11 summarises the psychometric testing of the reviewed PROMs. Importantly, none of any PROMs used in clinical studies of RAS have evidence for interpretability in this patient population.

Table 3.11 Summary of psychometric properties of identified PROMs in clinical studies of patients with RAS

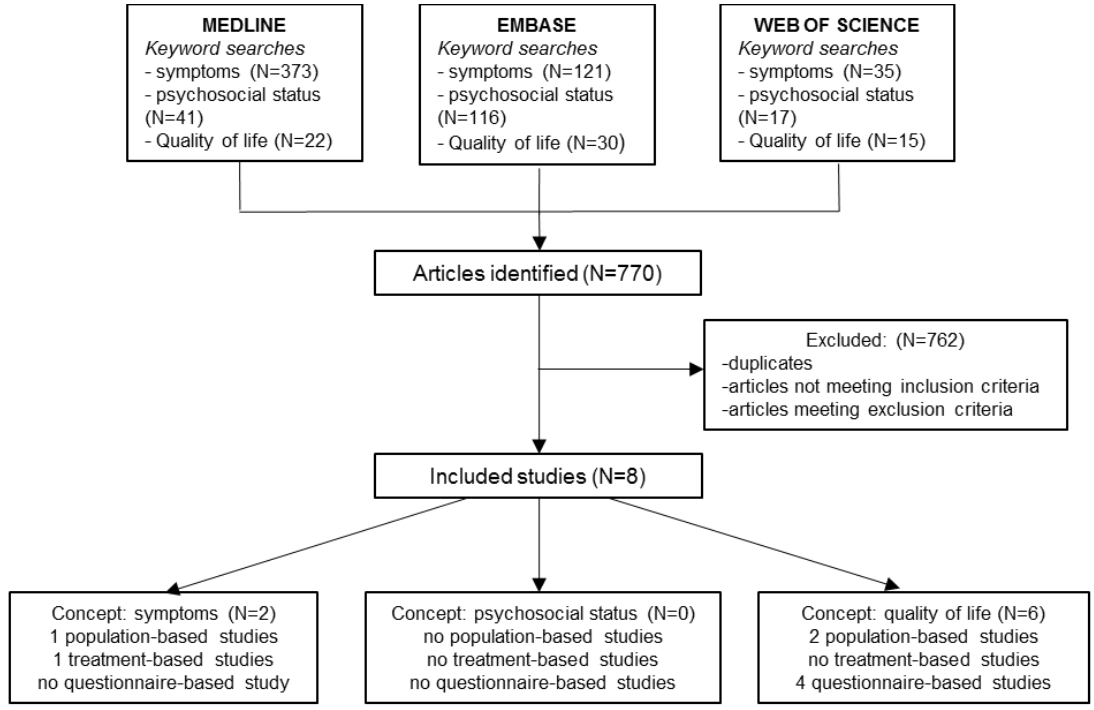
Authors	PROMs	Questionnaire language/country	Main Methods of Evaluation	No of patients	Major reported outcomes
(Mumcu et al., 2006)	OHIP-14	Turkish/Turkey	Internal consistency	24	Cronbach's α = 0.95
	OHQOL-UK	Turkish/Turkey	Internal consistency	24	Cronbach's α = 0.97
	SF-36	Turkish/Turkey	Internal consistency	24	Cronbach's α = 0.92
(Mumcu et al., 2007)	OHIP-14	Turkish/Turkey	Structural validity	28	FA revealed three subscales and explained 66.49% of overall variance in patients with active oral ulcers
(Mumcu et al., 2009)	Mumcu's composite index (CI)	Turkish/Turkey	Convergent validity (correlation with VAS for pain, number of oral ulcers, frequency of relapses); Discriminant validity between patients with oral ulcers (RAS and BD) and patients with dental infections; Internal consistency	31	Moderate to good convergent validity of total CI score with VAS for pain (r = 0.90), number of oral ulcers (r = 0.77) and frequency of relapse (r = 0.51); No CI score in patients with dental infections; Cronbach's α for functional disability score = 0.75
(Ni Riordain and McCreary, 2011)	COMDQ	English/Ireland	Convergent validity (correlation with VAS for pain and OHIP-14), Discriminant validity between patients with and without COMD, Internal consistency	12	Good convergent validity with VAS for pain (r = 0.883) and OHIP-14 (r = 0.819); Significant difference in COMDQ scores between patients with and without COMD; Cronbach's α = 0.929
(Ni Riordain and McCreary, 2012)	COMDQ	English/Ireland	Test-retest reliability, Responsiveness to change	?	Good test-retest reliability (ICC = 0.81); COMDQ is responsive to changes in the patient's overall conditions
(Li and He, 2013)	COMDQ	Chinese/China	Structural validity; Internal consistency; Test-retest reliability	84	EFA extracted four factors (consistent with original english version) and all items demonstrated adequate factor loadings; Cronbach's α = 0.894; ICC of total COMDQ scores = 0.83
(Ni Riordain et al., 2016)	COMDQ	English/UK	Convergent validity (correlation with VAS and OHIP-14), Internal consistency	42	Moderate to good convergent validity with VAS and OHIP-14; Cronbach's α = 0.93

3.5.3 The use of PROMs in clinical studies of patients with oral PV

3.5.3.1 Search results

Database searches of existing literature yielded 770 publications. Following removal of duplications and a review of the titles and abstracts of these studies, 8 articles were considered to meet the eligibility criteria (Figure 3.3). Overall, a total of 4 PROMs were identified for the assessment of patient reported outcomes in patients with oral PV. No any PROMs were PV-specific instrument.

Figure 3.3 Flow chart showing database search results and number and types of included studies of patients with oral PV



Note: questionnaire-based study related to the development and/or psychometric testing of PROMs for the use in PV patients with oral manifestations

3.5.3.2 PROMs assessing oral symptoms of PV

The VAS was the only PROM used for the assessment of oral symptoms in PV population with oral manifestations in three clinical studies (Nazemi Tabrizi et al., 2012, Czerninski et al., 2014, Gambino et al., 2014). Each study used different word descriptors in the VAS and NRS including oral symptoms (e.g. discomfort, itching, burning or pain) (Czerninski et al., 2014), pain (Gambino et al., 2014) and continuous and food-triggered pain (Nazemi-Tabrizi et al., 2012).

Out of these 3 studies using the VAS, only one study provided clear and accurate information, in the relevant material and methods section, regarding the use of the instrument and the measurement of results while the remaining two articles reported unclear or incorrect information. For example, one study stated that “pain was quantified using a VAS from 0 to 10”, which appear to reflect the NRS rather than the VAS.

3.5.3.3 PROMs assessing psychosocial status of oral PV

There were no any psychosocial PROMs assessing psychosocial status in patients with oral PV identified.

3.5.3.4 PROMs assessing quality of life of oral PV

A total of 3 PROMs have been used for the evaluation of quality of life in patients with MMP in the included studies including the COMDQ, OHIP-49 and SF-36; however, only the COMDQ has been examined for their psychometric properties (validity, reliability and responsiveness) in patients with oral PV.

3.5.3.5 Evidence for psychometric properties and interpretability of identified PROMs for the use in patients with oral PV

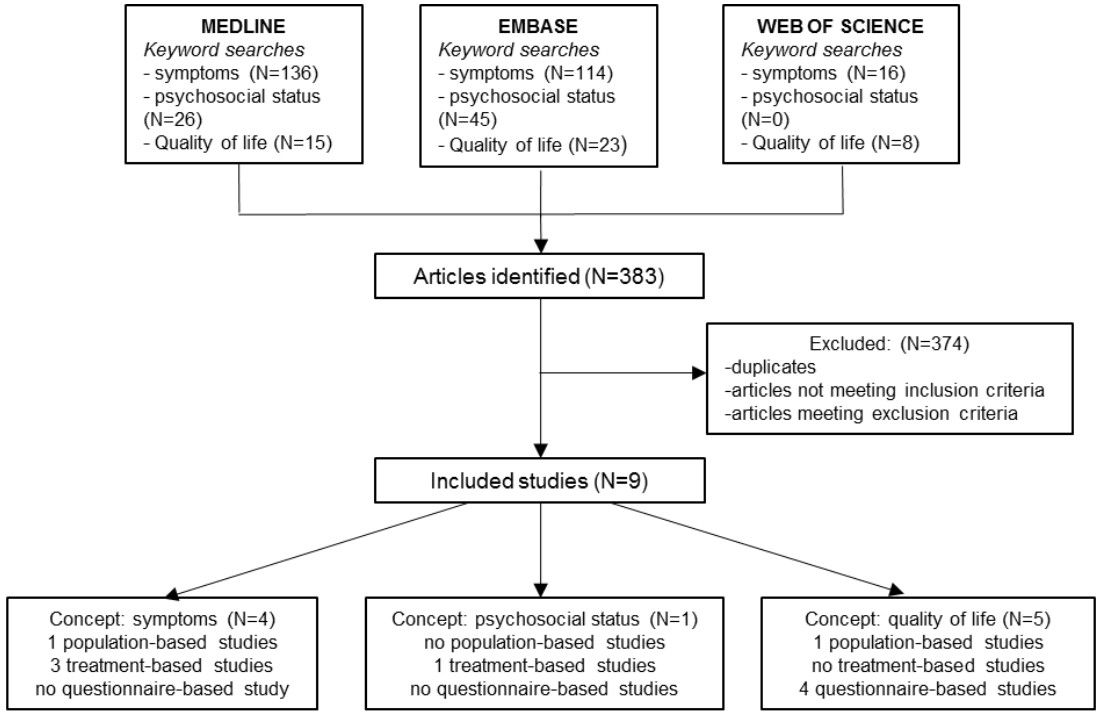
With respect to identified oral symptom-PROMs, the VAS has never been examined for its psychometric performance and interpretability in individuals with oral PV. Also, no evidence exists for psychometric testing or interpretability of psychosocial-PROMin individuals with oral PV documented in the literature. Of all QoL-PROMs identified, the COMDQ was the only PROM to have been examined for psychometric performance in individuals with oral PV and was found to have sufficient psychometric evidence on all main measurement properties including construct validity through convergent and discriminant validity testing, reliability (both test-retest reliability and internal consistency reliability) and responsiveness for use in this patient group (Ni Riordain and McCreary, 2011, Ni Riordain and McCreary, 2012). Importantly, none of the QoL-PROMs used in patients with oral PV has evidence or documentation of interpretability of their scores in this patient population.

3.5.4 The use of PROMs in clinical studies of patients with oral MMP

3.5.4.1 Search results

Initially 383 citations were identified from the literature searches, which included duplicates and spurious references. Following a review of the titles and abstracts of these studies, nine original studies met all the selection criteria and were included in the review (Figure 3.4). Overall, a total of 5 PROMs have been used for the assessment of patient reported outcomes in patients with oral manifestations of MMP. None of the PROMs were MMP-specific instrument.

Figure 3.4 Flow chart showing database search results and number and types of included studies of patients with oral MMP



Note: questionnaire-based study related to the development and/or psychometric testing of PROMs for the use in MMP patients with oral manifestations

3.5.4.2 PROMs assessing oral symptoms of MMP

The VAS was the only PROM used for the assessment of symptom intensity in patients with oral MMP in four clinical studies (Oliveira et al., 2009, Arduino et al., 2012, Cafaro et al., 2012, Czerninski et al., 2014). The following word descriptors for the VAS were used: oral symptoms

(e.g. discomfort, itching, burning or pain) (Cafaro et al., 2012, Czerninski et al., 2014) and pain (Oliveira et al., 2009, Arduino et al., 2012).

3.5.4.3 PROMs assessing psychosocial status of oral MMP

The profile of mood state (POMS) was the only psychosocial PROM identified for the application in MMP population with oral manifestations in one case report (Oliveira et al., 2009).

3.5.4.4 PROMs assessing quality of life of oral MMP

A total of 2 PROMs have been used for the evaluation of quality of life in patients with oral MMP including the OHIP-49 and SF-36 in one cross-sectional study (Lopez-Jornet et al., 2009).

3.5.4.5 Evidence for psychometric properties and interpretability of identified PROMs for the use in patients with oral MMP

None of any identified PROMs have been validated for use in patients with oral MMP. While the COMDQ was examined for their psychometric properties (validity, reliability and responsiveness) during its development phase in patients with MMP (Ni Riordain and McCreary, 2011, Ni Riordain and McCreary, 2012), this PROM still has never been used for the assessment of quality of life in clinical studies of patients with oral MMP.

3.5.5 Identification of PROMs which have been appropriately validated in immunologically mediated oral mucosal diseases

Of all identified PROMs used in immunologically mediated oral mucosal diseases, the COMDQ is the only QoL-PROM specific to patients with chronic oral mucosal diseases, that has appropriate documentation of psychometric evidence in all of the conditions of interest (OLP, RAS, PV, MMP). Furthermore, it is the only instrument that incorporated inputs from

patients with these conditions during its development process, and this reflects good level of content validity for immunologically mediated oral mucosal diseases. Apart from the COMDQ, both OHIP-14 and OHQOL-UK are other OH-QoL-PROMs with good psychometric evidence for use in OLP and RAS. The OHIP-14 is considered the most extensively used OH-QoL-PROM in the field of dentistry while OHQOL-UK is the only instrument capturing all aspects of OH-QoL that are relevant and specific to the UK population. As both PROMs are generic, they can be used to compare levels of OH-QoL of patients with immunologically mediated oral mucosal diseases and other oral and dental conditions.

As for PROMs assessing oral symptoms, both the NRS and VAS are the most frequently used instruments in the literature of immunologically mediated oral mucosal diseases. Both instruments have been demonstrated good psychometric properties for their use in the OLP population, but they have yet been validated in other oral mucosal conditions.

There are currently no psychosocial PROMs undergoing psychometric validation in patients with immunologically mediated oral mucosal diseases and further psychometric studies of these PROMs are required.

3.6 DISCUSSION

3.6.1 The use of PROMs in clinical studies of patients with OLP

Oral lichen planus can give rise to longstanding painful symptoms to the oral mucosa, often leading to psychological distress and a reduction in the quality of life of affected individuals (Eisen, 2002, Thongprasom et al., 2010, Ni Riordain et al., 2011a). Patient reported outcome measures are crucial in assessing and measuring the effect of the disease, as well as medical interventions, as perceived by the affected patients, and provide information that are complementary to the clinician-based clinical assessment of the condition (Devlin et al., 2010). A wide range of PROMs have been used in clinical studies of OLP; however, there remains

no comprehensive review of these instruments, and more importantly, there is no thorough critical assessment of their psychometric properties and interpretability. As a consequence little guidance is available for clinicians as regards to which instruments have been appropriately validated and therefore could be used for treatment and research of OLP.

In the present study, three PROMs (VAS, NRS and CSS) have been used to assess oral symptoms of OLP, with the VAS being the most common. However, there was a wide variability and lack of consistency in the type of oral symptoms measured by this instrument, as reflected by a number of different descriptors including "pain," "pain at rest," "discomfort," "burning sensation" and many others (Table 3.3). This heterogeneity makes study comparison and data pooling difficult. In addition, the material and method sections of the reviewed studies provided the necessary information about the use and interpretation of the VAS only in 44% of instances (Jensen et al., 1986, Jensen and McFarland, 1993). In the remaining studies, information on the VAS was either absent or incorrect; for example, one study stated that "*patients rated their symptoms on a scale from 0 to 10*," which appear to reflect the NRS rather than the VAS.

Both the VAS and NRS have been validated in patients with OLP resident in the US, and the NRS was found to have better construct validity than the VAS, as demonstrated by higher correlations with clinical manifestations (Chainani-Wu et al., 2008). Other strengths of the NRS over the VAS include its simplicity of scoring, better compliance owing to its comprehensibility and ease of completion, as well as the fact that it can be used in greater variety of patients including the elderly and those with motor problems (Hawker et al., 2011). Therefore, the NRS may be considered a better instrument than the VAS for the measurement of oral symptoms in the OLP population. Nevertheless, there is no any studies providing information regarding the interpretability of PROMs of oral symptoms in the OLP population, which raises concerns regarding the clinical meaning of their results (Mokkink et al., 2010, Cook et al., 2014).

The present review also identified a wide range of PROMs focusing on the psychosocial status of OLP patients. Studies have used instruments relevant to psychological constructs (anxiety, depression, stress, distress, coping with illness, hardiness, health locus of control, psychological symptoms and well-being, spirituality and vulnerability), as well as emotional (mood, emotion regulation, anger, loneliness) and social constructs (social support).

Anxiety and depression were the most frequently assessed psychosocial concepts in OLP population, and the STAI, BDI and HADS were the most commonly used PROMs in OLP studies. All three instruments have demonstrated good psychometric properties in a general population (Spielberger and Gorsuch, 1983, Beck et al., 1988, Snaith, 2003); however, all of them lack psychometric evidence in OLP samples. Instruments focusing upon other psychosocial constructs were few (Rojo-Moreno et al., 1998, Pippi et al., 2016), and again there was no evidence of their psychometric testing or interpretability in the OLP population. Overall, the present findings raise concerns as to whether these instruments are indeed relevant, comprehensive, valid and reliable for capturing the psychosocial status of individuals with OLP. Nonetheless, the HADS may have a potential to be a PROM of choice for use in patients with OLP as it comprises 14 simple-to-follow items with detailed, straightforward instruction (Snaith, 2003) and can capture both anxiety and depression, whereas STAI and BDI have more questions, require more time to complete and provide information on only one psychological concept.

Assessment of quality of life in OLP individuals is important as it reflects the patient's subjective perception of the impact of a disease and related treatment on physical, psychological and social aspects of life (McGrath et al., 2003, U.S. Department of Health and Human Services Food and Drug Administration, 2009). A number of quality of life PROMs have been used in patients with OLP, and can be divided into instruments assessing oral health-related quality of life (OH-QoL) and those assessing general aspects of quality of life.

In the present review six OH-QoL PROMs were identified, but only three have had their psychometric properties tested in the OLP population: the OHIP-14, OHQOL-UK and COMDQ. The OHIP-14 is the most frequently used PROMs for the assessment of quality of life in OLP literature. This was initially developed for use in older Australian adults and is a shortened version of the original OHIP-49 containing 14 items with a subset of 2 questions for each of the 7 domains of OH-QoL, which is based upon Locker's conceptual framework of oral health (Locker, 1988, Slade and Spencer, 1994). The OHQOL-UK was developed upon adult UK population's perceptions of how oral health affects quality of life (McGrath and Bedi, 2001). Therefore both the OHIP-14 and OHQOL-UK were developed without the input from patients with OLP and therefore may not be able to capture all relevant aspects associated with the disease and related treatment. The COMDQ is an oral medicine-specific PROM developed for the assessment of quality of life in patients with chronic oral mucosal disease (Ni Riordain et al., 2011b). It is the only validated PROM that was developed with input from patients with OLP. In addition, the COMDQ has the highest number of validation studies of patients with OLP compared to the other OH-QoL PROMs. Regarding the measurement of general aspect of quality of life, only two PROMs have been used in studies of OLP patients including the SF-36 and SF-12. Neither of them had their psychometric properties or interpretability tested in the OLP population.

The present review found that there are no studies reporting the interpretability of PROMs in patients with OLP. Interpretability gives meaning to the scores from these instruments in a clinical context, which facilitate better understanding of PROM results (Mokkink et al., 2010). The numerical scores derived from PROMs should be easily translated into clinically meaningful information, relevant to patients, clinicians and researchers. An interpretability parameter such as the minimal important difference (MID), the smallest magnitude of change in PROM scores which constitutes a clinically meaningful change, can therefore facilitate the

translation of these scores (Tubach et al., 2007). There is thus a need for further studies determining interpretability of PROMs in patients with OLP.

The treatment of OLP is not curative, rather the goal is to minimise symptoms and improving patient's quality of life. Although a wide array of topical and systemic medications are available for patients with OLP, there is currently weak evidence supporting the superiority of any of these medications over placebo (Escudier et al., 2007, Lodi et al., 2012) and future large randomised placebo-controlled trials (RCTs) are needed. These RCTs will require the careful selection of validated outcome measures, both clinical measures and PROMs. Although the present study identified some promising PROMs in several patient-reported concepts with appropriate psychometric properties for use in clinical studies of patients with OLP, there is currently a lack of uniformity in the choice of outcome measures including both PROMs and clinical measures of signs and disease activity (Wang and van der Waal, 2015) across the OLP literature. Therefore, there is an urgent need for a consensus on the core outcome set for clinical trials of OLP. This could enhance the quality of future clinical research, leading to more robust evidence supporting the use of OLP medications and eventually better patient care.

3.6.2 The use of PROMs in clinical studies of patients with RAS

Recurrent aphthous stomatitis is a common oral ulcerative condition associated with pain and other oral symptoms, which can have a significant negative impact upon normal oral functioning, psychosocial functioning and OH-QoL in affected individuals (Llewellyn and Warnakulasuriya, 2003, Tabolli et al., 2009). Therefore, in the clinical evaluation of patients with RAS, it is of paramount importance to assess the effects of this oral condition and its treatment from the perspective of the patient. The selection of an appropriate instrument to measure subjective RAS-related patient-reported outcomes requires careful consideration of the psychometric properties as well as the interpretability of the instruments. The present study

reviewed the use of PROMs in clinical studies of patients with RAS as well as published evidence supporting the psychometric properties and interpretability specifically for this patient population.

In the present study, three generic PROMs including the VAS, NRS and GCPS were identified for the assessment of oral symptoms in patients with RAS, with the VAS being the most frequently used instrument. Nevertheless, further investigation into the use of these instruments in the RAS literature revealed inconsistency in reporting the type of oral symptoms measured by VAS, as shown by a wide spectrum of different word descriptors for VAS (Table 3.8), and this study heterogeneity makes it difficult to pool VAS data for the comparison and meta-analysis. Also, it was observed that only 41% of studies of RAS provided clear instruction of the use of the VAS in the methodology section, whereas in the remaining studies information on the VAS were either absent, unclear or incorrect. While both the VAS and NRS have been widely used in clinical studies of RAS, neither has been investigated for psychometric performance specifically for patients with RAS. Therefore, further testing of the psychometric properties of the VAS and NRS in the RAS population is recommended.

Regarding the assessment of psychosocial status, anxiety and depression were the most frequently evaluated concepts in RAS patients, and the HADS, STAI and BDI were the most commonly used psychosocial-PROMs in the RAS literature. Nevertheless, all identified psychosocial-PROMs lack psychometric evidence in the RAS population, and this raises concerns as to whether these instruments are indeed relevant to RAS patients and whether they are suitable for assessing the psychosocial status of individuals with RAS.

Evaluation of quality of life in patients with RAS is also crucial. The present study identified six OH-QoL PROMs, but only three have had their measurement properties examined in the RAS population: the OHIP-14, OHQOL-UK and COMDQ. However, both OHIP-14 and OHQOL-UK

were developed without the input from patients with RAS and therefore may not be able to capture all relevant aspects associated with the disease and related treatment. In comparison, the COMDQ is the only validated QoL-PROM that was developed with input from patients with RAS. In addition, COMDQ has the highest number of validation studies of patients with RAS compared to the other OH-QoL PROMs, and may therefore be considered the most appropriate QoL-PROM for the assessment of quality of life in this patient population.

This review also identified one oral ulcer composite index, which aims to determine the impact of oral ulcer activity in patients with RAS and BD (Mumcu et al., 2009). This index, however, has not been widely adopted for use in clinical research of RAS, and apart from Turkish original language, there is no evidence of translation nor of cultural validation of this index. In addition, the rationale behind weights of three subscale scores to generate total composite index score appears to be unclear. Further validation studies for this composite index are recommended.

Importantly, there are no studies reporting the interpretability of any PROM used in clinical research of patients with RAS, and this casts doubts on the clinical meaningfulness of the PROM results in clinical studies of patients with RAS (Tubach et al., 2006). There is thus a need for further studies determining interpretability of PROMs in patients with RAS.

The goal for RAS management is usually to minimize oral symptoms and improve patient's oral functioning and quality of life. Although different groups of medications are available for RAS patients, there is currently no robust evidence supporting the efficacy of any of these medications, and future larger randomized RCTs are required. These RCTs will require the careful selection of validated outcome measures, both clinician-centred and PROMs. Although the present study identified that some PROMs showed appropriate psychometric properties for use in clinical studies of RAS, there is currently a lack of uniformity regarding the choice of outcome measures including both PROMs and clinical scoring systems across the RAS

literature (Brocklehurst et al., 2012). The comprehensive development of a core outcome set (COS) for clinical trials of RAS has been initiated and presented at the recent European Association of Oral Medicine (EAOM) conference in 2016 (Taylor et al., 2016). The methodology incorporated both patients with RAS (n = 6) and experts (n = 70), leading to a COS of 13 core outcomes for interventional studies in RAS. This COS includes all six key outcomes highlighted by patients, namely ulcer size, ulcer duration, frequency of ulcer attack, number of ulcers, pain and diet. The use of COS for RAS will improve the quality and uniformity of data in future clinical trials, allowing comparison between treatments and data pooling in systematic reviews and meta-analyses.

3.6.3 The use of PROMs in clinical studies of patients with oral PV and MMP

Pemphigus vulgaris and mucous membrane pemphigoid are characterized as autoimmune bullous mucocutaneous disorders, and oral mucous membrane is frequently the initial and exclusively affected area of involvement of these conditions (Kneisel and Hertl, 2011, McMillan et al., 2015, Taylor et al., 2015). Oral lesions of PV and MMP are usually long-standing and can give rise to varying degree of pain and discomfort as well as can substantially affecting day-to-day activities of affected patients (Ni Riordain et al., 2011a). Appropriate patient reported outcome measures are therefore crucial for accurately monitoring symptoms, quality of life and psychosocial status in patients with oral PV and MMP. Although there are some review articles of outcome measures for autoimmune blistering diseases existing in the literature (Hanna et al., 2016, Rencz et al., 2015, Zhao and Murrell, 2015), these studies focused primarily upon the instruments used in the dermatology clinical setting. Since several patients with PV and MMP have only oral involvement, the present study therefore reviewed the use of PROMs in the clinical studies of oral PV and MMP with the emphasis on their psychometric properties and interpretability.

The present study found a total of five PROMs utilized in clinical studies of oral PV and MMP including the VAS, SF-36, OHIP-49 (all these three were used in both PV and MMP studies), and the POMS and COMDQ (used in PV studies only). However, the COMDQ is the only PROM with psychometric evidence for the application in oral PV and MMP (Ni Riordain and McCreary, 2011, Ni Riordain and McCreary, 2012). The remaining identified instruments currently lack evidence supporting their measurement properties in these patient groups, and these findings therefore reflect questionable credibility of clinical research using these PROMs. Further validation studies of the VAS, SF-36, OHIP-49 and POMS in PV and MMP population are required to be conducted.

Local pain and discomfort are the main oral complaint in patients with PV and MMP. According to the present review, the VAS is the only PROM used for assessing these symptoms in these patient groups. However, it should be noted that the use of VAS may not be suitable for use in certain patient groups. For example elderly patients and those with motor problems may find it difficult to place a mark on a 10-cm VAS line. In a study comparing pain recorded with the NRS and VAS in patients with temporomandibular disorders (TMD) the authors found NRS to have greater precision and responsiveness (Conti et al., 2001). Nevertheless, further studies of psychometric performance of both the VAS and NRS are recommended in patients with oral PV and MMP.

An assessment of quality of life in patients with oral PV and MMP is crucial since oral symptoms and related functional limitation, as well as the side effects of systemic medications used, can pose significant impacts on several domains of patient's quality of life - including physical and psychosocial domains. Most previous studies have used generic QoL-PROM (SF-36) and OH-QoL PROM (OHIP-14) for the assessment of quality of life in oral PV and MMP patients. However, both instruments only measure general and oral health-specific quality of life regardless of the underlying disease, and therefore may be of little relevance in

capturing specific issues related to disease and treatment burden of oral PV and MMP. More importantly, there was no involvement of patients with oral PV and MMP during the initial development and validation of both the SF-36 and OHIP-14. On the other hand, the COMDQ was found to be the only identified QoL instrument that was developed using input from patients with various chronic oral mucosal diseases including oral PV and MMP, and have good documentation of psychometric evidence for use in these patient groups. At present COMDQ could therefore be considered to be an appropriate measurement instrument for evaluating quality of life specific to oral PV and MMP.

Although there are a range of other validated dermatology-specific quality of life measures used in the literature of oral PV and MMP, including the Dermatology Life Quality Index (DLQI) (Finlay and Khan, 1994), the Autoimmune Bullous Disease Quality of Life (ABQOL) (Sebaratnam et al., 2013), and the Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL) (Tjokrowidjaja et al., 2013). Nevertheless, these instruments have not been validated for use in an Oral Medicine setting and thus limiting their usefulness for measuring quality of life in patients with oral PV and MMP.

Again, the present review found no studies reporting the interpretability of any PROMs used in clinical research of patients with oral PV and MMP, and this casts doubt on the clinical meaningfulness of the PROM results for this patient group. There is thus a need for further studies determining interpretability of PROMs in individuals with oral PV and MMP.

3.7 CONCLUSION

There was a wide diversity of PROMs used in clinical studies of immunologically mediated oral mucosal diseases, which include instruments for oral symptoms, psychosocial status and QoL. The majority of these PROMs lack evidence of measurement properties and interpretability in these patient groups. Among identified instruments, the COMDQ appears to

be the most appropriately validated QoL instruments for use in all studied conditions. However, further validation and interpretability are required to assess whether these PROMs are fit-for-purpose, valid, reliable and provide meaningful, translatable or comparable results.

CHAPTER 4 PSYCHOMETRIC VALIDATION OF COMMON PSYCHOLOGICAL MEASURES AND PSYCHOLOGICAL STATUS IN IMMUNOLOGICALLY-MEDIATED ORAL MUCOSAL DISEASES

Measurement of psychological status in patients with immunologically mediated oral mucosal diseases is very important as not only do these chronic oral conditions pose an impact on physical oral health, but also affect patient's psychological status, and this could have negative consequences to overall quality of life of affected individuals. The findings from chapter 3 showed that over 40 psychological PROMs have been utilized in clinical research of oral mucosal diseases, and anxiety, depression and stress are the most frequently assessed psychological constructs in patients with immunologically mediated oral mucosal diseases. Within the identified PROMs assessing anxiety, depression and stress, the Hospital Anxiety and Depression Scale and the 10-item Perceived Stress Scale are among the most widely used instruments measuring anxiety, depression and stress in immunologically mediated oral mucosal diseases.

4.1 THE HOSPITAL ANXIETY AND DEPRESSION SCALE

The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-report questionnaire, initially designed as a screening measure of anxiety and depression in non-psychiatric hospital patients, without items reflecting physical health problems e.g. headaches, insomnia, dizziness and anergia (Zigmond and Snaith, 1983). Later, this scale has proven to perform well with other non-hospital groups including community settings (Snaith, 2003). The HADS contains 14 items equally divided into 2 subscales including anxiety (HADS-A) and depression (HADS-D). The response of each item of the HADS is scored on a 4-point Likert scale of 0 to 3, with 3 indicating higher frequency of symptoms. The total scores of the anxiety and depression subscale range from 0 to 21, with the score interval of 0-7, 8-10 and 11-21 referring

to normal, borderline abnormal and abnormal respectively. The total score of the HADS (HADS-T) indicates the level of overall emotional distress, ranging from 0 to 42 (Snaith, 2003).

The HADS developers proposed the scale as a two-factor scale measuring anxiety and depression separately. However, content validity of the HADS appears to be somewhat questionable (Coyne and van Sonderen, 2012). Due to the omission of somatic symptoms and its narrow focus towards only cognitive and emotional components of anxiety and depression (e.g. anhedonia, the inability to feel pleasure), the constructs measured by the scale do not comprehensively and accurately cover the diagnostic criteria for generalized anxiety disorders and major depressive disorders. In addition, there is currently ongoing debate among experts regarding the scale's underlying dimensionality and its ability to distinguish between anxiety and depression, both of which are commonly comorbid and often difficult to distinguish (Cosco et al., 2012). Despite mixed evidence supporting structural validity of the HADS, this instrument continues to be extensively used across a spectrum of medical conditions including cancer and cardiovascular diseases, with well-established normative data in various populations (Norton et al., 2013). In addition, the results from a comprehensive review (chapter 3) also demonstrated that the HADS is amongst the most frequently used instrument in clinical studies of RAS and OLP.

4.2 THE 10-ITEM PERCEIVED STRESS SCALE

The 10-item Perceived Stress Scale (PSS-10) is a self-report scale developed to assess perceived stress level in the general population (Cohen et al., 1983). Conceptually, the PSS-10 measures the degree to which situations over the last month in the respondent's life are appraised as unpredictable, uncontrollable and overloading. Each item is rated on a 5-point Likert-type scale ranging from 0 (never) to 4 (very often), with higher scores reflecting greater level of psychological stress. The PSS-10 was originally designed to be a unidimensional measure of perceived stress but psychometric evidence from subsequent studies revealed

the existence of two subscales in the PSS-10 comprising perceived stress subscale (6 negatively phrased items) and perceived self-efficacy subscale (4 positively phrased items) (Nielsen et al., 2016). Similar to the HADS, there remains no consensus regarding the underlying structure underpinning the PSS-10 (Lee, 2012).

4.3 KNOWLEDGE GAP

Despite extensive use of the HADS and PSS-10 in the literature of OLP and RAS, underlying factor structures and psychometric robustness of both psychological measures have yet to be fully investigated in patients with immunologically mediated oral mucosal diseases. It remains therefore unclear whether both psychological measures are structurally valid, reliable and appropriate measure for use as outcome measures in clinical practice and research involving this patient group.

4.4 AIMS

The aims of this chapter were:

1. To examine psychometric properties including structural validity and internal consistency reliability of the HADS and PSS-10 for use in patients with common immunologically mediated oral mucosal diseases (OLP and RAS).
2. To assess the prevalence of anxiety, depression, distress, and perceived stress in a cohort of patients with common immunologically mediated oral mucosal diseases (OLP and RAS)
3. To investigate the association between psychological comorbidities and associated demographics and clinical factors in patients with common immunologically mediated oral mucosal diseases (OLP and RAS)

4.5 METHODS

4.5.1 Study design

This was a cross-sectional, secondary analysis of baseline data from the Determination of Minimal Important Difference and Patient Acceptable Symptom State of Patient Reported Outcome Measures in Immunologically mediated Oral Mucosal Diseases (MEAN-IT) study, which was approved by the London – Queen Square Research Ethics Committee (REC reference 17/LO/1825; approval date 3 November 2017).

4.5.2 Participants

The study participants comprised 260 patients with OLP and 120 patients with RAS who attended review appointments at the Oral Medicine clinic of the UCLH Eastman Dental Hospital, London, United Kingdom. The eligibility criteria are listed in Table 4.1. Participant recruitment was based upon a convenience sampling. All potentially eligible participants, in all Consultant lead Oral Medicine clinics between January 2018 and June 2019 were approached and invited to participate. All participants provided written informed consent to participate in the study.

Table 4.1 Study eligibility criteria

Inclusion criteria	Exclusion criteria
- Aged 18 years or older - Able to read, understand and complete questionnaires	- Having coexisting chronic neuropathic orofacial pain, such as post-traumatic trigeminal neuropathic pain, persistent idiopathic facial pain or burning mouth syndrome
- Agree to participate and provide written informed consent	- Severe systemic disease (ASA 3 or more) and/or some psychiatric conditions which might affect the participation of the study such as schizophrenia
Having one of the following conditions	
1. Oral lichen planus	
- Clinically and histopathologically-confirmed OLP based upon modified WHO diagnostic criteria (van der Meij and van der Waal, 2003)	- Evidence of oral epithelial dysplasia in biopsy specimen - Evidence of proven hypersensitivity to dental materials - Evidence of oral lichenoid lesions associated with graft-versus-host disease and systemic lupus erythematosus
2. recurrent aphthous stomatitis	

- Having recurrent oral ulceration (ulcer episodes of at least twice a year)	- Having RAS-like ulcerations associated with systemic disorders such as Behcet's disease, Sweet syndrome, Ulcerative colitis, Crohn's disease, Celiac disease, auto-inflammatory syndromes, or haematological abnormalities (severe anaemia, cyclic or chronic neutropenia)

The sample size of this study was in line with recommendation from the COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) Risk of Bias checklist, which stipulates that a sample size for a factor analysis study should include at least 100 and more than 7 times the number of items of the outcome measures examined (at least 98 and 70 for factor analysis of the HADS and PSS-10, respectively).

4.5.3 Procedure

A comprehensive oral examination was carried out on all study participants to assess the clinical types, oral sites of involvement and disease activity. Disease activity of OLP was evaluated by using the Oral Disease Severity Score (ODSS) (Escudier et al., 2007). Participants with OLP were categorised into three clinical variants: (i) keratotic (presence of white reticular, papular or plaque-like lesions without apparent erythema/ulceration), (ii) erythematous (presence of atrophic/erythematous lesions with/without reticular/popular/ plaque-like features AND no evidence of erosion/ulceration), and (iii) erosive/ulcerative (presence of erosive or ulcerative lesions with/without the presence of keratotic and/or erythematous changes of OLP) (Bruch and Treister, 2018). For participants with RAS, disease activity was evaluated by taking history of each participant, and specific information about oral ulcers over the past three months was recorded. The activity score was calculated based on the standardized Ulcer Severity Score (USS) (Tappuni et al., 2013). Types of RAS were recorded based upon clinical appearance and behavior of RAS into 3 groups: minor RAS (shallow small ulcers (<1cm), usually last 7-10 days), major RAS (deeper and larger ulcers (≥1 cm), lasting several weeks, which may heal with scar formation) and herpetiform RAS (few millimeter ulcers, usually > 10 ulcers, last 7-10 days) (Scully and Porter, 2008).

Participants were then asked to complete the demographic form and a set of patient-reported questionnaires including the numerical rating scale (NRS) for pain, the HADS and the PSS-10. Information regarding medical history, social history and past OLP/RAS-related history including disease duration, extra-oral involvement of lichen planus (either patient-reported or confirmed by a dermatologist), and treatment was obtained from electronic patient records.

4.5.4 Outcomes

The outcome for the validation part of the study was evidence supporting structural validity and internal consistency reliability of the HADS and PSS-10 for use in patients with OLP and RAS. For structural validity, values of the fit indices were assessed against predefined standard to confirm whether the data of patients with OLP and RAS fit the underlying structure of the studied scales. For internal consistency reliability, reliability coefficients were calculated and compared with acceptable quality criteria.

The outcomes for the cross-sectional study section were as follows: (i) prevalence of psychological symptoms including anxiety, depression, distress and stress as measured by the HADS and PSS-10 in individuals with OLP and RAS; (ii) Bivariate analyses of potential predictors of psychological symptoms including demographics and clinical factors. Demographic variables that may have contributed to the presence of psychological comorbidities including age (continuous variables), gender (female/male), ethnicity (White/Mixed/Asian/Black), smoking (non-smoker/ex-smoker/current smoker), alcohol consumption (no/up to 14 units/more than 14 units per week) and systemic comorbidities (no/one/at least two comorbidities) were recorded. Potential associated clinical factors including clinical types (keratotic/erythematous/ulcerative for OLP and minor/major/ herpetiform for RAS), pain intensity (NRS), disease duration (time since symptom onset; years), disease severity (ODSS for OLP and USS for RAS), presence of extraoral lichen

planus (for OLP group) and treatment types (no treatment or topical anaesthetic agents only/topical corticosteroids only/topical corticosteroids and other topical treatment/topical and systemic treatment) were also recorded.

4.5.5 Outcome measures

Clinical scoring

The Oral Disease Severity Score (ODSS) is a validated clinical scoring system for the measurement of the severity of oral mucosal conditions including OLP (Escudier et al., 2007). The ODSS assesses the presence and extent of mucosal lesions as well as the severity of clinical presentations in 17 oral subsites. A total score is calculated by the summation of clinician-assessed site and activity scores with a 0-10 verbal rating scale for average oral pain over the past 2 weeks, with theoretical combined scores ranging from 0 to 106. Clinical sensitivity and inter-rater reliability were found to be adequate for use in the OLP population.

The Ulcer Severity Score (USS) is a validated RAS-specific scoring system for monitoring the severity of recurrent oral ulcers (Tappuni et al., 2013). Six RAS-related characteristics over the preceding three months including average number of the ulcers, average ulcer size, average ulcer duration, ulcer-free period, affected oral sites, and ulcer-related pain were evaluated to generate the RAS parameter scores of the USS. A total USS score is the summation of all six parameters scores with the maximum total score of 80.

Patient-reported outcome measures

The Numerical Rating Scale (NRS) for pain is a segmented numeric version of the VAS for pain. Participants were asked to select one whole number from 0 to 10 (11-point scale) that best reflected the intensity of the current oral pain they were experiencing from OLP. The NRS has been investigated for construct validity and the findings showed psychometric adequacy for use in the OLP population (Chainani-Wu et al., 2008).

The Hospital Anxiety and Depression Scale (HADS) is a brief screening measure of anxiety and depression through 14 items, consisting of a 7-item anxiety (HADS-A) and a 7-item depression (HADS-D) subscale. The HADS-A subscale includes items concerning generalized symptoms of anxiety e.g. feelings of tension, fear, worry and panic while the items on the HADS-D subscale largely focus upon anhedonia (loss of pleasure), a cardinal symptom of depression. For each item, participants were asked to rate items according to how they had felt in the past week on a 4-point Likert-type scale (0-3), with the total subscale score ranging from 0 to 21 in each subscale. Higher scores denote greater intensity of anxiety or depressive symptoms. A cut-off HADS-A or HADS-D score of 8 or above is indicative of the presence of anxiety and depression (Bjelland et al., 2002), and the HADS total (HADS-T) score of 15 or over indicates the presence of emotional distress (Schellekens et al., 2016).

The 10-item Perceived Stress Scale (PSS-10) is a 10-item self-report measure of stress appraisal. Participants were asked to stipulate how often they experienced a particular thought or feeling during the preceding month on a 5-point Likert scale from never (0) to very often (4). Six items of the PSS-10 are negatively phrased (item 1, 2, 3, 6, 9, 10; negative perception subscale) while the remaining four (item 4, 5, 7, 8; positive perception subscale) are positively phrased items and require reverse coding. Total PSS-10 score was calculated by summing scores across all the items, providing a total score range of 0-40. A higher score represents greater perceived stress. PSS-10 scores of 14 or above are indicative of moderate-to-high level of perceived stress (Alharbi and Alshehry, 2019).

4.5.6 Statistical Analysis

Statistical analyses were carried out using STATA version 15.1 (StataCorp, College Station, TX, U.S.A.) and MPlus version 8.2 (Muthén & Muthén, 2015). Preliminary item analyses were performed to examine median, interquartile range (IQR) and skewness as well as floor and ceiling effects (>15% of participants endorsing the lowest and highest possible option,

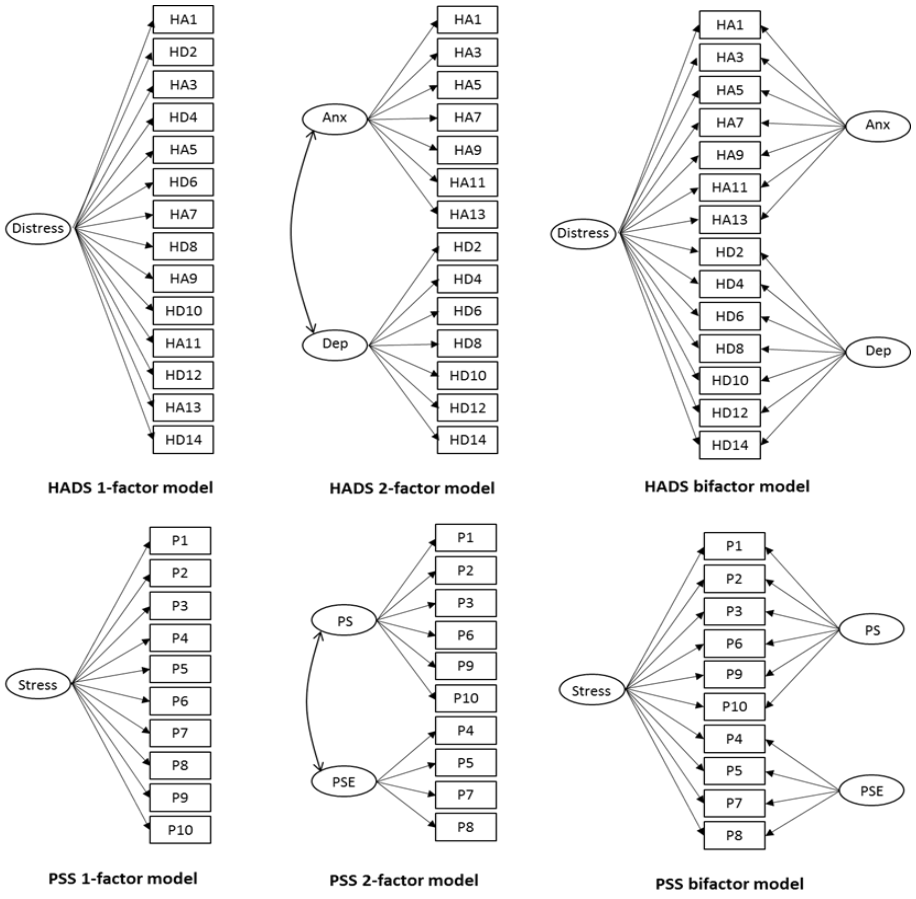
respectively) of each item in the HADS and PSS-10 (Terwee et al., 2007). Descriptive analyses for demographic and clinical characteristics were summarized using frequencies and percentages for categorical variables, and as the majority of continuous variables were non-normally distributed from the histogram and the Kolmogorov-Smirnov test, median and IQR were used as summary statistics.

Validity and reliability of the HADS and PSS-10

Structural validity of the HADS and PSS-10 was examined through confirmatory factor analysis (CFA) to test whether the data from the OLP or RAS population fit the previously proposed factor structures of both scales. Without sufficient evidence supporting structural validity, measurements cannot be adequately interpreted. A mean- and variance-adjusted weighted least square (WLSMV) estimator was applied to test the covariance matrix for the CFA (Millsap and Yun-Tein, 2004, Beauducel and Herzberg, 2006).

Three CFAs were performed to test the fit of the HADS data with the four most commonly identified factor structures including the uni-dimensional distress model, the original two-factor model and the bi-factor model (Figure 4.1). To test factor structures of the PSS-10 in the OLP or RAS population, three CFAs were used to test the fitness of OLP data with the following hypothesized models: one-, two- and bi-factor model (Figure 4.1). The bi-factor model allows all the items to load on a general factor reflecting unidimensionality of the scale, and in addition, onto specific group factors indicating multidimensionality of the scale.

Figure 4.1 Structural models of the HADS and PSS-10 applied in the confirmatory factor analyses using the OLP and RAS population



Abbreviation: Anx = anxiety subscale, Dep = depression subscale, PS = perceived stress subscale, PSE = perceived self-efficacy subscale

Acceptability of model fit was assessed by the use of fit indices including root mean square of error approximation (RMSEA), standardized root mean squared residual (SRMR), comparative fit index (CFI) and Tucker-Lewis index (TLI). RMSEA and SRMR values closer to 0 indicate better fit, with values below 0.08 and 0.05 indicating acceptable and good fit, respectively. CFI and TLI values greater than 0.95 are considered acceptable (Hu and Bentler, 1999a).

Cronbach's alpha coefficients were computed to assess *internal consistency reliability* of both total and subscale scores of the HADS and PSS-10 based upon the best fitted model from the CFA results. Internal consistency reliability is the degree to which items within a scale are interrelated and thus reliably measure the underlying concept of interest, and Cronbach's

alpha (α) of at least 0.70 was considered acceptable (Terwee et al., 2007, Mokkink et al., 2010). For the bi-factor models, two additional variance-based reliability indices, which are considered superior to α for a multidimensional construct, were computed including McDonald's omega coefficient (ω) and coefficient omega hierarchical (ω-h). The ω computes bifactor-model-based reliability of the total score combining variance from both general and specific group factors while the ω-h estimates reliability of summed scores explained by only one construct with all other factor variance removed (Zinbarg et al., 2005, Brunner et al., 2012). For the general factor, the difference between ω and ω-h demonstrates reliability of the total score attributable to specific factors after controlling for a general factor. High coefficient ω-h (>0.8) indicates that total score can be considered unidimensional. For the specific group factor, ω-h reflects capacity of a subscale score to reliably measure the underlying factor variance by itself, and low ω-h values deter the use of subscale scores. Both omega coefficients were calculated using the omega software (Watkins, 2013). Regardless of factorial structure and results of psychometric analysis, a cross-sectional analysis of psychological profile of patients with OLP was demonstrated based upon the originally proposed structure of both scales for a comparison with previous studies.

Cross-sectional analyses of psychological symptoms in patients with OLP and RAS

For the purpose of cross-sectional analysis, participants were dichotomized by the presence/absence of anxiety, depressive, emotional distress and moderate-to-high perceived stress using the following cut-off scores of self-report outcome measures: 8 for the HADS-A, 8 for the HADS-D, 15 for the HADS-T and 14 for the PSS-10, respectively. To identify potential predictors of anxiety, depressive and psychological distress symptoms in the OLP population, bivariate analysis between subgroups was conducted using the chi-square or Fisher's exact tests for categorical variables as appropriate while Mann-Whitney U test or independent sample t-tests were performed for comparisons of medians and means of continuous variables between subgroups respectively. All tests were two-tailed and a p-value of less than 0.05 was

considered statistically significant. Variables with statistical significance from bivariate analysis were entered into univariate logistic regression, and the crude odds ratio (OR), 95% confidence interval (CI) and p-value were calculated. Each of the demographic and clinical variables with a p-value of less than 0.1 on univariate analyses were then entered into separate multivariate logistic regression models using a forward stepwise procedure. Each of the explanatory variables was adjusted for the same set of variables (listed below in the results section). Adjusted odds ratios (Adj-ORs) with 95 % CI for each independent variable were calculated. Logistic regression was only conducted in a cohort of participants with OLP due to relatively small number of participants with RAS.

4.6 RESULTS

The results of this chapter are divided into two sections based upon the disease of interest.

4.6.1 Results of the OLP cohort

4.6.1.1 Psychometric validation of the HADS and PSS-10 for use in patients with OLP

Descriptive item analyses

Descriptive item score statistics, response distribution and skewness for the response of 260 participants with OLP to the HADS and PSS-10 are summarized in Table 4.2. The score distribution for the lowest response options ranged from 16.15% to 38.85% for the HADS-A items, between 18.08% to 73.08% for the HADS-D items and between 7.69% to 30.38% for the PSS-10 items. All skewness values of both scales were positive except for item P3 of the PSS-10, implying a long distribution tail towards larger values than the mean (positive skew). No ceiling effects were observed but all items of the HADS and seven PSS-10 items showed floor effects.

Table 4.2 Descriptive item statistics, response distribution and skewness for each of the HADS and PSS-10 item for a cohort of patients with OLP

Items	med (IQR)	mean (SD)	score distribution (%)					skewness
			0	1	2	3	4	
HADS-anxiety								
HA1 Tense-wound up	1 (1, 2)	1.17 (0.79)	42 (16.15)	152 (58.46)	45 (17.31)	21 (8.08)	_	0.66
HA3 Frightened feelings	1 (0, 2)	0.98 (0.92)	98 (37.69)	84 (32.31)	64 (24.64)	14 (5.38)	_	0.47
HA5 Worrying thought	1 (0, 2)	1.1 (0.93)	76 (29.23)	107 (41.15)	52 (20)	25 (9.62)	_	0.52
HA7 At ease-relaxed	1 (0, 1)	0.89 (0.75)	84 (32.31)	126 (48.46)	45 (17.31)	5 (1.92)	_	0.46
HA9 Butterflies in stomach	1 (0, 1)	0.78 (0.72)	93 (35.77)	138 (53.08)	21 (8.08)	8 (3.08)	_	0.84
HA11 Restless	1 (0, 2)	1.02 (0.87)	82 (31.54)	105 (40.38)	59 (22.69)	14 (5.38)	_	0.45
HA13 Sudden panic	1 (0, 1)	0.83 (0.79)	101 (38.85)	109 (41.92)	44 (16.92)	6 (2.31)	_	0.6
HADS-depression								
HA2 Enjoy things	1 (0, 1)	0.68 (0.70)	114 (43.85)	118 (45.38)	24 (9.23)	4 (1.54)	_	0.79
HA4 Laugh-see funny side	0 (0, 1)	0.38 (0.64)	180 (69.23)	63 (24.23)	14 (5.38)	3 (1.15)	_	1.69
HA6 Cheerful	0 (0, 1)	0.57 (0.71)	142 (54.62)	92 (35.38)	22 (8.46)	4 (1.54)	_	1.1
HA8 Slowed down	1 (1, 2)	1.26 (0.9)	47 (18.08)	131 (50.38)	50 (19.23)	32 (12.31)	_	0.51
HA10 Lost interest	0 (0, 1)	0.57 (0.80)	157 (60.38)	63 (24.23)	35 (13.46)	5 (1.92)	_	1.16
HA12 Excitement	0 (0, 1)	0.64 (0.83)	143 (55)	79 (30.38)	27 (10.38)	11 (4.23)	_	1.2
HA14 Enjoy leisures	0 (0, 1)	0.34 (0.64)	190 (73.08)	56 (21.54)	9 (3.46)	5 (1.92)	_	2.1
PSS-10								
P1 Upset	2 (1, 3)	1.95 (1.19)	33 (12.69)	56 (21.54)	98 (37.69)	38 (14.62)	35 (13.46)	0.13
P2 Life-uncontrollable	2 (1, 2)	1.77 (1.19)	45 (17.31)	59 (22.69)	93 (35.77)	37 (14.23)	26 (10)	0.19
P3 Nervous-stressed	2 (2, 3)	2.16 (1.09)	24 (9.23)	37 (14.23)	102 (39.23)	68 (26.15)	29 (11.15)	-0.23
P4 Ability to handle problems	1 (0, 2)	1.06 (0.89)	79 (30.38)	100 (38.46)	68 (26.15)	12 (4.62)	1 (0.38)	0.42
P5 Things going your way	1 (1, 2)	1.38 (0.91)	43 (16.54)	106 (40.77)	85 (32.69)	22 (8.46)	4 (1.54)	0.35
P6 Unable to cope	2 (1, 2)	1.56 (1.08)	46 (17.69)	83 (31.92)	85 (32.89)	32 (12.31)	14 (5.38)	0.36
P7 Control irritations	1 (1, 2)	1.24 (0.92)	62 (23.85)	97 (37.31)	79 (30.38)	21 (8.08)	1 (0.38)	0.26
P8 On top of things	1 (1, 2)	1.35 (0.92)	48 (18.46)	102 (39.23)	82 (31.54)	26 (10)	2 (0.77)	0.26
P9 Angry	2 (1, 3)	1.92 (1.01)	20 (7.69)	66 (25.38)	108 (41.54)	48 (18.46)	18 (6.92)	0.12
P10 Difficulties-overloaded	1 (1, 2)	1.49 (1.14)	56 (21.54)	83 (31.92)	76 (29.23)	27 (10.38)	18 (6.92)	0.49

Confirmatory factor analysis

The goodness-of-fit indicators of four HADS and three PSS-10 confirmatory factor analysis models are displayed in Table 4.3. For the HADS CFA results, one-factor model provided a poor fit to the OLP data according to RMSEA value and was thus rejected. The original 2-factor had acceptable-to-good level of fit indices. Notably, the bifactor model was found superior to other tested models in all fit statistics (RMSEA = 0.051, SRMR = 0.035, CFI = 0.989, TLI = 0.984), with all goodness-of-fit statistics falling within acceptable (RMSEA) and good (SRMR, CFI, TLI) model fit. This supported the utility of bifactor model to better explain the HADS results in the OLP population. As for the PSS-10, RMSEA values did not reach critical value of 0.08, indicating poor model fit of the original 1-factor and 2-factor models though other fit indices were found acceptable. Similar to the HADS, the bifactor model outperformed other tested models in all goodness-of-fit statistics (RMSEA = 0.076, SRMR = 0.021, CFI = 0.991, TLI = 0.984).

Table 4.3 Confirmatory factor analysis model fit statistics for the HADS and PSS-10 in a cohort of patients with OLP

	RMSEA	SRMR	CFI	TLI
HADS				
1-factor model	0.111	0.069	0.936	0.925
2-factor model	0.07	0.049	0.975	0.97
bifactor model	0.051	0.035	0.989	0.984
PSS-10				
1-factor model	0.155	0.05	0.947	0.932
2-factor model	0.112	0.035	0.973	0.964
bifactor model	0.076	0.021	0.991	0.984

Reliability

Since the CFA results revealed the bifactor model as the best fitting latent structure of the HADS and PSS-10, reliability estimates of total and subscale scores of both scales including Cronbach's α, McDonald's ω, and coefficient ω hierarchical were computed and shown in Table 4.4. The conventional Cronbach's α values of all total scales and subscales were in the acceptable range, reflecting adequate internal consistency reliability of the scales. Regarding the bifactor model-based reliability, McDonald's ω coefficients of general factor and specific group factors of both HADS and PSS-10 were satisfactory. High ω-h of total HADS and PSS-10 scores indicated general distress factor and general stress factor accounted substantially for composite score variance of the HADS (0.838) and the PSS-10 (0.88) respectively, and this supported the utility of overall HADS and PSS-10 scores. However, low range of ω-h values in all subscale scores of both scales indicated that reliability variance of subscale scores after controlling for influence from general factor is considerably low (<0.3 in all subscales), and the use of subscale scores of the HADS and PSS-10 in the OLP population should be done with caution.

Table 4.4 Reliability estimates of overall and subscale scores of the HADS and PSS-10 in a cohort of patients with OLP

	Cronbach's α	McDonald's ω	ω-h
HADS-*total (distress)*	0.9	0.966	0.838
HADS-*anxiety subscale*	0.87	0.91	0.275
HADS-*depression subscale*	0.84	0.974	0.164
PSS-*total (stress)*	0.9	0.941	0.88
PSS-*perceived stress subscale*	0.89	0.933	0.031
PSS-*perceived self-efficacy subscale*	0.78	0.828	0.268

4.6.1.2 Psychological status in patients with OLP: a cross-sectional study

Descriptive characteristics of study participants

The demographic and clinical characteristics of the 260 study participants are summarized in Table 4.5. The proportion of females was higher than that of males with a ratio of 4:1 (80% Female). The median age of OLP patients was 65.99 years (IQR = 55.21-71.11 years). The median OLP disease duration was about 6 years. Based upon the ODSS record form, atrophic/erosive OLP was the most common clinical variant in this sample (44.62%). Approximately one quarter of patients had at least one site of extraoral involvement, and genitalia (17.31%) and skin (14.23%) were the two most frequently coexisting sites of lichen planus involvement in this sample. The vast majority of patients (85%) had at least one disease comorbidity, and the most frequent systemic conditions were hypertension (33.85%), hypercholesterolaemia (18.08%), osteoarthritis (15%), diabetes mellitus (11.92%) and hypothyroidism (10.38%). Topical corticosteroids were the most frequently prescribed treatment for OLP (63.08%) in this study cohort.

Bivariate analysis of demographic and OLP-related variables by the presence of anxiety symptoms, depressive symptoms and psychological distress are presented in Table 4.5. All the significant variables with P values below 0.1 including patient's age, gender, ethnicity, history of smoking and alcohol consumption, number of comorbidities, disease duration, pain-VAS and total oral disease severity score were entered into univariate and multivariate logistic regression, shown in Table 4.6.

Table 4.5 Descriptive statistics of demographics and OLP-related variables of study participants and bivariate analysis of factors associated with the presence of anxiety symptoms, depressive symptoms, psychological distress and moderate-to-high perceived stress in patients with OLP (N=260)

Characteristics	All subjects (N=260)	HADS-A<8 (N=158, 60.77%)	HADS-A≥8 (N=102, 39.23%)	P value	HADS-D<8 (N=206, 79.23%)	HADS-D≥8 (N=54, 20.77%)	P value	HADS-T<15 (N=188, 72.31%)	HADS-T≥15 (N=55, 27.69%)	P value	PSS-10<14 (N=105, 40.38%)	PSS-10≥14 (N=155, 59.62%)	P value
Demographics													
Age (years): median (IQR)	65.99 (55.21, 71.11)	67.63 (58.45, 71.53)	62.45 (54.00, 69.52)	***0.001***[a]	66.03 (56.20, 70.70)	65.95 (54.30, 71.96)	0.821[a]	66.78 (56.78, 71.25)	63.36 (53.21, 70.01)	***0.036***[a]	67.26 (58.51, 71.34)	64.58 (54.30, 70.70)	0.075[a]
Gender (n, %)				0.446[c]			0.760[c]			0.628[c]			0.058[c]
Female	208 (80)	124 (59.62)	84 (40.38)		164 (78.85)	44 (21.15)		149 (71.63)	59 (28.37)		78 (37.50)	130 (62.50)	
Male	52 (20)	34 (65.38)	18 (34.62)		42 (80.77)	10 (19.23)		39 (75)	13 (25)		21 (51.92)	25 (48.08)	
Ethnicity (n, %)				0.170[b]			***0.002***[b]			***0.000***[b]			***0.004***[b]
White	183 (70.38)	119 (65.03)	64 (34.97)		156 (85.25)	27 (14.75)		146 (79.78)	37 (20.22)		86 (46.99)	97 (53.01)	
Mixed	6 (2.31)	3 (50)	3 (50)		4 (66.67)	2 (33.33)		4 (66.67)	2 (33.33)		2 (33.33)	4 (66.67)	
Asian	62 (23.85)	31 (50)	31 (50)		39 (62.9)	23 (37.1)		33 (53.23)	29 (46.77)		14 (22.58)	48 (77.42)	
Black	9 (3.46)	5 (55.56)	4 (44.44)		7 (77.78)	2 (22.22)		5 (55.56)	4 (44.44)		3 (3.33)	6 (66.67)	
Smoking (n, %)													
Non-smoker	197 (75.77)	127 (64.47)	70 (35.53)		160 (81.22)	37 (18.78)		146 (74.11)	51 (25.89)		86 (43.65)	111 (56.35)	
Ever smoker	63 (24.23)	31 (49.21)	32 (50.79)	***0.031***[c]	46 (73.02)	17 (26.98)	0.162[c]	42 (66.67)	21 (33.33)	0.25[c]	19 (30.16)	44 (69.84)	0.057[c]
Ex-smoker	52 (20)	24 (46.15)	28 (53.85)	**0.05**[b]	37 (71.15)	15 (28.85)	0.286[b]	33 (63.46)	19 (36.54)	0.235[b]	14 (26.92)	38 (73.08)	0.086[c]
Current smoker	11 (4.23)	7 (63.64)	4 (36.36)		9 (81.82)	2 (18.18)		9 (81.82)	2 (18.18)		5 (45.45)	6 (54.55)	
Alcohol consumption (n, %)													
No	85 (32.69)	44 (51.76)	41 (48.24)		53 (62.35)	32 (37.65)		47 (55.29)	38 (44.71)		23 (27.06)	62 (72.94)	
Yes	175 (67.31)	114 (65.14)	61 (34.86)	***0.038***[c]	153 (87.43)	22 (12.57)	***0.000***[c]	141 (80.57)	34 (19.43)	***0.000***[c]	82 (46.86)	93 (53.14)	***0.002***[c]
≤ 14 Units/week	150 (57.69)	98 (65.33)	52 (34.67)	0.106[c]	130 (86.67)	20 (13.33)	***0.000***[b]	118 (78.67)	32 (21.33)	***0.000***[b]	67 (44.67)	83 (55.33)	***0.004***[c]
> 14 Units/week	23 (8.85)	15 (65.22)	8 (34.78)		21 (91.30)	2 (8.7)		22 (95.65)	1 (4.35)		14 (60.87)	9 (39.13)	
Comorbidity (n, %)				0.322[c]			***0.001***[b]			***0.021***[c]			0.560[c]
No	39 (15)	26 (66.67)	13 (33.33)		35 (89.74)	4 (10.26)		32 (82.05)	7 (17.95)		18 (46.15)	21 (53.85)	
1 comorbidity	65 (25)	43 (66.15)	22 (33.85)		59 (90.77)	6 (9.23)		53 (81.54)	12 (18.46)		29 (43.08)	37 (56.92)	
≥ 2 comobidities	156 (60)	89 (57.05)	67 (42.95)		112 (71.79)	44 (28.21)		103 (66.03)	53 (33.97)		59 (37.82)	97 (62.18)	
OLP-related variables													
Disease duration (years), median (IQR)	6.37 (2.83, 10.84)	6.57 (3.39, 11.35)	6.14 (2.44, 10.17)	0.396a	6.47 (3.20, 11.1)	5.08 (2.30, 9.35)	0.273a	6.62 (3.18, 11.01)	5.45 (2.31, 10.03)	0.341a	7.31 (3.45, 14.29)	5.87 (2.40, 9.60)	0.01a

Note: [a] Mann-Whitney test; [b] Fisher's exact test; [c] Chi-square test; italic and bold values are p-value < .05

Table 4.5 Descriptive statistics of demographics and OLP-related variables of study participants and bivariate analysis of factors associated with the presence of anxiety symptoms, depressive symptoms, psychological distress and moderate-to-high perceived stress in patients with OLP (N=260) (cont.)

Characteristics	All subjects (N=260)	HADS-A<8 (N=158, 60.77%)	HADS-A≥8 (N=102, 39.23%)	P value	HADS-D<8 (N=206, 79.23%)	HADS-D≥8 (N=54, 20.77%)	P value	HADS-T<15 (N=188, 72.31%)	HADS-T≥15 (N=55, 27.69%)	P value	PSS-10<14 (N=105, 40.38%)	PSS-10≥14 (N=155, 59.62%)	P value
OLP-related variables													
Predominant clinical types (n, %)													
Keratotic	41 (15.77)	24 (58.54)	17 (41.46)	0.824[c]	35 (85.37)	6 (14.63)	0.547[c]	30 (73.17)	11 (26.83)	0.986[c]	14 (34.15)	27 (65.85)	0.427[c]
Reticular	30 (11.54)	16 (53.33)	14 (46.67)	0.807[b]	25 (83.33)	5 (16.67)	0.493[b]	22 (73.33)	8 (26.67)	0.998[b]	10 (33.33)	20 (66.67)	0.717[b]
Plaque-like	11 (4.23)	8 (72.73)	3 (27.27)		10 (90.91)	1 (9.09)		8 (72.73)	3 (27.27)		4 (36.36)	7 (63.64)	
Erythematous	184 (70.77)	114 (61.96)	70 (38.04)		143 (77.72)	41 (22.28)		133 (72.28)	51 (27.72)		79 (42.93)	105 (57.07)	
Atrophic/Erosive	116 (44.62)	72 (62.07)	44 (37.93)		86 (74.14)	30 (25.86)		83 (71.55)	33 (28.45)		52 (44.83)	64 (55.17)	
Desquamative gingivitis	68 (26.15)	42 (61.76)	26 (38.24)		57 (83.82)	11 (16.18)		50 (73.53)	18 (26.47)		27 (39.71)	41 (60.29)	
Ulcerative	35 (13.46)	20 (57.14)	15 (42.86)		28 (80)	7 (20)		25 (71.43)	10 (28.57)		12 (34.29)	23 (65.71)	
Pain-NRS: median (IQR)	3 (1, 5)	3 (1, 5)	4 (2, 6)	***0.000***[a]	3 (1,5)	5 (3, 7)	***0.000***[a]	3 (1,5)	5 (3, 7)	***0.000***[a]	2 (1, 4)	4 (2, 6)	***0.000***[a]
ODSS-site: median (IQR)	6 (4, 8)	6 (4, 8)	6 (3, 8)	0.954[a]	6 (3, 8)	6 (4, 9)	0.216[a]	6 (3.5, 8)	6 (4, 9)	0.354[a]	5 (3, 8)	6 (4, 8)	0.321[a]
ODSS-activity: median (IQR)	6 (3, 11)	6 (3, 10)	7 (2, 11)	0.552[a]	6 (2, 10)	8.5 (4, 11)	0.052[a]	6 (3, 10)	7 (2.5, 11)	0.243[a]	5 (2, 9)	7 (3, 12)	0.173[a]
ODSS-total: median (IQR)	15 (10, 24)	14 (9, 24)	18 (10, 25)	0.23[a]	14.5 (9, 22)	20 (13, 26)	***0.016***[a]	15 (9, 22)	19.5 (10, 25.5)	0.058[a]	13 (8, 21)	17 (10, 26)	***0.035***[a]
Presence of extraoral LP (n, %)													
No	189 (72.69)	116 (61.38)	73 (38.62)		153 (80.95)	36 (19.05)		142 (75.13)	47 (24.87)		78 (41.27)	111 (58.73)	
Yes	71 (27.31)	42 (59.15)	29 (40.85)	0.744[c]	53 (74.65)	18 (25.35)	0.264[c]	46 (64.79)	25 (35.21)	0.097[c]	27 (38.03)	44 (61.97)	0.635[c]
Yes/Genital area	45 (17.31)	24 (53.33)	21 (46.67)	0.261[c]	32 (71.11)	13 (28.89)	0.140[c]	28 (62.22)	17 (37.78)	0.096[c]	16 (35.56)	29 (64.44)	0.468[c]
Yes/Skin	37 (14.23)	22 (59.46)	14 (40.54)	0.86[c]	28 (75.68)	9 (24.32)	0.565[c]	25 (67.57)	12 (32.43)	0.487[c]	14 (37.84)	23 (62.16)	0.733[c]
Number of extraoral sites (n, %)													
1 Extraoral site	56 (21.54)	35 (62.5)	21 (37.5)	0.509[c]	42 (75)	14 (25)	0.531[c]	36 (64.29)	20 (35.71)	0.248[c]	23 (41.07)	33 (58.93)	0.593[c]
≥2 Extraoral sites	15 (5.77)	7 (46.67)	8 (53.33)		11 (73.33)	4 (26.67)		10 (66.67)	5 (33.33)		4 (26.67)	11 (73.33)	
Treatment (n, %)				0.754[b]			0.102[b]			0.887[b]			0.286[b]
No Tx/Tanes	34 (13.08)	23 (67.65)	11 (32.35)		31 (91.18)	3 (8.82)		26 (76.47)	8 (23.53)		16 (47.06)	18 (52.94)	
TCS alone	164 (63.08)	98 (59.76)	66 (40.24)		130 (79.27)	34 (20.73)		119 (72.56)	45 (27.44)		70 (42.68)	94 (57.32)	
TCS with other topical Tx	52 (20)	30 (57.69)	22 (42.31)		39 (75)	13 (25)		36 (69.33)	16 (30.77)		17 (32.69)	35 (67.31)	
Topical and systemic Tx	10 (3.85)	7 (70)	3 (30)		6 (60)	4 (40)		7 (70)	3 (30)		2 (20)	8 (80)	

Note: [a] Mann-Whitney test; [b] Fisher's exact test; [c] Chi-square test; italic and bold values are p-value < .05

Table 4.6 Univariate and multivariate logistic regression of factors associated with the presence of anxiety symptoms, depressive symptoms, psychological distress and moderate-to-high perceived stress in patients with OLP (N=260)

Variables	Presence of anxiety symptoms (HADS-A≥8)				Presence of depressive symptoms (HADS-D≥8)				Presence of psychological distress (HADS-D≥15)				Presence of moderate-to-high stress (PSS-T≥14)			
	Crude OR [95%CI]	P-value	Adj-OR [95%CI]	P-value	Crude OR [95%CI]	P-value	Adj-OR [95%CI]	P-value	Crude OR [95%CI]	P-value	Adj-OR [95%CI]	P-value	Crude OR [95%CI]	P-value	Adj-OR [95%CI]	P-value
Demographic variable																
Age	**0.97 [0.95-0.99]**	**0.007**	**0.96 [0.94-0.99]**	**0.004**	1 [0.98-1.03]	0.776	1 [0.96-1.03]	0.853	0.98 [0.95-1.00]	0.055	**0.96 [0.94-0.99]**	**0.019**	0.98 [0.96-1.00]	0.102	0.99 [0.96-1.01]	0.449
Male (female = ref.)	0.78 [0.41-1.47]	0.447	0.80 [0.39-1.66]	0.552	0.89 [0.41-1.91]	0.76	1.03 [0.41-2.61]	0.945	0.84 [0.42-1.69]	0.628	0.96 [0.42-2.20]	0.926	0.56 [0.30-1.02]	0.06	0.51 [0.25-1.05]	0.067
Ethnicity (white = ref.)																
Mixed	1.86 [0.36-9.48]	0.455	2.09 [0.36-12.13]	0.411	2.89 [0.5-16.56]	0.234	6.89 [0.77-61.82]	0.085	1.97 [0.35-17.13]	0.443	2.96 [0.41-21.16]	0.279	1.77 [0.32-9.92]	0.51	1.88 [0.29-12.36]	0.511
Asian	**1.86 [1.04-3.33]**	**0.037**	1.14 [0.56-2.34]	0.721	**3.41 [1.77-6.58]**	**0**	2.06 [0.89-4.76]	0.092	**3.47 [1.87-6.42]**	**0**	1.94 [0.91-4.14]	0.088	**3.04 [1.57-5.90]**	**0.001**	2.02 [0.92-4.42]	0.079
Black	1.49 [0.39-5.73]	0.564	0.72 [0.16-3.25]	0.669	1.65 [0.33-8.37]	0.545	0.60 [0.10-3.73]	0.58	3.16 [0.81-12.34]	0.098	1.38 [0.30-6.45]	0.682	1.77 [0.43-7.31]	0.428	0.87 [0.19-4.13]	0.865
Ever smoker (non-smokers = ref.)	**1.87 [1.06-3.32]**	**0.032**	**2.31 [1.22-4.35]**	**0.01**	1.60 [0.82-3.1]	0.165	**2.55 [1.15-5.67]**	**0.021**	1.43 [0.78-2.64]	0.252	2.01 [0.98-4.13]	0.056	1.79 [0.98-3.29]	0.059	**2.78 [1.39-5.53]**	**0.004**
Alcohol drinker (non-drinkers = ref.)	**0.57 [0.34-0.97]**	**0.039**	0.61 [0.32-1.14]	0.12	**0.24 [0.13-0.45]**	**0**	**0.26 [0.12-0.54]**	**0**	**0.30 [0.17-0.53]**	**0**	**0.35 [0.18-0.69]**	**0.002**	**0.42 [0.24-0.74]**	**0.002**	**0.51 [0.26-0.98]**	**0.045**
Comorbidity (no = ref.)																
1 comorbidity	1.02 [0.44-2.37]	0.957	1.48 [0.57-3.85]	0.417	0.89 [0.23-3.37]	0.864	1.10 [0.25-4.90]	0.901	1.04 [0.37-2.90]	0.948	1.67 [0.51-5.55]	0.4	1.13 [0.51-2.52]	0.76	1.18 [0.48-2.89]	0.72
≥ 2 comobidities	1.51 [0.72-3.15]	0.277	**2.72 [1.11-6.70]**	**0.029**	**3.44 [1.15-10.2]**	**0.027**	**4.93 [1.34-18.13]**	**0.016**	2.35 [0.97-5.68]	0.057	**4.55 [1.50-13.84]**	**0.008**	1.41 [0.69-2.86]	0.342	1.66 [0.71-3.87]	0.24
Clinical variable																
Disease duration	0.97 [0.93-1.01]	0.192	1.00 [0.96-1.04]	0.974	0.99 [0.94-1.04]	0.671	1.00 [0.95-1.04]	0.911	0.98 [0.93-1.03]	0.339	1.01 [0.97-1.05]	0.648	**0.95 [0.92-0.99]**	**0.006**	**0.95 [0.91-0.99]**	**0.009**
NRS for pain	**1.22 [1.10-1.36]**	**0**	**1.29 [1.11-1.49]**	**0.001**	**1.26 [1.11-1.43]**	**0**	**1.20 [1.01-1.44]**	**0.043**	**1.27 [1.13-1.43]**	**0**	**1.25 [1.06-1.47]**	**0.008**	**1.27 [1.13-1.41]**	**0**	**1.27 [1.09-1.48]**	**0.002**
ODSS-total (disease severity)	1.01 [0.99-1.03]	0.449	0.97 [0.94-1.00]	0.063	**1.03 [1-1.06]**	**0.034**	0.99 [0.95-1.03]	0.655	1.02 [1-1.05]	0.075	0.98 [0.95-1.02]	0.285	1.02 [1.00-1.05]	0.1	0.99 [0.95-1.02]	0.39

Note: Bold values are p-values < .05

Prevalence and associated factors related to the presence of anxiety symptoms in patients with OLP.

The median score of HADS-A in the present population was 7 (IQR 3, 9). The prevalence of anxiety symptoms (determined by HADS-A score of ≥ 8) in patients with OLP was 39.23% (n =102; 54 (20.77%) with mild anxiety (8 ≤ HADS-A ≤ 10), 40 (15.38%) with moderate anxiety (11 ≤ HADS-A ≤ 15), 8 (3.08%) with severe anxiety (HADS-A ≥16)). Based on univariate analysis, younger age, Asian ethnicity, no alcohol consumption and those reporting higher levels of painful oral symptoms were significantly associated with the presence of anxiety symptoms in patients with OLP. There was no significant difference in the number of disease comorbidities and oral disease severity (based upon ODSS scores) between the anxious OLP group and non-anxious OLP group. After adjusting for other confounders in multivariate analysis, older ages (AOR: 0.96 (0.94-0.99); p = 0.004) were less likely to have symptoms of anxiety with OLP. On the contrary, anxiety symptoms were found to be independently and positively associated with history of smoking (AOR: 2.31 (1.22-4.35); p = 0.01) and greater pain intensity (AOR: 1.29 (1.11-1.49); p = 0.001) in OLP patients (Table 4.6). The association of anxiety symptoms with Asian ethnicity and alcohol consumption in patients with OLP did not survive multivariate analysis but the positive association with having at least two disease comorbidities emerged (AOR: 2.72 (1.11-6.70); p =0.029).

Prevalence and associated factors related to the presence of depressive symptoms in patients with OLP.

The median score of depressive symptoms using HADS-D in OLP patients was 4 (IQR 1, 6). Based upon cut-off HADS-D score of 8.0, the prevalence of depressive symptoms in OLP patients was 20.77% (n = 54; 31 (11.92%) with mild depression (8 ≤ HADS-D ≤ 10), 20 (7.69%) with moderate depression (11 ≤ HADS-D ≤ 15), 3 (1.15%) with severe depression (HADS-D ≥16)). Univariate analysis demonstrated that Asian ethnicity, no alcohol consumption, having two disease comorbidities, greater oral pain and higher OLP disease severity were predictive

factors for having depressive symptoms in the OLP patients. When potential confounders were controlled in multivariate models, those who have more than one disease comorbidity (AOR: 4.93 (1.34-18.13); p = 0.016) and reporting greater painful oral symptoms (AOR: 1.20 (1.01-1.44); p = 0.043) remained significantly associated with an increased likelihood of having depressive symptoms in patients with OLP. Alcohol consumption was unexpectedly found to be a negative predictor of depressive symptoms (AOR: 0.26 (0.12-0.54), p <0.000). After adjusting for other confounders, there was no significant difference in Asian ethnicity and the degree of OLP disease severity between depressed and non-depressed OLP groups while the positive association between depressive symptoms and ever-smokers emerged (AOR: 2.55 (1.15-5.67); p =0.021). (Table 4.6).

Prevalence and associated factors related to the presence of psychological distress in patients with OLP.

The median HADS-T score in the OLP sample was 10 (IQR 5, 16). Based on the HADS-T cut-off score of 15, psychological distress was observed in 27.69% of patients with OLP (n = 55). In a univariate analysis, Asian ethnicity, alcohol consumption and greater intensity of oral pain were associated with distress in OLP patients. After confounders were adjusted, painful oral symptoms (AOR: 1.25 (1.06-1.47), p = 0.008) remained independent predictors of distress in OLP. OLP patients who were of older ages (AOR: 0.96 (0.94-0.99), p = 0.019) and consumed alcohol (AOR: 0.35 (0.18-0.69), p = 0.002) had a significantly lower likelihood of emotional distress. The positive association between emotional distress and having at least two disease comorbidities emerged (AOR: 4.55 (1.50-13.84); p =0.008) (Table 4.6). The remaining factors including history of smoking and severity of OLP were found not to be significant predictors after controlling for demographic and other OLP-related variables.

Prevalence and associated factors related to the presence of moderate-to-high perceived stress in patients with OLP.

The median score of total PSS-10 in the present OLP cohort was 16 (IQR 11, 21). Using the cut-off PSS-10 score of 14, moderate-to-high perceived stress was reported in 59.62% of patients (n = 155). Univariate analysis showed that Asian ethnicity, alcohol drinkers, disease duration and level of oral symptoms were associated with the presence of moderate-to-high stress in patients with OLP. When other confounding factors were taken into account, greater level of oral pain remained to be independent predictor of having moderate-to-high stress in patients with OLP (AOR: 1.27 (1.09-1.48), p = 0.002). Among patients with OLP, those having longer disease duration (AOR: 0.95 (0.91-0.99), p = 0.009) or alcohol drinkers (AOR: 0.51 (0.26-0.98), p = 0.045) were less likely to report moderate-to-high level of stress. While the association of moderate-to-high stress with Asian ethnicity patients with OLP did not survive multivariate analysis, the positive association with history of smoking emerged (AOR: 2.78 (1.39-5.53); p =0.004).

4.6.2 Results of the RAS cohort

4.6.2.1 Psychometric validation of the HADS and PSS-10 for use in patients with RAS

Descriptive item analyses

The descriptive item statistics for the HADS and PSS-10 responses of 120 participants with RAS are shown in Table 4.7. No data of the HADS and PSS-10 were missing, indicating good feasibility of in the present study. Skewness values of all items were generally acceptable (range between -1 and 1) except three HADS-D items, which were marginally high (up to 1.44).

Table 4.7 Descriptive statistics for each of the HADS and PSS-10 item

Items	med (IQR)	mean (SD)	score distribution (%)					skewness
			0	1	2	3	4	
HADS-anxiety								
HA1 Tense-wound up	1 (1, 2)	1.38 (0.69)	9 (7.5)	62 (51.67)	44 (36.67)	5 (4.17)	_	0.14
HA3 Frightened feelings	1 (0, 2)	0.88 (0.95)	53 (44.17)	36 (30)	23 (19.17)	8 (6.67)	_	0.71
HA5 Worrying thought	1 (1, 2)	1.18 (0.92)	29 (24.17)	54 (45)	24 (20)	13 (10.83)	_	0.49
HA7 At ease-relaxed	1 (0, 2)	0.99 (0.75)	33 (27.5)	56 (46.67)	30 (25)	1 (0.83)	_	0.13
HA9 Butterflies in stomach	1 (0, 1)	0.74 (0.74)	48 (40)	59 (49.17)	9 (7.5)	4 (3.33)	_	0.95
HA11 Restless	1 (1, 2)	1.24 (0.86)	26 (21.67)	46 (38.33)	41 (34.17)	7 (5.83)	_	0.07
HA13 Sudden panic	1 (0, 1)	0.84 (0.87)	49 (40.83)	48 (40)	16 (13.33)	7 (5.83)	_	0.85
HADS-depression								
HD2 Enjoy things	1 (0, 1)	0.64 (0.68)	57 (47.5)	49 (40.83)	14 (11.67)	0 (0)	_	0.59
HD4 Laugh-see funny side	0 (0, 1)	0.48 (0.72)	77 (64.17)	31 (25.83)	10 (8.33)	2 (1.67)	_	1.44
HD6 Cheerful	1 (0, 1)	0.68 (0.67)	50 (41.67)	60 (50)	8 (6.67)	2 (1.67)	_	0.8
HD8 Slowed down	1 (1, 2)	1.12 (0.85)	28 (23.33)	59 (49.17)	24 (20)	9 (7.5)	_	0.51
HD10 Lost interest	0 (0, 1)	0.62 (0.79)	67 (55.83)	34 (28.33)	17 (14.17)	2 (1.67)	_	1
HD12 Excitement	0 (0, 1)	0.61 (0.76)	65 (54.17)	39 (32.5)	14 (11.67)	2 (1.67)	_	1.02
HD14 Enjoy leisures	0 (0, 1)	0.38 (0.57)	79 (65.83)	36 (30)	5 (4.17)	0 (0)	_	1.16
PSS-10								
P1 Upset	2 (1, 3)	1.93 (1.06)	14 (11.67)	21 (17.5)	52 (43.33)	25 (20.83)	8 (6.67)	-0.12
P2 Life-uncontrollable	2 (1, 2)	1.63 (1.13)	23 (19.17)	29 (24.17)	45 (37.5)	15 (12.50)	8 (6.67)	0.23
P3 Nervous-stressed	2 (2, 3)	2.43 (0.99)	4 (3.33)	13 (10.83)	49 (40.83)	35 (29.17)	19 (15.83)	-0.18
P4 Ability to handle problems	1 (1, 2)	1.33 (1.02)	27 (22.5)	46 (38.33)	31 (25.83)	13 (10.83)	3 (2.5)	0.5
P5 Things going your way	1 (1, 2)	1.55 (0.92)	12 (10)	50 (41.67)	41 (34.17)	14 (11.67)	3 (2.5)	0.41
P6 Unable to cope	2 (1, 2)	1.71 (1.13)	19 (15.83)	32 (26.67)	43 (35.83)	17 (14.17)	9 (7.5)	0.24
P7 Control irritations	1 (1, 2)	1.57 (0.99)	14 (11.67)	47 (39.17)	42 (35)	11 (9.17)	6 (5)	0.53
P8 On top of things	1 (1, 2)	1.47 (0.87)	10 (8.33)	61 (50.83)	35 (29.17)	11 (9.17)	3 (2.5)	0.72
P9 Angry	2 (1, 3)	1.95 (1.05)	11 (9.17)	27 (22.5)	48 (40)	25 (20.83)	9 (7.5)	0.01
P10 Difficulties-overloaded	2 (1, 2)	1.58 (1.09)	22 (18.33)	35 (29.17)	41 (34.17)	16 (13.33)	6 (5)	0.28

Structural validity

The fit indices for the original two-factor and one-factor model of the HADS suggested that both models were less than a good fit for use in patients with RAS (Table 4.8). The bi-factor model of HADS fit the RAS data reasonably well, and was the only model which demonstrated good acceptability threshold of SRMR (<0.05). As for the PSS-10, the results from the CFA exhibited an approximately equal fit of both two-factor and bi-factor models to the RAS data. Comparing the CFI value of the two PSS-10 models, the value for the bi-factor model just reached the threshold for good model fit (CFI = 0.95), indicating marginally superior of this model to the two-factor model of the PSS-10 in this RAS cohort.

Table 4.8 Confirmatory factor analysis model fit statistics for the HADS and PSS-10 in a cohort of patients with RAS

	RMSEA	SRMR	CFI	TLI
HADS				
1-factor model	0.14	0.11	0.83	0.8
2-factor model	0.1	0.09	0.91	0.89
bifactor model	0.06	0.05	0.98	0.97
PSS-10				
1-factor model	0.21	0.08	0.85	0.8
2-factor model	0.13	0.04	0.94	0.93
bifactor model	0.14	0.04	0.95	0.92

Reliability

The internal consistency reliability for the total and subscale scores of the HADS and PSS-10 were acceptable to good (Cronbach's α range = 0.76-0.89; see also Table 4.9). The values of ω coefficients of subscale and total scores were high, varying from 0.86 to 0.92 for the HADS, and from 0.82 to 0.93 for the PSS-10. In contrast, The values of ω-h, which estimates scale reliability with the effects of all other factors removed, for each subscale of the HADS and

PSS-10 were found to be considerably low, indicating low reliability of subscale scores of both instruments.

Table 4.9 Reliability estimates of overall and subscale scores of the HADS and PSS-10 in a cohort of patients with RAS

	Cronbach's α	McDonald's ω	ω-h
HADS-*total (distress)*	0.852	0.92	0.729
HADS-*anxiety subscale*	0.829	0.89	0.474
HADS-*depression subscale*	0.763	0.86	0.107
PSS-*total (stress)*	0.88	0.931	0.835
PSS-*perceived stress subscale*	0.888	0.926	0.025
PSS-*perceived self-efficacy subscale*	0.762	0.819	0.444

4.6.2.2 Psychological status in patients with RAS: a cross-sectional study

Descriptive characteristics of participants

The median age of all 120 RAS participants was 42.03 years (interquartile range = 33.22-53.58 years), and 71 (59.17%) were female. The median age since the first RAS episode was 19.25 years, with disease duration varying from 1 year to 58 years (median = 16.89 years). Minor RAS was the most prevalent clinical variant of RAS, accounted for 85% of participants, followed by major (11%) and herpetiform types (4%). Among 120 participants, 21 (17.5%) received at least one systemic medications including colchicine (11 patients), prednisolone (4 patients), pentoxifylline (4 patients), thalidomide (4 patients), azathioprine (3 patients) and dapsone (1 patient). Other demographic and disease characteristics of the study cohort are summarised in Table 4.10.

Table 4.10 Descriptive statistics of demographics and RAS-related variables of study participants and bivariate analysis of factors associated with the presence of anxiety symptoms, depressive symptoms, psychological distress and moderate-to-high perceived stress in patients with RAS (N=120)

Characteristics	All subjects (N=120)	HADS-A<8 (N=69, 57.5%)	HADS-A≥8 (N=51, 42.5%)	P value	HADS-D<8 (N=98, 81.67%)	HADS-D≥8 (N=22, 18.33%)	P value	HADS-T<15 (N=86, 71.67%)	HADS-T≥15 (N=34, 28.33%)	P value	PSS-T<14 (N=34, 28.33%)	PSS-T≥14 (N=86, 71.67%)	P value
Demographics													
Age (years): median (IQR)	42.03 (33.22, 53.58)	42.01 (34.04, 51.42)	43.84 (31.06, 54.01)	0.78[a]	41.65 (32.94, 52.22)	49.40 (35.28, 56.37)	0.21[a]	41.46 (33.14, 52.22)	47.50 (33.41, 54.62)	0.47[a]	39.07 (33.30, 51.02)	46.40 (32.94, 53.79)	0.56[a]
Gender (n, %)				0.493[c]			0.994[c]			0.109[c]			0.383[c]
Female	71 (59.17)	39 (54.93)	32 (45.07)		58 (81.69)	13 (18.31)		47 (66.20)	24 (33.80)		18 (25.35)	53 (74.65)	
Male	49 (40.83)	30 (61.22)	19 (38.78)		40 (81.63)	9 (18.37)		39 (79.59)	10 (20.41)		16 (32.65)	33 (67.35)	
Ethnicity (n, %)				***0.049[b]***			0.117[b]			***0.022[b]***			0.161[b]
White	93 (77.50)	58 (62.37)	35 (37.63)		79 (84.95)	14 (15.05)		72 (77.42)	21 (22.58)		31 (33.33)	62 (66.67)	
Mixed	5 (4.17)	1 (20)	4 (80)		4 (80)	1 (20)		2 (40)	3 (60)		0 (0)	5 (100)	
Asian	16 (13.33)	9 (56.25)	7 (43.75)		12 (75)	4 (25)		10 (62.5)	6 (37.5)		2 (12.5)	14 (87.5)	
Black	6 (5)	1 (16.67)	5 (83.33)		3 (50)	3 (50)		2 (33.33)	4 (66.67)		1 (16.67)	5 (83.33)	
Smoking (n, %)													
Non-smoker	99 (82.5)	56 (56.57)	43 (43.43)		81 (81.82)	18 (18.18)		71 (71.72)	28 (28.28)		29 (29.29)	70 (70.71)	
Ever smoker	21 (17.5)	13 (61.90)	8 (38.10)	0.653[c]	17 (80.95)	4 (19.05)	0.926[c]	15 (71.43)	6 (28.57)	0.979[c]	5 (23.81)	16 (76.19)	0.613[c]
Ex-smoker	13 (10.83)	8 (61.54)	5 (38.46)	0.94[b]	12 (92.31)	1 (7.69)	0.255[b]	11 (84.62)	2 (15.38)	0.284[b]	4 (30.77)	9 (69.23)	0.672[b]
Current smoker	8 (6.67)	5 (62.5)	3 (37.5)		5 (62.5)	3 (37.5)		4 (50)	4 (50)		1 (12.5)	7 (87.5)	
Alcohol consumption (n, %)													
No	39 (32.5)	20 (51.28)	19 (48.72)		27 (69.23)	12 (30.77)		25 (64.10)	14 (35.90)		7 (17.95)	32 (82.05)	
Yes	81 (67.5)	49 (60.49)	32 (39.51)	0.339[c]	71 (87.65)	10 (12.35)	***0.015[c]***	61 (75.31)	20 (24.69)	0.202[c]	27 (33.33)	54 (66.67)	0.08[c]
≤ 14 Units/week	77 (64.17)	47 (61.04)	30 (38.96)	0.535[b]	68 (88.31)	9 (11.69)	***0.037[b]***	59 (76.62)	18 (23.38)	0.202[b]	25 (32.47)	52 (67.53)	0.142[b]
> 14 Units/week	4 (3.33)	2 (50)	2 (50)		3 (75)	1 (25)		2 (50)	2 (50)		2 (50)	2 (50)	
Comorbidity (n, %)				0.682[c]			***0.05[c]***			0.074[c]			0.268[c]
No	57 (47.5)	34 (59.65)	23 (40.35)		48 (84.21)	9 (15.79)		44 (77.19)	13 (22.81)		20 (35.09)	37 (64.91)	
1 comorbidity	37 (30.83)	22 (59.46)	15 (40.54)		33 (89.19)	4 (10.81)		28 (75.68)	9 (24.32)		9 (24.32)	28 (75.68)	
≥ 2 comobidities	26 (21.67)	13 (50)	13 (50)		17 (65.38)	9 (34.62)		14 (53.85)	12 (46.15)		5 (19.23)	21 (80.77)	

Note: [a] Mann-Whitney test; [b] Fisher's exact test; [c] Chi-square test; IQR = Interquartile range; Italic and bold values are p-value < .05

Table 4.10 Descriptive statistics of demographics and RAS-related variables of study participants and bivariate analysis of factors associated with the presence of anxiety symptoms, depressive symptoms, psychological distress and moderate-to-high perceived stress in patients with RAS (N=120) (cont.)

Characteristics	All subjects (N=120)	HADS-A<8 (N=69, 57.5%)	HADS-A≥8 (N=51, 42.5%)	P value	HADS-D<8 (N=98, 81.67%)	HADS-D≥8 (N=22, 18.33%)	P value	HADS-T<15 (N=86, 71.67%)	HADS-T≥15 (N=34, 28.33%)	P value	PSS-T<14 (N=34, 28.33%)	PSS-T≥14 (N=86, 71.67%)	P value
RAS-related variables													
Age at onset (years): med (IQR)	19.25 (10.66, 35.36)	15.61 (11.33, 34.52)	19.40 (9.97, 38.15)	0.69[a]	16.22 (9.97, 34.52)	24.12 (14.54, 42.12)	0.21[a]	16.22 (9.90, 34.52)	20.47 (12.93, 42.12)	0.28[a]	14.89 (9.90, 33.45)	19.38 (11.33, 36.73)	0.34[a]
Disease duration (years): median (IQR)	16.89 (7.20, 27.70)	18.50 (8.54, 28.56)	15.55 (5.43, 26.56)	0.69[a]	18.73 (7.49, 28.56)	15.16 (5.43, 22.38)	0.70[a]	18.73 (7.49, 28.56)	15.16 (5.43, 25.43)	0.54[a]	19 (10.23, 26.85)	15.47 (5.16, 28.56)	0.45[a]
Clinical types (n, %)													
Minor	102 (85)	63 (61.76)	39 (38.24)	0.063[b]	87 (85.29)	15 (14.71)	***0.016[b]***	78 (76.47)	24 (23.53)	***0.016[b]***	33 (32.35)	69 (67.65)	0.082[b]
Major	13 (10.83)	4 (30.77)	9 (69.23)		9 (69.23)	4 (30.77)		6 (46.15)	7 (53.85)		1 (7.69)	12 (92.31)	
Herpetiform	5 (4.17)	2 (40)	3 (60)		2 (40)	3 (60)		2 (40)	3 (60)		0 (0)	5 (100)	
Ulcer severity score (USS)													
USS-ulcer size (mm): median (IQR)	4 (2.5, 6)	4 (2, 6)	4 (3, 6)	0.72[a]	4 (2, 6)	4.5 (3, 7)	0.328[a]	4 (2, 6)	4 (3, 7)	0.38[a]	3.5 (2, 6)	4 (3, 6)	0.58[a]
ulcer size < 1 cm (n, %)	108 (90)	66 (61.11)	42 (38.89)	***0.016[c]***	90 (83.33)	18 (16.67)	0.157[c]	81 (75)	27 (25)	***0.015[c]***	34 (31.48)	74 (68.52)	***0.022[c]***
ulcer size ≥ 1 cm (n, %)	12 (10)	3 (25)	9 (75)		8 (66.67)	4 (33.33)		5 (41.67)	7 (58.33)		0 (0)	12 (100)	
USS-number of ulcers: median (IQR)	2 (2, 4)	2 (2, 4)	2 (2, 4)	0.77[a]	2 (2, 4)	2.5 (2, 4)	0.96[a]	2 (2, 4)	2 (2, 4)	0.84[a]	2 (2, 3)	2 (2, 4)	0.37[a]
number of ulcers < 5 (n, %)	100 (83.33)	57 (57)	43 (43)	0.805[c]	83 (83)	17 (17)	0.399[c]	72 (72)	28 (28)	0.856[c]	33 (28.70)	82 (71.30)	0.67[c]
number of ulcers ≥ 5 (n, %)	20 (16.67)	12 (60)	8 (40)		15 (75)	5 (25)		14 (70)	6 (30)		1 (20)	4 (80)	
USS-ulcer duration (1/2 w): median (IQR)	3 (2,4)	3 (2, 4)	3 (2, 4)	0.934[a]	3 (2, 4)	3 (2, 4)	0.934[a]	3 (2, 4)	3 (2, 4)	0.38[a]	3 (2, 4)	3 (2, 4)	0.09[a]
ulcer duration < 4 weeks (n, %)	110 (91.67)	62 (56.36)	48 (43.64)	0.404[c]	91 (82.73)	19 (17.27)	0.389[c]	80 (72.73)	30 (27.27)	0.467[c]	32 (29.09)	78 (70.91)	0.723[c]
ulcer duration ≥ 4 weeks (n, %)	10 (8.33)	7 (70)	3 (30)		7 (70)	3 (30)		6 (60)	4 (40)		2 (20)	8 (80)	
USS-ulcer free period (10-w): median (IQR)	8 (6.5, 9)	8 (7, 9)	8 (6, 9)	0.827[a]	8 (6, 9)	9 (7, 10)	0.051[a]	8 (7, 9)	8 (6, 9)	0.666[a]	8 (7, 9)	8 (6, 9)	0.413[a]
ulcer free period > 4 weeks (n, %)	22 (18.33)	11 (50)	11 (50)	0.431[c]	19 (86.36)	3 (13.64)	0.529[c]	14 (63.64)	8 (36.36)	0.355[c]	5 (22.73)	17 (77.27)	0.518[c]
ulcer free period ≤ 4 weeks (n, %)	98 (81.67)	58 (59.18)	40 (40.82)		79 (80.61)	19 (19.39)		72 (73.47)	26 (26.53)		29 (29.59)	69 (70.41)	
USS-site score: median (IQR)	5 (4, 8)	5 (4, 7)	5 (4, 8)	0.465[a]	5 (4, 7)	6 (5, 8)	0.19[a]	5 (4, 7)	6 (4, 9)	0.18[a]	5 (3, 7)	5 (4, 8)	0.55[a]
USS-pain(mean pain in the past 3 M)	6 (4, 7)	6 (4, 7)	6 (4, 8)	0.193[a]	6 (4, 7)	6 (4, 8)	0.58[a]	6 (4, 7)	7 (5, 8)	***0.05[c]***	5 (3, 6)	7 (5, 8)	***0.0019[c]***
USS-total	29 (24, 35)	29 (24, 35)	29 (25, 36)	0.586[a]	28.5 (24, 35)	33 (25, 38)	0.217[a]	29 (24, 34)	30 (24, 38)	0.326[a]	28 (21, 32)	29 (25, 36)	***0.048[a]***
NRS for pain scale: median (IQR)	4 (1, 7)	3 (1, 6)	5 (1, 7)	0.264[a]	3 (1, 7)	5.5 (2, 7)	0.104[a]	3 (1, 6)	6 (2, 7)	***0.03[a]***	2 (1, 4)	5 (2, 7)	***0.014[a]***
Treatment (n, %)				0.350[c]			0.598[c]			0.979[c]			0.881[c]
Topical treatment	99 (82.5)	55 (55.56)	44 (44.44)		80 (80.81)	19 (19.19)		71 (71.72)	28 (28.28)		63 (63.64)	36 (36.36)	
Topical and systemic treatment	21 (17.5)	14 (66.67)	7 (33.33)		18 (85.71)	3 (14.29)		15 (71.43)	6 (28.57)		13 (61.90)	8 (38.10)	

Note: [a] Mann-Whitney test; [b] Fisher's exact test; [c] Chi-square test; IQR = Interquartile range; Italic and bold values are p-value < .05

Prevalence and associated factors related to the presence of psychological symptoms in patients with RAS

The prevalence of anxiety, depressive symptoms, emotional distress and moderate-to-high perceived stress in participants with RAS were 42.5%, 18.33%, 28.33% and 71.67%, respectively. Significant factors associated with the presence of these psychological symptoms in RAS participants were as follows: ethnicity (with anxiety and distress), non-alcoholic drinkers (with depression), at least two disease comorbidities (with depression), clinical types of RAS (with depression and distress), average ulcer size ≥ 1 cm (with anxiety, distress and stress), average ulcer pain based upon the USS-pain and NRS for pain (with distress and stress) and disease activity based upon total USS (with distress). The detailed subgroup analysis of the association between demographic and clinical factors and the presence of psychological symptoms in the present sample are shown in Table 4.10.

4.7 DISCUSSION

4.7.1 Psychometric validation of the HADS and PSS-10 and a cross-sectional study of psychological status in patients with OLP

The present study aimed to validate two commonly used psychological measures – the Hospital Anxiety and Depression Scale and the 10-item Perceived Stress Scale – in patients with OLP and is the first study examining their internal structures using CFA in this patient population. The present study results found that both the HADS and PSS-10 demonstrate a robust bifactor structure among patients with OLP, rather than their original models and other proposed models in the literature. This finding is consistent with recent validation studies of both scales in other medical conditions (Norton et al., 2013, Iani et al., 2014, Luciano et al., 2014, Lee et al., 2017, Perera et al., 2017, Reis et al., 2017). Though this bifactor model acknowledges the presence of two subscales within both measures, once the variance of the general factor of distress in the HADS and general factor of stress in the PSS-10 are controlled, subscale reliability coefficients (ω-h) do not reach the threshold necessary for a

psychometrically meaningful interpretation. Hence both measures do not seem to have sufficient evidence supporting the utility of their subscale scores. As both scales are dominated by the presence of an underlying strong general factor, the HADS and PSS-10 should be employed as valid and reliable measures of overall psychological distress and perceived stress in patients with OLP, respectively.

The measurement of psychological distress, as indicated by the use of the HADS total score, may be useful for patients with OLP when considering intervention for the management of concomitant anxiety and depression (e.g. cognitive behavioural therapy or certain classes of antidepressants) (Kroenke et al., 2016). Future studies of anxiety and depression in OLP should adopt other contemporary psychological instruments, such as the Generalised Anxiety Disorder Scale (GAD-7) and the Patient Health Questionnaire-9 (PHQ-9) as they were designed according to the Diagnostic and Statistical Manual of Mental Disorders, 5th ed (DSM-5) to aid screening and diagnosis of generalized anxiety disorders and major depressive disorders (Kroenke et al., 2007, Wittkampf et al., 2009).

Both the GAD-7 and PHQ-9 have been well-validated as unidimensional scales with 16 combined items compared to the 14-item HADS. Additionally, very recently the composite scale of both measures (Patient Health Questionnaire Anxiety and Depression Scale; PHQ-ADS) has been psychometrically proven as a valid and reliable measure of distress in patients with chronic musculoskeletal pain, those undergoing dialysis therapy, or patients in oncology clinical settings (Kroenke et al., 2016, Chilcot et al., 2018). Further validation of GAD-7 and PHQ-9 in common oral mucosal diseases such as OLP is recommended.

The present study is the first prospective cross-sectional study with over 250 patients, providing the prevalence of psychological symptoms as well as examining the association of psychological comorbidities with various demographic and clinical variables in patients

diagnosed with OLP in one tertiary Oral Medicine referral centre in the UK. The present findings revealed the prevalence of anxiety symptoms, depressive symptoms and emotional distress in OLP of 39.23%, 20.77% and 27.69%, respectively. The reported prevalence of anxiety in OLP in this study was similar to the findings of a study of Croatian patients (Gavic et al., 2014); however, the present study found a much lower prevalence of depression (54.08%) compared to the same study. The discrepancies in the prevalence figures between the two studies may be explained by the difference in the use of instruments measuring psychological comorbidities, the differences in ethnic and sociocultural background between the study populations, as well as variation in the methodological qualities of the different studies.

Notably, when considering anxiety and depression as comorbidities of OLP, the high prevalence of anxiety symptoms in the study OLP population led to this being the second most common comorbidity of oral lichen planus, after hypertension. Although the present study found a high prevalence of anxiety and depressive symptoms in this patient population, only 3.08% (8/260) and 5% (13/260) of patients had a definitive diagnosis of anxiety and depression, respectively, and were currently receiving anti-depressant therapy. This means that a relatively high proportion of patients with OLP who have possible psychological comorbidities may not be aware of the associated symptoms and are not receiving optimal treatment or support. Screening for psychological comorbidities in patients with OLP using a psychometrically adequate outcome measures is therefore crucial in aiding identification of patients requiring additional psychological assessment and those who may benefit from appropriate psychological treatment and support, which could in turn improve their overall quality of life.

As expected, some demographic factors had certain roles in the presence of psychological comorbidities in patients with OLP. Regarding age, the present results found that younger

patients were more likely to be anxious and have emotional distress than older patients. Although the present result is contradicted by one study (Vallejo et al., 2001), this finding is consistent with previous research regarding patients with cancer. This may be due to greater disruption to everyday living in younger aged patients, while the older age group may already have a certain degree of impairment of physical function, and may be cognitively and emotionally better prepared to accept and cope with illness (Linden et al., 2012). Similar research in survivors of various types of cancers also added that this inverse association between age and psychological morbidities has been attributed by greater worries of recurrence and death in young patients (Hinz et al., 2009, Rogers et al., 2016), and we suggest that perhaps young patients with OLP may have greater concerns about potential transformation of OLP lesions into oral cancer.

OLP patients who currently smoke tobacco or previously smoked appeared to be more anxious or depressed than those who had never smoked, and this positive association between tobacco smoking and mental illness is generally in line with previously research (Farrell et al., 1998). With respect to the causal relationship, a recent systematic review found overall inconsistent evidence as regards the direction of this association (Fluharty et al., 2017). It was shown that nearly half of published studies found baseline anxiety or depression results in smoking or increased smoking behaviour, supporting self-medication hypothesis, which suggests that individuals smoke in order to alleviate their psychological symptoms. The same systematic review also reported that about one-third of the studies observed that baseline exposure to smoking can lead to development of anxiety and depression, and this supported the hypothesis that smoking can increase individual's susceptibility to anxiety and depression. However, some studies reported bidirectional relationship between the two, and very few studies showed null results. Further research using different methodology are required in order to draw stronger causal inferences between smoking and psychological symptoms.

Interestingly, the present study demonstrated a decreased likelihood of having comorbid depression and emotional distress in OLP patients who consumed alcohol, and this finding was consistent with several studies supporting evidence of elevated risk of depression among alcohol abstainers. Some recent studies have suggested a curvi-linear J-shaped relationship between alcohol consumption and depression, indicating that non-drinkers and heavy drinkers have an increased risk of having depressive symptoms than light-to-moderate drinkers (Kim et al., 2015, Skogen et al., 2009). Lower level of depressive symptoms in occasional drinkers might be partly attributable to therapeutic window of low dose alcohol, which could mask symptoms of depression or provide temporary mood enhancement. On the other hands, alcohol is also a depressant, which when consumes regularly and heavily, can increase the risk of developing depressive symptoms. Another possible explanation is that occasional alcohol drinking has a general protective influence with depressive symptoms which may be attributable to social circumstances surrounding drinking, whilst some abstainers could have personal and social background characteristics such as poor social support, which predispose to depression and emotional distress (Rodgers et al., 2007).

The present study did not find an association between any of the psychological comorbidities and the clinical type, extent or severity of OLP lesions based on site and activity scores of ODSS. This finding is in keeping with several previous studies (Radwan-Oczko et al., 2018, Lopez-Jornet et al., 2016, Shah et al., 2009). In contrast, some previous studies have reported higher depression levels in patients with erosive OLP than in those with non-erosive lesions (Vallejo et al., 2001, Garcia-Pola and Huerta, 2000, Rojo-Moreno et al., 1998). Another recent study observed significantly higher level of anxiety in OLP patients who had greater disease activity based upon ad hoc clinical disease activity scoring system (Zucoloto et al., 2019). The present findings, however, demonstrated that once variables including oral pain were controlled for in the multivariate model, the severity of clinical signs of OLP were found not to be risk predictors of depression and distress in OLP. This means that psychological symptoms can occur in patients with OLP regardless of the clinical type of disease and the severity of

clinical signs. This may be partly due to the chronic, unpredictable, and potentially malignant nature of OLP, or the distress may even occur independently to OLP.

The present study demonstrated that significantly higher levels of painful oral symptoms were observed in a subgroup of OLP patients who had anxiety, depression or emotional distress than those without psychological comorbidities. This is in agreement with the body of evidence from a comprehensive review, which highlighted the strong and consistent association between somatic symptoms including pain across various chronic medical conditions and comorbid anxiety and depression (Katon et al., 2007). Psychological comorbidities may lead to heightened awareness of physical symptoms and the burden of symptoms and resulting functional impairment are likely to provoke or worsen episodes of anxiety and depression (Katon et al., 2007). Interestingly, research in other medical conditions found an association of anxiety and depression with poor adherence to self-care regimens, leading to repeated medication changes, continued escalation of medication regimens, and repeated diagnostic procedures including multiple biopsies. Recognition of the association between subjective symptoms of OLP and comorbid anxiety and depression should therefore be an important consideration in the management of patients with OLP.

A particular strength of this study is the sample size, which is notably larger than previous studies on psychological comorbidities in OLP. However, it should be noted that all the prevalence figures in this study may not reflect the true prevalence of psychological illnesses in patients with OLP, as these prevalence figures were estimated based on the HADS, which is a screening tool. The figures shown above may in fact be an overestimation or underestimation of the actual prevalence. Future prevalence studies of psychological comorbidities should use structural psychiatric interviews based upon the International Classification of Diseases (ICD-10) or the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) to ensure definitive diagnoses of anxiety, depression and emotional

distress are made. Information on socioeconomic status of participants including educational level, marital and job status as well as other variables such as sleep disturbance, which have been shown to be related to the development of psychological symptoms (Adamo et al., 2015), were not assessed in the present study. The measurement of subjective oral symptoms in the present study was recorded using both VAS and NRS, which measure overall symptom intensity alone. The incorporation of other self-report symptom instruments such as the short-form McGill Pain Questionnaire (SF-MPQ), which measures both quality and quantity of subjective symptoms, or the novel Oral Lichen Planus Symptom Severity Measure (OLP-SSM) would provide better profile of oral symptoms as reported by patients with OLP (Burke et al., 2019b, Main, 2016).

Regarding generalizability of the study results, the OLP sample in this study was based upon patients in one tertiary referral Oral Medicine centre, and thus may not represent the whole OLP population including asymptomatic cases of OLP who did not seek for professional treatment. The exclusion of non-English speakers may also reduce external validity of the study. In addition, given the nature of this cross-sectional study, there is still no answer to the question as to whether OLP leads to the development of psychological morbidities or whether the opposite is true, or whether both conditions exacerbate each other in a cyclical relationship. Future prospective longitudinal studies are therefore of importance.

4.7.2 Psychometric validation of the HADS and PSS-10 and a cross-sectional study of psychological status in patients with RAS

The present study examines validity and reliability of the HADS and PSS-10 in a cohort of patients with RAS. Results from the CFA demonstrated that a bi-factor model, with all items loading onto general factor with two group factors, provides the best fit to the HADS and PSS-10 data of patients with RAS than the original model proposed by the authors of both scales. These findings were consistent with recent validation studies of the HADS and PSS-10 in a

variety of medical diagnoses (Burns et al., 2014, Reis et al., 2019), and demonstrated evidence of structural validity of both measures in a sample of RAS.

To further test the appropriateness of using subscale and total scores of both measures, reliability coefficients of the bi-factor model were calculated. Although values of omega coefficient (ω) were in an acceptable range in both scales, values of coefficient ω-h of the group factors were relatively low (range = 0.02-0.47) when compared with coefficient ω-h of the general factors (0.73 for the HADS total score and 0.84 for the PSS-10 total score). Coefficient ω-h estimates actual reliability of a latent factor (both general and group) once the effects of other factors are controlled. As a result, the present findings supported the summation of total scores of both the HADS and PSS-10, while the interpretation of subscale scores as reliable indices of group constructs (i.e. anxiety and depression in the HADS) is limited. Considering the psychometric evidence of the present study, the HADS and PSS-10 should be used as unidimensional scales of overall emotional distress and perceived stress with the use of total scores only in patients with RAS.

Previous studies have found that patients with RAS had higher level of anxiety (Cardoso et al., 2017, Al-Omiri et al., 2012), depression (Polat et al., 2018), distress (Tabolli et al., 2009) and psychological stress (Gallo Cde et al., 2009) when compared to healthy individuals, while some studies did not find the difference between two groups (Picek et al., 2012, Zwiri, 2015). Reported prevalence of these psychological comorbidities generally varies across different study settings, study population and measurement methods. The prevalence of anxiety symptoms in the present RAS cohort was higher than that reported in a previous study of Croatian patients (42.5% versus 24.47%) whereas the figures for depressive symptoms was much lower compared to the same study (18.3% versus 47.06%) (Gavic et al., 2014). Notably, more than two-thirds of participants in this study had moderate-to-high level of perceived stress over the past month. This was in agreement with a previous Brazilian study (Gallo Cde

et al., 2009), which found significantly higher number of RAS patients had moderate-to-high and high stress levels when compared to healthy individuals. Based upon these, it appeared that there was a significant mental health burden among patients with RAS.

The present study suggested that certain subgroups of patients with RAS might be at greater risk of having comorbid psychological symptoms when compared to other RAS subgroups. A significantly higher proportion of patients from non-white ethnic groups in this RAS cohort had comorbid anxiety and emotional distress than those from white ethnicity. These findings were consistent with the most recent Adult Psychiatric Morbidity Survey (2014) in England, which found that those identifying as black, mixed and Asian were more likely to report symptoms of a common mental disorder than a white population in England. A significantly higher number of non-alcohol drinkers with RAS in this study have depressive symptoms when compared to those who consume alcohol. This finding matched several studies in different conditions including oral lichen planus, which found the increased risk of having depressive symptoms among those who do not drink alcohol. One possible explanation of this association might be a result of certain social confounding factors. In cultures where alcohol use is acceptable, mid-range alcohol drinkers may be more culturally and socially well-adjusted, and these traits might indirectly prevent them from having depression (Skogen et al., 2009).

Regarding related clinical characteristics of RAS, the present results found that those with average larger ulcer size (≥ 1 cm) appeared to report symptoms of anxiety, distress and moderate-to-high perceived stress more than those having smaller size of oral ulcers. Correspondingly, it was shown that greater number of patients with major RAS reported having psychological symptoms compared to patients with minor RAS. It should be noted that due to the cross-sectional design of this study, it is not possible to draw a causal relationship of this association between ulcer size and comorbid psychological symptoms. However, this finding might be attributed to the fact that major RAS ulcers are larger, deeper, more painful, longer

lasting and associated with significant functional impairment (Akintoye and Greenberg, 2014), resulting in more psychological distress and stress in comparison with minor RAS ulcers.

In terms of oral pain, a previous study found positive associations between pain intensity and level of anxiety, depression and stress in patients with RAS (Gavic et al., 2014). The present study did not support the link between oral pain and the presence of either anxiety or depression. Instead, it appeared that overall emotional distress, which includes overarching symptoms of both anxiety and depression based upon the HADS total score, had an association with oral symptoms in this RAS cohort. Oral symptoms and associated functional impairment could initiate or exacerbate psychological symptoms, and in turn, the presence of a mental health disorder may increase awareness and lower tolerance of physical symptoms and, as a consequence, cause further psychological symptoms.

Disease activity of RAS, as determined by the total USS score, was found to be associated with only moderate-to-high level of perceived stress and not with other psychological symptoms. In the RAS literature, experiencing stressful life events was associated with roughly a three-fold increase in the likelihood of having new RAS episode, and an increase in stress severity appeared not to have an impact on the progression and frequency of recurrence of the RAS episodes (Huling et al., 2012). The present bivariate analyses confirmed the findings of this previous work and did not find any association between psychological factors and either duration of RAS episodes or ulcer-free periods. Although the present result found no link between the number of oral ulcers and psychological factors, it was interesting to note that all five patients with herpetiform RAS in this sample experienced moderate-to-high level of perceived stress over the past month. Nevertheless, with a small number of participants with herpetiform type of RAS, this finding should be interpreted with caution and further investigation into the association of stress and this rare variant of RAS is required.

Based upon the present findings, there is some association between psychological stress or distress and patient's perceived oral symptoms and disease activity. In light of this, management of RAS should include psychological assessment using validated outcome measures to identify patients requiring additional psychological assessment and those who may benefit from appropriate psychological treatment and support. Depending on the severity of identified psychological distress or stress, it is the clinician's responsibility to make onward referral of patients for appropriate management from the general practitioner, psychologist, or psychiatrist. The recognition and treatment of these psychological problems could not only help improving the perceived disease activity and quality of life of patients with RAS, but might also help reducing unnecessary medical costs and resource.

A number of caveats need to be noted in the present study. The prevalence figures of comorbid psychological illnesses in this study were estimated by the HADS, which is a screening instrument, and therefore the findings need to be interpreted cautiously. The present study did not evaluate the factors related to socioeconomic factors of patients such as educational level, marital and job status, which could be potential confounding factors of the present results. The use of a cross-sectional design limits its ability to draw a valid conclusion whether psychological symptoms was pre-existent to RAS diagnosis or a consequence of having RAS. The generalisability of the study results may be limited as study participants were recruited in one tertiary oral medicine unit, and thus the results might not be transferrable to the real-world RAS population. The exclusion of non-English users may also lessen the external validity of the study.

4.8 CONCLUSION

The HADS and PSS-10 are valid and reliable as general measures of psychological distress and perceived stress in patients with OLP and RAS. Based upon the present findings, there is a significant mental burden among patients with immunologically mediated oral mucosal

diseases, which makes screening for psychological symptoms a prudent and sensible practice in this patient group. The knowledge of demographic and clinical characteristics related to comorbid psychological symptoms in patients with immunologically mediated oral mucosal disesases may facilitate clinicians in providing better holistic care and may contribute to improve the quality of life of patients with these conditions.

CHAPTER 5 DEVELOPMENT AND VALIDATION OF A SHORT VERSION OF CHRONIC ORAL MUCOSAL DISEASE QUESTIONNAIRE (COMDQ-15)

5.1 THE CHRONIC ORAL MUCOSAL DISEASE QUESTIONNAIRE

The Chronic Oral Mucosal Disease Questionnaire (COMDQ) is a self-reported questionnaire assessing QoL specific to individuals with chronic oral mucosal diseases including but not limited to oral lichen planus, recurrent aphthous stomatitis, pemphigus vulgaris and mucous membrane pemphigoid (Ni Riordain et al., 2011b). The COMDQ comprises 26 items capturing 4 domains including pain and functional limitation, medication and treatment, social and emotional, and patient support. Patients are asked to respond to each item on a 5-point Likert scale, ranging from 'not at all' to 'extremely' with four items reverse scored. All the responses are added to give an overall score out of 104. This self-administered scale has been proven to be psychometrically sufficient in a series of validation studies conducted in several countries (Ni Riordain and McCreary, 2011, Ni Riordain and McCreary, 2012, Li and He, 2013, Ni Riordain et al., 2016, Shirzad et al., 2018). The COMDQ was found to have good level of content validity owing to incorporation of patient's views and preferences via qualitative interview during its development process (Ni Riordain et al., 2011b).

5.2 KNOWLEDGE GAP

Despite its indicated need and utility, the COMDQ appears to be under-implemented in both clinical research and routine Oral Medicine practice. This might be related to time needed to complete all 26 items of the questionnaires (high response burden to patients), which can conflict with the current time constraints of the healthcare service (Morris et al., 1998). Therefore, the development of a shorter version of COMDQ with optimal balance between its brevity, key content coverage and psychometric performance could improve clinical feasibility and widespread adoption of this instrument into clinical practice.

5.3 AIMS

The aim of the present chapter was to develop the short version of the COMDQ without altering the dimensional structure and psychometric quality.

5.4 METHODS

5.4.1 Study design

This was a development and validation study using baseline data from the Determination of Minimal Important Difference and Patient Acceptable Symptom State of Patient Reported Outcome Measures in Immunologically mediated Oral Mucosal Diseases (MEAN-IT) study, which had favourable opinion from the London – Queen Square Research Ethics Committee (REC reference 17/LO/1825; approval date 3 November 2017).

5.4.2 Participants

From January 2018 to August 2019, a convenient sample of 520 patients with chronic oral mucosal conditions including oral lichen planus (OLP), recurrent aphthous stomatitis (RAS), pemphigus vulgaris (PV) and mucous membrane pemphigoid (MMP) was recruited from the Oral Medicine clinic, UCLH Eastman Dental Hospital, London, United Kingdom. All potentially eligible participants, in all Consultant lead Oral Medicine clinics were invited to participate. The inclusion and exclusion criteria of study participants are listed in Table 5.1. Patient participation was voluntary, and the data were handled anonymously.

Table 5.1 Study eligibility criteria

Inclusion criteria	Exclusion criteria
- Aged 18 years or older - Able to understand and complete questionnaires	- Having coexisting chronic neuropathic orofacial pain, such as post-traumatic trigeminal neuropathic pain, persistent idiopathic facial pain or burning mouth syndrome
- Agree to participate and provide written informed consent	- Severe systemic disease (ASA 3 or more) and/or some psychiatric conditions which might affect the participation of the study such as schizophrenia
Having one of the following conditions	
1. *Oral lichen planus*	
- Clinical and histopathologically-confirmed OLP based upon modified WHO diagnostic criteria	- Evidence of oral epithelial dysplasia in biopsy specimen - Evidence of proven hypersensitivity to dental materials - Evidence of oral lichenoid lesions associated with graft-versus-host disease and systemic lupus erythematosus
2. *Recurrent aphthous stomatitis*	
- Having recurrent oral ulceration (ulcer episodes of at least twice a year)	- Having RAS-like ulcerations associated with systemic disorders such as Behcet's disease, Sweet syndrome, Ulcerative colitis, Crohn's disease, Celiac disease, auto-inflammatory syndromes, or haematological abnormalities (severe anaemia, cyclic or chronic neutropenia)
3. *Pemphigus vulgaris*	
- DIF/IIF or ELISA-proven PV	
4. *Mucous membrane pemphigoid*	
- DIF/IIF or ELISA-proven MMP	

For robust psychometric evaluation to be performed, the numerical ratio between respondents and items should be at least 10:1 for conducting factor analyses (DeVellis, 2017). As two different types of factor analyses, namely exploratory factor analysis (EFA) and confirmatory factor analysis (CFA), were employed for development and validation process of the short version of the 26-item COMDQ, a total number of 520 participants were required for the present study.

5.4.3 Outcome measure

The Chronic Oral Mucosal Disease Questionnaire (COMDQ) comprises 26 items in four subscales including Pain and Functional limitation (PF, 9 items), Medication and treatment (MT, 6 items), Social and Emotional (SE, 7 items) and Patient Support (PS, 4 items). The items were answered on a 5-point Likert-type scale (0-4), ranging from “not at all” to “extremely”. Total COMDQ score is calculated by summation of the responses of all items, giving the possible maximum score of 104 (Ni Riordain et al., 2011b).

5.4.4 Procedures

The COMDQ data of 520 participants of the MEAN-IT study were extracted for the present study. In addition, the following demographic and clinical data were collected for the purpose of sample descriptions and contrasted group comparisons: age, gender, ethnicity and clinical types of OLP (reticular/plaque, atrophic/erosive, ulcerative) and RAS (minor, major, herpetiform). The COMDQ items and subscales were initially analysed using descriptive statistics for preliminary item reduction. The cross-sectional samples of the MEAN-IT study were randomly split into two approximately equal datasets (N=260), namely “development sample” and “validation sample”. The COMDQ data from the development sample were analysed using EFA to identify underlying factor (subscale) of the COMDQ and associated items in each factor, and the results were used as further evidence for item reduction and generation of the short-versioned COMDQ. To validate short-form COMDQ, CFA was performed to test the hypothesized factor structure of this brief COMDQ determined from the EFA with an independent validation sample. Reliability and validity of new scale were also compared with its original version.

5.4.5 Statistical analyses

Statistical analyses were performed using MPlus version 8.2 (Muthén & Muthén, 2015) and STATA version 15.1 (StataCorp, College Station, TX, U.S.A.). Descriptive demographic and

clinical characteristics of the sample were first summarised using mean, standard deviation and proportion. Descriptive Item statistics including mean, standard deviations, floor and ceiling effects (proportion of item endorsement at the lowest and highest response options) were calculated. For preliminary item reduction process, items with floor effects of ≥ 60% suggesting less relevant items were first eliminated. Next, adjusted item-total correlations were calculated, and an item with low correlation (<0.3) was considered discarded due to poor metric performance compared to the remainder of the scale. Then a matrix of inter-item polychoric correlations was constructed, and one item from each of item pairs with high correlations (>0.7) was considered deleted to minimize information redundancy.

EFA using weighted least square means and variance-adjusted (WLSMV) estimator and oblique rotation (Promax) was carried out on the development sample. The WLSMV estimator is appropriate for the ordered categorical nature of the COMDQ data, and oblique rotations allow for correlations between underlying factors(Li, 2016). The optimal number of factor extraction was based upon eigenvalues ≥ 1, further inspection of the corresponding scree plot (number of dots above the elbow of the plot where the notable decline in factors levels off), and factor interpretability according to item content within each extracted factor. Items retention was based upon at least 0.4 loadings on a certain factor. For the item reduction, Item were considered removed if they failed to load with sufficient strength (<.03) on any factor or had high cross-loading (>0.3)(Tabachnick and Fidell, 2013).

With the remaining half of the data (validation sample), a CFA was performed to determine whether identified factor structure could be replicated on different sample. To confirm model fit, several fit indices including root mean square of error approximation (RMSEA), standardized root mean squared residual (SRMR), comparative fit index (CFI) and Tucker-Lewis index (TLI) were calculated. RMSEA and SRMR values closer to 0 indicate better fit, with values below 0.08 and 0.05 indicating acceptable and good fit, respectively. CFI and TLI

values greater than 0.95 are considered acceptable(Hu and Bentler, 1999b). For measures of internal consistency reliability, Cronbach's alpha coefficient (α) for each subscale was computed, and a reliability value of 0.70 or above indicates good reliability of the scale(Nunnally and Bernstein, 2010). Criterion validity of the short-form COMDQ was evaluated by assessing the strength of the correlations between subscale scores of the short and original version of the COMDQ. The primary hypotheses were that scores of short-version COMDQ would be significantly and positively correlated with scores of its original scale.

5.5 RESULTS

5.5.1 Sample characteristics

Study sample consisted of 520 participants with chronic oral mucosal diseases including 306 patients with OLP, 130 patients with RAS, 33 patients with PV and 51 patients with MMP. The average age of the participants was 58.39 years and 71.73% were female. The majority of sample (71.35%) were Caucasians, followed by 22.31% Asians, 3.85% Blacks and 2.5% mixed ethnic groups. In comparison with other conditions, patients with RAS reported highest mean COMDQ scores (47.31 ± 16.35) indicating the worst oral health-related quality of life, followed by PV (42.73 ± 17.91), and OLP (39.38 ± 19.40). The sample was randomly split into two subsamples, and Table 5.2 summarised descriptive characteristics of two random samples, and both were similar in all variables.

Table 5.2 Demographic and clinical characteristics of the study sample

Characteristics	Development sample (N=260)	Validation sample (N=260)	P-value (χ 2 test or t-test)
OLP (n)	154	152	
mean age (years)	62.81 ± 11.78	63.34 ± 11.46	0.69
gender (n, % Female)	120 (77.92)	119 (78.29)	0.94
clinical types (n, %)			0.99
reticular/plaque	29 (18.83)	28 (18.42)	
atrophic/erosive	103 (66.88)	103 (67.76)	
ulcerative	22 (14.29)	21 (13.82)	
RAS (n)	63	67	
mean age (years)	42.08 ± 14.56	46.21 ± 14.87	0.11
gender (% Female)	38 (60.32)	39 (58.21)	0.81
clinical types (n, %)			0.99
minor	55 (87.30)	59 (88.06)	
major	7 (11.11)	7 (10.45)	
herpetiform	1 (1.59)	1 (1.49)	
PV (n)	18	15	
mean age (years)	57.41 ± 20.65	55.69 ± 15.66	0.79
gender (% Female)	12 (66.67)	10 (66.67)	1
MMP (n)	25	26	
mean age (years)	67.52 ± 8.63	67.71 ± 11.96	0.95
gender (% Female)	18 (72)	17 (65.38)	0.61

5.5.2 Item and subscale analyses of the original COMDQ

Individual item analyses including mean, standard deviation, floor and ceiling effects using the whole sample are listed in Table 5.3. Item PF9 (discomfort/denture) was dropped in this stage due to its floor effect of > 90%, suggesting low impact of this item on the vast majority of respondents. The following correlation analyses for the remaining 25 items involved the development sample only. Four out of the 25 items had adjusted item-total correlations below 0.3 (Table 5.3). Item MT2 (medication satisfaction) and PS1 (satisfaction on available information) were discarded while item PS2 (support from family) and PS3 (support from

friends/colleagues) were retained, as they were felt to represent distinct domain of “patient support” consistent to a conceptual framework of the original COMDQ.

Further inspection of inter-item polychoric correlation matrix revealed 18 item pairs with correlations over 0.7, indicating content redundancy, and inclusion of both items in the pair are unnecessary. Dropping item PF2 (limitation/food types), PF4 (limitation/food texture), PF6 (limitation/food temperature), PF8 (limitation/oral hygiene care), MT6 (frustration on no disease cure), SE3 (stress due to oral condition), SE5 (worry about the future), and PS4 (isolation due to oral disease) eliminated 14 of these 18 strong inter-item correlations.

5.5.3 Exploratory factor analysis

Exploratory factor analysis using Promax rotation on the remaining 15 items yielded 4 factors with eigenvalues greater than 1 (Table 5.4), and this was further confirmed by the corresponding scree plot. All the items had factor loadings over 0.3 on their designated factors except for item MT1 (medication need), which was moved to the original Pain and Functional limitation subscale. No cross-loading was observed, and therefore no items met criteria for elimination at this stage. The new 15-item version of the COMDQ (COMDQ-15) was then created (Appendix). Three factors (Medication and Treatment, Social and Emotional, Patient Support) were named according to the original scale while the original “Pain and Functional limitation” factor was changed to “Physical Discomfort” to better reflect content of the remaining items within this factor. This new 4-factor solution of the 15-item COMDQ served as the hypothesized model for the subsequent CFA.

Table 5.3 Descriptive item analysis of the whole sample (N=520) and adjusted item-total and item-subscale correlations of development sample (N=260)

Item	mean	sd	floor effect (%)	ceiling effect (%)	adjusted item-total correlation
Pain and Functional limitation					
PF1 discomfort/food types	2.41	1.21	8.27	20.77	0.5696
PF2 limitation/food types	2.06	1.18	10.77	11.15	0.6386
PF3 discomfort/food texture	2.23	1.22	11.15	15	0.6091
PF4 limitation/food texture	1.93	1.22	16.15	8.85	0.6487
PF5 discomfort/food temperature	1.7	1.23	20.58	7.88	0.5774
PF6 limitation/food temperature	1.63	1.23	23.08	6.15	0.5684
PF7 discomfort/oral hygiene care	2.02	1.19	12.31	10.77	0.6726
PF8 limitation/oral hygiene care	1.42	1.28	32.5	6.92	0.6423
PF9 discomfort/denture	0.21	0.71	90.38*	1.15	N/A
Medication and Treatment					
MT1 medication need	1.73	1.31	22.69	11.15	0.4979
MT2 medication satisfaction	1.29	1.24	33.27	6.73	0.2391
MT3 concerns on side effects	1.42	1.32	33.27	10	0.4178
MT4 frustration on standard medication	2.03	1.47	22.31	22.12	0.5724
MT5 limitation from medication use	0.77	1.03	54.81	2.31	0.5339
MT6 frustration on no disease cure	2.72	1.25	5	36.92	0.5648
Social and Emotional					
SE1 depression due to oral disease	1.75	1.17	13.85	8.65	0.798
SE2 anxiety due to oral disease	1.42	1.17	25.38	5.96	0.7025
SE3 stress due to oral disease	1.51	1.24	24.23	9.23	0.7569
SE4 frustration on disease unpredictability	1.97	1.22	11.54	12.69	0.7212
SE5 worries about the future	2.08	1.33	13.85	19.04	0.3687
SE6 pessimism about the future	1.27	1.25	36.35	6.35	0.5989
SE7 social disruption	1.12	1.22	42.12	5.96	0.7152
Patient Support					
PS1 satisfaction on available information	1.38	1.01	20.96	2.31	0.2857
PS2 support from family	1.22	1.14	32.31	4.42	0.2212
PS3 support from friends/colleagues	1.42	1.27	30.96	8.65	0.2493
PS4 isolation due to oral disease	0.84	1.15	55.96	4.04	0.6407

Table 5.4 Factor loadings of the remaining 15 COMDQ items using exploratory factor analysis with Promax rotation

Item	Extracted factors			
	Physical Discomfort	Medication & Treatment	Social & Emotional	Patient Support
PF1 discomfort/food types	**0.625**	0.087	0.004	0.024
PF3 discomfort/food texture	**0.836**	-0.067	0.02	-0.014
PF5 discomfort/food temperature	**0.728**	-0.012	-0.013	-0.009
PF7 discomfort/oral hygiene care	**0.83**	0.018	0.009	-0.068
MT1 medication need	**0.369**	0.151	0.148	0.025
MT3 concerns on side effects	-0.085	**0.794**	-0.079	0.012
MT4 frustration on standard medication	0.049	**0.625**	0.098	0.081
MT5 limitation from medication use	0.086	**0.654**	0.091	-0.044
SE1 depression due to oral disease	0.237	-0.08	**0.805**	0.097
SE2 anxiety due to oral disease	-0.057	0.034	**0.897**	0.066
SE4 frustration on disease unpredictability	0.141	0.054	**0.707**	-0.01
SE6 pessimism about the future	-0.076	0.245	**0.68**	-0.18
SE7 social disruption	0.247	0.05	**0.584**	0.058
PS2 support from family	0.032	0.107	-0.104	**0.674**
PS3 support from friends/colleagues	-0.071	-0.056	0.131	**0.8**
Eigenvalues	*6.707*	*1.468*	*1.427*	*1.027*

Note: Factor loadings greater than 0.3 in **bold**

5.5.4 Confirmatory factor analysis

Confirmatory factor analysis was performed to test structural validity of the COMDQ-15 by replicating hypothesized model identified by EFA in validation sample (N=260). The goodness-of-fit indicators for the 4-factor solution of the COMDQ-15 compared to its original COMDQ-26 were reported in Table 5.5. CFA results of the COMDQ-15 demonstrated acceptable level of RMSEA and satisfactory level of the remaining fit indices; whereas, the original 26-item COMDQ was found to have insufficient level of structural validity based upon expected fit indices.

Table 5.5 Fit indices summary of the 4-factor solution of the COMDQ-15 and its original scale

	RMSEA	SRMR	CFI	TLI
15-item COMDQ				
4-factor model	0.08	0.04	0.97	0.97
26-item COMDQ				
4-factor model	0.121	0.08	0.93	0.92

5.5.5 Internal consistency reliability and criterion validity

The estimated values of Cronbach's alpha for 4 subscales of the COMDQ-15 were as followed: 0.86 for "Physical Discomfort", 0.71 for "Medication & Treatment", 0.91 for "Social & Emotional" and 0.70 for "Patient Support". Overall, the reliability coefficients indicated acceptable to good level of internal consistency reliability of the short version of the COMDQ. Criterion validity of the COMDQ-15 was satisfactory as both total and subscale scores of the short and original version of COMDQ were significantly and highly correlated (r_s range = 0.88-0.99; see also Table 5.6).

Table 5.6 Spearman's rank correlation coefficients between the subscale and total scores of the COMDQ-15 and their corresponding subscale and total score of the full version

COMDQ-15	The original COMDQ				
	Pain& Functional limitation	Medication & Treatment	Social & Emotional	Patient Support	Total score
Physical Discomfort	0.96*				
Medication & Treatment		0.93*			
Social & Emotional			0.99*		
Patient Support				0.88*	
Total score					0.99*

*All correlation coefficients were statistically significant with P < 0.01

5.6 DISCUSSION

The present study reports the development and initial validation of a 15-item brief version of the Chronic Oral Mucosal Disease Questionnaire, which retains content coverage of QoL related to chronic oral mucosal conditions from its original scale. In accordance with classical

test theory requirements, item analysis, structural validity, internal consistency reliability and criterion validity were studied to ensure that this short version maintains the psychometric quality of its full-length scale. Items with low functionality and conformity to the whole scale or those with information-redundant were removed to refine and create the most economical scale.

Content validity of the COMDQ-15 was inherited from the patient-centred qualitative study during the development of its original version (Ni Riordain et al., 2011b), and was ascertained by an attempt to preserve all the relevant aspects of hypothesized QoL construct during item reduction process. The underlying four theoretical subscales of the COMDQ-15 were identified by exploratory factor analysis and the stability of this factor structure was confirmed in a replication sample. The original item MT1 "medication need" was moved to the Physical Discomfort subscale, which appeared conceptually sensible considering greater level of physical discomfort generally increase the need for medication. Despite considerable shortening of its full-length scale, the COMDQ-15 had good to excellent level of internal consistency reliability and its subscales were significantly and strongly correlated with each corresponding original subscales ($r_s \geq 0.88$), indicating that this 15-item version appeared to be a valid and reliable summary of its original scale.

The notable advantage of having a short-form COMDQ is the lower respondent burden, making it easier to administer and thereby providing a more practical scale for use in routine clinical settings. Not only could shortened outcome measures increase patient acceptability in daily practice, but they could also enhance feasibility in clinical trials and other clinical studies. One example is the extensive usage of the shortened 14-item Oral Health Impact Profile (OHIP-14)(Slade, 1997) in oral mucosal disease literature. Two recent reviews found significantly higher frequency of use of the OHIP-14 than its original lengthy version (OHIP-49) as outcome measures in previous research of OLP (12 times use of the OHIP-14

compared to 6 for the OHIP-49) and RAS (9 times use of OHIP-14 compared to one study for the OHIP-49) (Wiriyakijja et al., 2018, Wiriyakijja et al., 2017). Considering the importance of measuring patient's QoL in oral mucosal diseases, the development of COMDQ-15 could improve implementation of this instrument in both clinical and research settings.

The present study has a number of limitations. Shortening questionnaires is always a trade-off between resources (e.g. time and cost) saved and the amount of information lost. Information concerning oral functional limitation (PF2, PF4, PF6, PF8) and patient satisfaction (MT2, PS1) were present in the original 26-item COMDQ but are no longer represented in the new shortened version. Clinicians and researchers who are interested in capturing these data should refer to the original COMDQ, which remains a valid and comprehensive measure of QoL in chronic oral mucosal conditions. In addition, although the present shortened scale appears to be psychometrically sound, it still requires additional psychometric testing particularly on sensitivity to change and interpretability of its score.

5.7 CONCLUSION

The COMDQ-15 is a brief, easy-to-use, valid and reliable instrument that can give an overview of the patient's perspective on QoL related to their chronic oral mucosal conditions. Although additional psychometric testing is needed to confirm sensitivity to change and interpretability of its score, the COMDQ-15 shows notable potential to assist clinicians in daily practice, so to assess the burden of chronic oral mucosal conditions upon QoL and measure relevant changes after medical intervention. It can also be easily adopted in clinical trials and other clinical studies. This marks another significant step towards the accurate and methodologically valid measurement of QoL in individuals with chronic oral mucosal diseases. It also highlights the importance of incorporating patients' views and perception into clinical decision making, so improving the quality of patient care in Oral Medicine.

CHAPTER 6 HEALTH RELATED QUALITY OF LIFE AND ITS ASSOCIATED PREDICTORS IN PATIENTS WITH IMMUNOLOGICALLY MEDIATED ORAL MUCOSAL DISEASES

6.1 KNOWLEDGE GAP

In recent years 'quality of life' (QoL) has increasingly become an important outcome for monitoring the impact of the disease and determining treatment success from the perspective of patients with chronic diseases (Fayers and Machin, 2016a). Based upon previous qualitative research, the burden of immunologically mediated oral mucosal diseases on a patient's quality of life has been associated with both physical impacts of the disease including oral discomfort and resulting impairment of eating, oral hygiene care and speech as well as negative psychosocial consequences of the disease due to its chronicity and unpredictable clinical behaviour (Ni Riordain et al., 2011a). Despite the significant impact of the disease upon different aspects of patient's QoL, only a small proportion of previous clinical research of immunologically mediated oral mucosal diseases incorporate QoL as study outcomes.

Previous clinical studies of QoL in immunologically mediated oral mucosal diseases mostly utilized generic measures of oral health-related QoL such as the OHIP-14, which have been developed for use in general population and appeared to be less sensitive to detect small changes (but clinically important differences) associated with certain conditions (chapter 3). It is considered appropriate to complement the results from non-specific QoL scales with QoL assessments obtained from instruments containing items with disease-specific perspectives.

Since the early 2010s, several QoL-specific instruments have been developed, and they comprise health aspects that are most important and pertinent to patients with immunologically mediated oral mucosal diseases. These instruments include the Chronic Oral Mucosal Disease Questionnaire (COMDQ) and its shortened 15-item version (COMDQ-15), and the

Oral Potentially Malignant Disorder Quality of Life (OPMDQoL) questionnaire (Wiriyakijja et al., 2019, Ni Riordain et al., 2011b, Tadakamadla et al., 2017). Despite their rigorous development and the robust psychometric evidence supporting their use in immunologically mediated oral mucosal diseases, adoption of these specific QoL instruments in clinical studies has been scarce (Rajan et al., 2014, Okumus et al., 2015, Tadakamadla et al., 2018), therefore limiting current knowledge of self-reported aspects of QoL unique to immunologically mediated oral mucosal diseases and hampering their pragmatic application into clinical practice. While clinician-rated disease activity based upon clinical oral presentation is of importance in the management of immunologically mediated oral mucosal conditions, it might not be perfectly correlated with how patients perceive and function. Information on level of QoL perceived by affected patients could be a complementary resource to help prioritize treatment decisions and the use of data from specific QoL instrument may provide a more complete approach to the management of these conditions. Understanding key determinants of worse QoL is also a prerequisite for the development of effective strategies for early identification of patients at risk and ultimately for improving the quality of care to the patients.

6.2 AIMS

The aims of the present chapter were:

1. To investigate levels of overall and aspects of quality of life (QoL) among patients with common immunologically mediated oral mucosal diseases (OLP, RAS) using both specific QoL measure (COMDQ-15) and general oral health-related QoL measure (OHIP-14).
2. To determine associated predictors of worse QoL in both patient cohort.

6.3 METHODS

6.3.1 Study design

This was a descriptive secondary analysis of baseline data from the Determination of Minimal Important Difference and Patient Acceptable Symptom State of Patient Reported Outcome Measures in Immunologically mediated Oral Mucosal Diseases (MEAN-IT) study, which had favourable opinion from the London – Queen Square Research Ethics Committee (REC reference 17/LO/1825; approval date 3 November 2017).

6.3.2 Participants

The study participants comprised 420 patients with immunologically mediated oral mucosal diseases (300 patients with OLP and 120 patients with RAS) attending the Oral Medicine clinic, UCLH Eastman Dental Hospital, London, United Kingdom for regular review appointments. Participant recruitment was based upon convenience sampling. All potentially eligible participants, in all Consultant lead Oral Medicine clinics from January 2018 to July 2019 were invited to participate. All participants provided written informed consent to take part in the study. The inclusion and exclusion criteria are listed in Table 6.1.

Table 6.1 Study eligibility criteria

Inclusion criteria	Exclusion criteria
- Aged 18 years or older - Able to read, understand and complete questionnaires	- Having coexisting chronic neuropathic orofacial pain, such as post-traumatic trigeminal neuropathic pain, persistent idiopathic facial pain or burning mouth syndrome
- Agree to participate and provide written informed consent	- Severe systemic disease (ASA 3 or more) and/or some psychiatric conditions which might affect the participation of the study such as schizophrenia
Having one of the following conditions	
1. Oral lichen planus	
- Clinically and histopathologically-confirmed OLP based upon modified WHO diagnostic criteria (van der Meij and van der Waal, 2003)	- Evidence of oral epithelial dysplasia in biopsy specimen - Evidence of proven hypersensitivity to dental materials - Evidence of oral lichenoid lesions associated with graft-versus-host disease and systemic lupus erythematosus
2. recurrent aphthous stomatitis	
- Having recurrent oral ulceration (ulcer episodes of at least twice a year)	- Having RAS-like ulcerations associated with systemic disorders such as Behcet's disease, Sweet syndrome, Ulcerative colitis, Crohn's disease, Celiac disease, auto-inflammatory syndromes, or haematological abnormalities (severe anaemia, cyclic or chronic neutropenia)

6.3.3 Procedure

A comprehensive oral examination was carried out on all study participants to assess the clinical types, oral sites of involvement and disease activity. Disease activity of OLP was evaluated by using the ODSS (Escudier et al., 2007). Participants were categorised into three groups on the basis of the clinical variant of OLP: (i) keratotic (presence of white reticular, papular or plaque-like lesions without apparent erythema/ulceration), (ii) erythematous (presence of atrophic/ erythematous lesions with/without reticular/popular/plaque-like features AND no evidence of erosion/ulceration), and (iii) erosive/ulcerative (presence of erosive or ulcerative lesions with/without the presence of keratotic and/or erythematous changes of OLP). For participants with RAS, disease activity was evaluated by taking history of each

participant, and specific information about oral ulcers over the past three months was recorded. The activity score was calculated based on the standardized USS (Tappuni et al., 2013). Types of RAS were recorded based upon clinical appearance and behavior of RAS into 3 groups: minor RAS (shallow small ulcers (<1cm), usually last 7-10 days), major RAS (deeper and larger ulcers (≥1 cm), lasting several weeks, which may heal with scar formation) and herpetiform RAS (few millimeter ulcers, usually > 10 ulcers, last 7-10 days) (Scully and Porter, 2008).

Participants were then asked to complete a demographic form and a set of patient-reported questionnaires associated with oral symptoms, psychological status (level of anxiety, depression, distress and perceived stress) and patient's perception of QoL relevant to their oral conditions over the past month. Information regarding medical history, social history and past OLP/RAS-related history including disease duration, extra-oral involvement of lichen planus (either patient-reported or confirmed by a dermatologist), and management was obtained from electronic patient records.

6.3.4 Outcomes

The primary outcome of the present study was level of overall and aspects of QoL in patients with different clinical phenotypes of OLP and RAS as indicated by total and subscale scores of the COMDQ-15 and OHIP-14. To determine associated predictors of QoL in patients with OLP, selected demographic characteristics, psychological and OLP-related factors were assessed. Demographic characteristics included age (continuous variable), gender (female/male), ethnicity (White/Mixed/Asian/Black), smoking status (non-smoker/ex-smoker/current smoker), alcohol use (no/up to 14 units/more than 14 units per week) and disease comorbidities (no/one/at least two disease comorbidities).

Regarding psychological factors, the HADS was used to measure level of anxiety, depression and distress, while level of perceived stress was evaluated by the PSS-10. Disease-related factors included disease duration (time since symptom onset (years)), clinical types (keratotic/erythematous/ulcerative for OLP and minor/major/ herpetiform for RAS), level of disease activity (ODSS for OLP and USS for RAS), level of oral pain (NRS), presence of self-reported extraoral lichen planus (LP) (no/yes-genital area/yes-skin) and treatment types (no treatment or topical anaesthetic agents only/topical corticosteroids only/topical corticosteroids and other topical treatment/topical and systemic treatment).

6.3.5 Outcome measures

Disease activity scoring

The Oral Disease Severity Score (ODSS) and *the Ulcer Severity Score (USS)* were used for the assessment of disease activity of OLP and RAS, respectively.

Patient-reported outcome measures

The Numerical Rating Scale (NRS) for pain estimated severity of oral pain currently experienced by a patient on a whole number scale of 0-10 (11-point scale) (Hawker et al., 2011).

The Hospital Anxiety and Depression Scale (HADS) is a 14-item, 0-3 Likert-type scale with seven questions (HADS-A) dedicated to the assessment of anxiety symptoms, and the other seven (HADS-D) to the assessment of depressive symptoms over the recall period of 1 week. Subscale scores of the HADS of 8 or over are indicative of the presence of anxiety or depressive symptoms, and the total score (HADS-T) from the sum scores of HADS-A and HADS-D of 15 or over indicate the presence of psychological distress (Bjelland et al., 2002, Schellekens et al., 2016).

The 10-item Perceived Stress Scale (PSS-10) is a 10-item, 0-4 Likert-type scale which examined participant's level of perceived stress over the past month. Four items of the PSS-10 (item 4, 5, 7, 8) are positively stated items and require reverse coding. Total PSS-10 score was obtained by the summation of all the item scores, providing a total score range of 0-40. A higher score represents greater perceived stress. Based upon total PSS-10 scores, scores of 0-13, 14-26 and 27-40 are considered mild, moderate and high level of perceived stress, respectively (Alharbi and Alshehry, 2019).

The 15-item Chronic Oral Mucosal Disease Questionnaire (COMDQ-15) is a recently developed brief version of the original 26-item COMDQ, which measured QoL specific to patients suffering from chronic oral mucosal conditions (Wiriyakijja et al., 2019). This 0-4 Likert-type scale evaluates 4 QoL domains including the "physical discomfort", "medication and treatment", "social and emotional", and "patient Support". The correlations between scores of the COMDQ-15 and its parent version were satisfactory (rs range = 0.88-0.99), indicated satisfactory of criterion validity. Also, the COMDQ-15 showed good level of structural validity for use in patients with chronic oral mucosal conditions.

The 14-item Oral Health Impact Profile (OHIP-14) is a 14-item, 5-point (0-4) Likert-type questionnaire assessing general oral health related QoL on seven domains (each with 2 items) including functional limitation (FL), physical pain (PhyP), psychological discomfort (PsyD), physical disability (PhyDis), psychological disability (PsyDis), social disability (SD) and handicap (H). The maximum possible subscale and total score of this scale are 8 and 56, respectively. The greater the OHIP-14 score the poorer of the patient's perception is of their general oral health related QoL (Slade, 1997).

6.3.6 Statistical analysis

Statistical analyses were undertaken using STATA version 15.1 (StataCorp, College Station, TX, U.S.A.). Participants with missing data were excluded from further analysis. Data distribution of scores of QoL outcomes (the COMDQ-15 and OHIP-14) and other patient-reported outcomes was first checked by the Kolmogorov-Smirnov test. As all the data was non-normally distributed, descriptive cross-sectional analyses were summarized using median and interquartile range (IQR) for continuous variable while frequencies and percentages were expressed for categorical variables. To identify potential determinants of QoL as measured by the COMDQ-15, univariate analyses were performed using non-parametric Mann-Whitney U test or Kruskal-Wallis tests with post-hoc Dunn's Bonferroni adjustment for categorical variables while spearman rho correlation coefficients were calculated for continuous variables.

Then the association between each significant variable from previous univariate analyses and worse QoL, when adjusted for demographic variables and all significant covariates, was investigated using multivariate linear regression (performed only for the OLP cohort due to relatively low number of participants in the RAS cohort). Each domain and total COMDQ-15 and OHIP-14 scores served as dependent variables for the models. All possible independent variables with a P-value of less than 0.1 from previous univariate analyses were entered together into the models. The assumptions of linear regression (non-collinearity, linearity, homoscedasticity, normality and independence) were confirmed for all models. Model goodness-of-fit was assessed using the adjusted R^2, representing the amount of variance in the dependent variable explained by the independent variables, correcting for the number of predictors in the model. Bonferroni's correction was performed to control inflation of type I error rate due to multiple testing, with adjusted P-value of 0.003 (0.05/number of tests per dependent variable = 0.05/19).

6.4 RESULTS

The results of this chapter are divided into two sections based upon the disease of interest.

6.4.1 Results of the OLP cohort

6.4.1.1 Descriptive characteristics of study participants

The main descriptive demographic and clinical characteristics of the 300 study participants are summarized in Table 6.2. The mean age of all participants was 63.2 ± 11.5 years (range: 27-88 years), with more females (78%) than males. The median time since symptom onset of OLP was 6.3 years (IQR = 2.7-10.5 years). Erythematous OLP was the most common clinical variant in this patient cohort (67%), followed by keratotic (18.3%; reticular/papular/plaque-like) and ulcerative OLP (14.7%). About one quarter of participants had at least one site of extraoral involvement, and genitalia (15.7%) and skin (12.7%) were the two most common sites of extraoral involvement of lichen planus in this sample. The vast majority of patients (83%) reported having at least one disease comorbidity, and the most frequent systemic conditions were hypertension (33%), hypercholesterolaemia (18.7%), osteoarthritis (14%), diabetes mellitus (12.7%) and hypothyroidism (12.3%).

6.4.1.2 Quality of life outcomes in patients with OLP

Bivariate analysis of demographics and OLP-related variables by QoL scores based upon the COMDQ-15 and OHIP-14 are present in Table 6.2 and Table 6.3, respectively. Overall, the results of total scores of both QoL scales were similar. Among patients with OLP in the present cohort, Asian ethnicity was found to have significantly worse QoL than white ethnicity while those who drank alcohol more than recommended alcohol limit (> 14 units/week) appeared to report better QoL level than alcohol abstainers. Regarding clinical types of OLP, patients with erosive/ulcerative OLP had significantly poorer overall QoL than those with keratotic OLP. While patients with erythematous OLP reported poorer QoL than those with keratotic OLP, the difference between two groups did not reach the Bonferroni corrected significance level (P = 0.003). Regarding treatment types, those who received topical steroids with other treatments

appeared to report worse QoL than those who did not receive any treatment or receive only topical anaesthetic agents.

Regarding correlation studies between QoL and other variables, it was observed that total scores of both QoL scales were positively and significantly associated with scores of the pain-NRS, HADS-anxiety, HADS-depression, total HADS (distress), PSS-10 (perceived stress), and total, site and activity scores of the ODSS (disease activity) in patients with OLP (P-values < 0.001 in all associations). As of the strength of association, the total COMDQ-15 had slightly stronger association with level of oral pain, perceived stress and total disease activity scores based upon spearman rho coefficients in patients with OLP when compared to the total OHIP-14. On the contrary, the total OHIP-14 showed greater magnitude of association with level of anxiety, depression and distress than total COMDQ-15 in this OLP cohort.

Table 6.2 Descriptive statistics of variables of study participants and bivariate analysis of factors associated with subscale and total scores of the COMDQ-15 in patients with OLP (N=300)

Study variables	N (%)	PD		MT		SE		PS		Total score	
		med (IQR)	P	med (IQR)	P	med (IQR)	P	med (IQR)	P	med (IQR)	P
Gender[a]: Female	234 (78)	10 (6, 14)	0.064	4 (1, 6)	0.58	6 (3, 10)	0.305	2 (1, 4)	0.468	22 (15, 32)	0.125
Male	66 (22)	9 (4, 12)		3 (1, 6)		5 (2, 10)		2 (0, 4)		19 (11, 31)	
Ethnicity[b]: White†	204 (68)	9 (5.5, 13)	**0.03**	3 (1, 5)	**0.000***	5 (2, 8)	**0.000***	2 (0, 4)	0.165	19 (13, 28.5)	**0.000***
Mixed	6 (2)	6.5 (3, 15)		2.5 (1, 8)		7.5 (1, 13)		1.5 (1, 3)		19 (5, 40)	
Asian	79 (26.33)	11 (8, 15)	†	5 (3, 8)	†*	9 (5, 15)	†*	2 (1, 4)		29 (19, 40)	†*
Black	11 (3.67)	10 (4, 15)		6 (4, 7)		12 (3, 15)		3 (2, 4)		30 (17, 37)	
Smoking[b]: Non-smoker	228 (76)	9 (6, 13)	0.507	4 (1, 6)	0.626	5.5 (3, 10)	0.687	2 (1, 4)	0.743	21 (13, 32)	0.95
Ex-smoker	59 (19.67)	9 (6, 14)		4 (1, 5)		6 (3, 10)		3 (0, 4)		21 (15, 30)	
Current smoker	13 (4.33)	13 (5, 17)		4 (1, 7)		5 (1, 12)		2 (1, 2)		23 (13, 37)	
Alcohol[b]: No†	104 (34.67)	10 (7, 15)	0.058	4 (2, 7)	**0.002***	8 (3.5, 13)	**0.002***	2 (1, 4)	0.45	24.5 (15, 36.5)	**0.002***
≤ 14 Units/week‡	173 (57.67)	9 (6, 13)		4 (1, 6)		5 (3, 10)	†	2 (0, 4)		21 (13, 30)	
> 14 Units/week	23 (7.67)	7 (5, 12)		1 (1, 3)	†*, ‡	3 (2, 6)	†*	1 (1, 3)		17 (9, 21)	†*
Comorbidity[b]: No†	71 (17)	8 (4, 12)	**0.004**	3 (1, 6)	0.19	4 (2, 8)	**0.015**	2 (0, 4)	0.961	17 (13, 25)	**0.007**
1 comorbidity‡	72 (24)	8 (5, 13)		3.5 (1, 6)		5 (3, 9.5)		2 (1, 4)		21 (13, 28)	
≥ 2 comobidities	177 (59)	10 (7, 15)	†	4 (2, 7)		7 (3, 12)	†	2 (1, 4)		24 (15, 35)	†
Clinical types[b]: Keratotic†	51 (18.33)	7 (3, 13)	**0.001***	2 (0, 5)	**0.013**	5 (2, 8)	**0.041**	2 (1, 4)	0.437	18 (11, 27)	**0.004**
Erythematous‡	201 (67)	10 (6, 13)	†	4 (1, 6)		5 (3, 10)		2 (0, 4)		21 (14, 31)	
Erosive/Ulcerative	44 (14.67)	12 (9, 15)	†*	5 (3, 7)	†	8 (4.5, 12)	†	2 (1, 5)		28 (20.5, 35)	†*, ‡
Extraoral LP[a]: No	226 (75.33)	9 (5, 13)		3 (1, 6)		6 (3, 10)		2 (1, 4)		20 (13, 31)	
Yes/genital	47 (15.67)	10 (7, 15)	0.092	4 (1, 6)	0.618	7 (3, 13)	0.194	2 (0, 4)	0.102	25 (14, 36)	0.285
Yes/skin	38 (12.67)	12 (7, 15)	**0.029**	5 (2, 8)	**0.009**	7.5 (4, 15)	**0.047**	3 (1, 5)	**0.05**	29 (17, 41)	**0.006**
Treatment[b]: No/only Tanes†	47 (15.67)	3 (2, 8)	**0.000***	0 (0, 3)	**0.000***	2 (1, 6)	**0.000***	1 (0, 4)	0.1	9 (5, 17)	**0.000***
TCS alone‡	178 (59.33)	10 (6, 13)	†*	4 (2, 6)	†*	6 (3, 10)	†*	2 (1, 4)		22 (15, 31)	†*
TCS + other TTx	65 (21.67)	13 (9, 16)	†*, ‡	5 (3, 6)	†*	8 (5, 13)	†*, ‡	2 (1, 4)		29 (20, 37)	†*, ‡
TTx + STx	10 (3.33)	10.5 (6, 15)	†	5 (1, 8)	†*	8 (5, 13)	†	2.5 (1, 5)		25 (18, 44)	†*
Age (years)[c]	65.5 (55.2, 71)	0.004	0.945	-0.094	0.103	-0.093	0.107	-0.168	**0.003**	-0.087	0.136
Disease duration (years)[c]	6.3 (2.7, 10.5)	0.049	0.394	0.061	0.295	-0.031	0.599	-0.005	0.931	0.027	0.646
NRS for pain[c]	3 (1, 5)	0.649	**0.000***	0.503	**0.000***	0.533	**0.000***	0.219	**0.000***	0.647	**0.000***
HADS-Anxiety[c]	6 (3, 9)	0.348	**0.000***	0.301	**0.000***	0.531	**0.000***	0.207	**0.000***	0.457	**0.000***
HADS-Depression[c]	4 (1, 6)	0.387	**0.000***	0.372	**0.000***	0.5	**0.000***	0.23	**0.000***	0.497	**0.000***
HADS-total (Distress)[c]	10 (5, 15)	0.398	**0.000***	0.352	**0.000***	0.564	**0.000***	0.241	**0.000***	0.517	**0.000***
PSS-10 (Perceived stress)[c]	16 (11, 21)	0.406	**0.000***	0.337	**0.000***	0.54	**0.000***	0.237	**0.000***	0.513	**0.000***
ODSS total (disease severity)[c]	15 (8, 24)	0.559	**0.000***	0.423	**0.000***	0.403	**0.000***	0.194	**0.000***	0.53	**0.000***
ODSS-site[c]	6 (3, 8)	0.395	**0.000***	0.307	**0.000***	0.282	**0.000***	0.142	**0.014**	0.382	**0.000***
ODSS-activity[c]	6 (2, 10)	0.47	**0.000***	0.338	**0.000***	0.319	**0.000***	0.184	**0.000***	0.436	**0.000***

Table 6.2 Descriptive statistics of variables of study participants and bivariate analysis of factors associated with subscale and total scores of the COMDQ-15 in patients with OLP (N=300) (cont.)

Study variables	N (%)	PD		MT		SE		PS		Total score	
		med (IQR)	P	med (IQR)	P	med (IQR)	P	med (IQR)	P	med (IQR)	P
All subjects	300 (100)	9 (6, 14)	-	4 (1, 6)	-	6 (3, 10)	-	2 (1, 4)	-	21 (14, 32)	-

Note: [a] Mann-Whitney U test; [b] Kruskal-Wallis test; [c] Spearman's rho correlation coefficients; † Significant difference with the first reference group; ‡ Significant difference with the second reference group; TCS = Topical corticosteroids; Tanes = Topical anesthetic agents; TTx = Topical treatment; STx = Systemic treatment; Bold value = P-value<0.05; * = Statistical significance at Bonferroni corrected P-value of 0.003

Table 6.3 Bivariate analysis of factors associated with subscale and total scores of the OHIP-14 in patients with OLP (N=300)

Study variables	FL		PhyP		PsyD		PhyDis		PsyDis		SD		H		Total score	
	med (IQR)	P	med (IQR)	P	med (IQR)	P	med (IQR)	P	med (IQR)	P	med (IQR)	P	med (IQR)	P	med (IQR)	P value
Gender[a]: Female	2 (0, 3)	0.224	4 (3, 6)	0.328	2 (1, 4)	0.057	3 (1, 5)	0.331	2 (0, 4)	**0.042**	1 (0, 3)	0.16	1 (0, 3)	0.166	15 (8, 26)	0.085
Male	1 (0, 3)		4 (3, 6)		2 (0, 4)		2 (0, 4)		1 (0, 3)		1 (0, 2)		1 (0, 2)		11 (5, 21)	
Ethnicity[b]: White†	1 (0, 3)	**0.014**	4 (3, 6)	**0.007**	2 (1, 4)	0.177	2 (0, 4)	**0.000***	1 (0, 3)	**0.002***	1 (0, 3)	0.24	1 (0, 2)	**0.016**	13 (7 ,22)	**0.001***
Mixed	1 (0, 2)		4 (3, 6)		2 (0, 4)		1 (0, 4)		2 (0, 3)		1 (0, 2)		1 (0, 2)		12 (4, 23)	
Asian	2 (0, 4)	†	5 (4, 7)	†*	3 (1, 6)		4 (2, 6)	†*	2 (1, 5)	†	1 (0, 4)		2 (0, 4)	†*	20 (11, 33)	†*
Black	3 (1, 5)		6 (3, 7)		2 (1, 8)		5 (2, 8)		3 (2, 7)	†	2 (0, 2)		1 (0, 3)		26 (10, 39)	
Smoking[b]: Non-smoker	1 (0, 3)	0.291	4 (3, 6)	0.724	2 (1, 4)	0.276	2 (0, 4)	0.672	2 (0. 3)	0.271	1 (0, 3)	0.352	1 (0, 2)	0.474	15 (7, 25)	0.451
Ex-smoker	2 (0, 3)		4 (3, 6)		2 (1, 5)		3 (1, 5)		2 (0, 4)		1 (0, 3)		1 (0, 2)		15 (9, 27)	
Current smoker	2 (0, 4)		4 (4, 7)		4 (0, 7)		3 (1, 6)		3 (1, 6)		2 (0, 5)		2 (0, 6)		19 (5, 43)	
Alcohol[b]: No†	2 (0, 4)	**0.008**	5 (4, 6)	**0.042**	3 (1, 5)	0.195	4 (2, 6)	**0.000***	2 (0, 4)	**0.028**	1 (0, 4)	**0.014**	1 (0, 3)	0.269	19 (9, 33)	**0.007**
≤ 14 Units/w eek	1 (0, 3)		4 (3, 6)		2 (1, 4)		2 (0, 4)	†*	2 (0, 3)		1 (0, 3)		1 (0, 2)		14 (8, 23)	†
> 14 Units/w eek	1 (0, 2)	†	4 (2, 5)		3 (0, 4)		1 (0, 3)	†*	1 (0, 2)	†	0 (0, 1)	†	1 (0, 2)		12 (5, 18)	†*
Comorbidity[b]: No†	1 (0, 2)	**0.013**	4 (2, 5)	**0.01**	2 (1, 4)	0.42	2 (0, 4)	**0.044**	2 (0, 3)	**0.03**	1 (0, 3)	0.496	1 (0, 2)	**0.026**	13 (5 ,21)	**0.03**
1 comorbidity‡	1 (0, 2)		4 (3, 5)		2 (1, 4)		2 (1, 4)		1 (0, 2)		1 (0, 2)		1 (0, 2)		13 (7, 22)	
≥ 2 comobidities	2 (0, 4)		5 (3, 6)		2 (1, 5)		3 (1, 5)		2 (0, 4)	‡	1 (0, 3)		1 (0, 3)		17 (8, 29)	
Clinical types[b]: Keratotic†	1 (0, 2)	0.116	4 (2, 4)	**0.000***	2 (0, 4)	0.084	1 (0, 3)	**0.006**	1 (0, 3)	0.129	0 (0, 2)	**0.001***	1 (0, 2)	0.082	10 (4, 21)	**0.006***
Erythematous‡	2 (0, 3)		4 (3, 6)	†	3 (1, 4)		3 (1, 4)	†	2 (0, 4)		1 (0, 3)		1 (0, 2)		15 (8, 24)	
Erosive/Ulcerative	2 (0, 3)		6 (4, 7)	†*, ‡	3 (1, 5)		4 (2, 5)	†*	2 (1, 5)		2 (1, 4)	†*, ‡*	2 (1, 3)		20 (11, 31)	†*
Extraoral LP[a]: No	1 (0, 3)		4 (3, 6)		2 (0, 4)		2 (0, 4)		2 (0, 3)		1 (0, 3)		1 (0, 2)		15 (7, 24)	
Yes/genital	2 (0, 4)	0.54	4 (4, 6)	0.302	3 (2, 5)	0.054	3 (0, 6)	0.388	2 (1, 4)	0.09	1 (0, 3)	0.603	1 (0, 3)	0.535	15 (7, 29)	0.3
Yes/skin	2 (1, 4)	0.06	5 (3, 7)	0.16	3 (2, 5)	**0.01**	4 (2, 6)	**0.003***	3 (1, 4)	0.06	2 (1, 3)	**0.03**	2 (0, 4)	0.115	20 (12, 33)	**0.01**
Treatment[b]: No/only Tanes†	0 (0, 1)	**0.000***	2 (0, 4)	**0.000***	1 (0, 2)	**0.000***	0 (0, 2)	**0.000***	0 (0, 1)	**0.000***	0 (0, 1)	**0.000***	0 (0, 1)	**0.000***	5 (2, 10)	**0.000***
TCS alone‡	2 (0, 3)	†*	4 (3, 6)	†*	2 (1, 5)	†*	3 (1, 4)	†*	2 (0, 4)	†*	1 (0, 3)	†*	1 (0, 2)	†*	16 (8, 24)	†*
TCS + other TTx	3 (1, 4)	†*, ‡*	6 (4, 7)	†*, ‡	4 (2, 5)	†*	4 (3, 6)	†*, ‡	3 (1, 4)	†*, ‡	2 (1, 4)	†*	2 (1, 3)	†*	22 (13, 30)	†*, ‡
TTx + STx	3 (0, 4)	†	5 (4, 7)	†*	2 (0, 4)		3 (1, 6)	†	3 (1, 4)	†	3 (0, 6)	†*	2 (1, 4)	†	21 (6, 36)	†*
Age (years)[c]	-0.065	0.262	-0.074	0.2	-0.188	**0.001***	-0.078	0.179	-0.125	**0.031**	-0.138	**0.017**	-0.087	0.131	-0.137	**0.018**
Disease duration (years)[c]	0.038	0.507	0.065	0.262	-0.034	0.564	-0.042	0.474	-0.032	0.586	-0.026	0.651	-0.013	0.825	-0.017	0.766
NRS for pain[c]	0.49	**0.000***	0.632	**0.000***	0.461	**0.000***	0.588	**0.000***	0.526	**0.000***	0.477	**0.000***	0.455	**0.000***	0.622	**0.000***
HADS-Anxiety[c]	0.429	**0.000***	0.377	**0.000***	0.465	**0.000***	0.394	**0.000***	0.536	**0.000***	0.446	**0.000***	0.52	**0.000***	0.534	**0.000***
HADS-Depression[c]	0.432	**0.000***	0.386	**0.000***	0.461	**0.000***	0.427	**0.000***	0.493	**0.000***	0.419	**0.000***	0.481	**0.000***	0.528	**0.000***
HADS-total[c]	0.468	**0.000***	0.42	**0.000***	0.513	**0.000***	0.442	**0.000***	0.567	**0.000***	0.473	**0.000***	0.551	**0.000***	0.583	**0.000***
PSS-10[c]	0.366	**0.000***	0.383	**0.000***	0.453	**0.000***	0.37	**0.000***	0.508	**0.000***	0.45	**0.000***	0.475	**0.000***	0.508	**0.000***
ODSS total[c]	0.381	**0.000***	0.534	**0.000***	0.378	**0.000***	0.482	**0.000***	0.369	**0.000***	0.373	**0.000***	0.326	**0.000***	0.494	**0.000***
ODSS-site[c]	0.272	**0.000***	0.355	**0.000***	0.266	**0.000***	0.349	**0.000***	0.254	**0.000***	0.237	**0.000***	0.211	**0.000***	0.343	**0.000***
ODSS-activity[c]	0.307	**0.000***	0.448	**0.000***	0.313	**0.000***	0.4	**0.000***	0.286	**0.000***	0.319	**0.000***	0.271	**0.000***	0.405	**0.000***

Table 6.3 Bivariate analysis of factors associated with subscale and total scores of the OHIP-14 in patients with OLP (N=300)

Study variables	FL		PhyP		PsyD		PhyDis		PsyDis		SD		H		Total score	
	med (IQR)	P	med (IQR)	P	med (IQR)	P	med (IQR)	P	med (IQR)	P	med (IQR)	P	med (IQR)	P	med (IQR)	P value
All subjects	2 (0, 3)		4 (3, 6)		2 (1, 4)		2 (0, 4.5)		2 (0, 4)		1 (0, 3)		1 (0, 2)		15 (7, 25)	

Note: [a] Mann-Whitney U test; [b] Kruskal-Wallis test; [c] Spearman's rho correlation coefficients; † Significant difference with the first reference group; ‡ Significant difference with the second reference group; TCS = Topical corticosteroids; Tanes = Topical anesthetic agents; TTx = Topical treatment; STx = Systemic treatment; Bold value = P-value<0.05; * = Statistical significance at Bonferroni corrected P-value of 0.003

6.4.1.3 Determinants of OLP-specific quality of life based upon the COMDQ-15 scores in patients with OLP

Based upon the bivariate analysis results (Table 6.2), the following variables (P < 0.1) were identified as potential determinants of worse QoL based upon total COMDQ-15 scores in patients with OLP: Asian ethnicity, alcohol abstainers, ulcerative OLP type, receiving active treatment of OLP (topical corticosteroids with/without other treatment), higher HADS-A scores, higher HADS-D scores, higher HADS-T scores, higher PSS-10 scores, greater pain-NRS, greater disease activity (ODSS-total, -site, -activity) scores, presence of self-reported skin lichen planus. The total HADS, total ODSS, ODSS-site score were not included in the final multivariate model due to collinearity with other variables.

After adjusting for potential confounders, greater level of pain intensity (β=0.36, P<0.001), the use of topical corticosteroids combination with other topical treatment (β=0.24, P<0.001), topical corticosteroids alone (β=0.24, P<0.001) and higher level of perceived stress (β=0.22, P<0.001) were retained as independent determinants of overall health-related QoL as measured by total COMDQ-15 scores based upon Bonferroni corrected significance threshold (P=0.003). This multivariate model explained about 60% of total variance in the total COMDQ-15 scores. Further details on the independent determinants of subscale COMDQ-15 scores are present in Table 6.4.

6.4.1.4 Determinants of general oral health related quality of life based upon the OHIP-14 scores in patients with OLP

From the bivariate analysis results (Table 6.3), covariates with P <0.1 (increased age female, Asian ethnicity, non-drinkers, having at least two disease comorbidities, ulcerative OLP, presence of self-reported skin and genital lichen planus, receiving active treatment of OLP, higher HADS-A scores, higher HADS-D scores, higher HADS-T scores, higher PSS-10 scores, greater pain-NRS and greater disease activity (ODSS-total, -site, -activity) scores)

were included in multivariate linear regression model for worse QoL based upon the OHIP-14 scores. The total HADS, total ODSS, ODSS-site score, although being significant at bivariate analysis, were excluded in the final model due to collinearity with other variables.

The final multivariate model showed that greater oral pain (β=0.32, P<0.001), higher level of anxiety symptoms (β=0.23, P <0.001) and the use of topical corticosteroids combination with other topical treatment (β=0.019, P<0.001) remained to be independent predictors of worse general oral health-related QoL based upon total OHIP-14 scores after adjusting for other demographic and OLP-related parameters. This final model explained about 56% of the variance in total OHIP-14 scores. Summary of independent determinants of subscale scores of the OHIP-14 are outlined in Table 6.5.

Table 6.4 Results of the univariate and multivariate linear regression analyses of the total and subscale COMDQ-15 scores

Dependent variables	Independent variables[a]	Univariate model				After adjusted for demographic variables[b]				Multivariate model				
		Unstandardized		Standardized coefficient β	P value	Unstandardized		Standardized coefficient β	P value	Unstandardized		Standardized coefficient β	P value	Adjusted R^2
		B	S.E.			B	S.E.			B	S.E.			
Total COMDQ-15	*Pain: NRS*	3.24	0.22	0.65	**0.000***	2.93	0.23	0.58	**0.000***	1.78	0.24	0.36	**0.000***	0.6
	Treatment: TCS & other TTx	17.37	2.14	0.58	**0.000***	15.95	2.04	0.53	**0.000***	7.2	1.72	0.24	**0.000***	
	Treatment: TCS	12.39	1.83	0.49	**0.000***	12.29	1.76	0.49	**0.000***	5.98	1.44	0.24	**0.000***	
	Stress: PSS-10	0.86	0.08	0.53	**0.000***	0.76	0.08	0.47	**0.000***	0.35	0.09	0.22	**0.000***	
	OLP activity: ODSS-activity	0.75	0.11	0.38	**0.000***	0.68	0.1	0.34	**0.000***	0.26	0.1	0.13	0.009	
	Ethnicity: Asian	8.6	1.56	0.31	**0.000***	8.31	1.72	0.3	**0.000***	2.8	1.21	0.1	0.021	
	Extraoral LP: skin LP	6.46	2.12	0.17	**0.002***	6.06	2.01	0.16	0.003	3.19	1.45	0.09	0.028	
	Treatment: systemic treatment	15.07	3.89	0.22	**0.000***	14.67	3.72	0.21	**0.000***	6.19	2.9	0.09	0.034	
Physical Discomfort	*Pain: NRS*	1.32	0.09	0.65	**0.000***	1.29	0.09	0.64	**0.000***	0.84	0.11	0.42	**0.000***	0.53
	Treatment: TCS & other TTx	7.74	0.84	0.64	**0.000***	7.29	0.84	0.6	**0.000***	3.67	0.75	0.3	**0.000***	
	Treatment: TCS	5.31	0.72	0.52	**0.000***	5.25	0.73	0.52	**0.000***	2.66	0.63	0.26	**0.000***	
	Stress: PSS-10	0.27	0.03	0.41	**0.000***	0.25	0.04	0.38	**0.000***	0.11	0.04	0.16	0.006	
	OLP activity: ODSS-activity	0.33	0.04	0.41	**0.000***	0.31	0.04	0.38	**0.000***	0.12	0.04	0.15	0.007	
	At least 2 disease comorbidities	2.47	0.78	0.24	**0.002***	2.62	0.83	0.26	**0.002***	1.26	0.57	0.12	0.028	
Medication & Treatment	*Pain: NRS*	0.63	0.06	0.5	**0.000***	0.54	0.07	0.42	**0.000***	0.33	0.08	0.26	**0.000***	0.36
	Treatment: TCS	2.88	0.48	0.45	**0.000***	2.89	0.47	0.45	**0.000***	1.59	0.46	0.25	**0.001***	
	Treatment: TCS & other TTx	3.38	0.56	0.44	**0.000***	3.06	0.54	0.4	**0.000***	1.33	0.55	0.18	0.015	
	Ethnicity: Asian	2.26	0.4	0.32	**0.000***	2.09	0.44	0.29	**0.000***	1.18	0.38	0.17	**0.002***	
	Treatment: systemic treatment	3.6	1.03	0.21	**0.001***	3.51	0.99	0.2	**0.000***	1.79	0.92	0.1	0.05	
Social & Emotional	*Pain: NRS*	1.11	0.1	0.53	**0.000***	0.94	0.1	0.45	**0.000***	0.53	0.11	0.25	**0.000***	0.5
	Anxiety: HADS-A	0.65	0.06	0.55	**0.000***	0.57	0.06	0.48	**0.000***	0.27	0.07	0.22	**0.000***	
	Stress: PSS-10	0.37	0.03	0.55	**0.000***	0.32	0.03	0.48	**0.000***	0.13	0.04	0.2	**0.001***	
	Treatment: TCS & other TTx	5.47	0.93	0.44	**0.000***	4.84	0.89	0.39	**0.000***	2.12	0.79	0.17	0.008	
	Ethnicity: Asian	3.91	0.64	0.34	**0.000***	3.62	0.71	0.31	**0.000***	1.71	0.54	0.15	**0.002***	
	Treatment: TCS	3.48	0.8	0.33	**0.000***	3.44	0.76	0.33	**0.000***	1.48	0.66	0.14	0.025	
Patient Support	Stress: PSS-10	0.07	0.02	0.26	**0.000***	0.07	0.02	0.24	**0.000***	0.06	0.02	0.2	0.016	0.08
	Older age	-0.03	0.01	-0.15	0.01	-0.03	0.01	-0.16	0.012	-0.03	0.01	-0.14	0.018	

Note: [a] only independent variables with P-value less than 0.05 in multivariate model are displayed in the Table; [b] adjusted for age, sex, ethnicity, smoking, alcohol consumption and number of disease comorbidities; *Italic* variables are significant variables at multivariale model; * Statistical significance at Bonferroni corrected P-value < 0.003; TCS = topical corticosteroids; TTx = topical treatment

Table 6.5 Results of the univariate and multivariate linear regression analyses of the total and subscale OHIP-14 scores

Dependent variables	Independent variables[a]	Univariate model				After adjusted for demographic variables[b]				Multivariate model				
		Unstandardized		Standardized coefficient β	P value	Unstandardized		Standardized coefficient β	P value	Unstandardized		Standardized coefficient β	P value	Adjusted R^2
		B	S.E.			B	S.E.			B	S.E.			
Total OHIP-14	*Pain: NRS*	3.11	0.24	0.61	**0.000***	2.8	0.24	0.55	**0.000***	1.65	0.26	0.32	**0.000***	0.56
	Anxiety: HADS-A	1.64	0.14	0.56	**0.000***	1.45	0.15	0.49	**0.000***	0.67	0.18	0.23	**0.000***	
	Treatment: TCS & other TTx	15.09	2.27	0.49	**0.000***	14.03	2.16	0.46	**0.000***	5.73	1.86	0.19	**0.002***	
	Depression: HADS-D	1.88	0.17	0.55	**0.000***	1.7	0.18	0.49	**0.000***	0.54	0.2	0.16	0.007	
	Treatment: TCS	9.97	1.94	0.39	**0.000***	10.26	1.86	0.4	**0.000***	3.93	1.55	0.15	0.012	
	OLP activity: ODSS-activity	0.7	0.11	0.34	**0.000***	0.62	0.11	0.3	**0.000***	0.27	0.11	0.13	0.012	
Functional Limitation	*Pain: NRS*	0.36	0.04	0.47	**0.000***	0.33	0.04	0.42	**0.000***	0.2	0.05	0.26	**0.000***	0.34
	Anxiety: HADS-A	0.19	0.02	0.44	**0.000***	0.17	0.02	0.38	**0.000***	0.09	0.03	0.19	0.008	
	Treatment: TCS & other TTx	2.01	0.35	0.43	**0.000***	1.81	0.34	0.39	**0.000***	0.8	0.33	0.17	0.017	
	Depression: HADS-D	0.23	0.03	0.45	**0.000***	0.2	0.03	0.39	**0.000***	0.08	0.04	0.15	0.034	
Physical Pain	*Pain: NRS*	0.54	0.04	0.62	**0.000***	0.52	0.04	0.6	**0.000***	0.36	0.05	0.41	**0.000***	0.46
	Treatment: TCS & other TTx	2.87	0.38	0.55	**0.000***	2.77	0.37	0.53	**0.000***	1.13	0.34	0.22	**0.001***	
	Treatment: TCS	1.94	0.32	0.45	**0.000***	1.97	0.32	0.45	**0.000***	0.81	0.28	0.19	0.005	
	Anxiety: HADS-A	0.19	0.03	0.39	**0.000***	0.17	0.03	0.34	**0.000***	0.07	0.03	0.15	0.023	
	OLP activity: ODSS-activity	0.14	0.02	0.4	**0.000***	0.13	0.02	0.37	**0.000***	0.05	0.02	0.13	0.018	
	Treatment: systemic treatment	2.49	0.68	0.21	**0.000***	2.53	0.68	0.21	**0.000***	1.19	0.57	0.1	0.039	
Psychological Discomfort	Depression: HADS-D	0.3	0.03	0.45	**0.000***	0.3	0.04	0.45	**0.000***	0.13	0.05	0.19	0.006	0.37
	Pain: NRS	0.46	0.05	0.45	**0.000***	0.42	0.05	0.42	**0.000***	0.18	0.06	0.18	0.003	
	OLP activity: ODSS-activity	0.11	0.02	0.27	**0.000***	0.1	0.02	0.25	**0.000***	0.06	0.02	0.15	0.014	
	older age	-0.04	0.01	-0.18	**0.002***	-0.05	0.01	-0.21	**0.001***	-0.03	0.01	-0.15	0.003	
	Treatment: TCS & other TTx	2.18	0.46	0.36	**0.000***	2.14	0.45	0.36	**0.000***	0.88	0.43	0.15	0.043	
	Stress: PSS-10	0.15	0.02	0.45	**0.000***	0.13	0.02	0.41	**0.000***	0.05	0.02	0.14	0.045	
Physical Disability	*Pain: NRS*	0.6	0.05	0.59	**0.000***	0.53	0.05	0.52	**0.000***	0.35	0.06	0.34	**0.000***	0.46
	Anxiety: HADS-A	0.25	0.03	0.43	**0.000***	0.21	0.03	0.35	**0.000***	0.11	0.04	0.19	0.005	
	Treatment: TCS & other TTx	3.04	0.45	0.5	**0.000***	2.75	0.43	0.45	**0.000***	1.04	0.4	0.17	0.011	
	OLP activity: ODSS-activity	0.14	0.02	0.35	**0.000***	0.13	0.02	0.32	**0.000***	0.06	0.02	0.15	0.01	
	Extraoral LP: skin LP	1.38	0.43	0.18	**0.001***	1.38	0.41	0.18	**0.001***	0.79	0.34	0.11	0.021	

Note: [a] only independent variables with P-value less than 0.05 in multivariate model are displayed in the Table; [b] adjusted for age, sex, ethnicity, smoking, alcohol consumption and number of disease comorbidities; *Italic* variables are significant variables at multivariale model; * Statistical significance at Bonferroni corrected P-value < 0.003; TCS = topical corticosteroids; TTx = topical treatment

Table 6.5 Results of the univariate and multivariate linear regression analyses of the total and subscale OHIP-14 scores (cont.)

Dependent variables	Independent variables	Univariate model				After adjusted for demographic variables				Multivariate model				
		Unstandardized		Standardized coefficient β	P value	Unstandardized		Standardized coefficient β	P value	Unstandardized		Standardized coefficient β	P value	Adjusted R^2
		B	S.E.			B	S.E.			B	S.E.			
Psychological	*Anxiety: HADS-A*	0.3	0.02	0.57	**0.000***	0.26	0.03	0.51	**0.000***	0.13	0.03	0.26	**0.000***	0.48
Disability	*Pain: NRS*	0.47	0.05	0.52	**0.000***	0.41	0.05	0.44	**0.000***	0.22	0.05	0.24	**0.000***	
	Treatment: TCS & other TTx	2.29	0.41	0.42	**0.000***	2.09	0.39	0.38	**0.000***	0.88	0.35	0.16	0.013	
	Depression: HADS-D	0.32	0.03	0.52	**0.000***	0.29	0.03	0.48	**0.000***	0.1	0.04	0.16	0.013	
	older age	-0.03	0.01	-0.14	0.013	-0.04	0.01	-0.19	**0.002***	-0.02	0.01	-0.13	0.009	
	Ethnicity: Black	2.1	0.68	0.18	**0.002***	1.74	0.66	0.15	**0.002***	1.05	0.52	0.09	0.043	
Social Disability	*Pain: NRS*	0.37	0.04	0.46	**0.000***	0.34	0.04	0.43	**0.000***	0.18	0.05	0.22	**0.000***	0.38
	Anxiety: HADS-A	0.21	0.02	0.46	**0.000***	0.2	0.03	0.44	**0.000***	0.08	0.03	0.18	0.012	
	Treatment: TCS	1.22	0.31	0.3	**0.000***	1.32	0.31	0.33	**0.000***	0.69	0.28	0.17	0.016	
	Stress: PSS-10	0.13	0.01	0.48	**0.000***	0.12	0.01	0.45	**0.000***	0.04	0.02	0.16	0.017	
	Treatment: TCS & other TTx	1.62	0.36	0.34	**0.000***	1.55	0.36	0.32	**0.000***	0.68	0.34	0.14	0.049	
	Treatment: systemic tx	2.25	0.66	0.3	**0.001***	2.38	0.66	0.22	**0.000***	1.55	0.57	0.14	0.007	
Handicap	*Anxiety: HADS-A*	0.22	0.02	0.52	**0.000***	0.2	0.02	0.48	**0.000***	0.11	0.03	0.26	**0.000***	0.38
	Pain: NRS	0.32	0.04	0.43	**0.000***	0.26	0.04	0.36	**0.000***	0.16	0.04	0.21	**0.000***	
	Depression: HADS-D	0.25	0.02	0.51	**0.000***	0.22	0.03	0.46	**0.000***	0.08	0.03	0.15	0.023	

Note: [a] only independent variables with P-value less than 0.05 in multivariate model are displayed in the Table; [b] adjusted for age, sex, ethnicity, smoking, alcohol consumption and number of disease comorbidities; *Italic* variables are significant variables at multivariale model; * Statistical significance at Bonferroni corrected P-value < 0.003; TCS = topical corticosteroids; TTx = topical treatment

6.4.2 Results of the RAS cohort

6.4.2.1 Descriptive characteristics of study participants

The median age of all 120 RAS participants was 42.03 years (interquartile range = 33.22-53.58 years), and 71 (59.17%) were female. The median age since the first RAS episode was 19.25 years, with disease duration varying from 1 year to 58 years (median = 16.89 years). Minor RAS was the most prevalent clinical variant of RAS, accounted for 85% of participants, followed by major (11%) and herpetiform types (4%). Among 120 participants, 21 (17.5%) received at least one systemic medications including colchicine (11 patients), prednisolone (4 patients), pentoxifylline (4 patients), thalidomide (4 patients), azathioprine (3 patients) and dapsone (1 patient). Other demographic and clinical characteristics of the study cohort are summarised in Table 6.6.

6.4.2.2 Quality of life outcomes in patients with RAS

Bivariate analysis of demographics and RAS-related variables by QoL scores according to the scores of COMDQ-15 and OHIP-14 are shown in Table 6.6 and Table 6.7, respectively. Patients with herpetiform RAS reported significantly worse overall QoL than other RAS phenotypes. Apart from clinical types of RAS, greater disease activity of RAS including higher number of oral ulcers, longer ulcer duration, shorter ulcer-free periods, higher number of involved oral sites and greater level of oral pain was found to be associated with poorer QoL in patients with RAS. Among participants in this RAS cohort, those taking systemic medication reported worse general oral health related QoL than those using topical treatment only as shown by the OHIP-14 results. In addition, alcohol abstainers appeared to have poorer QoL than those drinking alcohol based upon the COMDQ-15 results.

Regarding correlation studies between QoL and other variables, it was observed that total scores of both QoL scales were positively and significantly associated with scores of the pain-NRS, HADS-anxiety, HADS-depression, total HADS (distress), PSS-10 (perceived stress),

and total USS (disease activity) in patients with RAS. As for the strength of association, the total COMDQ-15 had slightly stronger association with level of oral pain, all studied psychological parameters and total disease activity scores based upon spearman rho coefficients in patients with RAS in comparison with the total OHIP-14.

Table 6.6 Descriptive statistics of variables of study participants and bivariate analysis of factors associated with subscale and total scores of the COMDQ-15 in patients with RAS (N=120)

Study variables	All subjects (N=120)	PhyDis		Med-Tx		Soc-Emo		PtSup		Total score	
		med (IQR)	P value	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value
Gender[a]: Female	71 (59.2)	12 (8, 15)	0.16	4 (2, 6)	0.48	9 (5, 14)	0.3	3 (2, 4)	0.29	28 (20, 37)	0.45
Male	49 (40.8)	11 (7, 14)		4 (3, 6)		9 (4, 12)		3 (2, 5)		25 (19, 36)	
Ethnicity[b]: White†	93 (77.5)	11 (7, 14)	0.25	4 (3, 6)	0.28	8 (4, 11)	**0.017**	3 (2, 4)	0.24	25 (19, 34)	0.06
Mixed	5 (4.2)	13 (12, 16)		5 (3, 6)		13 (9, 15)	†	3 (2, 5)		36 (27, 41)	
Asian	16 (13.3)	12 (9, 14.5)		6 (3.5, 7)		12 (7, 16.5)	†	2 (1, 3.5)		33 (24, 39)	
Black	6 (5)	14 (11, 15)		6 (5, 7)		11 (9, 15)		4 (3, 4)		35 (27, 39)	
Smoking[b]: Non-smoker	99 (82.5)	12 (8, 15)	0.84	4 (3, 6)	0.22	9 (5, 13)	0.91	3 (2, 4)	0.88	28 (19, 36)	0.68
Ex-smoker	13 (10.8)	12 (11, 14)		4 (3, 7)		8 (5, 13)		3 (2, 4)		26 (24, 39)	
Current smoker	8 (6.7)	13 (7, 15)		6 (4, 8.5)		7 (6, 14)		3 (2, 5)		26 (22, 41)	
Alcohol[b]: No†	39 (32.5)	13 (10, 16)	**0.006**	5 (3, 7)	0.56	10 (7, 16)	**0.015**	2 (2, 5)	0.68	32 (24, 40)	**0.015**
≤ 14 Units/week	77 (64.2)	11 (7, 14)	†	4 (3, 6)		8 (4, 11)	†	3 (2, 4)		25 (18, 34)	†
> 14 Units/week	4 (3.3)	11 (9, 14)		4.5 (3, 6)		7 (5.5, 11)		3.5 (2, 5)		27 (23, 33)	
Comorbidity[b]: No	57 (47.5)	11 (7, 14)	0.72	4 (2, 6)	0.77	9 (5, 13)	0.87	3 (2, 4)	0.88	27 (19, 37)	0.92
1 comorbidity	37 (30.8)	12 (9, 15)		5 (3, 6)		8 (5, 13)		3 (2, 4)		27 (20, 34)	
≥ 2 comobidities	26 (21.7)	11 (8, 14)		4 (3, 6)		9 (4, 14)		2.5 (2, 4)		28 (20, 37)	
Clinical types[b]: Minor†	102 (85)	11 (8, 14)	**0.002***	4 (3, 6)	**0.03**	8.5 (4, 11)	**0.000***	3 (2, 5)	0.95	26 (19, 34)	**<0.001**
Major‡	13 (10.8)	13 (12, 16)	†	6 (3, 6)		13 (7, 16)	†	3 (2, 4)		35 (25, 39)	†
Herpetiform	5 (4.2)	16 (15, 19)	†	7 (7, 7)	†, ‡	16 (16, 16)	†	3 (2, 3)		42 (41, 45)	†, ‡
Treatment[b]: TTx†	99 (82.5)	11 (8, 14)	0.39	4 (3, 6)	**0.01**	9 (4, 13)	0.1	3 (2, 5)	0.68	27 (19, 36)	0.11
TTx + STx	21 (17.5)	13 (9, 16)		6 (4, 8)	†	10 (7, 15)		3 (2, 4)		31 (24, 41)	
Age (years)[c]	42 (33.2, 53.6)	0.052	0.58	0.022	0.81	-0.004	0.97	-0.016	0.86	0.033	0.72
Disease duration (years)[c]	17.4 (8.5, 26.8)	0.199	**0.03**	0.021	0.81	0.038	0.68	-0.005	0.96	0.103	0.26
NRS for pain[c]	4 (1, 7)	0.422	**0.000***	0.165	0.07	0.432	**0.000***	0.129	0.16	0.449	**0.000***
HADS-Anxiety[c]	7 (4, 9.5)	0.121	0.189	0.152	0.1	0.327	**0.000***	0.106	0.25	0.267	**0.000***
HADS-Depression[c]	4 (2, 6)	0.343	**0.000***	0.288	**0.001***	0.526	**0.000***	0.165	0.07	0.499	**0.000***
HADS-total (Distress)[c]	11 (7, 15.5)	0.268	**0.003**	0.25	**0.006**	0.489	**0.000***	0.146	0.11	0.433	**0.000***
PSS-10 (Perceived stress)[c]	18 (12, 21.5)	0.379	**0.000***	0.278	**0.002***	0.551	**0.000***	0.251	**0.006**	0.532	**0.000***

Note: [a] Mann-Whitney U test; [b] Kruskal-Wallis test; [c] Spearman's rho correlation coefficients; † Significant difference with the first reference group; ‡ Significant difference with the second reference group; TTx = Topical treatment; STx = Systemic treatment; Bold value = P-value<0.05; * = Statistical significance at Bonferroni corrected P-value of 0.003

Table 6.6 Descriptive statistics of variables of study participants and bivariate analysis of factors associated with subscale and total scores of the COMDQ-15 in patients with RAS (N=120) (cont.)

Study variables	All subjects (N=120)	PhyDis		Med-Tx		Soc-Emo		PtSup		Total score	
		med (IQR)	P value	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value
USS total (disease severity)[c]	29 (24, 35)	0.46	**0.000***	0.278	**0.002***	0.435	**0.000***	-0.095	0.302	0.459	**0.000***
USS-size[c]	4 (2.5, 6)	0.133	0.15	-0.041	0.66	0.174	0.06	0.002	0.98	0.148	0.107
USS-number[c]	2 (2, 4)	0.269	**0.003**	0.267	**0.003**	0.27	**0.003**	-0.06	0.51	0.296	**0.001***
USS-duration[c]	3 (2, 4)	0.273	**0.003**	0.028	0.76	0.182	**0.047**	-0.127	0.167	0.207	**0.023**
USS-ulcer free period[c]	8 (6.5, 9)	0.291	**0.001***	0.224	**0.013**	0.32	**0.000***	-0.34	0.715	0.326	**0.000***
USS-site[c]	5 (4, 8)	0.269	**0.003**	0.238	**0.009**	0.259	**0.004**	0.112	0.224	0.308	**0.000***
USS-pain[c]	6 (4, 7)	0.414	**0.000***	0.154	0.09	0.358	**0.000***	-0.144	0.117	0.361	**0.000***
All subjects	120 (100)	12 (8, 14.5)	-	4 (3, 6)	-	9 (5, 13)	-	3 (2, 4)	-	27 (20, 37)	-

Note: [a] Mann-Whitney U test; [b] Kruskal-Wallis test; [c] Spearman's rho correlation coefficients; † Significant difference with the first reference group; ‡ Significant difference with the second reference group; TTx = Topical treatment; STx = Systemic treatment; Bold value = P-value<0.05; * = Statistical significance at Bonferroni corrected P-value of 0.003

Table 6.7 Descriptive statistics of variables of study participants and bivariate analysis of factors associated with subscale and total scores of the OHIP-14 in patients with RAS (N=120)

Study variables	FL		PhyP		PsyD		PhyDis		PsyDis		SD		H		Total score	
	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value
Gender[a]: Female	4 (2, 5)	0.33	6 (4, 7)	0.99	4 (2, 6)	0.5	4 (3, 6)	0.28	4 (2, 5)	0.94	4 (2, 6)	0.82	3 (1, 5)	0.77	27 (19, 38)	0.99
Male	3 (2, 4)		6 (4, 7)		4 (3, 6)		4 (3, 5)		4 (2, 6)		4 (2, 6)		2 (1, 5)		26 (22, 36)	
Ethnicity[b]: White†	3 (2, 5)	**0.03**	6 (4, 7)	0.32	4 (2, 6)	**0.02**	4 (3, 6)	0.51	4 (2, 5)	0.2	4 (2, 6)	0.85	2 (1, 4)	0.22	25 (17, 36)	0.23
Mixed	4 (3, 5)		7 (5, 7)		3 (3, 4)		5 (4, 6)		4 (4, 5)		4 (4, 5)		5 (4, 5)		35 (23, 36)	
Asian	5 (4, 6)	†	7 (5, 8)		5 (4, 8)		4 (2, 7)		5 (4, 7)		4 (2, 6)		3 (2, 6)		30 (24, 41)	
Black	4 (2, 6)		6 (5, 7)		6 (5, 7)		5 (4, 6)		5 (2, 6)		3 (2, 6)		3 (2, 6)		32 (26, 41)	
Smoking[b]: Non-smoker	4 (2, 5)	0.61	6 (4, 7)	0.55	4 (2, 6)	0.97	4 (3, 6)	0.38	4 (2, 5)	0.88	4 (2, 6)	0.49	3 (1, 5)	0.88	27 (20, 37)	0.83
Ex-smoker	3 (1, 5)		6 (5, 7)		4 (3, 5)		4 (3, 7)		4 (2, 6)		3 (2, 6)		2 (1, 4)		23 (22, 36)	
Current smoker	4 (2, 5)		6 (6, 7)		5 (2, 6)		6 (4, 6)		4 (1, 6)		5 (4, 6)		4 (1, 5)		32 (19, 40)	
Alcohol[b]: No†	4 (2, 5)	0.1	6 (5, 7)	0.11	4 (3, 7)	0.32	4 (3, 6)	0.21	4 (3, 6)	0.08	4 (2, 6)	0.64	3 (1, 6)	0.58	30 (22, 41)	0.15
≤ 14 Units/week	3 (2, 4)		5 (4, 7)		4 (2, 6)		4 (3, 5)		4 (2, 5)		4 (2, 5)		2 (1, 4)		25 (17, 36)	
> 14 Units/week	5 (4, 6)		6 (5, 8)		5 (4, 5)		6 (5, 7)		4 (3, 6)		5 (4, 6)		4 (2, 6)		32 (26, 40)	
Comorbidity[b]: No	4 (2, 6)	0.21	6 (4, 7)	0.09	4 (3, 6)	0.54	4 (3, 6)	0.67	4 (2, 6)	0.7	4 (2, 6)	0.5	3 (1, 5)	0.78	28 (21, 38)	0.46
1 comorbidity	3 (2, 5)		6 (5, 7)		4 (1, 6)		4 (3, 7)		4 (2, 5)		4 (2, 6)		2 (1, 5)		26 (22, 36)	
≥ 2 comobidities	4 (2, 4)		5 (4, 7)		4 (2, 6)		4 (2, 5)		4 (2, 5)		3 (2, 5)		2 (1, 4)		24 (18, 32)	
Clinical types[b]: Minor†	3 (2, 5)	**0.01**	5 (4, 7)	**0.02**	4 (2, 6)	**0.02**	4 (2, 5)	**0.01**	4 (2, 5)	0.09	3 (2, 5)	0.02	2 (1, 4)	0.09	25 (19, 35)	**0.006**
Major‡	4 (3, 5)		7 (7, 8)		6 (4, 6)		4 (3, 6)		4 (2, 6)		6 (4, 6)		4 (2, 5)		36 (24, 41)	
Herpetiform	7 (5, 7)	†	7 (7, 8)		7 (5, 8)		8 (6, 8)	†	6 (5, 7)		7 (4, 7)		5 (4, 6)		45 (39, 50)	†
Treatment[b]: TTx	4 (2, 5)	0.1	5 (4, 7)	**0.03**	4 (2, 6)	0.24	4 (2, 5)	**0.006**	4 (2, 5)	0.26	3 (2, 5)	**0.007**	2 (1, 4)	**0.047**	25 (19, 35)	**0.02**
TTx + STx	4 (3, 7)		7 (6, 8)		5 (3, 7)		6 (4, 8)		5 (3, 6)		5 (3, 7)		4 (2, 6)		38 (24, 45)	
Age (years)[c]	0.023	0.8	0.002	0.99	0.157	0.087	0.12	0.194	0.056	0.545	-0.093	0.314	0.052	0.575	0.055	0.55
Disease duration[c]	0.007	0.94	0.083	0.366	0.083	0.367	0.089	0.333	0.087	0.345	0.086	0.349	0.103	0.263	0.097	0.294
NRS for pain[c]	0.243	**0.007**	0.381	**0.000***	0.289	**0.001***	0.24	**0.008**	0.276	**0.002***	0.323	**0.000***	0.329	**0.000***	0.36	**0.000***
HADS-Anxiety[c]	0.121	0.188	0.057	0.538	0.269	**0.003**	0.28	**0.002***	0.256	**0.005**	0.206	**0.024**	0.278	**0.002***	0.239	**0.009**
HADS-Depression[c]	0.372	**0.000***	0.195	**0.033**	0.393	**0.000***	0.366	**0.000***	0.459	**0.000***	0.306	**0.000***	0.376	**0.000***	0.431	**0.000***
HADS-total (Distress)[c]	0.266	**0.003**	0.144	0.118	0.351	**0.000***	0.368	**0.000***	0.396	**0.000***	0.29	**0.001***	0.375	**0.000***	0.373	**0.000***
PSS-10 (stress)[c]	0.26	**0.004**	0.172	0.06	0.398	**0.000***	0.329	**0.002***	0.407	**0.000***	0.366	**0.000***	0.402	**0.000***	0.396	**0.000***

Note: [a] Mann-Whitney U test; [b] Kruskal-Wallis test; [c] Spearman's rho correlation coefficients; † Significant difference with the first reference group; ‡ Significant difference with the second reference group; TTx = Topical treatment; STx = Systemic treatment; Bold value = P-value<0.05; * = Statistical significance at Bonferroni corrected P-value of 0.00

Table 6.7 Descriptive statistics of variables of study participants and bivariate analysis of factors associated with subscale and total scores of the OHIP-14 in patients with RAS (N=120) (cont.)

Study variables	FL		PhyP		PsyD		PhyDis		PsyDis		SD		H		Total score	
	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value	med (IQR)	P value
USS (disease severity)[c]	0.432	**0.000***	0.434	**0.000***	0.309	**0.000***	0.385	**0.000***	0.292	**0.001***	0.323	**0.000***	0.268	**0.003**	0.402	**0.000***
USS-size[c]	0.184	**0.045**	0.173	0.059	0.054	0.56	0.098	0.285	0.077	0.403	0.204	**0.025**	0.162	0.078	0.158	0.09
USS-number[c]	0.241	**0.008**	0.23	**0.011**	0.289	**0.001***	0.396	**0.000***	0.22	**0.016**	0.177	0.053	0.173	0.059	0.289	**0.01**
USS-duration[c]	0.2	**0.028**	0.244	**0.007**	0.101	0.272	0.083	0.366	0.088	0.34	0.171	0.062	0.101	0.273	0.173	0.059
USS-ulcer free[c]	0.336	**0.000***	0.356	**0.000***	0.262	**0.004**	0.343	**0.000***	0.313	**0.000***	0.24	**0.008**	0.222	**0.015**	0.336	**0.000***
USS-site[c]	0.247	**0.007**	0.352	**0.000***	0.276	**0.002***	0.341	**0.000***	0.259	**0.004**	0.22	**0.016**	0.203	**0.026**	0.305	**0.001***
USS-pain[c]	0.319	**0.000***	0.352	**0.000***	0.255	**0.005**	0.26	**0.004**	0.243	**0.008**	0.239	**0.009**	0.232	**0.01**	0.314	**0.001***
All subjects	4 (2, 5)	-	6 (4, 7)	-	4 (2, 6)	-	4 (3, 6)	-	4 (2, 5)	-	4 (2, 6)	-	3 (1, 5)	-	26 (20, 38)	-

Note: [a] Mann-Whitney U test; [b] Kruskal-Wallis test; [c] Spearman's rho correlation coefficients; † Significant difference with the first reference group; ‡ Significant difference with the second reference group; TTx = Topical treatment; STx = Systemic treatment; Bold value = P-value<0.05; * = Statistical significance at Bonferroni corrected P-value of 0.003

6.5 DISCUSSION

6.5.1 Health-related quality of life and its associated predictors in patients with OLP

The present study provides a comprehensive evaluation of quality of life and assesses the ability of various demographic, clinical and psychological outcomes to predict quality of life outcomes in a sample of patients with OLP. Assessment of QoL outcomes in patients with OLP could incorporate patient's perspective to better understand how OLP and its related treatment could impact the whole of a patient's life, and QoL data could be an important resource to facilitate shared clinical decision making between clinicians and patients.

The present cross-sectional analysis supported findings from previous studies that patients with ulcerative OLP experienced greater impact of OLP on their QoL than those with other clinical variants (Parlatescu et al., 2019, Karbach et al., 2014). Based upon further COMDQ-15 item analysis, it was observed that patients with ulcerative OLP reported significantly greater level of oral discomfort when eating certain food textures/types and performing oral hygiene care, greater concerns about medication use as well as greater psychosocial burden of OLP. This finding is supported by previous literature, which found that ulceration in OLP lesions tends to become more painful than keratotic lesions of OLP (Radochová et al., 2014). In comparison, although patients with keratotic OLP reported low level of oral pain (median pain-NRS = 1), this patient group still experienced moderate levels of oral discomfort when having certain food types as reflected by the median scores of 2 in PF1 item of the COMDQ-15. This finding is in accordance with a previous study, which found dietary alteration and avoidance in patients with OLP regardless of the presence of erosive/ulcerative lesions (Czerninski et al., 2014). However, it should be noted that the presence of painful symptoms in keratotic OLP might be associated with underlying peripheral nerve injury resulting from chronic inflammatory process of OLP. Thus it is evident that regardless of clinical types, the presence of OLP can have a negative impact on patients' oral activities and the use of global

summary of oral symptoms such as the pain-NRS alone might not be a true reflection of the impact of oral symptoms on patient's everyday living.

Previous studies have attempted to explain factors associated with reduced QoL in patients with OLP although the findings were inconsistent and difficult to pool due to the use of different QoL measures and study methodology (Radwan-Oczko et al., 2018, Parlatescu et al., 2019). In the present study, after adjustment for potential confounders, independent determinants of overall worse QoL in patients with OLP include greater level of oral pain, the use of topical and/or systemic treatment, higher level of perceived stress, greater disease activity of OLP, Asian ethnicity and cutaneous involvement of lichen planus. Among these, the most prominent predictor for worse QoL in nearly all QoL dimensions in patients with OLP was greater level of oral pain. Painful oral symptoms are likely to be the most important reason for patients with symptomatic OLP to seek professional treatment (Ingafou et al., 2006). In light of this, effective pain management in this patient population is imperative. One recent study found that OLP patients who had comorbid psychological distress, including anxiety and depression, appeared to perceive higher intensity of oral pain than those with normal psychological state (Wiriyakijja et al, 2019b). Therefore, clinicians should not only focus on the treatment of visible clinical signs of OLP alone. Concomitant evaluation and appropriate management of psychological factors influencing the pain experience in patients with OLP may improve patient care.

The present analysis revealed that the increase in level of perceived stress and anxiety symptoms in OLP patients was an independent predictor for worse overall QoL, and this corroborates the finding of one recent study on OLP patients resident in Poland (Radwan-Oczko et al., 2018). Based upon multivariate models of subscale COMDQ-15 scores, the findings demonstrate that patients with greater level of psychological stress have a tendency to have more psychosocial burden ($P<0.001$), more perceived physical discomfort ($P=0.006$)

from OLP and less perceived support and understanding from family members and friends (P=0.016). Together with psychological stress, anxiety symptoms also negatively contribute to worse general oral health related QoL and increased psychosocial burden of OLP. In contrast, depressive symptoms did not persist as an independent determinant of QoL after adjusting for other factors, and this differs from the findings of previous research (Yang et al., 2018, Radwan-Oczko et al., 2018). Considering the influence of psychological factors on various aspects of patients' QoL, more attention should be paid to the screening of psychological symptoms using validated psychological measures in the management of OLP. Importantly, if abnormal psychological symptoms are detected, it is the clinician's responsibility to make timely onward referral to the general practitioner or appropriate specialist teams, which may include clinical psychologists or psychiatrists, in order to help improve the QoL of patients with OLP.

Clinical types of OLP appeared not to predict QoL outcomes in this OLP patient group once other confounders were controlled, and this did not support findings of previous studies (Karbach et al., 2014, Parlatescu et al., 2019). Nevertheless, it was observed that higher score of disease activity as assessed by the ODSS-activity score was an important determinant of worse QoL including the "physical discomfort" domain (P=0.007) and total COMDQ-15 scores (P=0.009), although the present results did not reach significance threshold (P<0.003). This was in agreement with a recent study of Brazillian patients with OLP, which found that patients with greater disease activity reported worse QoL outcomes as indicated by the total OHIP-14 score (Zucoloto et al., 2019). This finding underlines the important role of disease activity control to improve overall QoL outcomes particularly by lessening physical impact of the OLP lesions on daily oral activities in this patient group.

The present multivariate analysis showed Asian ethnicity was significantly associated with worse QoL in the domain "medication and treatment" and "social and emotional" of the

COMDQ-15 when compared to white ethnicity. In other words, Asian patients with OLP in this cohort were more likely to report a greater impact of OLP on their lives including concerns about medication and psychosocial burden than the major ethnic group. This might reflect potential sociocultural confounding factors including cultural difference in QoL perception, socioeconomic minority and communication problems and access to health care of this patient population in the UK. However, further studies exploring the ethnic factors on the perception of QoL in patients with OLP is required.

Apart from the demographic, psychological and disease-related variables, different choices of treatment prescribed were found to have influence on patient's QoL when compared to patients who did not receive any treatment or received topical anesthetic agents only. The present finding showed that those receiving topical corticosteroids with other adjuvant medications were likely to report worse overall QoL including the "physical discomfort" domain of the COMDQ-15 than those receiving topical corticosteroids alone and those receiving no active treatment. The use of systemic medications did not predict the "physical discomfort" domain but was found to increase scores of the total COMDQ-15 (P=0.034) and "medication and treatment" domain of the COMDQ-15 (P=0.05). The "medication and treatment" score of the COMDQ-15 is indicative of patient's concerns about OLP treatment including the side effects, limitation from routine use as well as frustration of no standard medication. As QoL in patients with OLP is not dependent on the impact of the disease alone, the use of QoL measure such as the COMDQ-15 could provide informative data on patient's concerns about the impact of treatment, which might not be expressed during routine consultation. Understanding a patient's concerns could improve shared decision-making and reassurance about treatment during consultations, and consequently improve the quality of care to the patients.

The vast majority of the clinical research and practice with OLP presently use non-specific patient-reported instruments for the assessment of subjective constructs such as pain, anxiety, depression or QoL including the NRS, the HADS or the OHIP-14 (Wiriyakijja et al., 2018). Although these instruments are useful for comparison between different patient groups, they may not always provide sufficient detail and appeared to be less sensitive to detect small but clinically meaningful changes associated with OLP. The present results also found that QoL as measured by the OHIP-14 was found to have poorer association with symptoms and signs of patients with OLP when compared to the use of COMDQ-15, which is a QoL measure specific to patients with oral mucosal conditions including OLP. Currently there are already a number of specific instruments developed with the input from patients with OLP. These include the Oral Lichen Planus Symptom Severity Measure (OLP-SSM) to assess daily experience of physical symptoms of OLP (Burke et al., 2019a), the COMDQ to quantify the level of QoL specific to chronic oral mucosal conditions, and the OPMDQoL to measure QoL specific to oral potentially malignant disorders (Tadakamadla et al., 2017). Utilizing these instruments could help clinicians and researchers assessing subjective constructs specific to patients with OLP with confidence.

6.5.2 Health-related quality of life and its associated predictors in patients with RAS

The present study aimed at examining level of health-related quality of life in patients with RAS as well as investigating potential determinants associated with poorer quality of life in this patient population. Previous studies showed that individuals with RAS reported worse quality of life when compared to healthy controls (Zwiri, 2015, Cardoso et al., 2017, Yang et al., 2018). Regarding clinical types of RAS, one study of Turkish patients with RAS found lower level of QoL was reported by patients with major RAS when compared to those with minor RAS as indicated by the OHIP-14 results (Hapa et al., 2011). The present descriptive analysis added to current literature that herpetiform RAS appeared to have a greater impact on patient's QoL including physical discomfort particularly when eating, socio-emotional aspect

and treatment-related concerns as well as having highest level of depressive symptoms and emotional distress than other RAS phenotypes based on further subgroup analysis.

Based upon bivariate analysis, some socio-demographic, clinical and psychological factors were found to be potential determinants of worse QoL in patients with RAS in the present cohort. Among RAS patients, It was observed that those who do not drink alcohol reported poorer overall QoL as measured by the COMDQ-15 than mild-to-moderate alcohol drinkers. The results were comparable to previous analysis of psychological comorbidities in patients with RAS from chapter 4. Again, this finding may reflect self-medication hypothesis, in which patients use substances such as alcohol or certain drug groups to alleviate psychological symptoms, and in this case short term use of alcohol could mask the underlying psychological problems of alcohol users. In addition, the association of drinking behaviour and level of QoL including psychological impact might be partly explained by social confounding factors related to alcohol drinking as mid-range alcohol drinkers might be more culturally and socially adjusted or better at regulating self-administered medication, and therefore might have less tendency to reported psychological symptoms than non-alcoholic users. The increase in the level of psychological factors including anxiety symptoms, depressive symptoms, emotional distress and perceived stress based on patient-reported instruments were found to be associated with worse overall QoL in individuals with RAS. These findings were in line with previous research (Yang et al., 2018, Al-Omiri et al., 2015) and previous analysis on a cohort of OLP patients, suggesting the significant contribution of patient's psychological status on the level of overall QoL in patients with RAS. Screening and proper management of psychological symptoms in this patient population is therefore imperative.

With respect to clinical factors, the present results demonstrated that the following ulcer-related characteristics were potential predictors of worse QoL as measured by the COMDQ-15 in patients with RAS: higher number of ulcers, longer duration of ulcers, shorter length of

ulcer-free periods, higher number of involved oral sites and greater level of oral pain. These findings were consistent with previous studies, which found significant associations between total scores of the OHIP-14 and RAS-related variables including pain, number of ulcers per attack, ulcer size and duration of ulcers (Hapa et al., 2011, Al-Omiri et al., 2015). This highlights the importance of good disease activity control in the management of RAS as this could help improve overall QoL of the affected patients.

The present results demonstrated that level of QoL as indicated by COMDQ-15 scores appeared to have greater strength of association with clinical signs and symptoms of RAS as well as psychological comorbidities including anxiety, depression and stress than the use of general measure such as the OHIP-14. These findings are consistent with the results from the OLP cohort, and may be partly explained by the fact that the COMDQ is a specific QoL measure concerning input from patients with chronic oral mucosal conditions during its development process. The use of COMDQ-15 could therefore be an appropriate measurement instrument providing an insight into perception of QoL as reflected by patients with RAS.

6.6 CONCLUSION

The quality of life of patients with immunologically mediated oral mucosal diseases is impaired and depends on several demographic, psychological and clinical determinants. As levels of QoL in this patient group are associated with other factors beyond oral pain and disease activity of affected patients, the knowledge and understanding of associated QoL determinants in patients with chronic oral mucosal diseases are imperative. Effective therapeutic management, coupled with appropriate assessment of psychological state and QoL could improve the quality of care received by patients with immunologically mediated oral mucosal diseases.

CHAPTER 7 RESPONSIVENESS AND MEANINGFUL CHANGE THRESHOLDS OF COMMON MEASURES OF PAIN AND HEALTH RELATED QUALITY OF LIFE IN IMMUNOLOGICALLY MEDIATED ORAL MUCOSAL DISEASES

7.1 CHALLENGES IN THE INTERPRETATION OF PATIENT REPORTED OUTCOMES

Although well-developed and validated PROMs have been increasingly applied in both clinical and research settings, interpretation of the scores generated by these PROMs can still be challenging (King, 2011). This challenge is particularly evident with respect to understanding clinical meaning of a change or difference in PROM scores from the perspective of the patient (Meadows, 2011). Clinicians are usually aware of relevant change of physiological or clinical outcomes such as blood pressure, ulcer size or serum creatinine levels due to an understanding of the well-established standard cut-point of these outcomes, as well as familiarity of these outcomes through clinical experience (Coon and Cappelleri, 2016). In contrast, the scores generated by PROMs to quantify latent (unobservable) constructs such as pain intensity and quality of life may be unfamiliar to both clinicians and researchers (Coon and Cappelleri, 2016). In addition, there may be insufficient available published data to facilitate the interpretation of what, for instance, the magnitude of a 5 point change means on a 0-56 scale of the OHIP-14, or whether a 1-point change in the 0-10 pain-NRS scale is clinically relevant to patients.

Data derived from PROMs is difficult to interpret due to a number of factors. Firstly, outcomes or scores as measured by a PROM are subjectively reliant on patients. One concept may have different meaning to an individual patient. Secondly, perception of each patient towards a concept of interest may shift over time based upon the context and perspective changes (response shift). For example, Thirdly, some patient-reported concepts are multi-domain containing different constructs and numeric values for these constructs are arbitrary to some extent. Fourthly, the scores on response options such as ordinal or Likert-type scale do not

have interval property, which means that the difference between ‘not at all’ (1) and ‘a little’ (2) may not equal to the difference between ‘a little’ (2) and ‘quite a bit’ (3) when using a set of option: 1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much as an example. Fifthly, items are usually combined in a multi-item scale and the scores from each patient are combined to yield a group result. Each step outlined represents a higher degree of abstraction. Finally, only a small number of clinicians have a prerequisite understanding of the properties of PROMs and can be able to interpret scores arising from these scales. In addition, there are surprisingly not many interpretation manuals of PROMs available (King, 2011).

To overcome issues related to interpretability of PROMs, a number of methods have been developed to facilitate interpretation of PROM scores. The present chapter outlines the concept of meaningful change thresholds, which deal with the clinical meanings of PROM change scores, while the discussion on the clinical relevance of PROM individual scores are present on chapter 8.

7.2 MEANINGFUL CHANGE THRESHOLDS

The concept of meaningful change thresholds was first described by Jaeschke et al in 1989. Since then the definition and terminology has varied considerably in the literature. However, these terms can be broadly categorized into two main concepts including minimal important change (MIC) and minimal important difference (MID). According to the COSMIN panel in 2010, MIC is defined as “the smallest change in score in the construct to be measured which patients perceive as important” while MID is “the smallest differences in the construct to be measured between patients that is considered important” (Mokkink et al., 2010).

7.2.1 Minimal important change

Minimal important change (MIC) reflects the smallest magnitude of within-patient change that is clinically important. The use of MIC could aid in shared decision-making in the routine

clinical practice (Vet et al., 2015). It can inform patients and clinicians about the magnitude of change in PROM scores that is justifiable for a change in the management, whether to introduce a new treatment, or to continue or withdraw current medication, or to increase or decrease the dosage. In addition, MIC helps inform judgements about a success of current treatment or intervention given to each patient. It can be implied that patients who achieve a PROM score of equal to or greater than MIC after a period of treatment might be beneficial from the given intervention. In other words, if an intervention produces a change or difference in PROM score that does not reach a level of MIC, it might not be perceived as beneficial by patients.

MIC also facilitates communication between clinicians and patients. During the discussion about possible treatment options, providing information about MIC will help patients understand the magnitude of benefits expected to gain after a treatment. Clinicians can explain how much a change in the scores of PROM perceived by patients has clinical implication such as eating spicy food more comfortably, or interacting with people with less embarrassment.

7.2.2 Minimal important difference

Minimal important difference (MID) is the smallest difference in mean scores between groups that could be considered clinically meaningful and is suitable for use in clinical research assessing treatment efficacy (Vet et al., 2015). Knowledge of MID allows investigators to interpret PROM data from patient's perspective and not merely statistical significance. Difference or change in scores of a certain magnitude may be statistical significance but does not imply clinical meaningful of such a difference or change. Results with statistical significance solely demonstrate that there is sufficient evidence to claim that the observed differences or changes are probably real events as opposed to chance events; and this tells us little regarding the magnitude of the difference as well as clinical importance of this

difference. Therefore, MID should be taken into consideration when assessing the effect of intervention in clinical trials using PROMs.

Knowledge of MID can be applied in responder analysis. The presentation of clinical trial results in terms of proportion of patients who have improved, remained unchanged or worsen has been adopted by several authors as a way of demonstrating results that is more clinically beneficial to clinicians (Osoba et al., 2005, Guyatt and Schunemann, 2007, Fayers and Machin, 2016b).

In addition, knowledge of MID can assist in calculating statistical power as well as determining the required sample size for clinical trials (Brozek et al., 2006, Revicki et al., 2008). MID can be applied as a complementary approach for enhancing interpretability of pooled data derived from PROMs in meta-analyses, instead of reporting only a standardized mean difference (Johnston et al., 2010). This would particularly facilitate interpretation of pooled data that comes from different PROMs measuring the same concept of interest.

7.3 KNOWLEDGE GAP

Various measures of pain and OH-QoL have been developed and/or used in clinical practice and research of immunologically mediated oral mucosal diseases (results from chapter 3). Unfortunately, only few studies have evaluated the responsiveness of these instruments (McGrath et al., 2003, Ni Riordain and McCreary, 2012), and surprisingly no studies have examined the clinical meaningfulness or interpretability of the PROM change scores for use in these patient groups.

7.4 AIMS

The aims of the present chapter were:

1. To evaluate responsiveness of common measures of pain and OH-QoL for use in common immunologically mediated oral mucosal diseases (OLP and RAS).

2. To establish cut-off scores corresponding to meaningful change thresholds including MIC and MID values of these instruments for use in patients with common immunologically mediated oral mucosal diseases (OLP and RAS).

7.5 METHODS

7.5.1 Study design

This was a prospective longitudinal validation study using baseline and 4-month follow-up data from the Determination of Minimal Important Difference and Patient Acceptable Symptom State of Patient Reported Outcome Measures in Immunologically mediated Oral Mucosal Diseases (MEAN-IT) study, which was approved by the London – Queen Square Research Ethics Committee (REC reference 17/LO/1825; approval date 3 November 2017).

7.5.2 Participants

Data were used from a total of 240 patients with immunologically mediated oral mucosal diseases (157 patients with OLP, 83 patients with RAS) who attended regular review appointments at the Oral Medicine clinic, UCLH Eastman Dental Hospital, London, United Kingdom from January 2018 to August 2019. They were prospectively followed from the initial baseline and a 4-month follow-up visit. The recruitment of the present study was based upon convenience sampling. All potentially eligible participants in all Consultant lead Oral Medicine clinics were invited to participate (conducted by PW). The inclusion and exclusion criteria of study participants are listed in Table 6.1. After obtaining verbal and written informed consent, all of the participants were prospectively followed from the initial baseline visit to the 4-month follow-up visit.

7.5.3 Procedures

During both study visits, a comprehensive oral examination was carried out on all study participants to assess the clinical types, oral sites of involvement and disease activity. Disease

activity of OLP was evaluated by using the ODSS (Escudier et al., 2007). Participants with OLP were categorised into three groups: (i) keratotic (presence of white reticular, papular or plaque-like lesions without apparent erythema/ulceration), (ii) erythematous (presence of atrophic/ erythematous lesions with/without reticular/popular/ plaque-like features AND no evidence of erosion/ulceration), and (iii) erosive/ulcerative (presence of erosive or ulcerative lesions with/without the presence of keratotic and/or erythematous changes of OLP) (Bruch and Treister, 2018). For participants with RAS, disease activity was evaluated by taking history of each participant, and specific information about oral ulcers over the past three months was recorded. The activity score was calculated based on the standardized USS (Tappuni et al., 2013). Types of RAS were recorded based upon clinical appearance and behavior of RAS into 3 groups: minor RAS (shallow small ulcers (<1cm), usually last 7-10 days), major RAS (deeper and larger ulcers (≥1 cm), lasting several weeks, which may heal with scar formation) and herpetiform RAS (few millimeter ulcers, usually > 10 ulcers, last 7-10 days) (Scully and Carrozzo, 2008).

Participants were then asked to complete a set of questionnaires including a demographic form (baseline visit only) and a set of patient-reported questionnaires. At the follow-up visit, participants were also asked to respond to an additional question about perception of change in their disease status on a 7-point patient global rating of change scale. The information regarding the age at symptom onset, disease duration (time since symptom onset), past medical history, social history, extra-oral manifestation and treatment of OLP/RAS was obtained from the review of electronic patient record.

7.5.4 Outcomes

The primary outcomes for the objectives of the present study were as follows: (i) evidence supporting responsiveness to change of the common measures of the VAS, NRS, OHIP-14, COMDQ-26 and COMDQ-15; (ii) cut-off values corresponding to magnitudes of meaningful

change thresholds including the MIC and MID on the scores of the studied measures of pain and OH-QoL.

7.5.5 Outcome measures

Clinical disease activity scoring

The Oral Disease Severity Score (ODSS) and *the Ulcer Severity Score (USS)* were used for the assessment of disease activity of OLP and RAS, respectively.

Patient-reported outcome measures

Measures of pain: *The Visual analog scale (VAS)* and *The Numerical Rating Scale (NRS)* for pain were used.

Measures of OH-QoL: *The 14-item Oral Health Impact Profile (OHIP-14), the 26-item* and *15-item Chronic Oral Mucosal Disease Questionnaire (COMDQ-26; COMDQ-15)* were used.

Anchor question

To assess the responsiveness and meaningful change thresholds of PROMs, criteria are required to confirm whether patients have experienced a change in their disease status - including being worse, improved or stable over time. In this study, the following *patient's global rating of change* (GRC) was used as external anchor/reference of change: "Thinking about all the ways your symptoms related to your oral mucosal conditions are affecting you, compared to the beginning of the study (4 months ago) how do you evaluate the severity of your oral mucosal conditions now?". The response options are on a 7-point Likert-type scale that includes 'very much better' (3), 'moderately better' (2), 'slightly better' (1), 'about the same' (0), 'slightly worse' (-1), 'moderately worse' (-2), 'very much worse' (-3). Participants answering 'moderately better' and 'very much better' were classified as having clinically important

improvement, while those responding to the remaining options were considered “not importantly improved”.

7.5.5 Statistical analysis

Statistical analyses were performed using STATA version 15.1 (StataCorp, College Station, TX, U.S.A.). Descriptive analyses of demographics and disease-related characteristics were summarized using frequencies and accompanying percentages for categorical variables, while median and interquartile range (IQR) were used as summary statistics for continuous variables. Score distribution of the studied PROMs including baseline, follow-up and change scores were presented using mean and standard deviation (SD) based upon the GRC. According to the small sample size of those reporting “very much worse”, “moderately worse” and “slightly worse”, the data were combined and presented as a “worsened” group (n=19). In addition, due to a small sample size in the total “worsened” group, assessment of the responsiveness and meaningful change thresholds were carried out only for the direction of improvement.

Responsiveness

Responsiveness is the ability of PROMs to detect change over time in the construct being measured. Two different approaches were performed to assess responsiveness of the studied PROMs including construct and criterion approaches. For the construct approach, Spearman’s correlation coefficient (rho) was used to test hypotheses of change values of the studied PROM scores and the GRC score. The following hypotheses were formulated:

1. Moderate and positive correlations between GRC scores and change scores of the pain-VAS, pain-NRS, total OHIP-14, total and subscales of the COMDQ-15 and COMDQ-26 (except for the patient support subscale of the COMDQ-15 and COMDQ-26).

2. Low and positive correlations between GRC scores and change scores of the patient support subscale of the COMDQ-15 and COMDQ-26.

Correlation coefficients of 0.3 or less, between 0.3 and 0.6, and 0.6 or greater were defined as low, moderate and high, respectively.

For the criterion approach, responsiveness of the PROMs was examined by checking the area under the curve (AUC) of the Receiver Operating Characteristic (ROC) curve analyses. The AUC represents the ability of PROM scores to correctly identify patients as improved or non-improved based upon the external anchor (GRC). The AUC values of 0.7 or above is considered acceptable (Terwee et al., 2007).

Meaningful improvement thresholds

Two methods were applied for the estimation of meaningful improvement thresholds including distribution-based and anchor-based methods. The distribution-based methods are based solely upon the distributional characteristics of the scores in the sample without the use of external reference. In this study, half a standard deviation at baseline (0.5 $SD_{baseline}$) and standard error of measurement (SEM) were calculated. The SEM was estimated by the following formula: $SEM=SD_{difference}/\sqrt{2}$, when $SD_{difference}$ is the standard deviation of the difference in scores at baseline and follow-up visit in the group reporting “about the same”.

To determine meaningful within-patient improvement thresholds, anchor-based MIC values were estimated as the ROC cut-off point of change scores of the PROMs with the least amount of misclassified patients between those who were “importantly improved” and “not importantly improved”. In other words, the MIC values were the optimal cut-off points, which maximise true-positive rate (TP; sensitivity) and true-negative rate (TN; specificity) on the ROC curve. To determine meaningful between-group difference thresholds, anchor-based MID values

were estimated by calculating the difference in mean change scores of the 'moderately improved' and 'about the same' group.

Multiple meaningful change threshold values from distribution-based and anchor-based methods were then triangulated to create the recommended threshold of MIC and MID for each studied PROM score. The triangulation process was based upon average values amongst all estimates with consideration of the limitation of the scale response. For instance, the recommended threshold values were narrowed down to integer value only.

7.6 RESULTS

The results of this chapter are divided into two sections based upon the disease of interest.

7.6.1 Results of the OLP cohort

7.6.1.1 Descriptive characteristics of the OLP cohort

Descriptive summary of baseline demographics and OLP-related characteristics of 157 study participants are present in Table 7.1. Mean and standard deviation of baseline, follow-up and change scores of all studied PROMs based upon the GRC are shown in Table 7.2. Of the 157 patients with OLP, 19 (12.1%) reported deterioration [one (0.01%) very much worse, five (0.03%) moderately worse and 13 (0.08%) slightly worse], 52 (33.1%) reported about the same and 86 (54.8%) reported improvement on the GRC.

Table 7.1 Demographic and clinical characteristics of the OLP cohort

Patient characteristics (n=157)	
Demographic variables	
Age (y; median, IQR)	65.5 (55.2, 70.4)
Female (n, %)	122 (77.7)
Ethnicity (n, %)	
White	105 (66.9)
Mixed	5 (3.2)
Asian	40 (25.5)
Black	7 (4.5)
Smoking (n, %)	
Non-smoker	119 (75.8)
Ex-smoker	30 (19.1)
Current smoker	8 (5.1)
Alcohol consumption (n, %)	
No	53 (33.8)
≤ 14 Units/week	89 (56.7)
> 14 Units/week	15 (9.6)
Comorbidity (n, %)	
No	20 (12.7)
1 comorbidity	37 (23.6)
≥ 2 comobidities	100 (63.7)
OLP-related characteristics	
Disease duration (y; median, IQR)	5.5 (2.4, 10.4)
Clinical types	
Keratotic	21 (13.4)
Erythematous	110 (70.1)
Ulcerative	26 (16.6)
Baseline ODSS score (median, IQR)	20 (13, 26)
Baseline ODSS-site	7 (4, 9)
Baseline ODSS-activity	8 (4, 13)
Presence of extraoral LP (n,%)	
Yes	40 (25.5)
Yes/genital	23 (14.7)
Yes/skin	23 (14.7)
Treatment	
Tanes	12 (7.6)
TCS	101 (64.3)
Tanes + TCS	36 (22.9)
Systemic treatment	8 (5.1)

Abbreviation: LP = lichen planus; Tanes = topical anaesthetic agents; TCS = topical corticosteroids

Table 7.2 Descriptive statistics of baseline, follow-up, and change scores of studied PROMs by response categories of the global rating of change scale

Instruments	Baseline scores (mean ± sd)	Follow-up scores (mean ± sd)	Change scores (mean ± sd)
VAS (0-100)			
worse[a] (n=19)	35.1 ± 23.6	57.0 ± 20.6	-21.9 ± 25.6
no change (n=52)	31.8 ± 23.6	32.8 ± 28.0	-0.9 ± 16.8
slightly better (n=37)	44.5 ± 24.8	34.7 ± 22.1	9.8 ± 17.8
moderately better (n=24)	48.2 ± 28.7	19.4 ± 23.3	28.8 ± 24.9
very much better (n=25)	19.7 ± 21.3	8.7 ± 9.0	11.1 ± 20.9
NRS (0-10)			
worse[a] (n=19)	3.4 ± 2.1	5.3 ± 2.4	-1.9 ± 2.2
no change (n=52)	3.5 ± 2.3	3.5 ± 3.0	-0.1 ± 1.7
slightly better (n=37)	4.5 ± 2.3	3.8 ± 2.1	0.7 ± 1.5
moderately better (n=24)	4.9 ± 2.8	2.2 ± 2.1	2.7 ± 1.8
very much better (n=25)	2.3 ± 2.1	1.2 ± 1.2	1.1 ± 2.1
OHIP-14 total (0-56)			
worse[a] (n=19)	23.0 ± 10.7	25.1 ± 11.8	-2.1 ± 8.1
no change (n=52)	19.2 ± 13.0	17.8 ± 13.9	1.3 ± 5.9
slightly better (n=37)	20.6 ± 12.8	18.1 ± 11.4	2.5 ± 6.7
moderately better (n=24)	22.8 ± 14.2	18.2 ± 12.7	4.5 ± 5.1
very much better (n=25)	13.6 ± 11.5	8.0 ± 8.0	5.6 ± 7.2
COMDQ-15 total (0-60)			
worse[a] (n=19)	26.8 ± 10.6	31.7 ± 9.8	-4.8 ± 6.6
no change (n=52)	23.4 ± 11.5	23.3 ± 12.8	0.1 ± 5.7
slightly better (n=37)	26.1 ± 11.1	25.0 ± 11.6	1.1 ± 5.9
moderately better (n=24)	31.8 ± 12.6	25.1 ± 11.0	6.6 ± 7.4
very much better (n=25)	20.3 ± 11.6	13.3 ± 7.2	7.0 ± 9.0
COMDQ-15-PD (0-20)			
worse[a] (n=19)	11.4 ± 4.0	13.1 ± 3.7	-1.6 ± 3.1
no change (n=52)	10.0 ± 5.0	9.6 ± 5.3	0.4 ± 2.3
slightly better (n=37)	10.6 ± 3.8	10.1 ± 4.4	0.6 ± 2.9
moderately better (n=24)	13.1 ± 4.7	10.2 ± 4.7	3.0 ± 3.5
very much better (n=25)	8.6 ± 5.2	5.6 ± 3.2	3.0 ± 4.0
COMDQ-15-MT (0-12)			
worse[a] (n=19)	3.8 ± 3.3	5.3 ± 3.4	-1.5 ± 3.0
no change (n=52)	3.6 ± 3.0	4.0 ± 3.0	-0.4 ± 1.8
slightly better (n=37)	4.8 ± 3.1	4.6 ± 2.8	0.2 ± 1.6
moderately better (n=24)	6.2 ± 3.3	4.9 ± 2.8	1.3 ± 2.0
very much better (n=25)	3.6 ± 3.2	3.0 ± 2.4	0.6 ± 2.6
COMDQ-15-SE (0-20)			
worse[a] (n=19)	8.5 ± 4.6	9.9 ± 4.7	-1.4 ± 2.8
no change (n=52)	6.9 ± 5.1	7.1 ± 5.3	-0.2 ± 3.4
slightly better (n=37)	8.2 ± 5.3	7.4 ± 5.1	0.8 ± 2.9
moderately better (n=24)	9.2 ± 5.8	6.7 ± 4.4	2.5 ± 3.9
very much better (n=25)	6.1 ± 4.4	3.2 ± 3.5	2.9 ± 3.6

Note: [a] worse group (n =19) included 13 slightly worse, 5 moderately worse and 1 very much worse

Table 7.2 Descriptive statistics of baseline, follow-up, and change scores of studied PROMs by response categories of the global rating of change scale (cont.)

Instruments	Baseline scores (mean ± sd)	Follow-up scores (mean ± sd)	Change scores (mean ± sd)
COMDQ-15-PS (0-8)			
worse[a] (n=19)	3.1 ± 2.2	3.4 ± 1.8	-0.3 ± 1.6
no change (n=52)	2.9 ± 2.3	2.7 ± 2.4	0.2 ± 1.7
slightly better (n=37)	2.6 ± 2.0	3.0 ± 1.8	-0.4 ± 1.7
moderately better (n=24)	3.3 ± 2.8	3.4 ± 2.4	-0.1 ± 2.0
very much better (n=25)	2.1 ± 1.8	1.5 ± 1.8	0.6 ± 1.6
COMDQ-26 total (0-104)			
worse[a] (n=19)	46.1 ± 17.9	53.6 ± 16.9	-7.5 ± 10.0
no change (n=52)	39.7 ± 18.3	39.4 ± 20.9	0.3 ± 9.2
slightly better (n=37)	44.5 ± 17.4	41.9 ± 17.8	2.6 ± 8.7
moderately better (n=24)	52.4 ± 19.4	41.8 ± 16.9	10.6 ± 10.7
very much better (n=25)	35.0 ± 18.2	24.1 ± 12.8	10.9 ± 14.2
COMDQ-26-PF (0-36)			
worse[a] (n=19)	18.2 ± 7.1	20.5 ± 6.9	-2.3 ± 4.1
no change (n=52)	15.5 ± 8.3	14.7 ± 8.7	0.9 ± 4.0
slightly better (n=37)	16.6 ± 6.0	15.5 ± 6.8	1.1 ± 4.0
moderately better (n=24)	20.0 ± 7.8	15.3 ± 7.6	4.7 ± 6.0
very much better (n=25)	13.3 ± 8.0	8.9 ± 6.0	4.4 ± 6.3
COMDQ-26-MT (0-24)			
worse[a] (n=19)	9.7 ± 4.6	12.6 ± 4.5	-2.8 ± 3.6
no change (n=52)	9.1 ± 4.7	9.7 ± 5.1	-0.6 ± 3.2
slightly better (n=37)	10.6 ± 4.9	10.4 ± 4.7	0.3 ± 2.6
moderately better (n=24)	13.3 ± 5.0	10.8 ± 4.3	2.5 ± 3.2
very much better (n=25)	8.5 ± 5.2	7.2 ± 4.2	1.3 ± 4.3
COMDQ-26-SE (0-28)			
worse[a] (n=19)	12.7 ± 6.7	14.6 ± 6.6	-1.9 ± 4.2
no change (n=52)	10.3 ± 7.1	10.6 ± 7.2	-0.2 ± 4.5
slightly better (n=37)	12.3 ± 7.2	11.2 ± 6.9	1.1 ± 4.1
moderately better (n=24)	13.7 ± 7.9	10.1 ± 6.1	3.6 ± 4.6
very much better (n=25)	9.3 ± 6.2	5.2 ± 4.9	4.1 ± 5.1
COMDQ-26-PS (0-16)			
worse[a] (n=19)	5.4 ± 2.8	5.9 ± 3.2	-0.5 ± 1.8
no change (n=52)	4.7 ± 3.2	4.7 ± 3.4	0.1 ± 2.3
slightly better (n=37)	4.9 ± 3.0	5.3 ± 2.8	-0.3 ± 2.4
moderately better (n=24)	5.5 ± 3.7	5.6 ± 2.9	0.0 ± 2.5
very much better (n=25)	3.9 ± 2.0	2.8 ± 2.4	1.1 ± 1.9

Note: [a]worse group (n =19) included 13 slightly worse, 5 moderately worse and 1 very much worse

7.6.1.2 Responsiveness

For construct approach, predefined hypotheses regarding expected magnitude and direction of correlation between PROM change scores and the GRC, values of Spearman rho coefficients and ascertainment of hypotheses are present in Table 7.3. The VAS and NRS for pain were similarly moderately responsive to change in OLP disease status over time. The total OHIP-14 was relatively less sensitive to detect patient's perception of change in OLP status over time compared to the total COMDQ-15 and COMDQ-26. With respect to the COMDQ subscale scores, values of Spearman rho coefficients confirmed the hypotheses in the majority of the subscales except for the MT subscale of the COMDQ-15, which was marginally insufficient to meet the requirement of the hypothesis.

For the criterion approach, the AUC values of change scores of the studied PROMs in the OLP cohort are present in Table 7.4. The results showed that only the AUC values of total COMDQ-15 and COMDQ-26, the PF subscale of the COMDQ-26 and the PD subscale of the COMDQ-15 achieved acceptable threshold of responsiveness (0.70).

7.6.1.3 Meaningful improvement thresholds

The MIC and MID estimation of all studied PROMs based on distribution-based and anchor-based methods are present in Table 7.4. After the triangulation process, the recommended MIC and MID values for improvement in total scores for each studied PROMs were as follows: the VAS (MIC = 16 mm, MID =18 mm), the NRS (MIC = MID = 2 points), the OHIP-14 (MIC = MID = 5 points), the COMDQ-15 (MIC = 5 points, MID = 6 points), the COMDQ-26 (MIC = MID = 9 points).

Table 7.3 Spearman correlation coefficients between the global rating of change and the change scores of studied PROMs of the OLP cohort

Instrument change scores	Hypothesis	spearman correlation coefficient	P-value	Supported hypothesis
VAS (0-100)	moderate positive correlation ($0.3 < r_s < 0.6$)	0.46	<0.001	yes
NRS (0-10)	moderate positive correlation ($0.3 < r_s < 0.6$)	0.46	<0.001	yes
OHIP-14 total	moderate positive correlation ($0.3 < r_s < 0.6$)	0.32	<0.001	yes
COMDQ-15 total	moderate positive correlation ($0.3 < r_s < 0.6$)	0.47	<0.001	yes
COMDQ-15-PD	moderate positive correlation ($0.3 < r_s < 0.6$)	0.4	<0.001	yes
COMDQ-15-MT	moderate positive correlation ($0.3 < r_s < 0.6$)	0.29	<0.001	no
COMDQ-15-SE	moderate positive correlation ($0.3 < r_s < 0.6$)	0.42	<0.001	yes
COMDQ-15-PS	low positive correlation ($r_s \leq 0.3$)	0.1	0.22	yes
COMDQ-26 total	moderate positive correlation ($0.3 < r_s < 0.6$)	0.49	<0.001	yes
COMDQ-26-PF	moderate positive correlation ($0.3 < r_s < 0.6$)	0.4	<0.001	yes
COMDQ-26-MT	moderate positive correlation ($0.3 < r_s < 0.6$)	0.36	<0.001	yes
COMDQ-26-SE	moderate positive correlation ($0.3 < r_s < 0.6$)	0.45	<0.001	yes
COMDQ-26-PS	low positive correlation ($r_s \leq 0.3$)	0.18	0.02	yes

Note: r_s = Spearman correlation coefficient

Table 7.4 Responsiveness parameter (AUC), MIC and MID estimates using different distribution-based and anchor-based methods, and recommended thresholds after triangulation process of the OLP cohort

Instruments	Distribution-based estimates		Anchor-based estimates						MIC Triangulation	MID Triangulation
	Half SD	SEM	Meaningful within-patient changes					Meaningful between-group differences		
			ROC analysis				mean change method	mean difference method		
			MIC	AUC	TP (%)	TN (%)				
VAS (0-100mm)	12.9	11.9	11	0.68	59	76	29	30	16	18
NRS (0-10)	1.3	1.2	2	0.69	53	84	2.7	2.7	2	2
OHIP-14 total	6.4	4.1	4	0.63	55	71	4.5	3.2	5	5
COMDQ-15 total	6	4.1	4	0.71	67	74	6.7	6.6	5	6
COMDQ-15-PD	2.3	1.6	2	0.71	69	73	3	2.5	2	2
COMDQ-15-MT	1.6	1.3	1	0.63	53	73	1.3	1.7	1	2
COMDQ-15-SE	2.6	2.4	1	0.68	73	62	2.5	2.7	2	3
COMDQ-15-PS	1.1	1.2	1	0.54	37	71	0.1	0.1	1	1
COMDQ-26 total	9.4	6.5	8	0.72	61	83	10.6	10.3	9	9
COMDQ-26-PF	3.9	2.8	3	0.71	69	72	4.7	3.8	4	4
COMDQ-26-MT	2.5	2.3	1	0.64	67	61	2.5	2.9	2	3
COMDQ-26-SE	3.6	3.2	2	0.69	65	72	3.6	3.8	3	4
COMDQ-26-PS	1.6	1.6	1	0.6	53	67	0.1	0.1	1	1

Note: Half SD = Half a standard deviation; SEM = standard error of measurement; ROC curve = receiver operating characteristic curve; MIC = minimal important change; AUC = area under the curve; TP = true positive rate; TN = true negative rate; MID = minimal important difference

7.6.2 Results of the RAS cohort

7.6.1.2 Descriptive characteristics of the RAS cohort

Descriptive summary of baseline characteristics of 83 participants with RAS are shown in Table 7.5. Mean and standard deviation of baseline, follow-up and change scores of all studied PROMs categorized by the GRC results are present in Table 7.6. Of all patients in this RAS cohort, 8 (9.64%) reported deterioration [three (3.61%) very much worse, one (1.20%) moderately worse and four (4.82%) slightly worse], 29 (34.94%) reported about the same and 46 (55.42%) reported improvement on the GRC.

7.6.2.2 Responsiveness

Using construct approach, predefined hypotheses regarding expected magnitude and direction of correlation between PROM change scores and the GRC, values of Spearman rho coefficients and ascertainment of hypotheses are present in Table 7.7. The VAS and NRS for pain were similarly moderately responsive to change in RAS disease status over time. Total scores of studied OH-QoL PROMs were all responsive to patient's perception of change in RAS status, and it was shown that the total OHIP-14 was relatively less sensitive in comparison to total COMDQ-15 and COMDQ-26. However, when testing hypotheses the majority of subscales of both COMDQ versions failed to meet the requirement of the hypothesis, and the results therefore did not support the use of COMDQ subscale scores in detecting changes in RAS status.

For the criterion approach, the AUC values of change scores of the studied PROMs in the RAS cohort are shown in Table 7.8. The results demonstrated that only the AUC values of total COMDQ-26 and the physical pain subscale of the OHIP-14 reached the acceptable threshold of responsiveness (0.70).

Table 7.5 Demographic and clinical characteristics of the RAS cohort

Patient characteristics (n=83)	
Demographic variables	
Age (y; mean ± sd)	45.3 ± 14.7
Age (y; median, IQR)	45.8 (34.7, 54.6)
Female (n, %)	49 (59.0)
Ethnicity (n, %)	
White	69 (83.1)
Mixed	2 (2.4)
Asian	10 (12.1)
Black	2 (2.4)
Smoking (n, %)	
Non-smoker	71 (85.5)
Ex-smoker	8 (9.6)
Current smoker	4 (4.8)
Alcohol consumption (n, %)	
No	24 (28.9)
≤ 14 Units/week	58 (69.9)
> 14 Units/week	1 (1.2)
Comorbidity (n, %)	
No	38 (45.8)
1 comorbidity	24 (28.9)
≥ 2 comobidities	21 (25.6)
RAS-related characteristics	
Disease duration (y; median, IQR)	15.5 (5.2, 26.8)
Clinical types	
Minor	70 (84.3)
Major	8 (9.6)
Herpetiform	5 (6.0)
Baseline USS score (median, IQR)	30 (24, 35)
Baseline USS-size	4 (3, 6)
Baseline USS-number	2 (2, 4)
Baseline USS-duration	3 (2, 6)
Baseline USS-ulcer-free period	8 (6, 9)
Baseline USS-site	6 (4, 8)
Baseline USS-pain	6 (4, 7)
Baseline NRS-pain (median, IQR)	3 (1, 6)
Baseline HADS-A (median, IQR)	7 (4, 10)
Baseline HADS-D (median, IQR)	3 (2, 7)
Baseline HADS-T (median, IQR)	10 (6, 17)
Baseline PSS-10 (median, IQR)	17 (9, 23)
Treatment	
Topical treatment	65 (78.3)
Topical and systemic treatment	18 (21.7)

Table 7.6 Descriptive statistics of baseline, follow-up, and change scores of studied PROMs by response categories of the global rating of change scale

Instruments	Baseline scores (mean ± sd)	Follow-up scores (mean ± sd)	Change scores (mean ± sd)
VAS (0-100)			
worse[a] (n=8)	52.1 ± 27.4	59.5 ± 27.8	-7.4 ± 9.2
no change (n=29)	30.6 ± 32.2	40.7 ± 29.4	-10.1 ± 28.7
slightly better (n=16)	24.5 ± 23.3	22.6 ± 22.1	1.9 ± 21.4
moderately better (n=21)	33.1 ± 28.4	26.1 ± 23.6	7.0 ± 25.6
very much better (n=9)	35.5 ± 29.7	18.2 ± 32.0	17.3 ± 37.4
NRS (0-10)			
worse[a] (n=8)	5.1 ± 2.4	6.1 ± 2.5	-1.0 ± 1.6
no change (n=29)	3.4 ± 3.1	4.4 ± 2.8	-1.0 ± 2.6
slightly better (n=16)	2.3 ± 2.4	2.6 ± 2.2	-0.2 ± 2.3
moderately better (n=21)	3.6 ± 2.8	2.9 ± 2.4	0.7 ± 2.5
very much better (n=9)	3.4 ± 2.9	1.4 ± 1.9	2.0 ± 3.0
OHIP-14 total (0-56)			
worse[a] (n=8)	33.6 ± 11.1	34.5 ± 11.9	-0.9 ± 14.4
no change (n=29)	28.6 ± 13.2	26.3 ± 12.8	2.3 ± 7.4
slightly better (n=16)	23.4 ± 13.2	19.9 ± 13.8	3.6 ± 5.5
moderately better (n=21)	30.6 ± 10.7	24.5 ± 9.8	6.1 ± 8.8
very much better (n=9)	25.2 ± 14.2	17.2 ± 12.8	8.0 ± 4.2
COMDQ-15 total (0-60)			
worse[a] (n=8)	32.9 ± 11.4	36.3 ± 10.1	-3.4 ± 6.2
no change (n=29)	27.8 ± 11.7	26.7 ± 11.4	1.1 ± 5.9
slightly better (n=16)	22.9 ± 10.3	21.5 ± 11.0	1.4 ± 6.5
moderately better (n=21)	30.6 ± 8.8	24.9 ± 7.6	5.8 ± 5.6
very much better (n=9)	27.4 ± 11.0	22.2 ± 14.3	5.2 ± 7.2
COMDQ-15-PD (0-20)			
worse[a] (n=8)	12.6 ± 3.9	14.6 ± 4.2	-2.0 ± 1.3
no change (n=29)	11.2 ± 4.7	10.3 ± 4.8	0.9 ± 3.1
slightly better (n=16)	9.4 ± 4.4	8.8 ± 4.2	0.7 ± 4.6
moderately better (n=21)	11.6 ± 3.7	8.6 ± 2.9	3.0 ± 2.8
very much better (n=9)	11.2 ± 3.7	8.2 ± 5.6	3.0 ± 2.6
COMDQ-15-MT (0-12)			
worse[a] (n=8)	6.3 ± 3.5	6.6 ± 2.6	-0.4 ± 3.0
no change (n=29)	3.9 ± 2.7	4.1 ± 2.7	-0.2 ± 2.4
slightly better (n=16)	3.8 ± 2.5	3.6 ± 2.5	0.2 ± 1.4
moderately better (n=21)	6.0 ± 2.5	4.8 ± 2.3	1.2 ± 2.1
very much better (n=9)	4.7 ± 2.9	3.8 ± 3.2	0.9 ± 3.3
COMDQ-15-SE (0-20)			
worse[a] (n=8)	11.3 ± 5.3	11.4 ± 5.2	-0.1 ± 2.0
no change (n=29)	9.3 ± 5.5	8.6 ± 5.2	0.8 ± 3.5
slightly better (n=16)	6.9 ± 5.9	6.4 ± 5.4	0.5 ± 3.5
moderately better (n=21)	10.0 ± 4.6	8.4 ± 4.3	1.6 ± 2.4
very much better (n=9)	7.7 ± 4.2	5.9 ± 6.2	1.8 ± 3.3

Note: [a]worse group (n =8) included 4 slightlyworse, 1 moderatelyworse and 3 very much worse

Table 7.6 Descriptive statistics of baseline, follow-up, and change scores of studied PROMs by response categories of the global rating of change scale (cont.)

Instruments	Baseline scores (mean ± sd)	Follow-up scores (mean ± sd)	Change scores (mean ± sd)
COMDQ-15-PS (0-8)			
worse[a] (n=8)	2.8 ± 2.4	3.6 ± 2.1	-0.9 ± 1.9
no change (n=29)	3.4 ± 2.2	3.8 ± 2.3	-0.4 ± 1.2
slightly better (n=16)	2.8 ± 2.0	2.8 ± 2.5	0.1 ± 2.3
moderately better (n=21)	3.0 ± 1.7	3.0 ± 1.7	0.0 ± 1.5
very much better (n=9)	3.9 ± 2.3	4.3 ± 2.9	-0.4 ± 3.2
COMDQ-26 total (0-104)			
worse[a] (n=8)	54.9 ± 18.2	60.0 ± 18.3	-5.1 ± 10.9
no change (n=29)	46.6 ± 19.5	45.3 ± 20.0	1.2 ± 12.0
slightly better (n=16)	38.1 ± 16.0	36.0 ± 18.3	2.1 ± 11.3
moderately better (n=21)	52.0 ± 13.9	41.2 ± 13.3	10.8 ± 8.9
very much better (n=9)	44.9 ± 16.5	35.9 ± 22.5	9.0 ± 11.7
COMDQ-26-PF (0-36)			
worse[a] (n=8)	19.6 ± 8.9	20.8 ± 8.3	-1.1 ± 5.0
no change (n=29)	17.9 ± 7.9	16.2 ± 7.9	1.7 ± 5.2
slightly better (n=16)	13.2 ± 7.9	12.4 ± 7.2	0.8 ± 7.1
moderately better (n=21)	18.0 ± 6.9	13.2 ± 5.2	4.9 ± 4.9
very much better (n=9)	16.3 ± 5.7	13.1 ± 10.4	3.2 ± 6.0
COMDQ-26-MT (0-24)			
worse[a] (n=8)	14.0 ± 4.6	15.6 ± 3.9	-1.6 ± 4.6
no change (n=29)	9.9 ± 4.4	10.4 ± 5.1	-0.5 ± 3.4
slightly better (n=16)	9.9 ± 3.7	9.4 ± 4.5	0.5 ± 2.7
moderately better (n=21)	13.2 ± 3.9	10.5 ± 4.1	2.7 ± 3.1
very much better (n=9)	11.3 ± 4.8	8.1 ± 5.1	3.2 ± 4.3
COMDQ-26-SE (0-28)			
worse[a] (n=8)	15.1 ± 7.8	16.0 ± 7.1	-0.9 ± 3.0
no change (n=29)	13.2 ± 7.7	11.8 ± 7.1	1.3 ± 4.7
slightly better (n=16)	10.1 ± 8.5	9.2 ± 7.7	0.9 ± 5.1
moderately better (n=21)	14.3 ± 6.4	11.7 ± 6.1	2.6 ± 3.3
very much better (n=9)	10.2 ± 4.7	8.1 ± 7.8	2.1 ± 4.5
COMDQ-26-PS (0-16)			
worse[a] (n=8)	6.1 ± 4.6	7.6 ± 3.4	-1.5 ± 3.6
no change (n=29)	6.3 ± 3.6	6.9 ± 4.0	-0.6 ± 1.9
slightly better (n=16)	4.8 ± 2.8	4.9 ± 3.1	-0.1 ± 3.1
moderately better (n=21)	6.5 ± 1.8	5.9 ± 2.3	0.6 ± 1.7
very much better (n=9)	7.0 ± 3.5	6.6 ± 3.9	0.4 ± 5.0

Note: [a] worse group (n =8) included 4 slightly worse, 1 moderately worse and 3 very much worse

Table 7.7 Spearman correlation coefficients between the global rating of change and the change scores of studied PROMs of the RAS cohort

Instrument change scores	Hypothesis	spearman rank correlation coefficient	P-value	Supported hypothesis
VAS (0-100)	moderate positive correlation ($0.3 < r_s < 0.6$)	0.33	0.003	yes
NRS (0-10)	moderate positive correlation ($0.3 < r_s < 0.6$)	0.34	0.002	yes
OHIP-14 total	moderate positive correlation ($0.3 < r_s < 0.6$)	0.38	<0.001	yes
COMDQ-15 total	moderate positive correlation ($0.3 < r_s < 0.6$)	0.4	<0.001	yes
COMDQ-15-PD	moderate positive correlation ($0.3 < r_s < 0.6$)	0.43	<0.001	yes
COMDQ-15-MT	moderate positive correlation ($0.3 < r_s < 0.6$)	0.24	0.03	no
COMDQ-15-SE	moderate positive correlation ($0.3 < r_s < 0.6$)	0.23	0.04	no
COMDQ-15-PS	low positive correlation ($r_s \leq 0.3$)	0.18	0.1	no
COMDQ-26 total	moderate positive correlation ($0.3 < r_s < 0.6$)	0.41	<0.001	yes
COMDQ-26-PF	moderate positive correlation ($0.3 < r_s < 0.6$)	0.28	0.01	no
COMDQ-26-MT	moderate positive correlation ($0.3 < r_s < 0.6$)	0.41	<0.001	yes
COMDQ-26-SE	moderate positive correlation ($0.3 < r_s < 0.6$)	0.24	0.03	no
COMDQ-26-PS	low positive correlation ($r_s \leq 0.3$)	0.37	<0.001	no

Note: r_s = Spearman correlation coefficient

Table 7.8 Responsiveness parameter (AUC), MIC and MID estimates using different distribution-based and anchor-based methods, and recommended thresholds after triangulation process of the RAS cohort

Instruments	Distribution-based estimates		Anchor-based estimates						MIC Triangulation	MID Triangulation
	Half SD	SEM	Meaningful within-patient changes					Meaningful between-group differences		
			ROC analysis				mean change method	mean difference method		
			MIC	AUC	TP (%)	TN (%)				
VAS (0-100mm)	14.6	19.4	6	0.66	53	79	16	17.1	14	17
NRS (0-10)	1.4	1.9	1	0.61	73	49	1.8	1.7	2	2
OHIP-14 total	6.3	5.9	6	0.69	67	72	3.9	3.8	6	5
OHIP-14-FL	1.1	1	1	0.63	70	57	0.6	0.6	1	1
OHIP-14-PhyP	0.9	1.1	2	0.63	47	79	0.4	0.4	1	1
OHIP-14-PsyD	1.2	1.2	1	0.7	63	77	0.8	0.8	1	1
OHIP-14-PhyDis	1.1	1.4	1	0.59	53	64	0.3	0.1	1	1
OHIP-14-PsyDis	1.1	1.1	1	0.64	67	60	0.7	0.6	1	1
OHIP-14-Sdis	1.1	1.3	1	0.58	50	66	0.4	0.4	1	1
OHIP-14-H	1.1	1.1	1	0.59	57	62	0.4	0.3	1	1
COMDQ-15 total	5.4	4.7	3	0.69	77	60	4.4	4.7	4	5
COMDQ-15-PD	2.1	2.5	3	0.64	57	72	2.1	2.1	2	2
COMDQ-15-MT	1.4	1.7	1	0.65	60	70	1.2	1.4	1	2
COMDQ-15-SE	2.6	2.2	1	0.63	67	58	1	0.8	2	2
COMDQ-15-PS	1	1.3	1	0.52	48	65	0.1	0.4	1	1
COMDQ-26 total	8.8	8.4	5	0.7	77	64	8.7	9.6	8	9
COMDQ-26-PF	3.8	4.1	3	0.69	62	75	3	3.2	3	4
COMDQ-26-MT	2.2	2.7	2	0.67	60	74	3	3.2	2	3
COMDQ-26-SE	3.7	3.1	2	0.64	67	60	1.3	1.3	3	3
COMDQ-26-PS	1.6	2	1	0.68	63	72	1	1.2	1	2

Note: Half SD = Half a standard deviation; SEM = standard error of measurement; ROC curve = receiver operating characteristic curve; MIC = minimal important change; AUC = area under the curve; TP = true positive rate; TN = true negative rate; MID = minimal important difference

7.6.2.3 Meaningful improvement thresholds

The estimation of MIC and MID for improvement of all studied PROMs based on distribution-based and anchor-based methods are present in Table 7.8. After the triangulation process, the recommended MIC and MID values for improvement in total scores for each studied PROMs were as follows: the VAS (MIC = 14 mm, MID =17 mm), the NRS (MIC = MID = 2 points), the OHIP-14 (MIC = 6 points, MID = 5 points), the COMDQ-15 (MIC = 4 points, MID = 5 points), the COMDQ-26 (MIC = 8 points, MID = 9 points).

7.7 DISCUSSION

The present study examined two important characteristics – responsiveness and interpretability – of common measures of oral symptoms and OH-QoL to support their usage in clinical practice and OLP research. Regarding responsiveness of studied PROMs assessing pain, the present results demonstrated that responsiveness of the VAS and NRS in measuring change in patient's perception of OLP and RAS status were similar based upon hypothesis testing approach. This is in accordance with one previous study (Chainani-Wu et al., 2008), which found moderate-to-high correlation between the Change in Symptom Scale (CSS) and both measures of oral pain in a group of OLP patients residing in the US (r_{VAS} = 0.492, r_{NRS} = 0. 549). Based upon the criterion approach, it was observed that the changes in both the VAS and NRS scores of both disease cohorts had AUC values below the acceptable criteria for responsiveness (AUC of at least 0.70) (Terwee et al., 2007), and this does not reflect positive evidence of responsiveness of both pain scales in OLP and RAS. However, this finding may be explained by the fact that the anchor question for this study measures global change in disease status, and not specifically changes in pain level, and thus the anchor question used in the present study may be less suitable to evaluate the responsiveness of these pain scales.

As for the responsiveness of the OH-QoL PROMs, the COMDQ-26 was found to be the most sensitive OH-QoL instrument to detect improvement in OLP and RAS status, followed by the COMDQ-15 and the OHIP-14. Using the generally accepted criteria (AUC of at least 0.70), the present results confirmed adequate evidence supporting the responsiveness to improvement of total COMDQ-26 scores in both OLP and RAS, and total COMDQ-15 scores in OLP. The AUC of the improvement of total COMDQ-15 in the RAS cohort was marginally lower than the predefined criteria (AUC = 0.69), which might be due to the small number of included RAS patients. Regarding the subscale COMDQ scores, PF subscale of the COMDQ-26 and PD subscale of the COMDQ-15 were shown to have acceptable responsiveness to change only in the OLP cohort, while the remaining subscales performed lower than predefined threshold. Considering all of the evidence supporting the responsiveness of the COMDQ, it is recommended to use total scores of both COMDQ versions over the use of subscale scores, for the assessment of treatment efficacy in patients with OLP and RAS.

In comparison, the OHIP-14 showed a relatively poorer level of responsiveness than both the COMDQ versions and all of the included pain scales. One explanation for this finding may be because the OHIP-14 was first developed and validated for use as a self-reported measure of general impact of oral conditions, and mainly for those with dental problems (Slade, 1997). The content of some items of the OHIP-14 such as “have you had painful aching in your mouth?”, which appeared to reflect odontogenic pain, rather than pain associated with oral mucosal diseases, may not always be sensitive enough to detect changes related to OLP or RAS. For the continued use of the OHIP-14 in immunologically mediated oral mucosal diseases, it is important that researchers or clinicians are aware of the limited content validity and responsiveness of this scale for use in such patients, and further refinement of this widely adopted instrument is therefore required.

To enhance their clinical utility, meaningful improvement thresholds of common measures of pain and OH-QoL were calculated. For research purposes, understanding magnitude of minimal important difference (MID) can be valuable in study designs (e.g. facilitating sample size calculation in studies assessing patient-reported outcomes) as well as assessing treatment efficacy between treatment groups beyond statistical significance (de Vet et al., 2006, Wyrwich et al., 2013). In comparison, the values of minimal important change (MIC) could aid in shared clinical decision-making in the routine clinical setting. For example, It can inform patients and clinicians about the magnitude of change in PROM scores that may justify a change in management, such as introduction of a new treatment, continuation or withdrawal of a current medication, or to increase or decrease the dosage (King, 2011). It can be implied that patients who achieve a score of equal to or greater than thresholds of MIC after a period of treatment may be benefiting from the given intervention.

To the best of our knowledge, this is the first study which has attempted to determine the MID and MIC values for improvement in common measures of pain and OH-QoL in a cohort of patients with OLP and RAS. Our results revealed some variability in the values of meaningful improvement thresholds amongst the different quantitative techniques used. However, the present study adopted a triangulation process, which has been recently recommended by a group of authors, to establish recommended thresholds for further references (Coon and Cappelleri, 2016). It was often observed that the magnitude of within-patient change (MIC) was generally greater than that of between-group difference (MID) (Sully et al., 2019). The present results, however, showed that the values of MIC and MID of studied measures are relatively comparable.

However, it is acknowledged that the present study has several limitations. Due to small sample size of patients whose oral mucosal conditions were worsened, only MIC and MID values for improvement were calculated, and these values do not apply for use as reference

values for those having a deterioration of the condition. Based on the present results, assessment of responsiveness and meaningful change thresholds for worsening of all studied measures are indeterminate, and future research with larger sample size is recommended. Again due to the small sample size, the present study did not take into consideration the impact of baseline scores, which has been reported to influence the MIC and MID values (Escobar and Riddle, 2014, Crosby et al., 2003). Regarding generalisability of the present finding, the study cohort in this study was based upon patients in one tertiary referral oral medicine centre, and thus may not represent the real-world OLP and RAS population, including asymptomatic cases. The exclusion of non-English speakers may also reduce the external validity of the study.

7.8 CONCLUSION

The present study provides some evidence of responsiveness to improvement in the VAS, NRS, COMDQ-15 and COMDQ-26 as well as establishing meaningful improvement thresholds of the scores of these instruments. Published estimates of MID and MIC will allow researchers and clinicians to adopt these as standard for interpretation of improvement of pain and OH-QoL outcomes in OLP and RAS.

CHAPTER 8 THRESHOLDS OF PATIENT ACCEPTABLE SYMPTOM STATE IN MEASURES OF PAIN AND QUALITY OF LIFE IN IMMUNOLOGICALLY MEDIATED ORAL MUCOSAL DISEASES

8.1 PATIENT ACCEPTABLE SYMPTOM STATE

The patient acceptable symptom state (PASS) is a clinically relevant threshold and is the highest level of symptoms beyond which patients consider themselves good enough to continue in that state (Tubach et al., 2007). The concept of PASS has been adopted in a number of medical fields including Rheumatology and Orthopaedics (Christie et al., 2011, Seror et al., 2016, Emerson Kavchak et al., 2013). In comparison to MID which emphasizes on clinical meanings of PROM change scores (i.e. feeling better or worse), the PASS focuses on clinical relevance of PROM single scores, and is a relevant cut-point determining whether patients are in the state of being well. 'Being well' is somewhat differed from 'feeling better' since patients experiencing improvement following the treatment may not consider their condition satisfactory.

The PASS can be used as a patient-relevant monitoring tool that reflects patient's satisfactory to his/her current condition. Achieving PASS can be indicative of therapeutic success at the individual level and may be used as the target for treatment strategies particularly in case of symptomatic treatment in clinical practice. Knowledge about the proportion of therapeutic success/failure using the basis of the PASS can aid in better communication between patient and clinician since clinician can explain the anticipated effectiveness of the treatment in the way that is more clinically relevant to patient than traditional mean effects. Apart from its benefits in clinical settings, the PASS is a useful tool for standardised responder criteria for clinical trials (Seror et al., 2016, Tubach et al., 2006). Also, this threshold can be applied as entry criteria for clinical trials assessing symptomatic treatment (Seror et al, 2015). For example, only patients who do not achieve the PASS are eligible for the inclusion of the study.

8.2 KNOWLEDGE GAP

A number of patient-reported instruments measuring pain and OH-QoL have been used in the literature of immunologically mediated oral mucosal diseases. Nevertheless, there are no studies exploring clinical relevance of individual scores derived from these scales using the PASS.

8.3 AIMS

The aims of the present chapter were:

1. To determine the cut-off scores of the PASS in measures of pain and OH-QoL for use in patients with common immunologically mediated oral mucosal diseases (OLP and RAS).
2. To investigate demographic, psychological and clinical factors associated with achieving the PASS in patients with OLP and RAS.

8.4 METHODS

8.4.1 Study design

This was a cross-sectional secondary analysis of data from the Determination of Minimal Important Difference and Patient Acceptable Symptom State of Patient Reported Outcome Measures in Immunologically mediated Oral Mucosal Diseases (MEAN-IT) study, which had favourable opinion from the London – Queen Square Research Ethics Committee (REC reference 17/LO/1825; approval date 3 November 2017).

8.4.2 Participants

Data were drawn from a total of 393 patients with immunologically mediated oral mucosal diseases including 281 patients with OLP and 112 patients with RAS, who attended the Oral Medicine clinic, UCLH Eastman Dental Hospital, London, United Kingdom for regular hospital appointments. The eligibility criteria of study participants are listed in Table 6.1. The

recruitment of the MEAN-IT study was based upon convenience sampling. All potentially eligible participants, in all Consultant lead Oral Medicine clinics were invited to participate. All participants provided verbal and written informed consent to take part in the study. To ensure sufficient number of patients with different state of symptom level (acceptable/non-acceptable), the data included in this study consisted of two patient groups at different time points (baseline and 4-month follow-up) of the MEAN-IT study.

8.4.3 Procedures

A comprehensive oral examination was performed on all study participants to assess the clinical type, oral sites of involvement and disease activity (ODSS for patients with OLP and USS for patients with RAS). Participants with OLP were categorised into three groups: (i) keratotic (presence of white reticular, papular or plaque-like lesions without apparent erythema/ulceration), (ii) erythematous (presence of atrophic/ erythematous lesions with/without reticular/popular/ plaque-like features AND no evidence of erosion/ulceration), and (iii) erosive/ulcerative (presence of erosive or ulcerative lesions with/without the presence of keratotic and/or erythematous changes of OLP). For participants with RAS, clinical types were recorded based upon clinical appearance and behavior of RAS into 3 groups: minor RAS (shallow small ulcers (<1cm), usually last 7-10 days), major RAS (deeper and larger ulcers (≥1 cm), lasting several weeks, which may heal with scar formation) and herpetiform RAS (few millimeter ulcers, usually > 10 ulcers, last 7-10 days) (Scully and Carrozzo, 2008).

Participants were then asked to complete a set of questionnaires including a demographic form, a set of patient-reported questionnaires associated with oral symptoms, psychological status (level of anxiety, depression, distress and perceived stress) and OH-QoL, and an additional question to determine the PASS. Information regarding past medical history, social history and past OLP-related history including disease duration, extraoral manifestation (either

patient-reported or confirmed by a dermatologist), and current management of OLP/RAS was obtained from review of electronic patient records.

8.4.4 Outcomes

The primary outcome of the present study was the cut-off scores for the PASS in measures of pain and OH-QoL for use in patients with OLP and RAS. To examine associated determinants of achieving PASS, selected demographic characteristics, psychological and OLP-related factors were assessed. Demographic variables included age (continuous variable), (female/male), ethnicity (White/Mixed/Asian/Black), smoking status (non-smoker/ex-smoker/current smoker), alcohol use (no/up to 14 units/more than 14 units per week) and systemic comorbidities (no/one/ at least two disease comorbidities) were recorded.

Potential PASS-associated clinical factors including clinical types (keratotic/erythematous/ ulcerative for OLP and minor/major/herpetiform for RAS), disease duration (time since symptom onset), disease severity and presence of extraoral LP (no/yes-genital area/yes-skin) were also recorded. Psychological state of patients including symptoms of anxiety, depression, emotional distress and level of perceived stress were assessed using the HADS and PSS-10.

8.4.5 Outcome measures

Clinical disease activity scoring

The Oral Disease Severity Score (ODSS) and *the Ulcer Severity Score (USS)* were used for the assessment of disease activity of OLP and RAS, respectively.

Patient-reported outcome measures

Measures of pain: *The Visual analog scale (VAS)* and *The Numerical Rating Scale (NRS)* for pain were used.

Measures of OH-QoL: *The 14-item Oral Health Impact Profile (OHIP-14), The 26-item* and *15-item Chronic Oral Mucosal Disease Questionnaire (COMDQ-26; COMDQ-15)* were used.

Measures of psychological factors: *The Hospital Anxiety and Depression Scale (HADS)* and *10-item perceived stress scale (PSS-10)* were used.

Anchor question

To determine the PASS, additional question is required as gold standard to determine acceptability of current disease state from the patient's perspective. In this study, the following *PASS question* was used as external anchor: "Thinking about all the ways your symptoms related to your oral mucosal conditions are affecting you, do you consider that your current state is acceptable?". The response options (yes/no) dichotomised participants into the PASS+ group (achieving acceptable symptom state; "yes" to the PASS question) and the PASS- group (not achieving acceptable symptom state; "no" to the PASS question).

8.4.6 Statistical analyses

Statistical analyses were performed using STATA version 15.1 (StataCorp, College Station, TX, U.S.A.). Data distribution of all continuous outcomes was first checked by the Kolmogorov-Smirnov test. As all the data was skewed, descriptive cross-sectional analyses were summarized using median and interquartile range (IQR) for continuous variable Descriptive analyses of demographics and OLP-related characteristics were summarized using frequencies and accompanying percentages for categorical variables while median and interquartile range (IQR) were used as summary statistics for continuous variables.

Patient acceptable symptom state

Before establishing PASS cut-points, Spearman correlation coefficients between scores of studied measures and PASS anchor question were calculated to ensure validity of anchor question. The values of coefficient of at least 0.30 was considered acceptable. PASS cut-off scores were identified using the receiver-operator characteristic (ROC) curves to calculate sensitivity and specificity of each of the potential cut-points on each of the measures of pain and OHRQoL. The ROC curve plotted sensitivity (true-positive (TP) rate; Y-axis) against one minus specificity (false-positive rate; X-axis) at various cut-off scores of each studied instrument. Using ROC approach, the optimal cut-points corresponded to PASS thresholds were scores on studied measures that best distinguish participants answering 'yes' to the PASS anchor question (PASS+) from participants answering 'no' (PASS-) and were the points nearest to the uppermost left-hand corner of the ROC curve, where both sensitivity and specificity are maximized. The area under the curve (AUC) indicated the probability of the cut-off points in correctly discriminating between participants who achieved PASS and those who did not, and an AUC value of > 0.7 is considered satisfactory (Terwee et al., 2007).

Impact of associated factors on achieving the PASS

To identify associated factors of achieving the PASS in patients with OLP and RAS, bivariate analysis between subgroups based on demographics, psychological and clinical factors were performed using the chi-square or Fisher's exact tests for categorical variables as appropriate while Mann-Whitney U test or independent sample t-tests were performed for comparisons of medians and means of continuous variables between subgroups respectively. All tests were two-tailed and a p-value of less than 0.05 was considered statistically significant. Independent variables with statistical significance from bivariate analysis were entered into univariate logistic regression, and the crude odds ratio (OR), 95% confidence interval (CI) and p-value were calculated. Each of the variables with a p-value of less than 0.1 on univariate analyses were all entered into multivariate logistic regression model. Adjusted odds ratios (Adj-ORs) with 95 % CI for each independent variable were calculated.

8.5 RESULTS

The results of this chapter are divided into two sections based upon the disease of interest.

8.5.1 Results of the OLP cohort

8.5.1.1 Descriptive characteristics of the OLP cohort

Data of 281 participants with OLP including 144 from baseline dataset and 137 from 4-month follow-up dataset were included in the present analysis. Descriptive statistics of baseline demographics, psychological and OLP-related factors of all study participants including PASS+ and PASS- group are present in Table 8.1. The characteristics of sample between baseline and 4-month follow-up group of the MEAN-IT study were generally similar except for disease comorbidities, disease activity and types of treatment. The average age of all participants was 63.3 ± 11.3 years (range: 27-88 years), and the majority were female (76.9%). Approximately two-thirds (66.9%) of participants had erythematous OLP. Regarding PASS status, 193 participants (68.7%) rated their current OLP state as acceptable (PASS+ group) while 88 participants (31.3%) did not consider themselves in the PASS.

Table 8.1 Descriptive characteristics of 281 participants with OLP according to patient acceptable symptom state (PASS) status

Patient characteristics	Sample 1 (baseline group; N = 144)	Sample 2 (4-month F/U group; N = 137)	P-value	Total sample (Sample 1 + 2; N = 281)			
				Characteristics	PASS negative (N = 88; 31.3%)	PASS positive (N = 193; 68.7%)	P-value
Demographic variables							
Age (y; median, IQR)	66.1 (55.7, 70.9)	65.0 (55.4, 71.3)	0.75	65.5 (55.6, 71.0)	65.5 (55.6, 70.7)	65.5 (55.4, 71.3)	0.87
Female (n, %)	111 (77.1)	105 (76.6)	0.93	216 (76.9)	69 (78.4)	147 (76.2)	0.68
Ethnicity (n, %)			0.75				0.003
White	98 (68.1)	90 (65.7)		188 (66.9)	47 (25.0)	141 (75.0)	
Mixed	3 (2.1)	3 (2.2)		6 (2.1)	1 (16.7)	5 (83.3)	
Asian	36 (25.0)	40 (29.2)		76 (27.1)	36 (47.4)	40 (52.6)	
Black	7 (4.9)	4 (2.9)		11 (3.9)	4 (36.4)	7 (63.6)	
Smoking (n, %)			0.25				0.15
Non-smoker	109 (75.7)	102 (74.5)		211 (75.1)	61 (28.9)	150 (71.1)	
Ex-smoker	27 (18.8)	32 (23.4)		59 (21.0)	21 (35.6)	38 (64.4)	
Current smoker	8 (5.6)	3 (2.2)		11 (3.9)	6 (54.6)	5 (45.5)	
Alcohol consumption (n, %)			0.15				0.17
No	49 (34.0)	47 (34.3)		96 (34.2)	34 (35.4)	62 (64.6)	
≤ 14 Units/week	80 (55.6)	84 (61.3)		164 (58.4)	51 (31.1)	113 (68.9)	
> 14 Units/week	15 (10.4)	6 (4.4)		21 (7.5)	3 (14.3)	18 (85.7)	
Comorbidity (n, %)			0.01				0.51
No	15 (10.42)	33 (24.1)		48 (17.1)	15 (31.3)	33 (68.8)	
1 comorbidity	35 (24.3)	31 (22.6)		66 (23.5)	17 (25.8)	49 (74.2)	
≥ 2 comobidities	94 (65.3)	73 (55.3)		167 (59.4)	56 (33.5)	111 (66.5)	
OLP-related characteristics							
Disease duration (y; median, IQR)	5.8 (2.8, 10.8)	6.7 (3.4, 10.8)	0.5	6.4 (3.0, 10.8)	5.8 (3.1, 10.0)	6.6 (2.8, 10.8)	0.89
Clinical types			0.21				<0.001
Keratotic	21 (14.6)	31 (22.6)		52 (18.5)	7 (13.5)	45 (86.5)	
Erythematous	100 (69.4)	88 (64.2)		188 (66.9)	59 (31.4)	129 (68.6)	
Ulcerative	23 (16.0)	18 (13.1)		41 (14.6)	22 (53.7)	19 (46.3)	
ODSS score (median, IQR)	13 (9, 21)	11 (6, 19)	0.02	12.5 (7, 20)	19.5 (13, 26)	10 (6, 17)	<0.001
ODSS-site	5.5 (4, 7)	4 (3, 7)	0.07	5 (3, 7)	6 (4, 9)	4 (2, 6)	<0.001
ODSS-activity	5 (2, 10)	4 (1, 8)	0.01	5 (2, 9)	8 (5, 13)	4 (1, 7)	<0.001

Table 8.1 Descriptive characteristics of 281 participants with OLP according to patient acceptable symptom state (PASS) status (cont.)

Patient characteristics	Sample 1 (baseline group; N = 144)	Sample 2 (4-month F/U group; N = 137)	P-value	Total sample (Sample 1 + 2; N = 281)			
				Characteristics	PASS negative (N = 88; 31.3%)	PASS positive (N = 193; 68.7%)	P-value
HADS-A (median, IQR)	6 (3, 9)	7 (3, 9)	0.62	6 (3, 9)	8 (5, 12)	5 (3, 8)	<0.001
< 8: no anxiety symptoms	97 (67.4)	80 (58.4)	0.12	177 (63)	40 (22.6)	137 (77.4)	<0.001
≥ 8: with anxiety symptoms	47 (32.6)	57 (41.6)		104 (37)	48 (46.2)	56 (53.9)	
HADS-D (median, IQR)	4 (1, 6)	3 (1, 6)	0.2	3 (1, 6)	6 (4, 9)	2 (1, 5)	<0.001
< 8: no depressive symptoms	116 (80.6)	112 (81.8)	0.8	228 (81.1)	57 (25.0)	171 (75.0)	<0.001
≥ 8: with depressive symptoms	28 (19.4)	25 (18.3)		53 (18.9)	31 (58.5)	22 (41.5)	
HADS-T (median, IQR)	9.5 (5.5, 15)	9 (4, 15)	0.4	9 (5, 15)	15 (8.5, 20)	7 (4, 12)	<0.001
< 15: no psychological distress	105 (72.9)	100 (73.0)	0.99	205 (73.0)	43 (21.0)	162 (79.0)	<0.001
≥ 15: with psychological distress	39 (27.1)	37 (27.0)		76 (27.1)	45 (59.2)	31 (40.8)	
PSS-10 (median, IQR)	16 (10, 21)	15 (10, 20)	0.8	16 (10, 21)	20 (13, 25)	14 (8, 19)	<0.001
0-13: mild perceived stress	56 (38.9)	61 (44.5)	0.63	117 (41.6)	23 (19.7)	94 (80.3)	<0.001
14-26: moderate perceived stress	77 (53.5)	66 (48.2)		143 (50.9)	51 (35.7)	92 (64.3)	
27-40: severe perceived stress	11 (7.6)	10 (7.3)		21 (7.5)	14 (66.7)	7 (33.3)	
Presence of extraoral LP (n, %)	37 (25.7)	32 (23.4)	0.65	69 (24.6)	21 (23.9)	48 (24.9)	0.86
Treatment (n, %)			<0.001				<0.001
Tanes	12 (8.3)	34 (24.8)		46 (16.4)	4 (4.6)	42 (21.8)	
TCS	90 (62.5)	76 (55.5)		166 (59.1)	52 (59.1)	114 (59.1)	
TCS and other topical treatment	34 (23.6)	26 (19.0)		60 (21.4)	31 (35.2)	29 (15.0)	
Systemic treatment	8 (5.6)	1 (0.7)		9 (3.2)	1 (1.1)	8 (4.2)	

Note: TCS = topical corticosteroids

8.5.1.2 Factors associated with achieving the PASS in patients with OLP

As shown in Table 8.1, there were significant difference in ethnicity, clinical types of OLP, disease severity (ODSS), treatment types and all studied psychological factors between PASS+ and PASS- group. Univariate and multivariate analysis with crude and adjusted OR of these variables were shown in Table 8.2. Univariate analyses showed that Asians were less likely to be in PASS when compared to white ethnicity. In comparison to those with keratotic OLP, those having erythematous and ulcerative OLP had lower tendency to consider their OLP status as acceptable. As expected, patients with higher level of disease activity, anxiety symptoms (HADS-A), depressive symptoms (HADS-D), distress (HADS-T), perceived stress (PSS-10) were less likely to achieve the state of PASS. Patients using topical corticosteroids with or without other topical treatment were less likely to be in PASS when compared to those who did not use any treatment or only use topical anaesthetic agents.

Due to collinearity with other variables, ODSS-site score, ODSS-activity score and total HADS (distress) were not included in the final model of multivariate analysis. After potential confounders were controlled, achieving PASS was independently associated with lower disease activity scores (ODSS-total; AOR = 0.91 (95%CI: 0.87-0.94); $p < 0.001$) and lower level of depressive symptoms (HADS-D; AOR = 0.88 (95%CI: 0.75-1.00); $p = 0.048$).

Table 8.2 Results of univariate and multivariate logistic regression of factors associated with achieving PASS status in patients with OLP

Variables	Achieving PASS			
	Crude OR [95%CI]	P-value	Adj-OR [95%CI]	P-value
Demographic variable				
Ethnicity (white = ref.)				
Mixed	1.67 [0.19-14.63]	0.645	2.61 [0.11-64.7]	0.558
Asian	0.37 [0.21-0.65]	*<0.001*	0.57 [0.24-1.05]	0.055
Black	0.58 [0.16-2.08]	0.406	1.50 [0.29-7.72]	0.631
Clinical variable				
Clinical types (reticular = ref.)				
Erythematous	0.34 [0.14-0.80]	0.013	0.60 [0.22-1.67]	0.328
Ulcerative	0.13 [0.05-0.37]	<0.001	0.37 [0.11-1.26]	0.112
Disease severity score (ODSS-total)	0.90 [0.87-0.93]	<0.001	**0.91 [0.87-0.94]**	**<0.001**
Anxiety symptoms (HADS-A)	0.85 [0.80-0.91]	<0.001	0.95 [0.85-1.06]	0.381
Depressive symptoms (HADS-D)	0.78 [0.72-0.84]	<0.001	**0.88 [0.75-1.00]**	**0.048**
Perceived stress (PSS-10)	0.91 [0.87-0.94]	<0.001	0.96 [0.90-1.03]	0.27
Treatment (no treatment/Tanes = ref.)				
TCS	0.21 [0.07-0.61]	0.004	0.47 [0.13-1.72]	0.257
TCS + other topical treatment	0.09 [0.03-0.28]	<0.001	0.29 [0.05-1.09]	0.06
Systemic treatment	0.76 [0.08-7.74]	0.818	6.38 [0.44-92.5]	0.175

Note: TCS = topical corticosteroids

8.5.1.3 Thresholds for PASS in common measures of pain and OHRQoL for use in patients with OLP

The absolute magnitudes of Spearman correlation coefficients between scores of studied instrument and PASS anchor question were over 0.30 in all measures, supporting validity of the anchor question (data not shown). According to the ROC curve analysis, PASS threshold for the NRS and VAS for pain in patients with OLP was 3 and 28 mm, respectively. Regarding PASS cut-points for scores of OH-QoL instruments, values of 18, 26, 45 corresponded to PASS level of total scores of OHIP-14, COMDQ-15 and COMDQ-26, respectively. Detailed characteristics of PASS cut-points including area under the curve (AUC), sensitivity and

specificity in common measures of pain and OH-QoL for use in patients with OLP are provided in Table 8.3.

Table 8.3 PASS cut-off scores for self-reported measures of pain and OH-QoL in patients with OLP

Instruments	PASS	AUC	sensitivity	specificity
VAS (0-100mm)	≤ 28	0.78	76	77
NRS (0-10)	≤ 3	0.75	75	75
OHIP-14				
Total	≤ 18	0.74	69	78
Functional Limitation	≤ 1	0.64	68	60
Physical Pain	≤ 4	0.76	77	76
Psychological Discomfort	≤ 2	0.73	76	69
Physical Disability	≤ 3	0.72	64	80
Psychological Disability	≤ 1	0.72	81	63
Social Disability	≤ 1	0.68	64	72
Handicap	≤ 1	0.72	73	71
COMDQ-15				
Total	≤ 26	0.8	76	84
Physical Discomfort	≤ 10	0.79	80	80
Medication & Treatment	≤ 3	0.69	75	63
Social & Emotional	≤ 6	0.77	78	75
Patient Support	≤ 2	0.58	55	61
COMDQ-26				
Total	≤ 45	0.81	74	87
Pain & Functional Limitation	≤ 15	0.79	81	77
Medication & Treatment	≤ 9	0.76	80	30
Social & Emotional	≤ 9	0.76	82	71
Patient Support	≤ 3	0.65	77	52

8.5.2 Results of the RAS cohort

8.5.2.1 Descriptive characteristics of the RAS cohort

Data of 112 participants with RAS (35 from baseline dataset and 77 from 4-month follow-up MEAN-IT dataset) were included in the present analysis. Descriptive statistics of demographics, psychological and RAS-related factors of all study participants including PASS+ and PASS- group are displayed in Table 8.4. The characteristics of sample between baseline and 4-month follow-up group of the MEAN-IT study were generally similar except for clinical types, disease activity and pain scores. The average age of all participants was 44.1 ± 14.8 years (range: 18-89 years), and 60.7% were female. Regarding clinical types, nearly 90% of participants had minor RAS, followed by major (8%) and herpetiform RAS (2.7%). Half of study participants considered their RAS conditions as acceptable.

Table 8.4 Descriptive characteristics of 112 participants with RAS according to patient acceptable symptom state (PASS) status

Patient characteristics	Sample 1 (baseline group; N = 35)	Sample 2 (4-month F/U group; N = 77)	P-value	Total sample (Sample 1 + 2; N = 112)			
				Characteristics	PASS negative (N = 56; 50%)	PASS positive (N = 56; 50%)	P-value
Demographic variables							
Age (y; median, IQR)	38.3 (32.2, 52.6)	45.8 (35.0, 54.6)	0.16	41.9 (33.2, 53.8)	41.9 (32.5, 54.2)	44 (34.5, 53.7)	0.66
Female (n, %)	25 (71.4)	43 (55.8)	0.12	68 (60.7)	37 (66.1)	31 (55.4)	0.25
Ethnicity (n, %)			0.59				0.19
White	26 (74.3)	63 (81.8)		89 (79.5)	41 (73.2)	48 (85.7)	
Mixed	2 (5.7)	2 (2.6)		4 (3.57)	4 (7.1)	0 (0)	
Asian	5 (14.3)	10 (13.0)		15 (13.4)	9 (16.1)	6 (10.7)	
Black	2 (5.7)	2 (2.6)		4 (3.6)	2 (3.6)	2 (3.6)	
Smoking (n, %)			0.7				0.79
Non-smoker	28 (80)	66 (85.7)		94 (83.9)	46 (82.1)	48 (85.7)	
Ex-smoker	5 (14.3)	7 (9.1)		12 (10.7)	6 (10.7)	6 (10.7)	
Current smoker	2 (5.7)	4 (5.2)		6 (5.4)	4 (7.1)	2 (3.6)	
Alcohol consumption (n, %)			0.77				0.49
No	11 (31.4)	23 (29.9)		34 (30.4)	20 (35.7)	14 (25)	
≤ 14 Units/week	23 (65.7)	53 (68.8)		76 (67.9)	35 (62.5)	41 (73.2)	
> 14 Units/week	1 (2.9)	1 (1.3)		2 (1.8)	1 (1.8)	1 (1.8)	
Comorbidity (n, %)			0.43				0.85
No	15 (42.9)	36 (46.8)		51 (45.5)	24 (42.9)	27 (48.2)	
1 comorbidity	14 (40)	22 (28.6)		36 (32.1)	19 (33.9)	17 (30.4)	
≥ 2 comobidities	6 (17.1)	19 (24.7)		25 (22.3)	13 (23.2)	12 (21.4)	
RAS-related characteristics							
Disease duration (y; median, IQR)	20 (4.3, 25.4)	15.5 (5.4, 26.8)	0.96	16 (5.2, 26.6)	15.1 (5.7, 25.8)	17.7 (4.8, 28.0)	0.76
Clinical types			0.5				0.11
Minor	31 (88.6)	69 (89.6)		100 (89.3)	47 (83.9)	53 (94.6)	
Major	4 (11.4)	5 (6.5)		9 (8.0)	6 (10.7)	3 (5.4)	
Herpetiform	0 (0)	3 (3.9)		3 (2.7)	3 (5.4)	0 (0)	

Table 8.4 Descriptive characteristics of 112 participants with RAS according to patient acceptable symptom state (PASS) status (cont)

Patient characteristics	Sample 1 (baseline group; N = 35)	Sample 2 (4-month F/U group; N = 77)	P-value	Total sample (Sample 1 + 2; N = 112)			
				Characteristics	PASS negative (N = 56; 50%)	PASS positive (N = 56; 50%)	P-value
USS score (median, IQR)	30 (25, 37)	25.5 (22, 32)	0.003	26 (23, 34)	32 (25, 37)	25 (21, 28)	<0.001
USS-size	4 (3, 7)	3 (2, 4)	0.002	3 (2, 4)	3 (3, 6.5)	3 (2, 4)	0.007
USS-number	3 (2, 4)	2 (2, 3)	0.02	2 (2, 3)	2.5 (2, 4)	2 (2, 3)	0.11
USS-duration	3 (3, 5)	2 (2, 3)	<0.001	3 (2, 4)	3 (2, 4)	2 (2, 3)	0.007
USS-ulcer-free period	7 (5, 9)	7 (6, 9)	0.83	7 (6, 9)	8 (7, 9)	7 (4, 8)	<0.001
USS-site	5 (4, 8)	5 (4, 7)	0.48	5 (4, 7)	5.5 (4, 7.5)	5 (4, 7)	0.39
USS-pain	7 (5, 8)	6 (4, 7)	0.003	6 (4, 7)	7 (5, 8)	5 (3, 7)	<0.001
HADS-A (median, IQR)	7 (4, 10)	7 (4, 9)	0.71	7 (4, 10)	7.5 (5, 11)	7 (4, 9)	0.18
< 8: no anxiety symptoms	19 (54.3)	43 (55.8)	0.88	62 (55.4)	28 (50)	34 (60.7)	0.25
≥ 8: with anxiety symptoms	16 (45.7)	34 (44.2)		50 (44.6)	28 (50)	22 (39.2)	
HADS-D (median, IQR)	3 (2, 6)	3 (2, 7)	0.69	3 (2, 6)	5 (3, 8)	2 (1, 4)	<0.001
< 8: no depressive symptoms	30 (85.7)	60 (77.9)	0.34	90 (80.4)	41 (73.2)	49 (87.5)	0.06
≥ 8: with depressive symptoms	5 (14.3)	17 (22.1)		22 (19.6)	15 (26.8)	7 (12.5)	
HADS-T (median, IQR)	12 (7, 17)	10 (7, 16)	0.6	10.5 (7, 16)	12 (8.5, 18)	9 (6, 13)	0.003
< 15: no psychological distress	24 (68.6)	53 (68.8)	0.98	77 (68.8)	33 (58.9)	44 (78.6)	0.03
≥ 15: with psychological distress	11 (31.4)	24 (31.2)		35 (31.3)	23 (41.1)	12 (21.4)	
PSS-10 (median, IQR)	18 (14, 21)	17 (9, 23)	0.57	18 (11, 22)	18 (13.5, 23.5)	15 (9, 21)	0.04
0-13: mild perceived stress	6 (17.1)	31 (40.3)	0.002	37 (33.0)	14 (25)	23 (41.1)	0.02
14-26: moderate perceived stress	28 (80)	35 (45.5)		63 (56.3)	32 (57.1)	31 (55.4)	
27-40: severe perceived stress	1 (2.9)	11 (14.3)		12 (10.7)	10 (17.9)	2 (3.6)	
Treatment (n, %)			0.07				0.81
Topical treatment	32 (91.4)	59 (76.6)		91 (81.3)	46 (82.1)	45 (80.4)	
Topical and systemic treatment	3 (8.6)	18 (23.4)		21 (18.8)	10 (17.9)	11 (19.6)	

8.5.2.2 Factors associated with achieving the PASS in patients with RAS

Based upon Table 8.4, there was significant difference in RAS-related parameters (overall disease activity, ulcer size, ulcer duration, ulcer free period, pain level) and scores of all studied psychological instruments between PASS+ and PASS- group. Univariate and multivariate analysis with crude and adjusted OR of these parameters were shown in Table 8.5. Univariate analyses revealed that patients with greater average ulcer size, longer ulcer duration, shorter ulcer free period, anxiety symptoms (HADS-A), depressive symptoms (HADS-D), distress (HADS-T), perceived stress (PSS-10) were less likely to achieve the state of PASS.

Due to collinearity with other variables, USS-total score, USS-pain and total HADS (distress) were not included in the final model of multivariate analysis. After potential confounders were controlled, achieving PASS was independently associated with lower level of depressive symptoms (HADS-D; AOR = 0.77 (95%CI: 0.64-0.93); p = 0.007), larger ulcer size (USS-ulcer size; AOR = 0.75 (95% CI: 0.58-0.95); P = 0.019) and longer ulcer free period (USS-ulcer free; AOR = 0.78 (95%CI: 0.64-0.96); p = 0.017).

8.5.2.3 Thresholds for PASS in common measures of pain and OH-QoL for use in patients with RAS

According to the ROC curve analysis, PASS threshold for the NRS and VAS for pain in patients with OLP was 3 and 31 mm, respectively. As for the PASS cut-points for OH-QoL measures, scores of 24, 26, 43 corresponded to PASS level of total scores of OHIP-14, COMDQ-15 and COMDQ-26, respectively. Other characteristics of PASS cut-points including AUC, sensitivity and specificity in measures of pain and OH-QoL for application in RAS patients are outlined in Table 8.6.

Table 8.5 Results of univariate and multivariate logistic regression of factors associated with achieving PASS status in patients with RAS

Variables	Achieving PASS			
	Crude OR [95%CI]	P-value	Adj-OR [95%CI]	P-value
Clinical variable				
Ulcer size (USS-size)	**0.73 [0.60-0.89]**	**0.002**	**0.75 [0.58-0.95]**	**0.019**
Ulcer duration (USS-duration)	0.82 [0.66-1.01]	0.059	0.96 [0.73-1.26]	0.763
Ulcer free period (USS-ulcer free)	**0.76 [0.64-0.90]**	**0.001**	**0.78 [0.64-0.95]**	**0.012**
Anxiety symptoms (HADS-A)	0.93 [0.84-1.01]	0.1	1.00 [0.85-1.17]	0.99
Depressive symptoms (HADS-D)	**0.78 [0.68-0.89]**	**<0.001**	**0.77 [0.64-0.93]**	**0.007**
Perceived stress (PSS-10)	**0.95 [0.90-1.00]**	**0.036**	1.43 [0.44-1.13]	0.533
Treatment (topical treatment = ref.)				
Topical and systemic treatment	1.12 [0.43-2.91]	0.809	1.43 [0.44-4.68]	0.556

Table 8.6 PASS cut-off scores for self-reported measures of pain and OH-QoL in patients with RAS

Instruments	PASS	AUC	sensitivity	specificity
VAS (0-100mm)	≤ 31	0.71	73	68
NRS (0-10)	≤ 3	0.71	82	61
OHIP-14				
Total	≤ 24	0.67	66	68
Functional Limitation	≤ 3	0.66	63	70
Physical Pain	≤ 5	0.64	57	71
Psychological Discomfort	≤ 4	0.55	36	75
Physical Disability	≤ 3	0.64	70	59
Psychological Disability	≤ 3	0.63	64	61
Social Disability	≤ 3	0.68	70	66
Handicap	≤ 2	0.68	64	71
COMDQ-15				
Total	≤ 26	0.73	70	77
Physical Discomfort	≤ 9	0.69	79	59
Medication & Treatment	≤ 5	0.63	46	80
Social & Emotional	≤ 8	0.7	66	73
Patient Support	≤ 3	0.53	50	55
COMDQ-26				
Total	≤ 43	0.73	73	73
Pain & Functional Limitation	≤ 15	0.73	75	71
Medication & Treatment	≤ 11	0.68	66	70
Social & Emotional	≤ 9	0.68	79	57
Patient Support	≤ 5	0.59	70	48

8.6 DISCUSSION

The present study identified estimates of patient acceptable symptom state (PASS) cut-points among common measures of pain for use in patients with OLP and RAS in one tertiary Oral Medicine clinic in the UK. According to results of the correlation studies, all included measures of pain and OH-QoL were predictive of acceptable disease status based upon patient's perception. The results from ROC analysis showed that only PASS thresholds for NRS for pain and total COMDQ-15 were similar between OLP and RAS while the remaining PASS cut-offs for other studied measures were different between two conditions. Independent determinants of achieving PASS in patients with OLP and RAS include lower level of depressive symptoms and lower disease activity, which refer to lower ulcer size and longer duration of ulcer-free periods in patients with RAS. This finding accentuated the importance of holistic patient care of patients with immunologically mediated oral mucosal diseases. In other words, to aid affected individuals in entering acceptable symptom state, clinicians should not only focus on treating physical symptoms and signs of oral diseases, but identification and management of related psychological symptoms could improve patient's perception of acceptability on their disease status.

Incorporating PASS as target for clinically relevant treatment success could bring patient's perspective to the fore of shared decision-making and make it easier for both patient and clinician to understand clinically relevant meanings of pain and OH-QoL scores (Tubach et al., 2006). Reporting the proportion of treatment responders could facilitate meaningful interpretation and communication of study results in addition to statistically significant mean effects (King, 2011). While using meaningful change thresholds such as "minimal important change" as responder criteria are only suitable for longitudinal study design, PASS cut-points can be used for both cross-sectional and longitudinal studies. In addition, PASS threshold can be applied as entry criteria for clinical trials assessing the effectiveness of symptomatic

treatment (Seror et al., 2016). In other words, only patients who do not achieve PASS are eligible for the inclusion of the study.

Importantly, PASS should be used with caution when incorporating this concept in the management of potentially malignant condition including OLP. A recent meta-analysis estimated malignant transformation rate of OLP of approximately 1.1 % (Gonzalez-Moles et al., 2019), and the reported figure may be an underestimation due to inconsistent diagnostic criteria used as well as methodological quality of published studies. Therefore, even though some patients reach the stage of PASS, appropriate management and regular review appointment are necessary particularly when oral lesions suspected of malignancy and/or other risk factors of malignant transformation including tobacco, alcohol, HCV infection and atrophic-erosive OLP lesions are present. Thus, the application of PASS in clinical settings may only influence clinical judgement on the provision of symptomatic treatment in OLP cases without clinical signs and symptoms of oral epithelial dysplasia or cancer.

The results of the present study should be cautiously interpreted in light of its limitations. There is presently no international consensus on the gold standard of PASS anchor question, which is reflected by the variation in the use of PASS questions in the literature. The cross-sectional design limits the assessment of PASS performance and its associated factors in long-term follow-up, and thus further longitudinal studies are required. Our study participants were recruited from one tertiary Oral Medicine clinic in London, and thus the present findings might not be generalizable to real-world patients in other countries or different settings. Additionally, some factors including socioeconomic status, educational level, and initial disease activity, which may be related to PASS, were not investigated in the present study.

8.7 CONCLUSION

The present study established PASS cut-off thresholds as a tool facilitating clinically meaningful interpretation of pain and OH-QoL outcomes relevant to individuals with OLP and RAS. Identified PASS estimates could be utilized as endpoints in clinical practice as well as eligibility criteria for recruiting participants in clinical trials assessing effectiveness of symptomatic intervention. Factors including pain intensity, depressive symptoms, disease activity and ulcer-free periods may have a negative impact on patient's acceptability of disease status of OLP and RAS.

CHAPTER 9 GENERAL DISCUSSION

The field of PROMs in immunologically mediated oral mucosal diseases is of great interest, and is obviously relevant to the modern era of medicine toward "patient-centered care" (Devlin et al., 2010). Standardized PROMs measure how the disease and treatment pose an impact on any health aspect directly from the patient, and therefore are valuable instruments demonstrating clinical response to treatment as well as effectiveness of care from the perspective of patients (Devlin et al., 2010). Routine collection of PROMs has been proven to facilitate improvement of communication between patients and health care providers, increase in accountability of healthcare service and clinicians, and satisfaction of the patients to care (Valderas et al., 2008, Chen et al., 2013). An effective PROM should have good evidence of both psychometric or measurement properties (validity, reliability and responsiveness) and operational properties such as interpretability or feasibility (Mokkink et al., 2010). The utility of a PROM is population-specific and its appropriateness can be established by investigating its properties in specific population.

Various patient-reported constructs may be of interest in clinical practice and research of immunologically mediated oral mucosal diseases, including intensity of oral symptoms, oral limitation, psychological symptoms, and oral health-related quality of life. Considering their importance in both research and clinical settings, there has been a significant increase in the application of PROMs in immunologically mediated oral mucosal diseases since the introduction of QoL assessment in the clinical studies of OLP in the early 2000s (Hegarty et al., 2002). The topic of PROMs in immunologically mediated oral mucosal diseases have received global recognition in the 2014 sixth World Workshop in Oral Medicine (WWOM VI), and despite their apparent benefits on monitoring and managing the patients, the working group still found limited adoption and utility of PROMs in routine healthcare and research of oral mucosal diseases (Ni Riordain et al., 2015).

To address this issue, the present thesis revisited the literature to investigate the extent to which PROMs are utilized in literature of four important immunologically mediated oral mucosal diseases (Chapter 3). Overall, there are a variety of over 50 PROMs, which have been adopted for use in clinical studies of immunologically mediated oral mucosal diseases. The vast majority of these instruments have no psychometric evidence supporting their applications in specific populations of immunologically mediated oral mucosal diseases. Prior to applying high-quality measures in a specific context, it is crucial that the end users cautiously review their developmental characteristics, design intents and validation evidence to ensure its suitability in target population of interest. It should not be assumed that psychometric performance of each PROM is consistent and comparable across different groups of population (Hawkins et al., 2018). A well-validated PROM used in an inappropriate target population or for unintended applications could yield distorted or inaccurate findings (Patel et al., 2017).

Regarding the types of PROMs used in research of immunologically mediated oral mucosal diseases, the majority of clinical studies in the literature used generic instruments, which may not be sufficiently sensitive for specific issues that are unique to patients with immunologically mediated oral mucosal conditions. Perhaps, these generic measures may be selected due to the lack of condition-specific PROMs at the time of conducting research. Despite their continued use in the literature and validation evidence in broader and diverse population, there has been minimal work undertaken to examine the psychometric performance of these generic PROMs in a specific group of patients with immunologically mediated oral mucosal diseases. On the other hand, only a few condition-specfic PROMs have been identified. Amongst these instruments, the Chronic Oral Mucosal Disease Questionnaire (COMDQ), which has undergone rigorous psychometric testing with the highest number of published validation studies in immunologically mediated oral mucosal diseases, is still not extensively

incorporated in outcome assessment in this patient population (Ní Ríordáin and Wiriyakijja, 2017).

Apart from the scarcity of supporting evidence of measurement properties, there was also a lack of documentation on guidance for PROM score interpretation in immunologically mediated oral mucosal diseases. For instance, what magnitude of change in PROM scores corresponds to a meaningful change in the disease status of an individual patient (minimal important change; MIC) or what magnitude of difference in PROM scores patients represents a meaningful difference between groups of patients (minimal important difference; MID) (Mokkink et al., 2010). Without these score guidance, it is difficult to understand clinical meaningfulness of PROM scores, hindering the applications of research findings to inform clinical decision making, guidelines, product labeling and health policy (Noud et al., 2017).

Following identification of the issues related to the application of PROMs in immunologically mediated oral mucosal diseases, the present thesis attempted to fill in these literature gaps by providing some empirical evidence of measurement properties and interpretability among some of the most frequently used PROMs to promote evidence-based applications and meaningful interpretation of these measures in this patient population. Apart from that, the present thesis developed a short version of the COMDQ to improve acceptability of this condition-specific instrument for use in clinical and research settings of immunologically mediated oral mucosal diseases.

In chapter 4, validity and reliability of two commonly used psychological-PROMs in the literature of immunologically mediated oral mucosal diseases including the HADS and PSS-10 were investigated in a cohort of patients with OLP and RAS in one tertiary Oral Medicine clinic in the UK. Despite their widely use, there is a lack of clarity regarding underlying structural factors (forming subscales of the instruments), construct validity and reliability of

both scales across different patient groups. Evidence from the present factor analysis and reliability studies supported the application of the HADS and PSS-10 in the OLP and RAS population as general measures of psychological distress and perceived stress, respectively. The summary of the HADS and PSS-10 as two subscale scores (e.g. anxiety and depression for the HADS) appeared to have relatively low reliability compared to the use of total score in a cohort of patients with OLP and RAS, and this is supported by evidence from some recent validation studies on different patient groups (Iani et al., 2014, Luciano et al., 2014, Perera et al., 2017, Reis et al., 2017). The present results therefore demonstrate that the findings of previous research using the HADS to measure anxiety and depression outcomes in OLP and RAS might be somewhat unreliable. Apart from providing some evidence of validity and reliability of the HADS and PSS-10 in patients with OLP and RAS, the present findings highlight the necessity of performing psychometric validation of PROMs before practical use in different population than its design intent to ensure their appropriateness in measuring accurate construct of interest in a particular population.

In Chapter 5, a short-form of the original 26-item COMDQ was successfully developed and rigorously tested for psychometric properties in patients with four immunologically mediated oral mucosal diseases (OLP, RAS, PV and MMP). This process ended up with a more simplified version comprising 15 items (COMDQ-15) that retain the original conceptual dimension of the 26-item version. A series of psychometric testing demonstrated satisfied quality benchmarks for important measurement properties of this short version compared to its parent scale. A major strength of the COMDQ-15 is its lower respondent burden, thus improving its acceptability for the use in clinical settings. This could potentially facilitate the adoption of this condition-specific QoL scale, which could in turn advance our understanding of the overall impact of chronic oral mucosal conditions on patient's quality of life. However, it should be noted that is the use of a short version might not facilitate comprehensive assessment of QoL particularly in certain topic areas, including oral functional limitation.

Overall, the COMDQ-15 is a short, valid, reliable instrument, which could be useful for the assessment of QoL specific to patients with chronic oral mucosal diseases.

In chapter 6, QoL among patients with OLP and RAS were investigated using the newly developed COMDQ-15 and a widely used measure of general oral health-related QoL (OHIP-14). Based upon the present findings, affected patients with OLP and RAS experienced impairment in QoL, which appeared to be related to certain demographic, psychological and clinical determinants. In addition, it was observed that levels of perceived QoL as measured by the COMDQ-15 have greater association with disease activity including symptoms and signs of OLP and RAS than those measured by the OHIP-14. This emphasizes the importance of the use of condition-specific PROMs, which usually have superior content validity and could provide a more tailored assessment relevant to specific conditions than the use of generic PROMs (Ghimire et al., 2018). Incorporating condition-specific QoL PROMs into clinical practice and research of immunologically mediated oral mucosal diseases could provide a better insight into how the diseases and associated treatment interventions affect patients as well as guiding improvement in the quality and delivery of care in this patient group (Besson et al., 2019).

In chapter 7, responsiveness or ability of PROM to detect change of the disease status over time was examined in commonly used measures of pain and QoL in OLP and RAS. It was evident that condition-specific PROM such as the COMDQ was more responsive to detect improvement in patient's perception of OLP and RAS status than the generic scale (OHIP-14). This finding further supports superior psychometric properties of the COMDQ over the OHIP-14. In addition, relevant cut-off thresholds for meaningful improvement in scores of common measures of pain and QoL including the MIC and MID were established using both the anchor-based and distribution-based methods. Providing the MIC and MID estimates could greatly assist clinicians and researchers in utilizing these pain and QoL PROMs with confidence in

score interpretation. The MIC thresholds could be used as estimated benchmark to help clinicians judge if treatment had a subjectively meaningful effect for an individual patient while the MID could facilitate planning of clinical trials including evaluation of treatment effects on subjective patient-reported outcomes between treatment groups as well as calculation of sample size (de Vet et al., 2015).

In chapter 8, thresholds for patient acceptable symptom state (PASS) were calculated to facilitate meaningful interpretation of individual scores of common PROMs assessing pain and QoL in OLP and RAS. These estimated cut-off scores could be helpful for clinicians to establish level of symptoms and QoL that might be important for patients to achieve on PROM scores to be satisfied with their diseases and care. Furthermore, The established PASS thresholds could be utilized as entry criteria for clinical trials assessing symptomatic treatment for the management of patients with OLP and RAS.

The main strength of the present thesis is that a large cohort of participants with confirmed diagnosis of immunologically mediated oral mucosal diseases were recruited, and this facilitated developing robust evidence for the development of the COMDQ-15 and psychometric validation of other studied PROMs. This relatively large sample size also allowed an increase in the power for studying the association of various demographic, psychological and clinical factors on study outcomes including the presence of psychological comorbidities, worse quality of life and patient acceptable symptom state. Another strength of the present thesis is the use of only appropriately validated PROMs. The present thesis is also the first to determine cut-off threshold scores for MIC, MID and PASS of scores of common measures of pain and QoL in patients with OLP and RAS, and this information could be a good foundation for the planning of the clinical studies as well determining the efficacy of the therapy based upon the patient's perspective in the clinical practice .

There are several limitations of the present thesis that should be mentioned. The comprehensive reviews of the PROMs only summarized available reports on the measurement properties of existing PROMs used in immunologically mediated oral mucosal diseases but did not appraise the methodological quality of the validation studies. Therefore, overall quality of evidence cannot be concluded. The use of study sample exclusively from one Tertiary Oral Medicine clinic and the exclusion of non-English users may not represent the whole population of immunologically mediated oral mucosal diseases, thus limiting generalizability of the present findings. Owing to limited number of recruited participants with PV and MMP, robust psychometric and statistical analysis in chapter 4 and 6 to 8 could not be performed in these immuno-bullous patient populations. Clear causal relationship between studied factors cannot be established due to the drawbacks of the cross-sectional design. The prevalence of psychological comorbidities reported in the present thesis were estimated by the HADS, which is a screening instrument, and therefore the findings need to be interpreted cautiously. The present thesis did not evaluate patient's socio-economic factors such as educational level, marital and job status, which could be potential confounders of the present results. Due to the small number of recruited participants with worsened conditions, the MIC and MID values were only calculated for the direction of improvement. Again due to the small sample size in the longitudinal cohort, assessment of the impact of baseline PROM scores and disease severity status of patients on meaningful change thresholds did not appear robust enough to perform, and future research with larger sample size on this subject is required.

Overall, the results of the present thesis add high-quality psychometric evidence and/or documentations of interpretability of frequently used PROMs assessing psychological status, oral symptoms and quality of life in common immunologically mediated oral mucosal diseases to the existing literature. The next step of the present thesis will involve selection of the most suitable PROMs for the measurement of each patient-reported construct in immunologically mediated oral mucosal diseases. In order to achieve this, systematic reviews analyzing overall

quality of evidence – including methodological quality and reported measurement properties – of all validation studies of existing PROMs in immunologically mediated oral mucosal diseases based upon the consensus-based standards for the selection of health status measurement instruments (COSMIN) checklist are needed (Mokkink et al., 2018, Prinsen et al., 2018). Following this, the next step should aim at the development of standardized core outcome set (COSs) for studies assessing the effectiveness of treatment for immunologically mediated oral mucosal diseases. The COSs are required to ensure consistent collection and reporting of all the outcomes important to all key stakeholders, and to facilitate the production of transparent, homogenous, meaningful and efficient data in future research of immunologically mediated oral mucosal diseases (Williamson et al., 2012).

CHAPTER 10 FUTURE WORKS

The present thesis has thrown up many questions in need of further investigation. The study participants in the present thesis were from only one referral Oral Medicine center in London, UK, which reflected a mixed multi-cultural group of patients who usually had history of painful symptoms, and therefore the results of present study might not be translatable to general population of immunologically mediated oral mucosal diseases in the UK, or in other countries. Future larger studies recruiting broader groups of participants including from different variety of sources and locations would provide results with greater generalizability. This should include but not limited to patients with asymptomatic or inactive diseases, patients with multiple extraoral involvement of the diseases in different settings, child/adolescent patients with immunologically mediated oral mucosal diseases. Future work should assess further roles of certain determinants, which were not studied in the present thesis, including socioeconomic status, locus of control, coping and acceptance to chronic illnesses and experience to healthcare services in relation to perception of symptoms, psychological status and health related quality of life in patients with immunologically mediated oral mucosal diseases (e.g. newly diagnosis, moderate disease duration and long disease duration).

Future psychometric validation of PROMs measuring oral symptoms and psychological status in patients with oral PV and MMP are required in order guide clinicians and researchers for the selection of appropriate PROMs for outcome measurement in these patient groups. Further investigation into long-term psychological profiles and oral health-related quality of life of patients with oral PV and MMP are also recommended as disease burden, clinical behaviour, treatment outcomes and prognosis of both immunobullous conditions are different from OLP and RAS. Better insight into this matter could assist the development of recommendations to improve standard of care of oral PV and MMP. However, due to the rarity of both diseases, multicenter collaboration for large prospective studies into this matter is imperative.

The recently developed COMDQ-15 is still required cross-cultural validation to examine whether this QoL-specific PROM is applicable and meaningful for use in different countries and cultures than the UK population. In addition, future research are needed to establish external validity of identified meaningful improvement thresholds and patient acceptable symptom state thresholds, and this could be done by testing the performance and relevance of these cut-points in clinical studies or trials of immunologically mediated oral mucosal diseases.

Validated PROMs with good level of interpretability could also be incorporated as monitoring tool for prospective natural history studies in order to provide comprehensive understanding of immunologically mediated oral mucosal diseases and their progression over time. Future natural history studies of immunologically mediated oral mucosal diseases have a potential to assist the medical and research community to understand illness trends, treatment outcomes, disease burden, and some important demographic information about patient age and gender. The results of these promising studies could improve patient care, support, education and outreach, as well as expedite research of immunologically mediated oral mucosal diseases.

CHAPTER 11 CONCLUSION

Immunologically mediated oral mucosal diseases require significant patient and clinician input for optimal management. PROMs can provide a useful assessment of the impact of disease and associated treatment on physical, psychosocial functioning and health-related quality of life of affected individuals in order to guide proper management. There is a need in the field of Oral Medicine for identification and adoption of high-quality PROMs, which achieve specified levels of validation evidence. However, based up the present comprehensive reviews, the vast majority of existing PROMs lack evidence supporting their quality properties for the application in immunologically mediated oral mucosal diseases. The results of the present thesis provide robust psychometric evidence supporting validity, reliability and/or responsiveness of frequently used PROMs assessing oral symptoms, psychological status and quality of life in a cohort of patients with immunologically mediated oral mucosal diseases. The present thesis also included the development of a short version of the COMDQ, a novel condition-specific QoL PROM, to enhance its feasibility and acceptability in order to facilitate its incorporation into clinical and research settings. Established threshold values for the MIC, MID and PASS may be useful in interpreting the clinical relevance of PROM endpoints in the care of patients with immunologically mediated oral mucosal diseases or indeed research of this group of sometimes complex oral mucosal disorders.

REFEERENCES

ADAMO, D., RUOPPO, E., LEUCI, S., ARIA, M., AMATO, M. & MIGNOGNA, M. D. 2015. Sleep disturbances, anxiety and depression in patients with oral lichen planus: a case-control study. *J Eur Acad Dermatol Venereol,* 29**,** 291-7.

AKINTOYE, S. O. & GREENBERG, M. S. 2014. Recurrent aphthous stomatitis. *Dent Clin North Am,* 58**,** 281-97.

AKRAM, Z., ABDULJABBAR, T., VOHRA, F. & JAVED, F. 2018a. Efficacy of low-level laser therapy compared to steroid therapy in the treatment of oral lichen planus: A systematic review. *J Oral Pathol Med,* 47**,** 11-17.

AKRAM, Z., JAVED, F., HOSEIN, M., AL-QAHTANI, M. A., ALSHEHRI, F., ALZAHRANI, A. I. & VOHRA, F. 2018b. Photodynamic therapy in the treatment of symptomatic oral lichen planus: A systematic review. *Photodermatol Photoimmunol Photomed,* 34**,** 167-174.

AL-HASHIMI, I., SCHIFTER, M., LOCKHART, P. B., WRAY, D., BRENNAN, M., MIGLIORATI, C. A., AXELL, T., BRUCE, A. J., CARPENTER, W., EISENBERG, E., EPSTEIN, J. B., HOLMSTRUP, P., JONTELL, M., LOZADA-NUR, F., NAIR, R., SILVERMAN, B., THONGPRASOM, K., THORNHILL, M., WARNAKULASURIYA, S. & VAN DER WAAL, I. 2007. Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod,* 103 Suppl**,** S25.e1-12.

AL-OMIRI, M. K., KARASNEH, J., ALHIJAWI, M. M., ZWIRI, A. M., SCULLY, C. & LYNCH, E. 2015. Recurrent aphthous stomatitis (RAS): a preliminary within-subject study of quality of life, oral health impacts and personality profiles. *J Oral Pathol Med,* 44**,** 278-83.

AL-OMIRI, M. K., KARASNEH, J. & LYNCH, E. 2012. Psychological profiles in patients with recurrent aphthous ulcers. *Int J Oral Maxillofac Surg,* 41**,** 384-8.

AL JOHANI, K. A., HEGARTY, A. M., PORTER, S. R. & FEDELE, S. 2009. Calcineurin inhibitors in oral medicine. *J Am Acad Dermatol,* 61**,** 829-40.

ALAIZARI, N. A., AL-MAWERI, S. A., AL-SHAMIRI, H. M., TARAKJI, B. & SHUGAA-ADDIN, B. 2016. Hepatitis C virus infections in oral lichen planus: a systematic review and meta-analysis. *Aust Dent J,* 61**,** 282-7.

ALBANIDOU-FARMAKI, E., DELIGIANNIDIS, A., MARKOPOULOS, A. K., KATSARES, V., FARMAKIS, K. & PARAPANISSIOU, E. 2008. HLA haplotypes in recurrent aphthous stomatitis: a mode of inheritance? *Int J Immunogenet,* 35**,** 427-32.

ALBANIDOU-FARMAKI, E., MARKOPOULOS, A. K., KALOGERAKOU, F. & ANTONIADES, D. Z. 2007. Detection, enumeration and characterization of T helper cells secreting type 1 and type 2 cytokines in patients with recurrent aphthous stomatitis. *Tohoku J Exp Med,* 212**,** 101-5.

ALHARBI, H. & ALSHEHRY, A. 2019. Perceived stress and coping strategies among ICU nurses in government tertiary hospitals in Saudi Arabia: a cross-sectional study. *Ann Saudi Med,* 39**,** 48-55.

ALI, S. & WAHBI, W. 2017. The efficacy of aloe vera in management of oral lichen planus: a systematic review and meta-analysis. *Oral Dis,* 23**,** 913-918.

ALKHATEEB, A., KARASNEH, J., ABBADI, H., HASSAN, A. & THORNHILL, M. 2013. Association of cell adhesion molecule gene polymorphisms with recurrent aphthous stomatitis. *J Oral Pathol Med,* 42**,** 741-6.

ALRASHDAN, M. S., CIRILLO, N. & MCCULLOUGH, M. 2016. Oral lichen planus: a literature review and update. *Arch Dermatol Res,* 308**,** 539-51.

ALTENBURG, A., EL-HAJ, N., MICHELI, C., PUTTKAMMER, M., ABDEL-NASER, M. B. & ZOUBOULIS, C. C. 2014. The treatment of chronic recurrent oral aphthous ulcers. *Dtsch Arztebl Int,* 111**,** 665-73.

AMAGAI, M. 2008. Pemphigus vulgaris and its active disease mouse model. *Curr Dir Autoimmun,* 10**,** 167-81.

ARDUINO, P. G., LOPETUSO, E., CARCIERI, P., GIACOMETTI, S., CARBONE, M., TANTERI, C. & BROCCOLETTI, R. 2012. Professional oral hygiene treatment and detailed oral hygiene instructions in patients affected by mucous membrane pemphigoid with specific gingival localization: a pilot study in 12 patients. *Int J Dent Hyg,* 10**,** 138-41.

AXELL, T. & RUNDQUIST, L. 1987. Oral lichen planus--a demographic study. *Community Dent Oral Epidemiol,* 15**,** 52-6.

BACHTIAR, E. W., CORNAIN, S., SIREGAR, B. & RAHARJO, T. W. 1998. Decreased CD4+/CD8+ ratio in major type of recurrent aphthous ulcers: comparing major to minor types of ulcers. *Asian Pac J Allergy Immunol,* 16**,** 75-9.

BASCH, E., TORDA, P. & ADAMS, K. 2013. Standards for patient-reported outcome-based performance measures. *Jama,* 310**,** 139-40.

BAUM, S., ASTMAN, N., BERCO, E., SOLOMON, M., TRAU, H. & BARZILAI, A. 2016. Epidemiological data of 290 pemphigus vulgaris patients: a 29-year retrospective study. *Eur J Dermatol,* 26**,** 382-7.

BEAUDUCEL, A. & HERZBERG, P. Y. 2006. On the Performance of Maximum Likelihood Versus Means and Variance Adjusted Weighted Least Squares Estimation in CFA. *Structural Equation Modeling: A Multidisciplinary Journal,* 13**,** 186-203.

BECK, A. T., STEER, R. A. & CARBIN, M. G. 1988. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review,* 8**,** 77-100.

BERNARD, P., ANTONICELLI, F., BEDANE, C., JOLY, P., LE ROUX-VILLET, C., DUVERT-LEHEMBRE, S., ROUSSELLE, P. & PROST-SQUARCIONI, C. 2013. Prevalence and clinical significance of anti-laminin 332 autoantibodies detected by a novel enzyme-linked immunosorbent assay in mucous membrane pemphigoid. *JAMA Dermatol,* 149**,** 533-40.

BERNARD, P., VAILLANT, L., LABEILLE, B., BEDANE, C., ARBEILLE, B., DENOEUX, J. P., LORETTE, G., BONNETBLANC, J. M. & PROST, C. 1995. Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. *Arch Dermatol,* 131**,** 48-52.

BERTRAM, F., BROCKER, E. B., ZILLIKENS, D. & SCHMIDT, E. 2009. Prospective analysis of the incidence of autoimmune bullous disorders in Lower Franconia, Germany. *J Dtsch Dermatol Ges,* 7**,** 434-40.

BESSON, A., DEFTEREOS, I., CHAN, S., FARAGHER, I. G., KINSELLA, R. & YEUNG, J. M. 2019. Understanding patient-reported outcome measures in colorectal cancer. *Future Oncol,* 15**,** 1135-1146.

BIDARRA, M., BUCHANAN, J. A., SCULLY, C., MOLES, D. R. & PORTER, S. R. 2008. Oral lichen planus: a condition with more persistence and extra-oral involvement than suspected? *J Oral Pathol Med,* 37**,** 582-6.

BJELLAND, I., DAHL, A. A., HAUG, T. T. & NECKELMANN, D. 2002. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res,* 52**,** 69-77.

BLACK, M., MIGNOGNA, M. D. & SCULLY, C. 2005. Number II. Pemphigus vulgaris. *Oral Dis,* 11**,** 119-30.

BLACK, N. 2013. Patient reported outcome measures could help transform healthcare. *Bmj,* 346**,** f167.

BLACK, N. & JENKINSON, C. 2009. Measuring patients' experiences and outcomes. *Bmj,* 339**,** b2495.

BLAZAR, B. R., MURPHY, W. J. & ABEDI, M. 2012. Advances in graft-versus-host disease biology and therapy. *Nat Rev Immunol,* 12**,** 443-58.

BOULINGUEZ, S., SOMMET, A., BEDANE, C., VIRABEN, R. & BONNETBLANC, J. M. 2003. Oral nicorandil-induced lesions are not aphthous ulcers. *J Oral Pathol Med,* 32**,** 482-5.

BROCKLEHURST, P., TICKLE, M., GLENNY, A. M., LEWIS, M. A., PEMBERTON, M. N., TAYLOR, J., WALSH, T., RILEY, P. & YATES, J. M. 2012. Systemic interventions for recurrent aphthous stomatitis (mouth ulcers). *Cochrane Database Syst Rev***,** Cd005411.

BROOK, E. M., GLERUM, K. M., HIGGINS, L. D. & MATZKIN, E. G. 2017. Implementing Patient-Reported Outcome Measures in Your Practice: Pearls and Pitfalls. *Am J Orthop (Belle Mead NJ),* 46**,** 273-278.

BROZEK, J. L., GUYATT, G. H. & SCHUNEMANN, H. J. 2006. How a well-grounded minimal important difference can enhance transparency of labelling claims and improve interpretation of a patient reported outcome measure. *Health Qual Life Outcomes,* 4**,** 69.

BRUCH, J. M. & TREISTER, N. S. 2018. *CLINICAL ORAL MEDICINE AND PATHOLOGY,* [Place of publication not identified], SPRINGER INTERNATIONAL PU.

BRUNNER, M., NAGY, G. & WILHELM, O. 2012. A tutorial on hierarchically structured constructs. *J Pers,* 80**,** 796-846.

BUAJEEB, W., OKUMA, N., THANAKUN, S. & LAOTHUMTHUT, T. 2015. Direct Immunofluorescence in Oral Lichen Planus. *J Clin Diagn Res,* 9**,** Zc34-7.

BUNO, I. J., HUFF, J. C., WESTON, W. L., COOK, D. T. & BRICE, S. L. 1998. Elevated levels of interferon gamma, tumor necrosis factor alpha, interleukins 2, 4, and 5, but not interleukin 10, are present in recurrent aphthous stomatitis. *Arch Dermatol,* 134**,** 827-31.

BURKE, L. B., BRENNAN, M. T., NI RIORDAIN, R. & MADSEN, L. S. 2019a. Novel Oral Lichen Planus Symptom Severity Measure for assessing patients' daily symptom experience. *Oral Dis,* 25**,** 1564-1572.

BURKE, L. B., BRENNAN, M. T., NI RIORDAIN, R. & MADSEN, L. S. 2019b. Novel Oral Lichen Planus Symptom Severity Measure for assessing patients' daily symptom experience. *Oral Dis*.

BURNS, A., HOFER, S., CURRY, P., SEXTON, E. & DOYLE, F. 2014. Revisiting the dimensionality of the Hospital Anxiety and Depression Scale in an international sample of patients with ischaemic heart disease. *J Psychosom Res,* 77**,** 116-21.

CAFARO, A., BROCCOLETTI, R. & ARDUINO, P. G. 2012. Low-level laser therapy for oral mucous membrane pemphigoid. *Lasers Med Sci,* 27**,** 1247-50.

CALVERT, M., BRUNDAGE, M., JACOBSEN, P. B., SCHUNEMANN, H. J. & EFFICACE, F. 2013. The CONSORT Patient-Reported Outcome (PRO) extension: implications for clinical trials and practice. *Health Qual Life Outcomes,* 11**,** 184.

CAMACHO-ALONSO, F., LOPEZ-JORNET, P. & BERMEJO-FENOLL, A. 2007. Gingival involvement of oral lichen planus. *J Periodontol,* 78**,** 640-4.

CAMPISI, G., SPADARI, F. & SALVATO, A. 1997. [Sucralfate in odontostomatology. Clinical experience]. *Minerva Stomatol,* 46**,** 297-305.

CAPPELLERI, J. C. 2016. *Patient-reported outcomes : Measurement, implementation and interpretation,* Boca Raton, Chapman & Hall.

CARDOSO, J. A., DOS SANTOS JUNIOR, A. A., NUNES, M. L., DE FIGUEIREDO, M. A., CHERUBINI, K. & SALUM, F. G. 2017. Salivary Alpha-Amylase Enzyme, Psychological Disorders, and Life Quality in Patients with Recurrent Aphthous Stomatitis. *Int J Dent,* 2017**,** 5269856.

CARROZZO, M., FRANCIA DI CELLE, P., GANDOLFO, S., CARBONE, M., CONROTTO, D., FASANO, M. E., ROGGERO, S., RENDINE, S. & GHISETTI, V. 2001. Increased frequency of HLA-DR6 allele in Italian patients with hepatitis C virus-associated oral lichen planus. *Br J Dermatol,* 144**,** 803-8.

CARROZZO, M., PORTER, S., MERCADANTE, V. & FEDELE, S. 2019. Oral lichen planus: A disease or a spectrum of tissue reactions? Types, causes, diagnostic algorhythms, prognosis, management strategies. *Periodontol 2000,* 80**,** 105-125.

CARROZZO, M. & THORPE, R. 2009. Oral lichen planus: a review. *Minerva Stomatol,* 58**,** 519-37.

CARROZZO, M., UBOLDI DE CAPEI, M., DAMETTO, E., FASANO, M. E., ARDUINO, P., BROCCOLETTI, R., VEZZA, D., RENDINE, S., CURTONI, E. S. & GANDOLFO, S. 2004. Tumor necrosis factor-alpha and interferon-gamma polymorphisms contribute to susceptibility to oral lichen planus. *J Invest Dermatol,* 122**,** 87-94.

CHAINANI-WU, N., SILVERMAN, S., JR., REINGOLD, A., BOSTROM, A., LOZADA-NUR, F. & WEINTRAUB, J. 2008. Validation of instruments to measure the symptoms and signs of oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod,* 105**,** 51-8.

CHALLACOMBE, S. J., ALSAHAF, S. & TAPPUNI, A. 2015. Recurrent Aphthous Stomatitis: Towards Evidence-Based Treatment? *Current Oral Health Reports,* 2**,** 158-167.

CHAN, L. S. 2012. Ocular and oral mucous membrane pemphigoid (cicatricial pemphigoid). *Clin Dermatol,* 30**,** 34-7.

CHAN, L. S., AHMED, A. R., ANHALT, G. J., BERNAUER, W., COOPER, K. D., ELDER, M. J., FINE, J. D., FOSTER, C. S., GHOHESTANI, R., HASHIMOTO, T., HOANG-XUAN, T., KIRTSCHIG, G., KORMAN, N. J., LIGHTMAN, S., LOZADA-NUR, F., MARINKOVICH, M. P., MONDINO, B. J., PROST-SQUARCIONI, C., ROGERS, R. S., 3RD, SETTERFIELD, J. F., WEST, D. P., WOJNAROWSKA, F., WOODLEY, D. T., YANCEY, K. B., ZILLIKENS, D. & ZONE, J. J. 2002. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol,* 138**,** 370-9.

CHEN, H., SUI, Q., CHEN, Y., GE, L. & LIN, M. 2015. Impact of haematologic deficiencies on recurrent aphthous ulceration: a meta-analysis. *Br Dent J,* 218**,** E8.

CHEN, J., OU, L. & HOLLIS, S. J. 2013. A systematic review of the impact of routine collection of patient reported outcome measures on patients, providers and health organisations in an oncologic setting. *BMC Health Serv Res,* 13**,** 211.

CHENG, L. L. 2019. Limited Evidence Suggests That Patients With Recurrent Aphthous Stomatitis May Benefit From Using Sodium Lauryl Sulfate-free Dentifrices. *J Evid Based Dent Pract,* 19**,** 101349.

CHENG, Y. S., GOULD, A., KURAGO, Z., FANTASIA, J. & MULLER, S. 2016. Diagnosis of oral lichen planus: a position paper of the American Academy of Oral and Maxillofacial Pathology. *Oral Surg Oral Med Oral Pathol Oral Radiol,* 122**,** 332-54.

CHILCOT, J., HUDSON, J. L., MOSS-MORRIS, R., CARROLL, A., GAME, D., SIMPSON, A. & HOTOPF, M. 2018. Screening for psychological distress using the Patient Health Questionnaire Anxiety and Depression Scale (PHQ-ADS): Initial validation of structural validity in dialysis patients. *Gen Hosp Psychiatry,* 50**,** 15-19.

CHOLERA, M. & CHAINANI-WU, N. 2016. Management of Pemphigus Vulgaris. *Adv Ther,* 33**,** 910-58.

CHRISTIE, A., DAGFINRUD, H., GARRATT, A. M., RINGEN OSNES, H. & HAGEN, K. B. 2011. Identification of shoulder-specific patient acceptable symptom state in patients with rheumatic diseases undergoing shoulder surgery. *J Hand Ther,* 24**,** 53-60; quiz 61.

COHEN, S., KAMARCK, T. & MERMELSTEIN, R. 1983. A global measure of perceived stress. *J Health Soc Behav,* 24**,** 385-96.

CONTI, P. C., DE AZEVEDO, L. R., DE SOUZA, N. V. & FERREIRA, F. V. 2001. Pain measurement in TMD patients: evaluation of precision and sensitivity of different scales. *J Oral Rehabil,* 28**,** 534-9.

COOK, C., PAUL, M. & WYATT, V. 2014. Potential caveats in the use of interpretability of outcome measures. *Physical Therapy Reviews,* 19**,** 158-162.

COON, C. D. & CAPPELLERI, J. C. 2016. Interpreting Change in Scores on Patient-Reported Outcome Instruments. *Ther Innov Regul Sci,* 50**,** 22-29.

COSCO, T. D., DOYLE, F., WARD, M. & MCGEE, H. 2012. Latent structure of the Hospital Anxiety And Depression Scale: a 10-year systematic review. *J Psychosom Res,* 72**,** 180-4.

COYNE, J. C. & VAN SONDEREN, E. 2012. No further research needed: abandoning the Hospital and Anxiety Depression Scale (HADS). *J Psychosom Res,* 72**,** 173-4.

CRINCOLI, V., DI BISCEGLIE, M. B., SCIVETTI, M., LUCCHESE, A., TECCO, S. & FESTA, F. 2011. Oral lichen planus: update on etiopathogenesis, diagnosis and treatment. *Immunopharmacol Immunotoxicol,* 33**,** 11-20.

CRIVELLI, M. R., AGUAS, S., ADLER, I., QUARRACINO, C. & BAZERQUE, P. 1988. Influence of socioeconomic status on oral mucosa lesion prevalence in schoolchildren. *Community Dent Oral Epidemiol,* 16**,** 58-60.

CROSBY, R. D., KOLOTKIN, R. L. & WILLIAMS, G. R. 2003. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol,* 56**,** 395-407.
CUI, R. Z., BRUCE, A. J. & ROGERS, R. S., 3RD 2016. Recurrent aphthous stomatitis. *Clin Dermatol,* 34**,** 475-81.
CZERNINSKI, R., ZADIK, Y., KARTIN-GABBAY, T., ZINI, A. & TOUGER-DECKER, R. 2014. Dietary alterations in patients with oral vesiculoulcerative diseases. *Oral Surg Oral Med Oral Pathol Oral Radiol,* 117**,** 319-23.
DE ROSSI, S. S. & CIARROCCA, K. 2014. Oral lichen planus and lichenoid mucositis. *Dent Clin North Am,* 58**,** 299-313.
DE VET, H. C., TERWEE, C. B., OSTELO, R. W., BECKERMAN, H., KNOL, D. L. & BOUTER, L. M. 2006. Minimal changes in health status questionnaires: distinction between minimally detectable change and minimally important change. *Health Qual Life Outcomes,* 4**,** 54.
DE VET, H. C. W., TERWEE, C., MOKKINK, W. & KNOL, D. L. 2015. *Measurement in medicine : a practical guide*.
DEVELLIS, R. F. 2017. *Scale development : theory and applications*.
DEVLIN, N. J., APPLEBY, J., BUXTON, M., KING EDWARD'S HOSPITAL FUND FOR, L. & OFFICE OF HEALTH, E. 2010. *Getting the most out of PROMs : putting health outcomes at the heart of NHS decision-making,* London, King's Fund.
DI ZENZO, G., CARROZZO, M. & CHAN, L. S. 2014. Urban legend series: mucous membrane pemphigoid. *Oral Dis,* 20**,** 35-54.
EISEN, D. 2002. The clinical features, malignant potential, and systemic associations of oral lichen planus: a study of 723 patients. *J Am Acad Dermatol,* 46**,** 207-14.
EISEN, D., CARROZZO, M., BAGAN SEBASTIAN, J. V. & THONGPRASOM, K. 2005. Number V Oral lichen planus: clinical features and management. *Oral Dis,* 11**,** 338-49.
EL ACHHAB, Y., NEJJARI, C., CHIKRI, M. & LYOUSSI, B. 2008. Disease-specific health-related quality of life instruments among adults diabetic: A systematic review. *Diabetes Res Clin Pract,* 80**,** 171-84.
EMERSON KAVCHAK, A. J., COOK, C., HEGEDUS, E. J. & WRIGHT, A. A. 2013. Identification of cut-points in commonly used hip osteoarthritis-related outcome measures that define the patient acceptable symptom state (PASS). *Rheumatol Int,* 33**,** 2773-82.
ESCOBAR, A. & RIDDLE, D. L. 2014. Concordance between important change and acceptable symptom state following knee arthroplasty: the role of baseline scores. *Osteoarthritis Cartilage,* 22**,** 1107-10.
ESCUDIER, M., AHMED, N., SHIRLAW, P., SETTERFIELD, J., TAPPUNI, A., BLACK, M. M. & CHALLACOMBE, S. J. 2007. A scoring system for mucosal disease severity with special reference to oral lichen planus. *Br J Dermatol,* 157**,** 765-70.
FARNIK, M. & PIERZCHALA, W. A. 2012. Instrument development and evaluation for patient-related outcomes assessments. *Patient Relat Outcome Meas,* 3**,** 1-7.
FARRELL, M., HOWES, S., TAYLOR, C., LEWIS, G., JENKINS, R., BEBBINGTON, P., JARVIS, M., BRUGHA, T., GILL, B. & MELTZER, H. 1998. Substance misuse and psychiatric comorbidity: an overview of the OPCS National Psychiatric Morbidity Survey. *Addict Behav,* 23**,** 909-18.
FAYERS, P. M. & MACHIN, D. 2016a. The quality of life : the assessment, analysis and reporting of patient-reported outcomes.
FAYERS, P. M. & MACHIN, D. 2016b. *Quality of life the assessment, analysis and reporting of patient-reported outcomes,* Chichester, Wiley.
FEMIANO, F., GOMBOS, F. & SCULLY, C. 2003. Sweet's syndrome: recurrent oral ulceration, pyrexia, thrombophlebitis, and cutaneous lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod,* 95**,** 324-7.
FILIPOVICH, A. H. 2008. Diagnosis and manifestations of chronic graft-versus-host disease. *Best Pract Res Clin Haematol,* 21**,** 251-7.

FINLAY, A. Y. & KHAN, G. K. 1994. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol,* 19**,** 210-6.
FITZPATRICK, R., DAVEY, C., BUXTON, M. J. & JONES, D. R. 1998. Evaluating patient-based outcome measures for use in clinical trials. *Health Technol Assess,* 2**,** i-iv, 1-74.
FITZPATRICK, S. G., HIRSCH, S. A. & GORDON, S. C. 2014. The malignant transformation of oral lichen planus and oral lichenoid lesions: a systematic review. *J Am Dent Assoc,* 145**,** 45-56.
FLUHARTY, M., TAYLOR, A. E., GRABSKI, M. & MUNAFÒ, M. R. 2017. The Association of Cigarette Smoking With Depression and Anxiety: A Systematic Review. *Nicotine Tob Res,* 19**,** 3-13.
GALLO, C., BARROS, F., SUGAYA, N., NUNES, F. & BORRA, R. 2012. Differential expression of toll-like receptor mRNAs in recurrent aphthous ulceration. *J Oral Pathol Med,* 41**,** 80-5.
GALLO CDE, B., MIMURA, M. A. & SUGAYA, N. N. 2009. Psychological stress and recurrent aphthous stomatitis. *Clinics (Sao Paulo),* 64**,** 645-8.
GAMBINO, A., CARBONE, M., ARDUINO, P. G., CARCIERI, P., CARBONE, L. & BROCCOLETTI, R. 2014. Conservative approach in patients with pemphigus gingival vulgaris: a pilot study of five cases. *Int J Dent,* 2014**,** 747506.
GARCIA-POLA, M. J. & HUERTA, G. 2000. Ansiety as an etiologic factor in oral lichen planus. *Med Oral,* 5**,** 7-13.
GARRATT, A., SCHMIDT, L., MACKINTOSH, A. & FITZPATRICK, R. 2002. Quality of life measurement: bibliographic study of patient assessed health outcome measures. *Bmj,* 324**,** 1417.
GAVIC, L., CIGIC, L., BIOCINA LUKENDA, D., GRUDEN, V. & GRUDEN POKUP EC, J. S. 2014. The role of anxiety, depression, and psychological stress on the clinical status of recurrent aphthous stomatitis and oral lichen planus. *J Oral Pathol Med,* 43**,** 410-7.
GHIMIRE, P., HASEGAWA, H., KALYAL, N., HURWITZ, V. & ASHKAN, K. 2018. Patient-Reported Outcome Measures in Neurosurgery: A Review of the Current Literature. *Neurosurgery,* 83**,** 622-630.
GIULIANI, M., TROIANO, G., CORDARO, M., CORSALINI, M., GIOCO, G., LO MUZIO, L., PIGNATELLI, P. & LAJOLO, C. 2019. Rate of malignant transformation of oral lichen planus: A systematic review. *Oral Dis,* 25**,** 693-709.
GONZALEZ-MOLES, M. A., RUIZ-AVILA, I., GONZALEZ-RUIZ, L., AYEN, A., GIL-MONTOYA, J. A. & RAMOS-GARCIA, P. 2019. Malignant transformation risk of oral lichen planus: A systematic review and comprehensive meta-analysis. *Oral Oncol,* 96**,** 121-130.
GONZALEZ-MOLES, M. A., RUIZ-AVILA, I., RODRIGUEZ-ARCHILLA, A., MORALES-GARCIA, P., MESA-AGUADO, F., BASCONES-MARTINEZ, A. & BRAVO, M. 2003. Treatment of severe erosive gingival lesions by topical application of clobetasol propionate in custom trays. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod,* 95**,** 688-92.
GONZALEZ-MOLES, M. A. & SCULLY, C. 2005. Vesiculo-erosive oral mucosal disease--management with topical corticosteroids: (2) Protocols, monitoring of effects and adverse reactions, and the future. *J Dent Res,* 84**,** 302-8.
GRANDHE, N. P., DOGRA, S. & KANWAR, A. J. 2005. Multiple autoimmune syndrome in a patient with pemphigus vulgaris. *Acta Derm Venereol,* 85**,** 91-2.
GREENBERG, M. S. & PINTO, A. 2003. Etiology and Management of Recurrent Aphthous Stomatitis. *Curr Infect Dis Rep,* 5**,** 194-198.
GREENHALGH, J. & MEADOWS, K. 1999. The effectiveness of the use of patient-based measures of health in routine practice in improving the process and outcomes of patient care: a literature review. *J Eval Clin Pract,* 5**,** 401-16.
GUYATT, G. & SCHUNEMANN, H. 2007. How can quality of life researchers make their work more useful to health workers and their patients? *Qual Life Res,* 16**,** 1097-105.
GUYATT, G. H., OSOBA, D., WU, A. W., WYRWICH, K. W. & NORMAN, G. R. 2002. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc,* 77**,** 371-83.

HAISRAELI-SHALISH, M., LIVNEH, A., KATZ, J., DOOLMAN, R. & SELA, B. A. 1996. Recurrent aphthous stomatitis and thiamine deficiency. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod,* 82**,** 634-6.

HANDFIELD-JONES, S., ALLEN, B. R. & LITTLEWOOD, S. M. 1985. Dapsone use with oral-genital ulcers. *Br J Dermatol,* 113**,** 501.

HANNA, S., KIM, M. & MURRELL, D. F. 2016. Validation studies of outcome measures in pemphigus. *Int J Womens Dermatol,* 2**,** 128-139.

HAPA, A., AKSOY, B., POLAT, M., ASLAN, U. & ATAKAN, N. 2011. Does recurrent aphthous stomatitis affect quality of life? A prospective study with 128 patients evaluating different treatment modalities. *J Dermatolog Treat,* 22**,** 215-20.

HARMAN, K. E., BROWN, D., EXTON, L. S., GROVES, R. W., HAMPTON, P. J., MOHD MUSTAPA, M. F., SETTERFIELD, J. F. & YESUDIAN, P. D. 2017. British Association of Dermatologists' guidelines for the management of pemphigus vulgaris 2017. *Br J Dermatol,* 177**,** 1170-1201.

HARMAN, K. E., SEED, P. T., GRATIAN, M. J., BHOGAL, B. S., CHALLACOMBE, S. J. & BLACK, M. M. 2001. The severity of cutaneous and oral pemphigus is related to desmoglein 1 and 3 antibody levels. *Br J Dermatol,* 144**,** 775-80.

HAWKER, G. A., MIAN, S., KENDZERSKA, T. & FRENCH, M. 2011. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken),* 63 Suppl 11**,** S240-52.

HAWKINS, M., ELSWORTH, G. R. & OSBORNE, R. H. 2018. Application of validity theory and methodology to patient-reported outcome measures (PROMs): building an argument for validity. *Qual Life Res,* 27**,** 1695-1710.

HAY, K. D. & READE, P. C. 1984. The use of an elimination diet in the treatment of recurrent aphthous ulceration of the oral cavity. *Oral Surg Oral Med Oral Pathol,* 57**,** 504-7.

HEGARTY, A. M., MCGRATH, C., HODGSON, T. A. & PORTER, S. R. 2002. Patient-centred outcome measures in oral medicine: are they valid and reliable? *Int J Oral Maxillofac Surg,* 31**,** 670-4.

HELLO, M., BARBAROT, S., BASTUJI-GARIN, S., REVUZ, J. & CHOSIDOW, O. 2010. Use of thalidomide for severe recurrent aphthous stomatitis: a multicenter cohort analysis. *Medicine (Baltimore),* 89**,** 176-82.

HERBST, A. & BYSTRYN, J. C. 2000. Patterns of remission in pemphigus vulgaris. *J Am Acad Dermatol,* 42**,** 422-7.

HIETANEN, J., HAYRINEN-IMMONEN, R., AL-SAMADI, A., TROKOVIC, N., KOSKENPATO, K. & KONTTINEN, Y. T. 2012. Recurrent aphthous ulcers--a Toll-like receptor-mediated disease? *J Oral Pathol Med,* 41**,** 158-64.

HINZ, A., KRAUSS, O., STOLZENBURG, J. U., SCHWALENBERG, T., MICHALSKI, D. & SCHWARZ, R. 2009. Anxiety and depression in patients with prostate cancer and other urogenital cancer: a longitudinal study. *Urol Oncol,* 27**,** 367-72.

HSU, D. Y., BRIEVA, J., SINHA, A. A., LANGAN, S. M. & SILVERBERG, J. I. 2016. Comorbidities and inpatient mortality for pemphigus in the U.S.A. *Br J Dermatol,* 174**,** 1290-8.

HU, L.-T. & BENTLER, P. M. 1999a. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling,* 6**,** 1-55.

HU, L. T. & BENTLER, P. M. 1999b. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling: A Multidisciplinary Journal,* 6**,** 1-55.

HUANG, Y. H., KUO, C. F., CHEN, Y. H. & YANG, Y. W. 2012. Incidence, mortality, and causes of death of patients with pemphigus in Taiwan: a nationwide population-based study. *J Invest Dermatol,* 132**,** 92-7.

HULING, L. B., BACCAGLINI, L., CHOQUETTE, L., FEINN, R. S. & LALLA, R. V. 2012. Effect of stressful life events on the onset and duration of recurrent aphthous stomatitis. *J Oral Pathol Med,* 41**,** 149-52.

IANI, L., LAURIOLA, M. & COSTANTINI, M. 2014. A confirmatory bifactor analysis of the Hospital Anxiety and Depression Scale in an Italian community sample. *Health Qual Life Outcomes,* 12**,** 84.

IKEDA, N., ISHII, T., IIDA, S. & KAWAI, T. 1991. Epidemiological study of oral leukoplakia based on mass screening for oral mucosal diseases in a selected Japanese population. *Community Dent Oral Epidemiol,* 19**,** 160-3.

IMAI, H., MOTEGI, M., MIZUKI, N., OHTANI, H., KOMATSUDA, A., HAMAI, K. & MIURA, A. B. 1997. Mouth and genital ulcers with inflamed cartilage (MAGIC syndrome): a case report and literature review. *Am J Med Sci,* 314**,** 330-2.

IMANGULI, M. M., ALEVIZOS, I., BROWN, R., PAVLETIC, S. Z. & ATKINSON, J. C. 2008. Oral graft-versus-host disease. *Oral Dis,* 14**,** 396-412.

INGAFOU, M., LEAO, J. C., PORTER, S. R. & SCULLY, C. 2006. Oral lichen planus: a retrospective study of 690 British patients. *Oral Dis,* 12**,** 463-8.

ISMAIL, S. B., KUMAR, S. K. & ZAIN, R. B. 2007. Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis, management and malignant transformation. *J Oral Sci,* 49**,** 89-106.

JENSEN, M. P., KAROLY, P. & BRAVER, S. 1986. The measurement of clinical pain intensity: a comparison of six methods. *Pain,* 27**,** 117-26.

JENSEN, M. P. & MCFARLAND, C. A. 1993. Increasing the reliability and validity of pain intensity measurement in chronic pain patients. *Pain,* 55**,** 195-203.

JOHNSTON, B. C., THORLUND, K., SCHUNEMANN, H. J., XIE, F., MURAD, M. H., MONTORI, V. M. & GUYATT, G. H. 2010. Improving the interpretation of quality of life evidence in meta-analyses: the application of minimal important difference units. *Health Qual Life Outcomes,* 8**,** 116.

JURGE, S., KUFFER, R., SCULLY, C. & PORTER, S. R. 2006. Mucosal disease series. Number VI. Recurrent aphthous stomatitis. *Oral Dis,* 12**,** 1-21.

KARASNEH, J. A., DARWAZEH, A. M., HASSAN, A. F. & THORNHILL, M. 2011. Association between recurrent aphthous stomatitis and inheritance of a single-nucleotide polymorphism of the NOS2 gene encoding inducible nitric oxide synthase. *J Oral Pathol Med,* 40**,** 715-20.

KARBACH, J., AL-NAWAS, B., MOERGEL, M. & DAUBLANDER, M. 2014. Oral health-related quality of life of patients with oral lichen planus, oral leukoplakia, or oral squamous cell carcinoma. *J Oral Maxillofac Surg,* 72**,** 1517-22.

KASPERKIEWICZ, M., ELLEBRECHT, C. T., TAKAHASHI, H., YAMAGAMI, J., ZILLIKENS, D., PAYNE, A. S. & AMAGAI, M. 2017. Pemphigus. *Nat Rev Dis Primers,* 3**,** 17026.

KATON, W., LIN, E. H. & KROENKE, K. 2007. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen Hosp Psychiatry,* 29**,** 147-55.

KAVUSI, S., DANESHPAZHOOH, M., FARAHANI, F., ABEDINI, R., LAJEVARDI, V. & CHAMS-DAVATCHI, C. 2008. Outcome of pemphigus vulgaris. *J Eur Acad Dermatol Venereol,* 22**,** 580-4.

KEOGAN, M. T. 2009. Clinical Immunology Review Series: an approach to the patient with recurrent orogenital ulceration, including Behcet's syndrome. *Clin Exp Immunol,* 156**,** 1-11.

KHANDWALA, A., VAN INWEGEN, R. G. & ALFANO, M. C. 1997. 5% amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers: I. Clinical demonstration of acceleration of healing and resolution of pain. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod,* 83**,** 222-30.

KHARFI, M., KHALED, A., ANANE, R., FAZAA, B. & KAMOUN, M. R. 2010. Early onset childhood cicatricial pemphigoid: a case report and review of the literature. *Pediatr Dermatol,* 27**,** 119-24.

KHUDHUR, A. S., DI ZENZO, G. & CARROZZO, M. 2014. Oral lichenoid tissue reactions: diagnosis and classification. *Expert Rev Mol Diagn,* 14**,** 169-84.
KIM, S. A., KIM, E., MORRIS, R. G. & PARK, W. S. 2015. Exploring the non-linear relationship between alcohol consumption and depression in an elderly population in Gangneung: the Gangneung Health Study. *Yonsei Med J,* 56**,** 418-25.
KING, M. T. 2011. A point of minimal important difference (MID): a critique of terminology and methods. *Expert Rev Pharmacoecon Outcomes Res,* 11**,** 171-84.
KLEINMAN, D. V., SWANGO, P. A. & PINDBORG, J. J. 1994. Epidemiology of oral mucosal lesions in United States schoolchildren: 1986-87. *Community Dent Oral Epidemiol,* 22**,** 243-53.
KNEISEL, A. & HERTL, M. 2011. Autoimmune bullous skin diseases. Part 1: Clinical manifestations. *J Dtsch Dermatol Ges,* 9**,** 844-56; quiz 857.
KOOPAI, M., MORTAZAVI, H., KHATAMI, A. & KHODASHENAS, Z. 2018. Salivary and Serum Anti-Desmoglein 1 and 3 ELISA and Indirect Immunofluorescence in Pemphigus Vulgaris: Correlations with Serum ELISA, Indirect Immunofluorescence and Disease Severity. *Acta Dermatovenerol Croat,* 26**,** 91-99.
KOUROSH, A. S. & YANCEY, K. B. 2011. Therapeutic approaches to patients with mucous membrane pemphigoid. *Dermatol Clin,* 29**,** 637-41.
KRABBE, P. F. M. 2017. The measurement of health and health status concepts : methods and applications from a multidisciplinary perspective. : methods and applications from a multidisciplinary perspective.
KRAMER, I. R., LUCAS, R. B., PINDBORG, J. J. & SOBIN, L. H. 1978. Definition of leukoplakia and related lesions: an aid to studies on oral precancer. *Oral Surg Oral Med Oral Pathol,* 46**,** 518-39.
KRIDIN, K., ZELBER-SAGI, S., KHAMAISI, M., COHEN, A. D. & BERGMAN, R. 2016. Remarkable differences in the epidemiology of pemphigus among two ethnic populations in the same geographic region. *J Am Acad Dermatol,* 75**,** 925-930.
KROENKE, K., SPITZER, R. L., WILLIAMS, J. B., MONAHAN, P. O. & LOWE, B. 2007. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. *Ann Intern Med,* 146**,** 317-25.
KROENKE, K., WU, J., YU, Z., BAIR, M. J., KEAN, J., STUMP, T. & MONAHAN, P. O. 2016. Patient Health Questionnaire Anxiety and Depression Scale: Initial Validation in Three Clinical Trials. *Psychosom Med,* 78**,** 716-27.
KURAGO, Z. B. 2016. Etiology and pathogenesis of oral lichen planus: an overview. *Oral Surg Oral Med Oral Pathol Oral Radiol,* 122**,** 72-80.
KUTEN-SHORRER, M., WOO, S. B. & TREISTER, N. S. 2014. Oral graft-versus-host disease. *Dent Clin North Am,* 58**,** 351-68.
KYTE, D. G., CALVERT, M., VAN DER WEES, P. J., TEN HOVE, R., TOLAN, S. & HILL, J. C. 2015. An introduction to patient-reported outcome measures (PROMs) in physiotherapy. *Physiotherapy,* 101**,** 119-25.
LAEIJENDECKER, R., VAN JOOST, T., TANK, B., ORANJE, A. P. & NEUMANN, H. A. 2005. Oral lichen planus in childhood. *Pediatr Dermatol,* 22**,** 299-304.
LE CLEACH, L. & CHOSIDOW, O. 2012. Clinical practice. Lichen planus. *N Engl J Med,* 366**,** 723-32.
LEE, C. P., CHOU, Y. H., LIU, C. Y. & HUNG, C. I. 2017. Dimensionality of the Chinese hospital anxiety depression scale in psychiatric outpatients: Mokken scale and factor analyses. *Int J Psychiatry Clin Pract,* 21**,** 283-291.
LEE, E. H. 2012. Review of the psychometric evidence of the perceived stress scale. *Asian Nurs Res (Korean Soc Nurs Sci),* 6**,** 121-7.
LEE, Y. C., SHIN, S. Y., KIM, S. W. & EUN, Y. G. 2013. Intralesional injection versus mouth rinse of triamcinolone acetonide in oral lichen planus: a randomized controlled study. *Otolaryngol Head Neck Surg,* 148**,** 443-9.

LI, C.-H. 2016. Confirmatory factor analysis with ordinal data: Comparing robust maximum likelihood and diagonally weighted least squares. *Behavior Research Methods,* 48**,** 936-949.
LI, M. & HE, S. L. 2013. Reliability and validity of the Chinese version of the chronic oral mucosal diseases questionnaire. *J Oral Pathol Med,* 42**,** 194-9.
LINDEN, W., VODERMAIER, A., MACKENZIE, R. & GREIG, D. 2012. Anxiety and depression after cancer diagnosis: prevalence rates by cancer type, gender, and age. *J Affect Disord,* 141**,** 343-51.
LIU, C., ZHOU, Z., LIU, G., WANG, Q., CHEN, J., WANG, L., ZHOU, Y., DONG, G., XU, X., WANG, Y., GUO, Y., LIN, M., WU, L., DU, G., WEI, C., ZENG, X., WANG, X., WU, J., LI, B., ZHOU, G. & ZHOU, H. 2012. Efficacy and safety of dexamethasone ointment on recurrent aphthous ulceration. *Am J Med,* 125**,** 292-301.
LLEWELLYN, C. D. & WARNAKULASURIYA, S. 2003. The impact of stomatological disease on oral health-related quality of life. *Eur J Oral Sci,* 111**,** 297-304.
LOCKER, D. 1988. Measuring oral health: a conceptual framework. *Community Dent Health,* 5**,** 3-18.
LODI, G., CARROZZO, M., FURNESS, S. & THONGPRASOM, K. 2012. Interventions for treating oral lichen planus: a systematic review. *Br J Dermatol,* 166**,** 938-47.
LODI, G., PELLICANO, R. & CARROZZO, M. 2010. Hepatitis C virus infection and lichen planus: a systematic review with meta-analysis. *Oral Dis,* 16**,** 601-12.
LOPEZ-JORNET, P. & CAMACHO-ALONSO, F. 2010. Quality of life in patients with oral lichen planus. *J Eval Clin Pract,* 16**,** 111-3.
LOPEZ-JORNET, P., CAMACHO-ALONSO, F. & LUCERO BERDUGO, M. 2009. Measuring the impact of oral mucosa disease on quality of life. *Eur J Dermatol,* 19**,** 603-6.
LOPEZ-JORNET, P., CAYUELA, C. A., TVARIJONAVICIUTE, A., PARRA-PEREZ, F., ESCRIBANO, D. & CERON, J. 2016. Oral lichen planus: salival biomarkers cortisol, immunoglobulin A, adiponectin. *J Oral Pathol Med,* 45**,** 211-7.
LUCIANO, J. V., BARRADA, J. R., AGUADO, J., OSMA, J. & GARCIA-CAMPAYO, J. 2014. Bifactor analysis and construct validity of the HADS: a cross-sectional and longitudinal study in fibromyalgia patients. *Psychol Assess,* 26**,** 395-406.
LUKACS, J., SCHLIEMANN, S. & ELSNER, P. 2015. Lichen planus and lichenoid reactions as a systemic disease. *Clin Dermatol,* 33**,** 512-9.
MAIN, C. J. 2016. Pain assessment in context: a state of the science review of the McGill pain questionnaire 40 years on. *Pain,* 157**,** 1387-99.
MAKSYMOWYCH, W. P., GOOCH, K., DOUGADOS, M., WONG, R. L., CHEN, N., KUPPER, H. & VAN DER HEIJDE, D. 2010. Thresholds of patient-reported outcomes that define the patient acceptable symptom state in ankylosing spondylitis vary over time and by treatment and patient characteristics. *Arthritis Care Res (Hoboken),* 62**,** 826-34.
MATTHEWS, R. W., SCULLY, C. M., LEVERS, B. G. & HISLOP, W. S. 1987. Clinical evaluation of benzydamine, chlorhexidine, and placebo mouthwashes in the management of recurrent aphthous stomatitis. *Oral Surg Oral Med Oral Pathol,* 63**,** 189-91.
MATTSSON, U., JONTELL, M. & HOLMSTRUP, P. 2002. Oral lichen planus and malignant transformation: is a recall of patients justified? *Crit Rev Oral Biol Med,* 13**,** 390-6.
MATTSSON, U., MAGNUSSON, B. & JONTELL, M. 2010. Squamous cell carcinoma in a patient with oral lichen planus treated with topical application of tacrolimus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod,* 110**,** e19-25.
MCCARTAN, B. E. & HEALY, C. M. 2008. The reported prevalence of oral lichen planus: a review and critique. *J Oral Pathol Med,* 37**,** 447-53.
MCGRATH, C. & BEDI, R. 2001. An evaluation of a new measure of oral health related quality of life--OHQoL-UK(W). *Community Dent Health,* 18**,** 138-43.
MCGRATH, C., HEGARTY, A. M., HODGSON, T. A. & PORTER, S. R. 2003. Patient-centred outcome measures for oral mucosal disease are sensitive to treatment. *Int J Oral Maxillofac Surg,* 32**,** 334-6.

MCMILLAN, R., TAYLOR, J., SHEPHARD, M., AHMED, R., CARROZZO, M., SETTERFIELD, J., GRANDO, S., MIGNOGNA, M., KUTEN-SHORRER, M., MUSBAH, T., ELIA, A., MCGOWAN, R., KERR, A. R., GREENBERG, M. S., HODGSON, T. & SIROIS, D. 2015. World Workshop on Oral Medicine VI: a systematic review of the treatment of mucocutaneous pemphigus vulgaris. *Oral Surg Oral Med Oral Pathol Oral Radiol,* 120**,** 132-42.e61.

MCPARLAND, H. & WARNAKULASURIYA, S. 2012. Oral lichenoid contact lesions to mercury and dental amalgam--a review. *J Biomed Biotechnol,* 2012**,** 589569.

MEADOWS, K. A. 2011. Patient-reported outcome measures: an overview. *Br J Community Nurs,* 16**,** 146-51.

MERGONI, G., ERGUN, S., VESCOVI, P., METE, O., TANYERI, H. & MELETI, M. 2011. Oral postinflammatory pigmentation: an analysis of 7 cases. *Med Oral Patol Oral Cir Bucal,* 16**,** e11-4.

MESSADI, D. V. & YOUNAI, F. 2010. Aphthous ulcers. *Dermatol Ther,* 23**,** 281-90.

MIGNOGNA, M. D., LO RUSSO, L. & FEDELE, S. 2005. Gingival involvement of oral lichen planus in a series of 700 patients. *J Clin Periodontol,* 32**,** 1029-33.

MIHAI, S. & SITARU, C. 2007. Immunopathology and molecular diagnosis of autoimmune bullous diseases. *J Cell Mol Med,* 11**,** 462-81.

MILLSAP, R. E. & YUN-TEIN, J. 2004. Assessing Factorial Invariance in Ordered-Categorical Measures. *Multivariate Behavioral Research,* 39**,** 479-515.

MOHAN, M. P. & RAMESH, T. C. 2003. Multiple autoimmune syndrome. *Indian J Dermatol Venereol Leprol,* 69**,** 298-9.

MOKKINK, L. B., DE VET, H. C. W., PRINSEN, C. A. C., PATRICK, D. L., ALONSO, J., BOUTER, L. M. & TERWEE, C. B. 2018. COSMIN Risk of Bias checklist for systematic reviews of Patient-Reported Outcome Measures. *Qual Life Res,* 27**,** 1171-1179.

MOKKINK, L. B., TERWEE, C. B., PATRICK, D. L., ALONSO, J., STRATFORD, P. W., KNOL, D. L., BOUTER, L. M. & DE VET, H. C. 2010. The COSMIN study reached international consensus on taxonomy, terminology, and definitions of measurement properties for health-related patient-reported outcomes. *J Clin Epidemiol,* 63**,** 737-45.

MORRIS, J., PEREZ, D. & MCNOE, B. 1998. The use of quality of life data in clinical practice. *Qual Life Res,* 7**,** 85-91.

MUMCU, G., HAYRAN, O., OZALP, D. O., INANC, N., YAVUZ, S., ERGUN, T. & DIRESKENELI, H. 2007. The assessment of oral health-related quality of life by factor analysis in patients with Behcet's disease and recurrent aphthous stomatitis. *J Oral Pathol Med,* 36**,** 147-52.

MUMCU, G., INANC, N., ERGUN, T., IKIZ, K., GUNES, M., ISLEK, U., YAVUZ, S., SUR, H., ATALAY, T. & DIRESKENELI, H. 2006. Oral health related quality of life is affected by disease activity in Behcet's disease. *Oral Dis,* 12**,** 145-51.

MUMCU, G., SUR, H., INANC, N., KARACAYLI, U., CIMILLI, H., SISMAN, N., ERGUN, T. & DIRESKENELI, H. 2009. A composite index for determining the impact of oral ulcer activity in Behcet's disease and recurrent aphthous stomatitis. *J Oral Pathol Med,* 38**,** 785-91.

MURTI, P. R., DAFTARY, D. K., BHONSLE, R. B., GUPTA, P. C., MEHTA, F. S. & PINDBORG, J. J. 1986. Malignant potential of oral lichen planus: observations in 722 patients from India. *J Oral Pathol,* 15**,** 71-7.

MUSTAFA, M. B., PORTER, S. R., SMOLLER, B. R. & SITARU, C. 2015. Oral mucosal manifestations of autoimmune skin diseases. *Autoimmun Rev,* 14**,** 930-51.

NAIR, J. R. & MOOTS, R. J. 2017. Behcet's disease. *Clin Med (Lond),* 17**,** 71-77.

NAJAFI, S., MOHAMMADZADEH, M., RAJABI, F., ZARE BIDOKI, A., YOUSEFI, H., FARHADI, E. & REZAEI, N. 2018. Interleukin-4 and Interleukin-4 Receptor Alpha Gene Polymorphisms in Recurrent Aphthous Stomatitis. *Immunol Invest,* 47**,** 680-688.

NATAH, S. S., KONTTINEN, Y. T., ENATTAH, N. S., ASHAMMAKHI, N., SHARKEY, K. A. & HAYRINEN-IMMONEN, R. 2004. Recurrent aphthous ulcers today: a review of the growing knowledge. *Int J Oral Maxillofac Surg,* 33**,** 221-34.

NAZEMI-TABRIZI, M.-J., HATAMI, P., GHIASI, M., DANESHPAZHOOH, M. & CHAMS-DAVATCHI, C. 2012. Randomized trial of tacrolimus 0.1% ointment versus triamcinolone acetonide 0.1% paste in the treatment of oral pemphigus vulgaris. *Iranian Journal of Dermatology,* 15**,** 42-46.

NAZEMI TABRIZI, M. J., HATAMI, P., GHIASI, M., DANESH PAZHOUH, M. & CHAMS DAVATCHI, C. 2012. Randomized trial of tacrolimus 0.1% ointment versus triamcinolone acetonide 0.1% paste in the treatment of oral pemphigus vulgaris *Iranian Journal of Dermatology* 15**,** -.

NG, P. P., THNG, S. T., MOHAMED, K. & TAN, S. H. 2005. Comparison of desmoglein ELISA and indirect immunofluorescence using two substrates (monkey oesophagus and normal human skin) in the diagnosis of pemphigus. *Australas J Dermatol,* 46**,** 239-41.

NI RIORDAIN, R., HODGSON, T., PORTER, S. & FEDELE, S. 2016. Validity and reliability of the Chronic Oral Mucosal Diseases Questionnaire in a UK population. *J Oral Pathol Med,* 45**,** 613-6.

NI RIORDAIN, R. & MCCREARY, C. 2010. The use of quality of life measures in oral medicine: a review of the literature. *Oral Dis,* 16**,** 419-30.

NI RIORDAIN, R. & MCCREARY, C. 2011. Validity and reliability of a newly developed quality of life questionnaire for patients with chronic oral mucosal diseases. *J Oral Pathol Med,* 40**,** 604-9.

NI RIORDAIN, R. & MCCREARY, C. 2012. Further reliability and responsiveness of the Chronic Oral Mucosal Diseases Questionnaire. *Oral Dis,* 18**,** 60-6.

NI RIORDAIN, R., MEANEY, S. & MCCREARY, C. 2011a. Impact of chronic oral mucosal disease on daily life: preliminary observations from a qualitative study. *Oral Dis,* 17**,** 265-9.

NI RIORDAIN, R., MEANEY, S. & MCCREARY, C. 2011b. A patient-centered approach to developing a quality-of-life questionnaire for chronic oral mucosal diseases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod,* 111**,** 578-86, 586.e1-2.

NI RIORDAIN, R., SHIRLAW, P., ALAJBEG, I., AL ZAMEL, G. Y., FUNG, P. L., YUAN, A. D., MCCREARY, C., STOOPLER, E. T., DE ROSSI, S. S., LODI, G., GREENBERG, M. S. & BRENNAN, M. T. 2015. World Workshop on Oral Medicine VI: Patient-reported outcome measures and oral mucosal disease: current status and future direction. *Oral Surg Oral Med Oral Pathol Oral Radiol,* 120**,** 152-60.e11.

NÍ RÍORDÁIN, R. & WIRIYAKIJJA, P. 2017. Patient reported outcome and experience measures of oral disease in oral medicine. *Br Dent J,* 223**,** 713.

NIELSEN, M. G., ORNBOL, E., VESTERGAARD, M., BECH, P., LARSEN, F. B., LASGAARD, M. & CHRISTENSEN, K. S. 2016. The construct validity of the Perceived Stress Scale. *J Psychosom Res,* 84**,** 22-30.

NOLAN, A., MCINTOSH, W. B., ALLAM, B. F. & LAMEY, P. J. 1991. Recurrent aphthous ulceration: vitamin B1, B2 and B6 status and response to replacement therapy. *J Oral Pathol Med,* 20**,** 389-91.

NORTON, S., COSCO, T., DOYLE, F., DONE, J. & SACKER, A. 2013. The Hospital Anxiety and Depression Scale: a meta confirmatory factor analysis. *J Psychosom Res,* 74**,** 74-81.

NOUD, M., HOVIS, K., GELBARD, A., SATHE, N. A., PENSON, D. F., FEURER, I. D., MCPHEETERS, M. L. & FRANCIS, D. O. 2017. Patient-Reported Outcome Measures in Upper Airway-Related Dyspnea: A Systematic Review. *JAMA Otolaryngol Head Neck Surg,* 143**,** 824-831.

NUNNALLY, J. C. & BERNSTEIN, I. H. 2010. *Psychometric theory,* New Delhi, Tata McGraw-Hill Ed.

OJHA, J., BHATTACHARYYA, I., STEWART, C. & KATZ, J. 2007. Cicatricial pemphigoid with severe gingival and laryngeal involvement in an 18-year-old female. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod,* 104**,** 363-7.

OKUMUS, O., KALKAN, S., KESER, G. & PEKINER, F. N. 2015. Awareness assessment in Turkish subpopulation with chronic oral mucosal diseases. *Eur J Dent,* 9**,** 564-572.

OLIVEIRA, P. C., REIS JUNIOR, J. A., LACERDA, J. A., SILVEIRA, N. T., SANTOS, J. M., VITALE, M. C. & PINHEIRO, A. L. 2009. Laser light may improve the symptoms of oral lesions of cicatricial pemphigoid: a case report. *Photomed Laser Surg,* 27**,** 825-8.

OSOBA, D., BEZJAK, A., BRUNDAGE, M., ZEE, B., TU, D. & PATER, J. 2005. Analysis and interpretation of health-related quality-of-life data from clinical trials: basic approach of The National Cancer Institute of Canada Clinical Trials Group. *Eur J Cancer,* 41**,** 280-7.

PARLATESCU, I., TOVARU, M., NICOLAE, C. L., SFEATCU, R. & DIDILESCU, A. C. 2019. Oral health-related quality of life in different clinical forms of oral lichen planus. *Clin Oral Investig*.

PATEL, D. A., SHARDA, R., HOVIS, K. L., NICHOLS, E. E., SATHE, N., PENSON, D. F., FEURER, I. D., MCPHEETERS, M. L., VAEZI, M. F. & FRANCIS, D. O. 2017. Patient-reported outcome measures in dysphagia: a systematic review of instrument development and validation. *Dis Esophagus,* 30**,** 1-23.

PATRICK, D. L., BURKE, L. B., GWALTNEY, C. J., LEIDY, N. K., MARTIN, M. L., MOLSEN, E. & RING, L. 2011a. Content validity--establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 1--eliciting concepts for a new PRO instrument. *Value Health,* 14**,** 967-77.

PATRICK, D. L., BURKE, L. B., GWALTNEY, C. J., LEIDY, N. K., MARTIN, M. L., MOLSEN, E. & RING, L. 2011b. Content validity--establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force report: part 2--assessing respondent understanding. *Value Health,* 14**,** 978-88.

PAYERAS, M. R., CHERUBINI, K., FIGUEIREDO, M. A. & SALUM, F. G. 2013. Oral lichen planus: focus on etiopathogenesis. *Arch Oral Biol,* 58**,** 1057-69.

PERERA, M. J., BRINTZ, C. E., BIRNBAUM-WEITZMAN, O., PENEDO, F. J., GALLO, L. C., GONZALEZ, P., GOUSKOVA, N., ISASI, C. R., NAVAS-NACHER, E. L., PERREIRA, K. M., ROESCH, S. C., SCHNEIDERMAN, N. & LLABRE, M. M. 2017. Factor structure of the Perceived Stress Scale-10 (PSS) across English and Spanish language responders in the HCHS/SOL Sociocultural Ancillary Study. *Psychol Assess,* 29**,** 320-328.

PETTI, S., RABIEI, M., DE LUCA, M. & SCULLY, C. 2011. The magnitude of the association between hepatitis C virus infection and oral lichen planus: meta-analysis and case control study. *Odontology,* 99**,** 168-78.

PICEK, P., BULJAN, D., ROGULJ, A. A., STIPETIC-OVCARICEK, J., CATIC, A., PLESTINA, S., BORAS, V. V. & VIDOVIC-JURAS, D. 2012. Psychological status and recurrent aphthous ulceration. *Coll Antropol,* 36**,** 157-9.

PIPPI, R., ROMEO, U., SANTORO, M., DEL VECCHIO, A., SCULLY, C. & PETTI, S. 2016. Psychological disorders and oral lichen planus: matched case-control study and literature review. *Oral Dis,* 22**,** 226-34.

POLAT, C., DUZER, S., AYYILDIZ, H., SEC, S., AKSOY, N., SAKALLIOGLU, O., AKYIGIT, A. & CETINER, H. 2018. Association Between Anxiety, Depression, and Salivary Cortisol Levels in Patients with Recurrent Aphthous Stomatitis. *Turk Arch Otorhinolaryngol,* 56**,** 166-169.

PORTER, S., FLINT, S., SCULLY, C. & KEITH, O. 1992. Recurrent aphthous stomatitis: the efficacy of replacement therapy in patients with underlying hematinic deficiencies. *Ann Dent,* 51**,** 14-6.

PRINSEN, C. A. C., MOKKINK, L. B., BOUTER, L. M., ALONSO, J., PATRICK, D. L., DE VET, H. C. W. & TERWEE, C. B. 2018. COSMIN guideline for systematic reviews of patient-reported outcome measures. *Qual Life Res,* 27**,** 1147-1157.

RAD, M., HASHEMIPOOR, M. A., MOJTAHEDI, A., ZAREI, M. R., CHAMANI, G., KAKOEI, S. & IZADI, N. 2009. Correlation between clinical and histopathologic diagnoses of oral lichen planus based on modified WHO diagnostic criteria. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod,* 107**,** 796-800.

RADOCHOVÁ, V., DŘÍZHAL, I. & SLEZÁK, R. 2014. A retrospective study of 171 patients with oral lichen planus in the East Bohemia - Czech Republic - single center experience. *J Clin Exp Dent,* 6**,** e556-61.

RADWAN-OCZKO, M., ZWYRTEK, E., OWCZAREK, J. E. & SZCZESNIAK, D. 2018. Psychopathological profile and quality of life of patients with oral lichen planus. *J Appl Oral Sci,* 26**,** e20170146.
RAJAN, B., AHMED, J., SHENOY, N., DENNY, C., ONGOLE, R. & BINNAL, A. 2014. Assessment of quality of life in patients with chronic oral mucosal diseases: a questionnaire -based study. *Perm J,* 18**,** e123-7.
RASHID, K. A., GURCAN, H. M. & AHMED, A. R. 2006. Antigen specificity in subsets of mucous membrane pemphigoid. *J Invest Dermatol,* 126**,** 2631-6.
REIS, D., LEHR, D., HEBER, E. & EBERT, D. D. 2017. The German Version of the Perceived Stress Scale (PSS-10): Evaluation of Dimensionality, Validity, and Measurement Invariance With Exploratory and Confirmatory Bifactor Modeling. *Assessment***,** 1073191117715731.
REIS, D., LEHR, D., HEBER, E. & EBERT, D. D. 2019. The German Version of the Perceived Stress Scale (PSS-10): Evaluation of Dimensionality, Validity, and Measurement Invariance With Exploratory and Confirmatory Bifactor Modeling. *Assessment,* 26**,** 1246-1259.
RENCZ, F., GULACSI, L., TAMASI, B., KARPATI, S., PENTEK, M., BAJI, P. & BRODSZKY, V. 2015. Health-related quality of life and its determinants in pemphigus: a systematic review and meta-analysis. *Br J Dermatol,* 173**,** 1076-80.
REVICKI, D., HAYS, R. D., CELLA, D. & SLOAN, J. 2008. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J Clin Epidemiol,* 61**,** 102-9.
RODENAS, J. M., ORTEGO, N., HERRANZ, M. T., TERCEDOR, J., PINAR, A. & QUERO, J. H. 1992. Cyclic neutropenia: a cause of recurrent aphthous stomatitis not to be missed. *Dermatology,* 184**,** 205-7.
RODGERS, B., PARSLOW, R. & DEGENHARDT, L. 2007. Affective disorders, anxiety disorders and psychological distress in non-drinkers. *J Affect Disord,* 99**,** 165-72.
ROGERS, R. S., 3RD 1997. Recurrent aphthous stomatitis: clinical characteristics and associated systemic disorders. *Semin Cutan Med Surg,* 16**,** 278-83.
ROGERS, R. S., 3RD & EISEN, D. 2003. Erosive oral lichen planus with genital lesions: the vulvovaginal-gingival syndrome and the peno-gingival syndrome. *Dermatol Clin,* 21**,** 91-8, vi-vii.
ROGERS, Z., ELLIOTT, F., KASPARIAN, N. A., BISHOP, D. T., BARRETT, J. H. & NEWTON-BISHOP, J. 2016. Psychosocial, clinical and demographic features related to worry in patients with melanoma. *Melanoma Res,* 26**,** 497-504.
ROJO-MORENO, J. L., BAGAN, J. V., ROJO-MORENO, J., DONAT, J. S., MILIAN, M. A. & JIMENEZ, Y. 1998. Psychologic factors and oral lichen planus. A psychometric evaluation of 100 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod,* 86**,** 687-91.
ROOPASHREE, M. R., GONDHALEKAR, R. V., SHASHIKANTH, M. C., GEORGE, J., THIPPESWAMY, S. H. & SHUKLA, A. 2010. Pathogenesis of oral lichen planus--a review. *J Oral Pathol Med,* 39**,** 729-34.
ROOSAAR, A., YIN, L., SANDBORGH-ENGLUND, G., NYREN, O. & AXELL, T. 2006. On the natural course of oral lichen lesions in a Swedish population-based sample. *J Oral Pathol Med,* 35**,** 257-61.
RUAH, C. B., STRAM, J. R. & CHASIN, W. D. 1988. Treatment of severe recurrent aphthous stomatitis with colchicine. *Arch Otolaryngol Head Neck Surg,* 114**,** 671-5.
SADLER, E., LAZAROVA, Z., SARASOMBATH, P. & YANCEY, K. B. 2007. A widening perspective regarding the relationship between anti-epiligrin cicatricial pemphigoid and cancer. *J Dermatol Sci,* 47**,** 1-7.
SANTANA, M. J. & FEENY, D. 2014. Framework to assess the effects of using patient-reported outcome measures in chronic care management. *Qual Life Res,* 23**,** 1505-13.
SANTORO, F. A., STOOPLER, E. T. & WERTH, V. P. 2013. Pemphigus. *Dent Clin North Am,* 57**,** 597-610.
SCARDINA, G. A., MESSINA, P., CARINI, F. & MARESI, E. 2006. A randomized trial assessing the effectiveness of different concentrations of isotretinoin in the management of lichen planus. *Int J Oral Maxillofac Surg,* 35**,** 67-71.

SCHELLEKENS, M. P. J., VAN DEN HURK, D. G. M., PRINS, J. B., MOLEMA, J., VAN DER DRIFT, M. A. & SPECKENS, A. E. M. 2016. The suitability of the Hospital Anxiety and Depression Scale, Distress Thermometer and other instruments to screen for psychiatric disorders in both lung cancer patients and their partners. *J Affect Disord,* 203**,** 176-183.

SCHLOSSER, B. J. 2010. Lichen planus and lichenoid reactions of the oral mucosa. *Dermatol Ther,* 23**,** 251-67.

SCHMIDT, E., GOEBELER, M., HERTL, M., SARDY, M., SITARU, C., EMING, R., HOFMANN, S. C., HUNZELMANN, N., KERN, J. S., KRAMER, H., ORZECHOWSKI, H. D., PFEIFFER, C., SCHUSTER, V., SPORBECK, B., STICHERLING, M., WORM, M., ZILLIKENS, D. & NAST, A. 2015. S2k guideline for the diagnosis of pemphigus vulgaris/foliaceus and bullous pemphigoid. *J Dtsch Dermatol Ges,* 13**,** 713-27.

SCHMIDT, E., KASPERKIEWICZ, M. & JOLY, P. 2019. Pemphigus. *Lancet,* 394**,** 882-894.

SCHMIDT, E. & ZILLIKENS, D. 2013. Pemphigoid diseases. *Lancet,* 381**,** 320-32.

SCULLY, C. 2006. Clinical practice. Aphthous ulceration. *N Engl J Med,* 355**,** 165-72.

SCULLY, C. & CARROZZO, M. 2008. Oral mucosal disease: Lichen planus. *Br J Oral Maxillofac Surg,* 46**,** 15-21.

SCULLY, C., CARROZZO, M., GANDOLFO, S., PUIATTI, P. & MONTEIL, R. 1999a. Update on mucous membrane pemphigoid: a heterogeneous immune-mediated subepithelial blistering entity. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod,* 88**,** 56-68.

SCULLY, C. & LO MUZIO, L. 2008. Oral mucosal diseases: mucous membrane pemphigoid. *Br J Oral Maxillofac Surg,* 46**,** 358-66.

SCULLY, C., PAES DE ALMEIDA, O., PORTER, S. R. & GILKES, J. J. 1999b. Pemphigus vulgaris: the manifestations and long-term management of 55 patients with oral lesions. *Br J Dermatol,* 140**,** 84-9.

SCULLY, C. & PORTER, S. 1989. Recurrent aphthous stomatitis: current concepts of etiology, pathogenesis and management. *J Oral Pathol Med,* 18**,** 21-7.

SCULLY, C. & PORTER, S. 2008. Oral mucosal disease: recurrent aphthous stomatitis. *Br J Oral Maxillofac Surg,* 46**,** 198-206.

SEBARATNAM, D. F., HANNA, A. M., CHEE, S. N., FREW, J. W., VENUGOPAL, S. S., DANIEL, B. S., MARTIN, L. K., RHODES, L. M., TAN, J. C., WANG, C. Q., WELSH, B., NIJSTEN, T. & MURRELL, D. F. 2013. Development of a quality-of-life instrument for autoimmune bullous disease: the Autoimmune Bullous Disease Quality of Life questionnaire. *JAMA Dermatol,* 149**,** 1186-91.

SEROR, R., BOOTSMA, H., SARAUX, A., BOWMAN, S. J., THEANDER, E., BRUN, J. G., BARON, G., LE GUERN, V., DEVAUCHELLE-PENSEC, V., RAMOS-CASALS, M., VALIM, V., DORNER, T., TZIOUFAS, A., GOTTENBERG, J. E., SOLANS LAQUE, R., MANDL, T., HACHULLA, E., SIVILS, K. L., NG, W. F., FAUCHAIS, A. L., BOMBARDIERI, S., PRIORI, R., BARTOLONI, E., GOEB, V., PRAPROTNIK, S., SUMIDA, T., NISHIYAMA, S., CAPORALI, R., KRUIZE, A. A., VOLLENWEIDER, C., RAVAUD, P., MEINERS, P., BRITO-ZERON, P., VITALI, C. & MARIETTE, X. 2016. Defining disease activity states and clinically meaningful improvement in primary Sjogren's syndrome with EULAR primary Sjogren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). *Ann Rheum Dis,* 75**,** 382-9.

SETTERFIELD, J. F., NEILL, S., SHIRLAW, P. J., THERON, J., VAUGHAN, R., ESCUDIER, M., CHALLACOMBE, S. J. & BLACK, M. M. 2006. The vulvovaginal gingival syndrome: a severe subgroup of lichen planus with characteristic clinical features and a novel association with the class II HLA DQB1*0201 allele. *J Am Acad Dermatol,* 55**,** 98-113.

SHAH, B., ASHOK, L. & SUJATHA, G. P. 2009. Evaluation of salivary cortisol and psychological factors in patients with oral lichen planus. *Indian J Dent Res,* 20**,** 288-92.

SHENGYUAN, L., SONGPO, Y., WEN, W., WENJING, T., HAITAO, Z. & BINYOU, W. 2009. Hepatitis C virus and lichen planus: a reciprocal association determined by a meta-analysis. *Arch Dermatol,* 145**,** 1040-7.

SHIP, II 1972. Epidemiologic aspects of recurrent aphthous ulcerations. *Oral Surg Oral Med Oral Pathol,* 33**,** 400-6.
SHIP, J. A., CHAVEZ, E. M., DOERR, P. A., HENSON, B. S. & SARMADI, M. 2000. Recurrent aphthous stomatitis. *Quintessence Int,* 31**,** 95-112.
SHIRZAD, A., BIJANI, A., MEHRYARI, M., MOTALLEBNEJAD, M. & MOHSENITAVAKOLI, S. 2018. Validity and reliability of the persian version of the chronic oral mucosal diseases questionnaire. *Caspian J Intern Med,* 9**,** 127-133.
SILVERMAN, S., JR., GORSKY, M., LOZADA-NUR, F. & GIANNOTTI, K. 1991. A prospective study of findings and management in 214 patients with oral lichen planus. *Oral Surg Oral Med Oral Pathol,* 72**,** 665-70.
SISTIG, S., CEKIC-ARAMBASIN, A., RABATIC, S., VUCICEVIC-BORAS, V., KLEINHEINZ, J. & PIFFKO, J. 2001. Natural immunity in recurrent aphthous ulceration. *J Oral Pathol Med,* 30**,** 275-80.
SKOGEN, J. C., HARVEY, S. B., HENDERSON, M., STORDAL, E. & MYKLETUN, A. 2009. Anxiety and depression among abstainers and low-level alcohol consumers. The Nord-Trondelag Health Study. *Addiction,* 104**,** 1519-29.
SLADE, G. D. 1997. Derivation and validation of a short-form oral health impact profile. *Community Dent Oral Epidemiol,* 25**,** 284-90.
SLADE, G. D. & SPENCER, A. J. 1994. Development and evaluation of the Oral Health Impact Profile. *Community Dent Health,* 11**,** 3-11.
SLEBIODA, Z., SZPONAR, E. & KOWALSKA, A. 2014. Etiopathogenesis of recurrent aphthous stomatitis and the role of immunologic aspects: literature review. *Arch Immunol Ther Exp (Warsz),* 62**,** 205-15.
SLOAN, J. A., BERK, L., ROSCOE, J., FISCH, M. J., SHAW, E. G., WYATT, G., MORROW, G. R. & DUECK, A. C. 2007. Integrating patient-reported outcomes into cancer symptom management clinical trials supported by the National Cancer Institute-sponsored clinical trials networks. *J Clin Oncol,* 25**,** 5070-7.
SNAITH, R. P. 2003. The Hospital Anxiety And Depression Scale. *Health Qual Life Outcomes,* 1**,** 29.
SPIELBERGER, C. D. & GORSUCH, R. L. 1983. *Manual for the State-Trait Anxiety Inventory (Form Y) : ("self-evaluation questionnaire"),* Palo Alto, CA, Consulting Psychologists Press, Inc.
STONE, O. J. 1991. Aphthous stomatitis (canker sores): a consequence of high oral submucosal viscosity (the role of extracellular matrix and the possible role of lectins). *Med Hypotheses,* 36**,** 341-4.
STREINER, D. L., NORMAN, G. R. & CAIRNEY, J. 2015. *Health measurement scales : a practical guide to their development and use,* Oxford, Oxford University Press.
SUBRAMANYAM, R. V. 2011. Occurrence of recurrent aphthous stomatitis only on lining mucosa and its relationship to smoking--a possible hypothesis. *Med Hypotheses,* 77**,** 185-7.
SUGERMAN, P. B. & SAVAGE, N. W. 2002. Oral lichen planus: causes, diagnosis and management. *Aust Dent J,* 47**,** 290-7.
SUGERMAN, P. B., SAVAGE, N. W., WALSH, L. J., ZHAO, Z. Z., ZHOU, X. J., KHAN, A., SEYMOUR, G. J. & BIGBY, M. 2002. The pathogenesis of oral lichen planus. *Crit Rev Oral Biol Med,* 13**,** 350-65.
SULLY, K., TRIGG, A., BONNER, N., MORENO-KOEHLER, A., TRENNERY, C., SHAH, N., YUCEL, E., PANJABI, S. & COCKS, K. 2019. Estimation of minimally important differences and responder definitions for EORTC QLQ-MY20 scores in multiple myeloma patients. *Eur J Haematol,* 103**,** 500-509.
SUN, A., CHU, C. T., LIU, B. Y., WANG, J. T., LEU, J. S. & CHIANG, C. P. 2000. Expression of interleukin-2 receptor by activated peripheral blood lymphocytes upregulated by the plasma level of interleukin-2 in patients with recurrent aphthous ulcers. *Proc Natl Sci Counc Repub China B,* 24**,** 116-22.
SURESH, L. & NEIDERS, M. E. 2012. Definitive and differential diagnosis of desquamative gingivitis through direct immunofluorescence studies. *J Periodontol,* 83**,** 1270-8.

SVECOVA, D., PARNICKA, Z., PASTYRIKOVA, L., URBANCEK, S., LUHA, J. & BUC, M. 2015. HLA DRB1* and DQB1* alleles are associated with disease severity in patients with pemphigus vulgaris. *Int J Dermatol,* 54**,** 168-73.

TABACHNICK, B. G. & FIDELL, L. S. 2013. *Using multivariate statistics,* Boston, Pearson Education.

TABOLLI, S., BERGAMO, F., ALESSANDRONI, L., DI PIETRO, C., SAMPOGNA, F. & ABENI, D. 2009. Quality of life and psychological problems of patients with oral mucosal disease in dermatological practice. *Dermatology,* 218**,** 314-20.

TADAKAMADLA, J., KUMAR, S., LALLOO, R., GANDHI BABU, D. B. & JOHNSON, N. W. 2018. Impact of oral potentially malignant disorders on quality of life. *J Oral Pathol Med,* 47**,** 60-65.

TADAKAMADLA, J., KUMAR, S., LALLOO, R. & JOHNSON, N. W. 2017. Development and validation of a quality-of-life questionnaire for patients with oral potentially malignant disorders. *Oral Surg Oral Med Oral Pathol Oral Radiol,* 123**,** 338-349.

TAPPUNI, A. R., KOVACEVIC, T., SHIRLAW, P. J. & CHALLACOMBE, S. J. 2013. Clinical assessment of disease severity in recurrent aphthous stomatitis. *J Oral Pathol Med,* 42**,** 635-41.

TAYLOR, J., GLENNY, A., WALSH, T., BROCKLEHURST, P. & PEMBERTON, M. Core outcome set for recurrent aphthous stomatitis: a collaborative approach. Oral Diseases, 2016. WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA, 16-16.

TAYLOR, J., MCMILLAN, R., SHEPHARD, M., SETTERFIELD, J., AHMED, R., CARROZZO, M., GRANDO, S., MIGNOGNA, M., KUTEN-SHORRER, M., MUSBAH, T., ELIA, A., MCGOWAN, R., KERR, A. R., GREENBERG, M. S., HODGSON, T. & SIROIS, D. 2015. World Workshop on Oral Medicine VI: a systematic review of the treatment of mucous membrane pemphigoid. *Oral Surg Oral Med Oral Pathol Oral Radiol,* 120**,** 161-71.e20.

TERWEE, C. B., BOT, S. D., DE BOER, M. R., VAN DER WINDT, D. A., KNOL, D. L., DEKKER, J., BOUTER, L. M. & DE VET, H. C. 2007. Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol,* 60**,** 34-42.

TERWEE, C. B., PRINSEN, C. A. C., CHIAROTTO, A., WESTERMAN, M. J., PATRICK, D. L., ALONSO, J., BOUTER, L. M., DE VET, H. C. W. & MOKKINK, L. B. 2018. COSMIN methodology for evaluating the content validity of patient-reported outcome measures: a Delphi study. *Qual Life Res,* 27**,** 1159-1170.

THONGPRASOM, K., CARROZZO, M., FURNESS, S. & LODI, G. 2011. Interventions for treating oral lichen planus. *Cochrane Database Syst Rev***,** Cd001168.

THONGPRASOM, K. & DHANUTHAI, K. 2008. Steriods in the treatment of lichen planus: a review. *J Oral Sci,* 50**,** 377-85.

THONGPRASOM, K., YOUNGNAK-PIBOONRATANAKIT, P., PONGSIRIWET, S., LAOTHUMTHUT, T., KANJANABUD, P. & RUTCHAKITPRAKARN, L. 2010. A multicenter study of oral lichen planus in Thai patients. *J Investig Clin Dent,* 1**,** 29-36.

THORNHILL, M. H., BACCAGLINI, L., THEAKER, E. & PEMBERTON, M. N. 2007. A randomized, double-blind, placebo-controlled trial of pentoxifylline for the treatment of recurrent aphthous stomatitis. *Arch Dermatol,* 143**,** 463-70.

TJOKROWIDJAJA, A., DANIEL, B. S., FREW, J. W., SEBARATNAM, D. F., HANNA, A. M., CHEE, S., DERMAWAN, A., WANG, C. Q., LIM, C., VENUGOPAL, S. S., RHODES, L. M., WELSH, B., NIJSTEN, T. & MURRELL, D. F. 2013. The development and validation of the treatment of autoimmune bullous disease quality of life questionnaire, a tool to measure the quality of life impacts of treatments used in patients with autoimmune blistering disease. *Br J Dermatol,* 169**,** 1000-6.

TREISTER, N. S., COOK, E. F., JR., ANTIN, J., LEE, S. J., SOIFFER, R. & WOO, S. B. 2008. Clinical evaluation of oral chronic graft-versus-host disease. *Biol Blood Marrow Transplant,* 14**,** 110-5.

TUBACH, F., DOUGADOS, M., FALISSARD, B., BARON, G., LOGEART, I. & RAVAUD, P. 2006. Feeling good rather than feeling better matters more to patients. *Arthritis Rheum,* 55**,** 526-30.

TUBACH, F., RAVAUD, P., BEATON, D., BOERS, M., BOMBARDIER, C., FELSON, D. T., VAN DER HEIJDE, D., WELLS, G. & DOUGADOS, M. 2007. Minimal clinically important improvement and patient acceptable symptom state for subjective outcome measures in rheumatic disorders. *J Rheumatol,* 34**,** 1188-93.

TUBACH, F., WELLS, G. A., RAVAUD, P. & DOUGADOS, M. 2005. Minimal clinically important difference, low disease activity state, and patient acceptable symptom state: methodological issues. *J Rheumatol,* 32**,** 2025-9.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION. 2009. *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.* [Online]. Available: https://www.fda.gov/media/77832/download [Accessed February 4, 2020 2020].

VALDERAS, J. M., ALONSO, J. & GUYATT, G. H. 2008. Measuring patient-reported outcomes: moving from clinical trials into clinical practice. *Med J Aust,* 189**,** 93-4.

VALLEJO, M. J., HUERTA, G., CERERO, R. & SEOANE, J. M. 2001. Anxiety and depression as risk factors for oral lichen planus. *Dermatology,* 203**,** 303-7.

VAN DER MEIJ, E. H., MAST, H. & VAN DER WAAL, I. 2007. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective five-year follow-up study of 192 patients. *Oral Oncol,* 43**,** 742-8.

VAN DER MEIJ, E. H. & VAN DER WAAL, I. 2003. Lack of clinicopathologic correlation in the diagnosis of oral lichen planus based on the presently available diagnostic criteria and suggestions for modifications. *J Oral Pathol Med,* 32**,** 507-12.

VAN DER WAAL, I. 2009a. Oral lichen planus and oral lichenoid lesions; a critical appraisal with emphasis on the diagnostic aspects. *Med Oral Patol Oral Cir Bucal,* 14**,** E310-4.

VAN DER WAAL, I. 2009b. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. *Oral Oncol,* 45**,** 317-23.

VENUGOPAL, S. S. & MURRELL, D. F. 2012. Diagnosis and clinical features of pemphigus vulgaris. *Immunol Allergy Clin North Am,* 32**,** 233-43, v-vi.

VET, H. C. W. D., TERWEE, C., MOKKINK, W. & KNOL, D. L. 2015. *Measurement in medicine : a practical guide*.

VIGO, G. & ZULIAN, F. 2012. Periodic fevers with aphthous stomatitis, pharyngitis, and adenitis (PFAPA). *Autoimmun Rev,* 12**,** 52-5.

WANG, J. & VAN DER WAAL, I. 2015. Disease scoring systems for oral lichen planus; a critical appraisal. *Med Oral Patol Oral Cir Bucal,* 20**,** e199-204.

WARE, J. E., JR., KOSINSKI, M., BAYLISS, M. S., MCHORNEY, C. A., ROGERS, W. H. & RACZEK, A. 1995. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. *Med Care,* 33**,** As264-79.

WARNAKULASURIYA, S., JOHNSON, N. W. & VAN DER WAAL, I. 2007. Nomenclature and classification of potentially malignant disorders of the oral mucosa. *J Oral Pathol Med,* 36**,** 575-80.

WELDRING, T. & SMITH, S. M. 2013. Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs). *Health Serv Insights,* 6**,** 61-8.

WHITE, C. M., CHAMBERLIN, K. & EISENBERG, E. 2019. Curcumin, a turmeric extract, for oral lichen planus: A systematic review. *Oral Dis,* 25**,** 720-725.

WILLIAMSON, P. R., ALTMAN, D. G., BLAZEBY, J. M., CLARKE, M., DEVANE, D., GARGON, E. & TUGWELL, P. 2012. Developing core outcome sets for clinical trials: issues to consider. *Trials,* 13**,** 132.

WIRIYAKIJJA, P., FEDELE, S., PORTER, S., MERCADANTE, V. & NI RIORDAIN, R. 2017. Patient-reported outcome measures in recurrent aphthous stomatitis: A critical assessment of quality properties. *Oral Dis,* 23**,** 1168-1179.

WIRIYAKIJJA, P., FEDELE, S., PORTER, S. R., MERCADANTE, V. & NI RIORDAIN, R. 2018. Patient-reported outcome measures in oral lichen planus: A comprehensive review of the literature with focus on psychometric properties and interpretability. *J Oral Pathol Med,* 47**,** 228-239.

WIRIYAKIJJA, P., PORTER, S., FEDELE, S., HODGSON, T., MCMILLAN, R., SHEPHARD, M. & NI RIORDAIN, R. 2019. Development and validation of a short version of Chronic Oral Mucosal Disease Questionnaire (COMDQ-15). *J Oral Pathol Med*.

WITTKAMPF, K., VAN RAVESTEIJN, H., BAAS, K., VAN DE HOOGEN, H., SCHENE, A., BINDELS, P., LUCASSEN, P., VAN DE LISDONK, E. & VAN WEERT, H. 2009. The accuracy of Patient Health Questionnaire-9 in detecting depression and measuring depression severity in high-risk groups in primary care. *Gen Hosp Psychiatry,* 31**,** 451-9.

WU, D., XIN, J., LIU, J. & ZHOU, P. 2018. The association between interleukin polymorphism and recurrent aphthous stomatitis: A meta-analysis. *Arch Oral Biol,* 93**,** 3-11.

WYRWICH, K. W., NORQUIST, J. M., LENDERKING, W. R. & ACASTER, S. 2013. Methods for interpreting change over time in patient-reported outcome measures. *Qual Life Res,* 22**,** 475-83.

XIA, J., LI, C., HONG, Y., YANG, L., HUANG, Y. & CHENG, B. 2006. Short-term clinical evaluation of intralesional triamcinolone acetonide injection for ulcerative oral lichen planus. *J Oral Pathol Med,* 35**,** 327-31.

XIE, S., DING, L., XIONG, Z. & ZHU, S. 2012. Implications of Th1 and Th17 cells in pathogenesis of oral lichen planus. *J Huazhong Univ Sci Technolog Med Sci,* 32**,** 451-457.

XU, H. H., WERTH, V. P., PARISI, E. & SOLLECITO, T. P. 2013. Mucous membrane pemphigoid. *Dent Clin North Am,* 57**,** 611-30.

YANG, C., LIU, L., SHI, H. & ZHANG, Y. 2018. Psychological problems and quality of life of patients with oral mucosal diseases: a preliminary study in Chinese population. *BMC Oral Health,* 18**,** 226.

YOUNG, A. L., BAILEY, E. E., COLACO, S. M., ENGLER, D. E. & GROSSMAN, M. E. 2011. Anti-laminin-332 mucous membrane pemphigoid associated with recurrent metastatic prostate carcinoma: hypothesis for a paraneoplastic phenomenon. *Eur J Dermatol,* 21**,** 401-4.

ZAIN, R. B., IKEDA, N., RAZAK, I. A., AXELL, T., MAJID, Z. A., GUPTA, P. C. & YAACOB, M. 1997. A national epidemiological survey of oral mucosal lesions in Malaysia. *Community Dent Oral Epidemiol,* 25**,** 377-83.

ZHAO, C. Y. & MURRELL, D. F. 2015. Outcome measures for autoimmune blistering diseases. *J Dermatol,* 42**,** 31-6.

ZIGMOND, A. S. & SNAITH, R. P. 1983. The hospital anxiety and depression scale. *Acta Psychiatr Scand,* 67**,** 361-70.

ZINBARG, R. E., REVELLE, W., YOVEL, I. & LI, W. 2005. Cronbach's α, Revelle's β, and Mcdonald's ωH: their relations with each other and two alternative conceptualizations of reliability. *Psychometrika,* 70**,** 123-133.

ZUCOLOTO, M. L., SHIBAKURA, M. E. W., PAVANIN, J. V., GARCIA, F. T., DA SILVA SANTOS, P. S., MACIEL, A. P., DE BARROS GALLO, C., SOUZA, N. V., INNOCENTINI, L., HUMBERTO, J. S. M. & MOTTA, A. C. F. 2019. Severity of oral lichen planus and oral lichenoid lesions is associated with anxiety. *Clin Oral Investig*.

ZWIRI, A. M. 2015. Anxiety, Depression and Quality of Life among Patients with Recurrent Aphthous Ulcers. *J Contemp Dent Pract,* 16**,** 112-7.

APPENDIX

APPENDIX 1 CASE REPORT FORM-INVESTIGATOR FORM

Patient Initials:	Screening n. :	Study n.:

Determination of Minimal Important Difference and Patient Acceptable Symptom State of Patient Reported Outcome Measures in Immunologically Mediated Oral Mucosal Diseases (The MEAN-IT study), IRAS 222002

CASE REPORT FORM

Determination of Minimal Important Difference and Patient Acceptable Symptom State of Patient Reported Outcome Measures in Immunologically Mediated Oral Mucosal Diseases
(The **MEAN-IT** study)

Investigator form

Chief Investigator: Dr. Stefano Fedele
University College London
Eastman Dental Institute
256 Gray's Inn Road
WC1X 8LD
London, UK

Appointment Schedule

	Visit Date Scheduled	Actual Visit Date
Study visit 1 **(Baseline visit)**		
Study visit 2 **(Follow-up visit)** **+4 months post visit 1**		

INDEX

PART A
Screening (Visit 1 Pre-Entry Activities)

Date of screening: ____ / ____/ ____

1. DEMOGRAPHICS

Patient ID _____ **Patient Screening Number** _____

Date of Birth: _ _ / _ _ / _ _ _ _ **Age:** _____ **years**
DD/ MM / YYYY

Gender (please tick box)**:** ☐ Male ☐ Female

Ethnic Group:

White

British	☐
Irish	☐
Any other white background	☐

Mixed

White and Black Caribbean	☐
White and Black African	☐
White and Asian	☐
Any other mixed background	☐

Asian or Asian British		
	Indian	☐
	Pakistani	☐
	Bangladeshi	☐
	Any other Asian background	☐
Black or Black British		
	Caribbean	☐
	African	☐
	Any other Black background	☐
Other Ethnic Groups		
	Chinese	☐
	Any other Asian background	☐
	Other	☐
	Please specify……..	
Vital signs:	Pulse (bpm) …….	
	Blood Pressure (mmHg):……/…	
Social History:	Smoking: current smoker	☐
	Never smoked	☐
	Previous smoker	☐

Year started [ ] Year stopped *(If previous smoker)* [ ]

Cigarettes ☐ cigars ☐ pipe ☐

Average number/day: ……

Alcohol: (Units/week) ……

2. MEDICAL HISTORY (general – not oral mucosal diseases)

Please list most significant systemic diseases and relevant medications

No.	Diagnosis		Medication	
1		Since:		Since:
2		Since:		Since:
3		Since:		Since:
4		Since:		Since:

3. DIAGNOSIS OF IMMUNOLOGICALLY MEDIATED ORAL MUCOSAL DISEASES

3.1 Type of immunologically mediated oral mucosal diseases

☐ Oral lichen planus (OLP) (please complete 3.2)

☐ Recurrent aphthous stomatitis (RAS) (please complete 3.3)

☐ Pemphigus vulgaris (PV) (please complete 3.4)

☐ Mucous membrane pemphigoid (MMP)
(Please complete 3.5)

2. MEDICAL HISTORY (general – not oral mucosal diseases)

Please list most significant systemic diseases and relevant medications

No.	Diagnosis		Medication	
1		Since:		Since:
2		Since:		Since:
3		Since:		Since:
4		Since:		Since:

3. DIAGNOSIS OF IMMUNOLOGICALLY MEDIATED ORAL MUCOSAL DISEASES

3.1 Type of immunologically mediated oral mucosal diseases

☐ Oral lichen planus (OLP) (please complete 3.2)

☐ Recurrent aphthous stomatitis (RAS) (please complete 3.3)

☐ Pemphigus vulgaris (PV) (please complete 3.4)

☐ Mucous membrane pemphigoid (MMP)
(Please complete 3.5)

3.2 Diagnosis of Oral lichen planus (OLP)

Time at diagnosis of OLP: _ _ / _ _ / _ _ _ _
DD/ MM / YYYY

Confirmation of OLP diagnosis:

1. Histopathological report from oral pathologist ☐

Evidence of oral epithelial dysplasia in biopsy specimen: ☐ YES ☐ NO

Evidence of proven hypersensitivity to dental materials: ☐ YES ☐ NO

(in case of oral lesions with lichenoid features adjacent to dental restoration)

3.3 Diagnosis of Recurrent aphthous stomatitis (RAS)

Time since the first RAS ulcer appeared: _ _ / _ _ / _ _ _ _
DD/ MM / YYYY

Confirmation of RAS diagnosis:

1. History of recurrent oral ulcers occurring at least twice a year ☐
2. No history of RAS-like ulceration associated with systemic disorders ☐
   (Such as Behcet's disease, Sweet syndrome, Ulcerative colitis, Crohn disease, Celiac disease), auto-inflammatory syndrome and haematological abnormalities (severe anaemia, cyclic or chronic neutropenia))

3.4 Diagnosis of Pemphigus vulgaris (PV)

Time at diagnosis of PV: __ / __ / ____
DD/ MM / YYYY

Confirmation of PV diagnosis:

1. DIF/IIF or ELISA-proven PV ☐

3.5 Diagnosis of Mucous membrane pemphigoid (MMP)

Time at diagnosis of MMP: __ / __ / ____
DD/ MM / YYYY

MMP diagnosis confirmation:

1. DIF/IIF or ELISA-proven MMP ☐

4. INCLUSION CRITERIA

All items must be checked "yes" for the patient to be eligible for entry into the study. Mark with **X** as appropriate.

	Yes	No
1. ≥ 18 years old		
2. To have one of the following immunologically mediated oral mucosal diseases 2.1 Oral lichen planus (OLP) - Histopathologically proven OLP - No evidence of proven hypersensitivity to dental restorative materials - Absence of histopathological signs of oral epithelial dysplasia in biopsy specimen - No evidence of lichenoid lesions associated with Graft versus Host Disease, Systemic Lupus Erythematosus 2.2 Recurrent aphthous stomatitis (RAS) - History of recurrent aphthous ulcers occurring at least twice a year - No evidence of RAS-like ulcerations associated with systemic Disorders 2.3 Pemphigus vulgaris (PV) - DIF/IIF or ELISA-proven PV 2.4 Mucous membrane pemphigoid (MMP) - DIF/IIF or ELISA-proven MMP		
3. To be able to understand questionnaires and speak and understand English language		
4. To be able to give consent		

5. EXCLUSION CRITERIA

All items must be checked "no" for the patient to be eligible for entry into the study. Mark with **X** as appropriate.

	Yes	No
• Severe systemic disease (on the basis of the classification of the American Society of Anesthesiology: ASA 3 or more) * and/or psychiatric conditions which might affect the participation of the study such as schizophrenia		
• Pregnancy		
• To have coexisting chronic neuropathic orofacial pain, such as post-traumatic trigeminal neuropathic pain, persistent idiopathic facial pain or burning mouth syndrome		
• To have RAS-like ulcerations associated with systemic disorders such as Behcet's disease, Sweet syndrome, Ulcerative colitis, Crohn's disease, Celiac disease, auto-inflammatory syndromes, or haematological abnormalities (severe anaemia, cyclic or chronic neutropenia)		

*ASA Physical Status 1 - A normal healthy patient
ASA Physical Status 2 - A patient with mild systemic disease
ASA Physical Status 3 - A patient with severe systemic disease
ASA Physical Status 4 - A patient with severe systemic disease that is a constant threat to life
ASA Physical Status 5 - A moribund patient who is not expected to survive without the operation
ASA Physical Status 6 - A declared brain-dead patient whose organs are being removed for donor purposes

PATIENT ELIGIBLE

[YES] **[NO]**

Patient Information Sheet to patient: [ ]

PATIENT ENROLLED

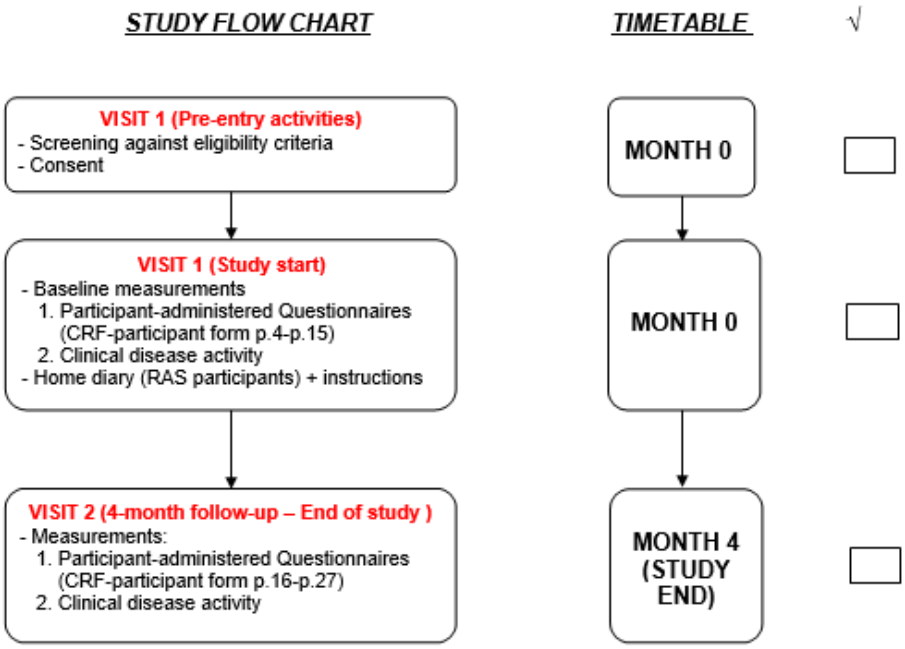
[YES] **[NO]**

Please make sure 3 copies* of informed consent are signed [ ]

**1 copy to patient, 1 copy to clinical notes, 1 copy added to this CRF*

Completed by : _____ Date ____/____/____

PART B
Study Measurements (enrolled individuals only)



6. STUDY VISIT 1 Date ……../……./…….

Please mark with √ items completed

6.1 BASELINE MEASUREMENTS

6.1.1 Participant-administered questionnaires **[ ]**

Please ensure participant complete all the items in the participant CRF on page 4 to page 15

6.1.2 History of medication use in participant **[ ]**

Please complete the following items

Did participant receive any medication for the treatment of oral mucosal disease in the last visit?

☐ YES (please complete the following items) ☐ NO (please go to 6.1.3)

Date of participant's last visit: _ _ / _ _ / _ _ _ _
DD/ MM / YYYY

Type of previous medication prescribed for the treatment of oral mucosal disease in the participant's last visit (please tick all that apply)

☐ Topical medication
☐ Systemic medication
☐ Intralesional corticosteroid injection

6. STUDY VISIT 1 Date ……../……./…….

Please mark with √ items completed

6.1 BASELINE MEASUREMENTS

6.1.1 Participant-administered questionnaires [ ]

Please ensure participant complete all the items in the participant CRF on page 4 to page 15

6.1.2 History of medication use in participant [ ]

Please complete the following items

Did participant receive any medication for the treatment of oral mucosal disease in the last visit?

☐ YES (please complete the following items) ☐ NO (please go to 6.1.3)

Date of participant's last visit: _ _ / _ _ / _ _ _ _
DD/ MM / YYYY

Type of previous medication prescribed for the treatment of oral mucosal disease in the participant's last visit (please tick all that apply)

☐ Topical medication
☐ Systemic medication
☐ Intralesional corticosteroid injection

List of previous medication prescribed for the treatment of oral mucosal disease in the participant's last visit

Medication (record generic or trade name)	Dosage	Frequency of use

6.1.3 Current medication use in participant [ ]

Please complete the following items

Will participant receive any medication for the treatment of oral mucosal disease in the present visit?

☐ YES (please complete the following items)

- ☐ Same as previous visit (please go to 6.1.4)
- ☐ Different from the previous visit (please complete the following items)

☐ NO (please go to 6.1.4)

Type of medication prescribed to the participant for the treatment of oral mucosal disease in the present visit (please tick all that apply)

- ☐ Topical medication
- ☐ Systemic medication
- ☐ Intralesional corticosteroid injection

List of medication prescribed to the participant for the treatment of oral mucosal disease in the present visit (please tick all that apply)

Medication (record generic or trade name)	Dosage	Frequency of use

6.1.4 Clinical disease activity [ ]

- For participants with OLP, PV, MMP

Please use *Escudier Severity Score (ESS)* for the measurement of Disease activity on page 16

- For participants with RAS

Please use Ulcer Severity Score (USS) for the measurement of Disease activity on page 17

Escudier Severity Score (ESS)

Predominant type (for OLP only): Reticular / Atrophic / Plaque / Desquamative gingivitis / Ulcerative

Sites (Possible score values)		Site score	Activity score (0-3), Double if site score = 2
Outer lips	(0-1)		
Inner lips	(0-1)		
R Buccal mucosa	(0 or 1 [<50%] or 2 [.50%])		
L Buccal mucosa	(0 or 1 [<50%] or 2 [.50%])		
Gingivae	(0-1 each segment)		
Lower R (distal)			
Lower central			
Lower L (distal)			
Upper R (distal)			
Upper central			
Upper L (distal)			
Dorsum tongue	(0 or 1 or 2)		
R ventral tongue	(0-1)		
L ventral tongue	(0-1)		
Floor of mouth	(0 or 1 or 2)		
Hard palate	(0 or 1 or 2)		
Soft palate	(0 or 1 or 2)		
Oropharynx	(0 or 1 or 2)		

Totals: SITE SCORE: ACTIVITY SCORE: PAIN SCORE (0-10):

TOTAL DISEASE SEVERITY SCORE:

Key

Activity Score:

0 = no lesion at site

1 = mild erythema (e.g. on gingivae, papillae only or less than 3mm along margins)

2 = marked erythema (e.g. full thickness on gingivae, extensive with atropy or oedema on nonkeratinised mucosa)

3 = Ulceration at this site

Site Score: 0 if no lesion at site

1 if less than 50% of area affected

2 if greater than 50%. Not defined anatomically

Patient Initials:	Screening n. :	Study n.:

Determination of Minimal Important Difference and Patient Acceptable Symptom State of Patient Reported Outcome Measures in Immunologically Mediated Oral Mucosal Diseases (The MEAN-IT study), IRAS 222002

Ulcer Severity Score (USS)

Diagnosis: Minor Major Herpetiform Atypical Other:

Size		Ulcer Characteristics	Score	Description of USS
2mm O 3mm O 4mm O 6mm O 8mm O 10mm O 12mm O	Average **Size** of ulcers (in mm)			Score = average size of ulcers in mm Maximum score – 20
	Average **Number** of ulcers			Score –average number of ulcers in a crop Maximum score = 20
	Average **Duration** of ulcers			Score = number of ½ weeks i.e. Half week (3 days) scores 1, one and a half week (10 days) scores 3. Maximum score = 10
	Ulcer-free period (in weeks)			Score = 10 minus the average ulcer-free period in weeks Maximum score = 10 (never free from ulcers)
	Pain as perceived by the patient (on a scale of 0-10)			1 for slight discomfort when ulcers are present 10 for excruciating ulcers interfering with eating and talking Maximum score = 10
	Mucosal site	Group 1 Labial mucosa Buccal mucosa Buccal Sulcus Soft palate Ventral of tongue Lateral of tongue Floor of mouth Group 2 Hard palate Attached gingiva Alveolar ridge Dorsum of tongue Tonsils Pillars of fauces Ulvula		Score = total of sites affected 1 for each site in group 1 (non- keratenised Mucosa) 2 for each site in group 2 (keratenised, specialised or oropharynx) Maximum score = 10 **Evidence of scarring** Yes ☐ No ☐ **Total USS**

6.2 DELIVERY OF HOME DIARY FOR RAS PARTICIPANTS [ ]

Completed by : _____ Date ____/____/____

7. STUDY VISIT 2 Date …../……./……

Please mark with √ items completed

7.1 MEASUREMENTS

7.1.1 Participant-administered questionnaires [ ]

Please ensure participant complete all the items in the participant CRF on page 16 to page 27

7.1.2 Clinical disease activity [ ]

- For participants with OLP, PV, MMP

Please use *Escudier Severity Score (ESS)* for the measurement of Disease activity on page 20

- For participants with RAS

Please use Ulcer Severity Score (USS) for the measurement of Disease activity on page 21

8. Termination Form

❑ Participant completed study

❑ Participant discontinued early

Please indicate the reason and explain in the comment section:

Comments: _____

_____

_____

_____

Investigator's Signature:_____ **Date** ____/____/_____

APPENDIX 2 CASE REPORT FORM-PARTICIPANT FORM

Patient Initials:	Screening n. :	Study n.:

Determination of Minimal Important Difference and Patient Acceptable Symptom State of Patient Reported Outcome Measures in Immunologically Mediated Oral Mucosal Diseases (The MEAN-IT study), IRAS 222002

CASE REPORT FORM

Determination of Minimal Important Difference and Patient Acceptable Symptom State of Patient Reported Outcome Measures in Immunologically Mediated Oral Mucosal Diseases

(The **MEAN-IT** study)

Participant form

Chief Investigator: Dr. Stefano Fedele
University College London
Eastman Dental Institute
256 Gray's Inn Road
WC1X 8LD
London, UK

Appointment Schedule

	Visit Date Scheduled	Actual Visit Date
Study visit 1 (Screening + Baseline visit)		
Study visit 2 (Follow-up visit) +4 months post visit 1		

INDEX

1. STUDY VISIT 1 Date ...../...../.....

1. Socio-demographics:

1.1 Date of Birth: ___ / ___ / _____ **1.2 Age (years):** ____

1.3 Gender: ☐ Male ☐ Female

1.4 Ethnic group:

☐ White British
☐ Other white backgrounds
☐ Indian
☐ Bangladeshi
☐ Pakistani
☐ Other Asian backgrounds
☐ Black African
☐ Black Caribbean
☐ Other black backgrounds
☐ Other, please specify: _____

1.5 Please select the furthest level of education you have completed:

☐ No qualifications
☐ Secondary education (O-Level/GCSE)
☐ Post-secondary education (College, A-Levels, NVQ3 or below, or similar)
☐ Vocational qualification (Diploma, Certificate, BTEC, NVQ 4 and above, or similar)
☐ Undergraduate degree (BA, BSc etc.)
☐ Postgraduate degree (MA, MSc, PhD etc.)

1.6 Please select band which best represent your total personal income before all deductions

☐ Less than £100 a week
☐ £100 but less than £200
☐ £200 but less than £300
☐ £300 but less than £400
☐ £400 but less than £500
☐ £500 but less than £600
☐ £600 but less than £700
☐ £700 but less than £800
☐ £800 but less than £900
☐ £900 but less than £1000
☐ Over £1000 a week

2. Hospital Anxiety and Depression score (HADS):

Instructions: Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response. (Please circle one answer per question)

I feel tense or 'wound up':	**A**
Most of the time	3
A lot of the time	2
Time to time, occasionally	1
Not at all	0

I still enjoy the things I used to enjoy:	**D**
Definitely as much	0
Not quite so much	1
Only a little	2
Not at all	3

I get a sort of frightened feeling like something awful is about to happen:	**A**
Very definitely and quite badly	3
Yes, but not too badly	2
A little, but it doesn't worry me	1
Not at all	0

I can laugh and see the funny side of things:	**D**
As much as I always could	0
Not quite so much now	1
Definitely not so much now	2
Not at all	3

Worrying thoughts go through my mind:	**A**
A great deal of the time	3
A lot of the time	2
From time to time but not too often	1
Only occasionally	0

I feel cheerful:	**D**
Not at all	3
Not often	2
Sometimes	1
Most of the time	0

I can sit at ease and feel relaxed:	**A**
Definitely	0
Usually	1
Not often	2
Not at all	3

I feel as if I am slowed down:	**D**
Nearly all of the time	3
Very often	2
Sometimes	1
Not at all	0

I get a sort of frightened feeling like 'butterflies in the stomach':	**A**
Not at all	0
Occasionally	1
Quite often	2
Very often	3

I have lost interest in my appearance:	**D**
Definitely	3
I don't take as much care as I should	2
I may not take quite as much care	1
I take just as much care as ever	0

I feel restless as if I have to be on the move:	**A**
Very much indeed	3
Quite a lot	2
Not very much	1
Not at all	0

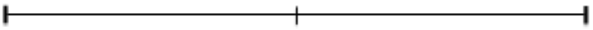
I look forward with enjoyment to things:	**D**
A much as I ever did	0
Rather less than I used to	1
Definitely less than I used to	2
Hardly at all	3

I get sudden feelings of panic:	**A**
Very often indeed	3
Quite often	2
Not very often	1
Not at all	0

I can enjoy a good book or radio or TV programme:	**D**
Often	0
Sometimes	1
Not often	2
Very seldom	3

3. Visual analog scale (VAS)

Instructions: Please mark the position on the line below that best represents the pain or discomfort you are currently experiencing from your oral condition



(no pain) (worst pain imaginable)

4. Numerical rating scale (NRS)

Instructions: Please circle only one number below that best represents the pain or discomfort you are currently experiencing from your oral condition

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst pain imaginable

5. Oral Health Impact Profile (OHIP-14):

Instructions: Please circle only one number on each line

Functional Limitations	Never	hardly ever	Occasionally	fairly often	very often
Have you had trouble *pronouncing any words* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Have you felt that your *sense of taste* has worsened because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Physical pain					
Have you had *painful aching* in your mouth?	0	1	2	3	4
Have you found it *uncomfortable to eat any foods* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Psychological discomfort					
Have you been *self-conscious* because of your teeth, mouth or dentures?	0	1	2	3	4
Have you *felt tense* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Physical disability					
Has your *diet been unsatisfactory* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Have you had to *interrupt meals* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Psychological disability					
Have you found it *difficult to relax* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Have you been *a bit embarrassed* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Social disability					
Have you been *a bit irritable with other people* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Have you had *difficulty doing your usual jobs* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Handicap					
Have you *felt that life in general was less satisfying* because of problems with your teeth, mouth or dentures?	0	1	2	3	4
Have you been *totally unable to function* because of problems with your teeth, mouth or dentures?	0	1	2	3	4

6. Perceived Stress Scale

Instructions: The questions in this scale ask you about your feelings and thoughts during the last month. In each case, you will be asked to indicate by **circling** how often you felt or thought a certain way.

1. In the last month, how often have you been upset because of something that happened unexpectedly?
0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

2. In the last month, how often have you felt that you were unable to control the important things in your life?
0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

3. In the last month, how often have you felt nervous and "stressed"?
0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

4. In the last month, how often have you felt confident about your ability to handle your personal problems?
0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

5. In the last month, how often have you felt that things were going your way?
0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

6. In the last month, how often have you found that you could not cope with all the things that you had to do?
0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

7. In the last month, how often have you been able to control irritations in your life?
0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

8. In the last month, how often have you felt that you were on top of things?
0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

9. In the last month, how often have you been angered because of things that were outside of your control?
0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?
0 = never 1 = almost never 2 = sometimes 3 = fairly often 4 = very often

7. Chronic Oral Mucosal Disease Questionnaire (COMDQ)

Instructions: Please answer the following questions by ticking one of the following boxes for each.

Pain and functional limitation

1.	How much do certain types of food/drink cause you discomfort (spicy food, acidic food)?	Not at all ☐0 Slightly ☐1 Moderately ☐2 Considerably ☐3 Extremely ☐4
2.	How much does your oral condition cause you to limit the types of food/ drinks you consume?	Not at all ☐0 Slightly ☐1 Moderately ☐2 Considerably ☐3 Extremely ☐4
3.	How much do certain food textures cause you discomfort (rough food, crusty food)?	Not at all ☐0 Slightly ☐1 Moderately ☐2 Considerably ☐3 Extremely ☐4
4.	How much does your oral condition cause you to limit the textures of the food you consume?	Not at all ☐0 Slightly ☐1 Moderately ☐2 Considerably ☐3 Extremely ☐4
5.	How much does the temperature of certain foods/drinks cause you discomfort?	Not at all ☐0 Slightly ☐1 Moderately ☐2 Considerably ☐3 Extremely ☐4

6.	How much does you oral condition cause you to limit the temperature of the foods/drinks you consume?	Not at all Slightly Moderately Considerably Extremely	☐0 ☐1 ☐2 ☐3 ☐4
7.	How much does your oral condition lead to discomfort when carrying out your daily oral hygiene routine (brushing, flossing, mouthwash usage)?	Not at all Slightly Moderately Considerably Extremely	☐0 ☐1 ☐2 ☐3 ☐4
8.	How much does your oral condition cause you to limit your daily oral hygiene routine (brushing, flossing, mouthwash usage)?	Not at all Slightly Moderately Considerably Extremely	☐0 ☐1 ☐2 ☐3 ☐4
9.	How much does your oral condition lead to discomfort when wearing a denture (false teeth)?	Not at all Slightly Moderately Considerably Extremely	☐0 ☐1 ☐2 ☐3 ☐4

Medication and treatment (including mouthwashes, gels, creams, ointments, injections, tablets, infusions)

1.	How much do you feel you need medication to help you with activities of daily life (talking, eating etc.)?	Not at all Slightly Moderately Considerably Extremely	☐0 ☐1 ☐2 ☐3 ☐4
2.	How satisfied are you with the medication being used to treat your oral condition?	Not at all Slightly Moderately Considerably Extremely	☐4 ☐3 ☐2 ☐1 ☐0
3.	How concerned are you about the possible side effects of the medications used to treat your oral condition?	Not at all Slightly Moderately Considerably Extremely	☐0 ☐1 ☐2 ☐3 ☐4
4.	How much does it frustrate you that there is no single standard medication to be used in your oral condition?	Not at all Slightly Moderately Considerably Extremely	☐0 ☐1 ☐2 ☐3 ☐4
5.	How much does the use of the medication limit you in your every day life (routine / the way you apply or take your medications)?	Not at all Slightly Moderately Considerably Extremely	☐0 ☐1 ☐2 ☐3 ☐4

6.	How much does it bother you that there is no cure for your oral condition?	Not at all ☐0 Slightly ☐1 Moderately ☐2 Considerably ☐3 Extremely ☐4

Social and emotional

1.	How much does your oral condition get you down?	Not at all ☐0 Slightly ☐1 Moderately ☐2 Considerably ☐3 Extremely ☐4
2.	How much does your oral condition cause you anxiety?	Not at all ☐0 Slightly ☐1 Moderately ☐2 Considerably ☐3 Extremely ☐4
3.	How much does your oral condition cause you stress?	Not at all ☐0 Slightly ☐1 Moderately ☐2 Considerably ☐3 Extremely ☐4
4.	How much does the unpredictability of your oral condition bother you?	Not at all ☐0 Slightly ☐1 Moderately ☐2 Considerably ☐3 Extremely ☐4

5.	How much does your oral condition cause you to worry about the future (spread of the condition, possible cancer risk)?	Not at all ☐0 Slightly ☐1 Moderately ☐2 Considerably ☐3 Extremely ☐4
6.	How much does your oral condition make you pessimistic about the future?	Not at all ☐0 Slightly ☐1 Moderately ☐2 Considerably ☐3 Extremely ☐4
7.	How much does your oral condition disrupt social activities in your life (social gatherings, eating out parties)?	Not at all ☐0 Slightly ☐1 Moderately ☐2 Considerably ☐3 Extremely ☐4

Patient Support

1.	How satisfactory do you consider the information available to you regarding your oral condition?	Not at all ☐4 Slightly ☐3 Moderately ☐2 Considerably ☐1 Extremely ☐0
2.	How satisfied are you with the level of support and understanding shown to you by family regarding this oral condition?	Not at all ☐4 Slightly ☐3 Moderately ☐2 Considerably ☐1 Extremely ☐0

3.	How satisfied are you with the level of support and understanding shown to you by friends/work colleagues regarding your oral condition?	Not at all ☐4 Slightly ☐3 Moderately ☐2 Considerably ☐1 Extremely ☐0
4.	How isolated do you feel as a result of this oral condition?	Not at all ☐0 Slightly ☐1 Moderately ☐2 Considerably ☐3 Extremely ☐4

7. Evaluation of patient's oral mucosal condition:

EVALUATION OF CHANGE IN PATIENT'S CONDITIONS

Thinking about all the ways your symptoms related to your oral mucosal conditions are affecting you, compared to the beginning of the study (4 months ago), how do you evaluate the severity of your oral mucosal conditions now?
(Please tick only one box)

- ☐ Very much better
- ☐ Moderately better
- ☐ Slightly better
- ☐ About the same
- ☐ Slightly worse
- ☐ Moderately worse
- ☐ Very much worse

EVALUATION OF ACCEPTABLE SYMPTOM STATE

Thinking about all the ways your symptoms related to your oral mucosal conditions are affecting you, do you consider that your current state is acceptable?

☐ YES ☐ NO

APPENDIX 3 HOME DIARY FOR PARTICIPANTS WITH RAS

HOME DIARY

FOR STUDY PARTICIPANTS

Lay Title of the Project: Improving the interpretability of patient reported outcome measures (PROMs) in individuals with immunologically mediated oral mucosal diseases

[**Scientific title**: Determination of **M**inimal Important Diff**e**rence and Patient **A**cceptable Symptom State of Patient Reported Outcome Measures i**n** **I**mmunologically Media**t**ed Oral Mucosal Diseases (MEAN-IT)].

Version 1.0, 01/06/2017
Study MEAN-IT
Patient Identification Number for this trial:

Dear Participant,

Many thanks for agreeing to participate in this study (*MEAN-IT*). This diary is aimed at keeping a record of specific information about your oral ulcers during the study, including size of ulcers, number of ulcers, duration of ulcers, area/site of ulcers, and severity of pain arising from the ulcers. We would be grateful if you could complete the diary as outlined below and bring it to the study doctors at your hospital appointments.

A home diary is important for us to understand the frequency and severity of recurrent oral ulceration, which rely greatly on the patient history. Therefore your help is invaluable as regards completing this diary and keeping it updated.

If you have any further questions or would simply like to discuss the study in more detail, please do not hesitate to contact the study doctors outlined below who will be happy to speak with you.

Kind regards.

Yours sincerely,

Dr Stefano Fedele (Chief Investigator) 020 3456 1004 or s.fedele@ucl.ac.uk
Dr Richeal Ni Riordain (Principal Investigator) Richeal.NiRiordain@uclh.nhs.uk
Professor Stephen Porter (Principal Investigator) 020 3456 1000 or s.porter@ucl.ac.uk

1. DIARY USER MANUAL

1.1 Initials and Identification number (all pages)

Please write your initials and your study identification number (study doctors will provide this for you) on the top of each monthly page where indicated on the diary.

1.2 Oral ulcer information

Please write in the allocated tables on the information listed below.

- **Number** of oral ulcers: please record the average number of oral ulcers that you have in each period.
- **Size** of oral ulcers: please record the average size of oral ulcers that you experience in each period in millimetres (aid: we provide ulcer size diagram below to help you estimate the average size of ulcers)

- **Duration**: please record the average duration of each ulcer you have on each day during the period of study.
- **Mouth area** of oral ulcers: please record mouth area that your oral ulcers appear.
  Note: Mouth area of ulcer occurrence may include (inner) lips, (inner) cheeks, tongue (please specify: top/side/bottom of the tongue), roof of the mouth, gum and back of the mouth.
- **Pain** as a result of oral ulcers: please record average mouth pain that you experience as a result of your mouth ulcers on a scale from 0 to 10 when 0 representing no pain and 10 representing worst pain imaginable. For example, if you have two mouth ulcers, one with pain of 4/10 and another with pain of 6/10, you should record average pain of 5 (/10).

1.3 Completion of diary

Please complete the diary on the first and last day of every subsequent oral ulcer attack. On the first day of each ulcer attack, please record the starting date. On the last day of each ulcer attack, please record the end date and all relevant information about oral ulcers.

2. THE DIARY:

Please complete the box with the date (__/__/____) and record all the relevant information about oral ulcers.

Example **(in blue colour)**

Oral ulcer attack episode 1

Starting date 01/09/2017

End date 12/09/2017

oral ulcer characteristics	
Average number	4
Average size (mm)	3
Average duration per 1 ulcer (days)	10
Mouth area of ulcers (please tick in the box)	☐ outer lips ☑ inner lips ☐ inner cheeks ☐ tongue (top) ☑ tongue (side) ☐ tongue (bottom) ☐ roof of mouth ☐ gum ☐ back of mouth ☐ others: please specify_____
Average mouth pain (0-10)	5

Oral ulcer attack episode 2

Starting date 25/09/2017

End date 10/10/2017

oral ulcer characteristics	
Average number	3
Average size (mm)	3
Average duration per 1 ulcer (days)	10
Mouth area of ulcers (please tick in the box)	☐ outer lips ☐ inner lips ☑ inner cheeks ☐ tongue (top) ☐ tongue (side) ☐ tongue (bottom) ☑ roof of mouth ☐ gum ☐ back of mouth ☐ others: please specify_____
Average mouth pain (0-10)	2

Oral ulcer attack episode 1

Starting date ___/___/_____

End date ___/___/_____

oral ulcer characteristics	
Average number	
Average size (mm)	
Average duration per 1 ulcer (days)	
Mouth area of ulcers (please tick in the box)	☐ outer lips ☐ inner lips ☐ inner cheeks ☐ tongue (top) ☐ tongue (side) ☐ tongue (bottom) ☐ roof of mouth ☐ gum ☐ back of mouth ☐ others: please specify_____
Average mouth pain (0-10)	

Oral ulcer attack episode 2

Starting date ___/___/_____

End date ___/___/_____

oral ulcer characteristics	
Average number	
Average size (mm)	
Average duration per 1 ulcer (days)	
Mouth area of ulcers (please tick in the box)	☐ outer lips ☐ inner lips ☐ inner cheeks ☐ tongue (top) ☐ tongue (side) ☐ tongue (bottom) ☐ roof of mouth ☐ gum ☐ back of mouth ☐ others: please specify_____
Average mouth pain (0-10)	

APPENDIX 4 PUBLISHED ARTICLES ARISING FROM THE PRESENT THESIS

Wiriyakijja P, Fedele S, Porter SR, Mercadante V, Ni Riordain R. Patient-reported outcome measures in oral lichen planus: A comprehensive review of the literature with focus on psychometric properties and interpretability. *J Oral Pathol Med*. 2018;47(3):228-239. doi:10.1111/jop.12604

Wiriyakijja P, Fedele S, Porter S, Mercadante V, Ni Riordain R. Patient-reported outcome measures in recurrent aphthous stomatitis: A critical assessment of quality properties. *Oral Dis*. 2017;23(8):1168-1179. doi:10.1111/odi.12726

Wiriyakijja P, Porter S, Fedele S, Hodgson T, McMillan R, Shephard M, Ni Riordain R. Development and validation of a short version of Chronic Oral Mucosal Disease Questionnaire (COMDQ-15). *J Oral Pathol Med*. 2020;49(1):55-62. doi:10.1111/jop.12964

Wiriyakijja P, Porter S, Fedele S, Hodgson T, McMillan R, Shephard M, Ni Riordain R. Validation of the HADS and PSS-10 and psychological status in patients with oral lichen planus. *Oral Dis*. 2020;26(1):96-110. doi:10.1111/odi.13220

Wiriyakijja P, Porter S, Fedele S, Hodgson T, McMillan R, Shephard M, Ni Riordain R. Validation of the HADS and PSS-10 and a cross-sectional study of psychological status in patients with recurrent aphthous stomatitis. *J Oral Pathol Med*. 2020;49(3):260-270. doi:10.1111/jop.12991

Wiriyakijja P, Porter S, Fedele S, Hodgson T, McMillan R, Shephard M, Ni Riordain R. Meaningful improvement thresholds in measures of pain and quality of life in oral lichen planus [published online ahead of print, 2020 May 4]. *Oral Dis*. 2020;10.1111/odi.13379. doi:10.1111/odi.13379

Wiriyakijja P, Porter S, Fedele S, Hodgson T, McMillan R, Shephard M, Ni Riordain R. Health-related quality of life and its associated predictors in patients with oral lichen planus: a cross-sectional study**.** *Int Dent J.* [accepted, under process of online proofing before publication].

Chronic Oral Mucosal Disease Questionnaire-15 (COMDQ-15)

Instructions: Please answer the following questions by ticking one of the following boxes for each.

Physical discomfort	**Not at all**	**Slightly**	**Moderately**	**Considerably**	**Extremely**
How much do certain *types of food/drink* cause you discomfort (spicy food, acidic food)?	0	1	2	3	4
How much do certain *food textures* cause you discomfort (rough food, crusty food)?	0	1	2	3	4
How much does the *temperature of certain foods/drinks* cause you discomfort?	0	1	2	3	4
How much does your oral condition lead to discomfort when *carrying out your daily oral hygiene routine* (brushing, flossing, mouthwash usage)?	0	1	2	3	4
How much do you feel you *need medication* to help you with activities of daily life (talking, eating etc.)?	0	1	2	3	4
Medication and Treatment					
How concerned are you about the possible *side effects of the medications* used to treat your oral condition?	0	1	2	3	4
How much does it frustrate you that there is *no single standard medication* to be used in your oral condition?	0	1	2	3	4
How much does *the use of the medication limit* you in your *every day life* (routine / the way you apply or take your medications)?	0	1	2	3	4
Social and Emotional					
How much does your oral condition get you *down*?	0	1	2	3	4
How much does your oral condition cause you *anxiety*?	0	1	2	3	4
How much does the *unpredictability* of your oral condition bother you?	0	1	2	3	4
How much does your oral condition make you *pessimistic about the future*?	0	1	2	3	4
How much does your oral condition *disrupt social activities* in your life (social gatherings, eating out parties)?	0	1	2	3	4
Patient Support					
How satisfied are you with the *level of support and understanding* shown to you by *family* regarding this oral condition?	4	3	2	1	0
How satisfied are you with the *level of support and understanding* shown to you by *friends/work colleagues* regarding your oral condition?	4	3	2	1	0