Clinimetrics of musculoskeletal ultrasound in osteoarthritis

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Supervisors' Statement

As supervisors of Win Min's doctoral work, we certify that we consider his Thesis "**Clinical utilities of musculoskeletal ultrasound in osteoarthritis**" sufficiently well presented to be examined and certify that it does not exceed the prescribed word limit or any extended word limit for which prior approval has been granted.

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Candidate's Statement

I, Win Min, hereby declare that this submission is my own work and that it contains no material previously published or written by another person except where acknowledged in the text. Nor does it contain material which has been accepted for the award of another degree.

I, Win Min, understand that if I am awarded a higher degree for my Thesis entitled "Clinical utilities of musculoskeletal ultrasound in osteoarthritis" being lodged herewith for examination, the Thesis will be lodged in the University library and be available immediately for use. I agree that the University Librarian (or in the case of a department, the Head of the Department) may supply a photocopy or microform of the Thesis to an individual for research or study or to a library.

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"Hold fast to dreams,

For if dreams die

Life is a broken-winged bird,

That cannot fly."

Langston Hughes

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Publications and Presentations

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5. **Oo W.M**., Deveza L.A., Duong V., Fu K., Linklater J.M., Riordan E.A., Robbins S.R., and Hunter D.J., *Musculoskeletal ultrasound in symptomatic thumb-base osteoarthritis: clinical, functional, radiological and muscle strength associations*. BMC Musculoskeletal Disorders, 2019. 20(1): p. 220.

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Published works arising from osteoarthritis/ ultrasound research during the period of candidature

(i) As first-author publications

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2. **Oo W.M**., Yu S.P., Daniel M.S., and Hunter D.J., *Disease-modifying drugs in osteoarthritis: current understanding and future therapeutics*. Expert Opinion on Emerging Drugs, 2018. 23(4): p. 331-347.

3. **Oo WM**, Hunter DJ. *Disease modification in osteoarthritis: are we there yet?* Clinical and Experimental Rheumatology 2019;37 Suppl 120(5):135-140.

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2. Wang X., **Oo W.M**., and Linklater J.M., *What is the role of imaging in the clinical diagnosis of osteoarthritis and disease management?* Rheumatology (Oxford), 2018. 57(suppl_4): p. iv51-iv60.

3. Riordan E., Robbins S., Deveza L., Duong V., **Oo W.M**., Wajon A., Bennell K., Eyles J., Jongs R., Linklater J., and Hunter D., *Radial subluxation in relation to hand strength and radiographic severity in trapeziometacarpal osteoarthritis*. Osteoarthritis and Cartilage, 2018. 26(11): p. 1506-1510.

4. Deveza L.A., Bierma-Zeinstra S.M.A., van Spil W.E., **Oo W.M**., Saragiotto B.T., Neogi T., van Middelkoop M., and Hunter D.J., *Efficacy of bisphosphonates in specific knee osteoarthritis subpopulations: protocol for an OA Trial Bank systematic review and individual patient data meta-analysis.* BMJ Open, 2018. 8(12): p. e023889.

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1. **Oo W.M**., Linklater J., Bennell K, Yu S, Wang X., Duong V., and Hunter D. Are OMERACT knee ultrasound scores associated with pain, other symptoms, radiographic and MRI findings? American College of Rheumatology Annual Meeting 2019, Atlanta, USA.

2. **Oo W.M**., Linklater J., Wang X., Daniel M., Pryke D., Yu S., Deveza L., Duong V., and Hunter D., *AB1167 Reliability and Validity of Ultrasound Pathologies in Knee Osteoarthritis for Semi-quantitative and Qualitative Methods with MRI as a Reference.* Annals of the Rheumatic Diseases, 2019. 78(Suppl 2): p. 2044-2045.European League against Rheumatism Conference June 2019, Madrid, Spain

3. **Oo W.M**., Deveza L.A., Duong V., Fu K., Linklater J.M., Meneses S.R., Riordan E.A., and Hunter D.J., *Construct validity of musculoskeletal ultrasound in thumb-base osteoarthritis: comparison with clinical, functional and radiological findings.* Osteoarthritis and Cartilage, 2018. 26: p. S431. Osteoarthritis Research International Congress April 2018, Liverpool UK.

4. **Oo W.M**., Linklater J.M., and Hunter D.J., *Imaging in knee Osteoarthritis.* International Doctorate Student Conference, Zhejiang University, China (2017).

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2. **Oo W.M**, Linklater J.M., Saarakkala S., Samuels J., Conaghan P.G., Daniel M., Keen H., Deveza L., and Hunter D.J., *Clinimetrics of Ultrasonography in Osteoarthritis*: *A Systematic Literature Review*. Sydney Musculoskeletal, Bone & Joint Health Alliance Scientific meeting. Sydney October 2017.

Thesis outline

The thesis consists of eight chapters, each written so that they can be read independently. The University of Sydney permits published manuscripts arising from the candidature to be included in the Thesis. Six chapters of this Thesis consist of papers that were submitted for publication. Four of these chapters have been published with the remaining two currently under review. Each of these six chapters addresses one of the four specific aims.

This thesis provides the clinimetrics of MSKUS as an imaging tool in the pathophysiological manifestations of the OA disease process. **Chapter One** described the introduction to the context of the global burden of OA disease, the involvement of different joint tissues in OA pathogenic process and what pathologies the imaging tools such as plain radiograph, MSKUS and MRI could evaluate and their common grading scores and shortcomings. **Chapter Two** is a narrative review updating the clinimetrics of imaging tools focusing on plain radiograph, MSKUS and MRI. Specific to MSKUS and MRI, it synthesised the recent literature in OA tissue disorders visualised by these imaging tools, usage of scoring systems as outcome measures in clinical trials and prediction for disease progression, novel MRI imaging methods and new OMERACT MSKUS scoring system for knee OA. This study is presented as published in Current Opinion in Rheumatology.

Another narrative review is included in **Chapter Three** focusing on the pathophysiological manifestations of MSKUS in knee OA. This paper describes the clinical values of MSKUS for detecting cartilage, soft tissue and bony abnormalities; its clinical role as a monitoring tool in interventional trials or as a guidance tool for joint injections as well as its limitations. The review is presented as published in the Journal of Clinical Rheumatology. **Chapter Four** is a large systematic review and meta-analysis focussed on the psychometric properties of MSKUS in hip, knee and hand OA, including 100 papers after screening 1126 records. The systemic review evaluates each aspect of the following clinimetrics (1) inter-rater/intra-rater reliability; (2) construct validity; (3) criteria validity; (4) internal/ external responsiveness and (5) feasibility. Meta-analysis of clinimetrics was limited only to knee OA as there were insufficient studies for hip and hand OA for which qualitative

analysis was conducted. Sub-group meta-analyses were performed for each type of clinimetrics: (1) kappa or ICC for inter-rater or intra-rater reliability (2) construct validity against each comparison such as healthy control, pain, functional assessment, plain radiograph, MRI, or biomarkers, (3) internal or external responsiveness. These data were pooled, based on each ultrasound pathology (synovitis/effusion/osteophyte/etc.) to be clinically meaningful. It is presented as published in Osteoarthritis and Cartilage.

Chapter Five was to examine the inter-rater/intra-rater reliability and construct validity of MSKUS grading system developed by OMERACT for knee OA, comparing with the well-validated outcomes such as pain on numerical rating scales (NRS), Knee Injury and Osteoarthritis Outcome Score (KOOS) symptoms and pain sub-scores, Kellgren and Lawrence grade (KLG) on plain radiograph and MRI Osteoarthritis Knee Score (MOAKS). It was presented as submitted to Rheumatology (under review). **Chapter Six** reports the comparative detectability of low-grade inflammation in OA by SMI and cPD and their relative association with clinical and imaging outcomes such as pain, radiograph and MRI to determine its added clinical value. It is presented as submitted to Ultrasound in Medicine and Biology (under review).

Chapter Seven describes the intra-rater and inter-machine reliability, and associations of MSKUS disorders of thumb-base OA with pain, hand function, pinch and grip strength, and plain radiographs using a cross-sectional design. It is presented as published in BMC Musculoskeletal Disorders. Finally, **Chapter Eight** provides a summary of the principal findings of this Thesis, discusses the implications of these findings and proposes directions for future research.

Abstract

Osteoarthritis (OA) is one of the highly prevalent joint diseases, predisposing to severe disability and economic burden on the global community. In spite of being assumed as a degenerative disease of cartilage, recent evidence indicates that it is a complex, multi-factorial disease with multi-tissue alterations involving the whole joint. Traditionally, OA is imaged with plain radiographs, which has several limitations, such as radiation hazards and inability to visualize soft tissue pathologies which can contribute to pain and symptoms. On the other hand, the use of musculoskeletal ultrasound (MSKUS) permits visualisation of the superficial bony cortex and soft tissue pathologies, leading to study of OA phenotypes with respect to inflammatory and structural changes that cannot be visualized through a plain radiograph. This thesis focuses on a series of investigations on the topic of "clinical utility of MSKUS in osteoarthritis".

Firstly, we conducted two narrative reviews and one systematic review related to imaging in OA. The first narrative review updated the recent reports about the clinical utility of MRI, MSKUS and radiograph in knee OA while the latter specifically discussed the clinical utility of MSKUS for detecting soft-tissue, bone and cartilage disorders in knee OA. Then, we conducted a systematic review and meta-analysis related to the clinimetrics of each OA manifestation visualized with MSKUS, concluding that MSKUS was strongly correlated with patient's symptoms and MRI findings, had moderate measurement reliability, and low responsiveness to interventions.

Due to the operator-dependence nature of MSKUS, the Outcome Measures in Rheumatology (OMERACT) group developed standardized knee MSKUS scanning methods and grading scores for knee OA based on the international consensus and reliability testing. We examined the construct validity of these scores against pain, clinical symptoms, plain radiographs and MRI, displaying a good construct validity with validated outcome measures such as pain on the numerical rating scale, Knee Injury and Osteoarthritis Outcome Score (KOOS) scores, Kellgren-Lawrence grade (KLG) on radiograph and MRI Osteoarthritis Knee Score. We also investigated the clinical utility of novel Doppler technology known as Superb microvascular imaging (SMI) in knee OA. We found that SMI

can detect the low-grade inflammation implicated in OA disease process compared to conventional power Doppler and revealed a significant correlation with KOOS pain and symptoms sub-scores, KLG and MRI synovitis.

In addition, there was a paucity of research evidence for construct validity related to MSKUS in thumb-base OA. Therefore, we performed comprehensive MSKUS scanning and exanimated their associations with pain, function, muscle strength and radiographic scores. Our data showed that only power Doppler demonstrated a significant association with pain.

As we showed MSKUS had good reliability and validity, together with its easy accessibility and promising technological advancement, it can be a powerful tool for investigating OA phenotypes in clinical research. However, as our studies are cross-sectional, longitudinal data will be required to establish a cause-effect relationship and determine the clinical importance of variability of the MSKUS features with longitudinal changes in clinical and imaging outcomes.

Abbreviations

B=B-mode

BLOKS= Boston leeds osteoarthritis knee score

BMOs= Bone marrow oedema

CI= Confidence interval

COMP= Cartilage oligomeric matrix protein

cPD=conventional power Doppler

EULAR= European league against rheumatism

FIHOA=Functional index for hand OA

KOOS= Knee injury and osteoarthritis outcome score

JSN=Joint space narrowing

JSW=Joint space width

KLG=Kellgren Lawrence grading

MOAKS= MRI osteoarthritis knee score

MRI=Magnetic resonance imaging

NA=Non-applicable

NRS=Numerical rating scale

OA=Osteoarthritis

OARSI=Osteoarthritis research society international

OMERACT= Outcome measure in rheumatology

PD=Power Doppler

RhMSUS=Musculoskeletal ultrasound in rheumatology

SMI=Superb microvascular imaging

US=Ultrasound

VAS=Visual analogue scale

WORMS= Whole-organ magnetic resonance imaging score

CHAPTER ONE

Chapter One: Thesis introduction

1. The burden of osteoarthritis

Osteoarthritis (OA) is one of the most prevalent joint diseases in the elderly community and a leading cause of pain and disability [1] with about 15.4% of the adult population suffering from symptomatic OA in a 2015 Sweden epidemiological study [2]. In the Global Burden of Disease 2013 report, OA was the 10th highest contributor to global disability out of 291 health conditions studied, and it was estimated that globally 242 million people were living with activity-limiting OA [3]. In a mailed survey conducted in England including 26,705 adults ≥ 50 years old with 72% providing the response, 53.2% of respondents reported the presence of OA in at least one of four joints (hand, hip, foot, knee), and 21.8% reported OA to be disabling [4]. In the US alone, the annual financial cost for OA management has been estimated to be 185.5 billion in 2007 US dollars [5]. When compared to age and gender-matched peers, people with OA reported higher out-of-pocket health-related expenditures and the average direct costs of OA was estimated at approximately $2,600 per year for person [6]. By 2030, it was predicted that OA prevalence will increase by up to 35% and become the single greatest contributor to disability globally [4]. In addition, compared with the general population, OA patients had a 55% increase in all-cause mortality (standardized mortality ratio 1.55, 95% confidence interval 1.41 to 1.70) [7].

In Australia, the prevalence of OA was almost 8% (2.2 million people) in 2015 (56.2% of the total arthritis population) which was 5 times more common than rheumatoid arthritis. The health care expenses for OA disease amounted over 2.1 billion Australian dollars (AUD) in 2015 (≈AUD 970 for one OA patient, 1 AUD≈0.7 USD) [8]. In addition, the imaging costs varies across different imaging modalities according to Medicare Rebate in Australia. According to Medicare Benefits Schedule Review conducted in 2017, the imaging prices differ depending on the imaging modalities and indication with the MRI being the most expensive tool, i.e knee MRI≈ 400 AUD, knee ultrasound≈ 75 AUD, knee x-rays≈50 AUD [9]. Therefore, the imaging cost in OA population funded by the government or out-of-pocket expense by the patient should not be underestimated.

Currently, in spite of such an enormous global burden, there is no effective cure for OA . The available medications such as paracetamol or non-steroid anti-inflammatory drugs (NSAIDs), that are currently used to mitigate the pain of OA have a number of concerning side effects [10]. Regulatory bodies such as Food and Drug Administration (FDA) of the United States (US) and the European Medicines Agency (EMA) have not approved any disease-modifying drugs that can prevent, stop, or even limit the progression of OA [10, 11].

1.2. Imaging in osteoarthritis

OA is a complex, multi-factorial joint disease with multi-tissue alterations such as cartilage degeneration, synovial inflammation, meniscal extrusion, osteophyte formation, etc [12, 13]. Therefore, OA is now often viewed as the consequence of joint failure as a whole and comprehensive assessments of the whole joint structure are required for advancing our knowledge of pathologic changes and clarification of their relationship to symptoms and structural progression [13]. The imaging modalities used in OA research and clinical setting are plain radiograph, magnetic resonance imaging (MRI) and musculoskeletal ultrasound (MSKUS). The advantages and disadvantages of these imaging tools are described in **Table 1.1**. The clinical utilities of these imaging modalities are updated in **Chapter Two**.

Table 1.1. Advantages and disadvantages of imaging modalities

Imaging modality	Advantages	Disadvantages
Plain radiograph	Low cost, reference technique Short testing time Wide equipment availability Screening or baseline	Radiation Limitations in imaging soft tissue and subchondral structures
MRI	Sensitive Non-invasive technique No radiation burden 3D sectional imaging technique High spatial resolution Excellent soft-tissue contrast High accuracy and reliability	High cost and low availability Scanning time can be prolonged Not dynamic Contraindicated in patients with implanted devices
Ultrasound	Safety non-invasiveness No radiation burdens Low cost Absence of contraindications High temporal resolution Repeatability over time Wide equipment availability Bedside procedure Optimal patient acceptance Real-time imaging with a short acquisition time US-guided procedures	Limited number and width of acoustic windows Low contrast and strong boundary effects Operator dependency Long learning curve Lack of standardized definitions and scoring systems for findings

1.3. Plain radiograph in osteoarthritis

A plain radiograph is still the main imaging tool used in clinical practice and clinical trials as it is cheap, widely available and able to view structural changes such as osteophyte and joint space narrowing which is a surrogate marker of cartilage loss. The European League Against Rheumatism (EULAR) task force and Osteoarthritis Research Society International (OARSI) have recommended the use of radiography as the primary imaging modality for structural evaluation of OA disease process [14, 15]. It is still the required structural outcome for disease-modifying clinical trials to provide evidence of efficacy according to regulatory bodies.

The main semi-quantitative radiographic scores used in the clinical and research setting include the KLG [16] and OARSI osteophyte and joint space narrowing (JSN) grading scales [17]. All these scores are based on the extent of osteophyte and change in joint space which is the main construct of grading methods. The difference between the two grading systems is that KLG provides global scores as a composite of osteophyte and JSN while the OARSI scores assign the severity grades for each specific feature of OA separately. Hunter *et al* discussed the imaging acquisition, standardized positioning to get consistent results, use of different views for cross-sectional or longitudinal studies, technical details and potential pitfalls for these scoring systems, providing detail on how one might use and apply knee imaging in knee OA trials [15].

Although the plain radiograph can visualise bone changes such as osteophytes and sclerosis, it is unable to reveal soft-tissue changes which are also known to contribute to pain and symptoms in OA [18]. Joint space width measured on a plain radiograph is just a surrogate marker for cartilage thickness as direct visualisation of cartilage is not possible, leading to lack of sensitivity and specificity for detection of OA-related articular change [19]. In addition, there are several shortcomings, such as poor sensitivity to change longitudinally, challenges regarding positioning [20]. In a published narrative review of this thesis (Chapter Two), the role of hidden osteophyte at the intercondylar notch at the knee joint and the additional views of plain radiograph to increase sensitivity was discussed, providing further evidence of limitation of radiograph in OA diagnosis and

monitoring [13]. The ideal instrument should fulfil psychometric criteria such as validity (i.e. it really measures the cartilage) and reliability (i.e. the results are reproducible under other circumstances) and responsiveness (i.e. the measurement is highly responsive to sensitive change). However, plain radiograph does not fulfil those criteria [21].

Therefore, more advanced imaging such as MSKUS and MRI have become important tools in the OA research to capture multiple tissue changes implicated in OA. MSKUS may have some advantages including a higher sensitivity for detecting osteophytes than plain radiographs [22]. In addition, the use of MSKUS and MRI would permit the study of OA phenotypes with respect to inflammatory and structural changes that cannot be visualized with a plain radiograph [13, 23].

1.4. MRI in osteoarthritis

Due to strengths such as the ability to view all joint structures as the whole organ and advancement of MRI technology in recent decades, MRI has become the most widely utilized imaging tool in the research community to evaluate OA risk factors, identify predictors of disease progression and assess treatment change [13]. The role of structural changes evaluated with MRI and relevant clinical utilities are discussed in more detail in chapter 3.

MRI has played a principal role in changing our understanding of OA pathologies in recent decades when semi-quantitative grading methods were introduced for evaluating the significance of each specific pathology in OA disease process as a whole organ disease. These semi-quantitative scores are based on separate grading of the extent of involvement of MRI pathologies relevant to the pathophysiology of OA and usually include meniscal extrusion and tears, osteophyte in different locations around the joint, subchondral bone marrow lesions (BMLs), cartilage degeneration, subchondral cysts, synovial inflammation, effusion, ligament damage and periarticular cysts and bursitis[24]. It is believed that OA has different structural phenotypes and progresses through multiple pathogenic mechanisms. Thus, designing optimal pulse sequences, choosing the appropriate MRI

protocol, in particular, following validated grading systems and understanding artefacts that mimic pathological findings are critical [13, 25].

Since Peterfy *et al.* published the first MRI-based semi-quantitative scoring system known as Whole-organ magnetic resonance imaging score (WORMS) for knee OA in 2004 [26], three additional grading systems for the knee have been developed over the last decade: Knee Osteoarthritis Scoring System (KOSS) [27], the Boston Leeds Osteoarthritis Knee Score (BLOKS) [28] and MRI Osteoarthritis Knee Score (MOAKS) [29]. Although WORMS and BLOKS grading systems both revealed high reliability, these two methods should be combined as BLOKS outperformed WORMS for meniscal evaluation, while WORMS was superior for BMLs assessment [30, 31]. Therefore, MOAKS, a newly refined semi-quantitative MRI-based scoring system, was developed based on experts' experience of the existing scoring systems and the available comparative data for cross-sectional and longitudinal assessment of knee OA.

Although MRI is useful in detecting the whole joint structure, its shortcomings include high costs, prolonged duration of image acquisition and limited availability in the community care impeding its wide-spread use in clinical practice, and availability in community care [20]. In addition, it is contraindicated in certain conditions such as metal implants and claustrophobia [32].

1.5. Musculoskeletal ultrasound in osteoarthritis

In contrast, ultrasonography (US) possesses several advantages over MRI, such as easy accessibility, visibility on different soft tissue pathologies (e.g. active synovitis) without the use of contrast agents [33, 34]. Over the last few decades, MSKUS has become popular among the musculoskeletal research setting due to its inherent dynamic nature, no apparent contraindications, safety and portability in the community [34]. In addition, MSKUS has the ability to examine multiple joints at one session and the capacity to provide answers to rheumatic issues which cannot be solved only by clinical examinations [23, 35], enabling it to be used as point-of-care ultrasound in a clinical setting. Its clinical role and clinimetric properties in OA are detailed in **Chapters Three and Four**.

Chapter Three is a narrative review focusing on the clinical utilities of ultrasound in knee, discussing stages of cartilage abnormalities depending on OA severity, the detectability of soft tissue structures such as synovitis, meniscal tissue in knee OA, the morphological features of bony osteophyte on ultrasound and their respective staging scores, and updating the clinical and imaging correlation of the ultrasound [35], **Chapter Four** was to systemically review the clinimetrics of ultrasound in hip, knee and hand OA, limiting the meta-analysis to the knee joint, and performing the qualitative analysis for hip and hand joints due to paucity of included studies in hip and hand OA [23].

On the other hand, one of the limitations of MSKSUS is the operator-dependency [35]. In addition, as different research groups were utilising different scanning methods, in 2001, the European League against Rheumatism (EULAR) established the standardised scanning protocol for different joints including patient positioning and standard scans with extensive images [36] and then updated these protocol in 2017 [37]. Then, in 2005, Outcome Measure in Rheumatology (OMERACT) proposed definitions for MSKUS pathologies such as synovial effusion, synovial hypertrophy and bone erosion in rheumatic diseases [33], and then these definitions are extended to cover cartilage abnormalities, enthesitis, etc in 2019 [38]. There has been increased utilisation of these scores since its development and many studies have shown a variety of results with pain, function and other imaging measures [23].

1.5.1. Clinimetrics of musculoskeletal ultrasound scores

As an outcome measure to be used in clinical research and practice, it needs to fulfil the clinimetric measures such as reliability, validity, etc. In this aspect, since 1992, OMERACT has developed the OMERACT filter, which aims to establish validated, objective, and feasible measurement tools that demonstrate truth, discrimination, and feasibility [39]. The word “truth” captures issues of face, content, construct, and criterion validity; discrimination captures issues of reliability and sensitivity to change; feasibility determines which of the valid measures can actually be

applied [40]. In 2014, the OMERACT filter 2.0 was published, defining potential domains (‘‘what to measure’’) and measurement instruments (‘‘how to measure’’); and the process of identifying these based on consensus to include them in a core set [41]. Firstly, content validity of the core set was developed by specifying four key ‘‘Areas,’’ of a health condition including Death, Life Impact, and Resource Use; and Pathophysiological manifestations. Measurement of pathophysiological manifestations is essential to evaluate whether or not the effect of the intervention specifically targets the pathophysiology of the disease.

In 2016, based on this model, the OMERACT group produced semi-quantitative and dichotomous MSKUS knee OA scores, based on the current literature and international consensus to reflect the pathophysiological manifestation of the OA disease process. It evaluates synovitis, synovial hypertrophy, effusion, power Doppler signals, meniscal extrusion, osteophyte and cartilage thickness together with the representative image atlas and standardised scanning plane [42]. This scoring system in knee OA was demonstrated to be reliable among the experts in the group. However, reliability outside the group still needs to be tested. There has been no validation study for this scoring system to be used widely in clinical practice. This validation should involve the comparison with clinical measures as well as commonly used imaging scores such as plain radiographs and MRI.

Therefore, out of a variety of clinimetric properties, the current thesis examined the reliability and construct validity of the OMERACT ultrasound knee score (**Chapter Five**). Reliability is defined as the stability or consistency of the ultrasound score, i.e. how close it will provide the same results on repeated administrations (test-retest/intra-rater reliability or reproducibility) or in different ways (inter-rater reliability or inter-machine reliability) [43]. Validity was defined as the degree to which a scale measures what it is intended to measure [41]. Construct validity is examined by assessing to what extent the outcome scores (*e.g.* pain, function, other imaging tools, etc.) correlates with the relevant construct, i.e. pain, function, other imaging tools, etc. [44].

In addition to the development and refinement of the MSKUS grading systems for OA, the MSKUS technology has improved over the decade. Toshiba® has introduced the innovative Doppler

technology known as superb microvascular imaging (SMI) which is specifically designed for detecting tiny blood vessels [45]. SMI is more sensitive to very slow flows than conventional power Doppler in patients with rheumatoid arthritis (RA) [46]. The synovial inflammation implicated in the OA disease process is known to be low-grade and quantitatively much lower compared to rheumatoid arthritis [47]. Studies have reported that the prevalence of positive conventional power Doppler findings in OA populations was also low [48, 49]. Therefore, SMI technology might be useful in our attempt to understand the pathogenic mechanism of the OA disease process. However, there is no study on this. We addressed this issue in **Chapter Six**.

According to our meta-analytic review (Chapter Four) [23], we identified that knee OA was the most widely investigated (n=64), followed by hand OA (n=28), and hip OA (n=8) out of 100 papers. These may be due to the fact that limited ultrasound widow and visibility in the case of hip joint, and the multiple-joint involvement of the interphalangeal joints and the requirement of high frequency probes for superficial joints in the case of hand OA. In addition, hands are frequently involved joints in OA and were often less studied compared to knees. To illustrate the general applicability of MSK US in the appendicular joints and be presented as filling a gap in the literature, the ultrasound study in thumb-base OA was performed. As there is no MSKUS scoring system specific to this joint, methods [50] developed in 2008 by Keen *et al.* for multifocal hand OA were applied to investigate the reliability and association of MSKUS scores with pain, function, muscle strength and radiographic outcomes (**Chapter Seven**).

1.6. Aims of this thesis

With the development of technology and refinement of grading systems for MSKUS OA scores, the overarching research question was to examine the clinimetric properties of MSKUS in OA using the updated scores and novel technology.

There were four specific aims of this thesis that addressed this question:

1. To identify and update the imaging literature (**Chapters Two, Three and Four**)

2. To investigate the construct validity of the OMERACT ultrasound knee score against pain, function, radiographic changes and MRI-detected abnormalities (**Chapter Five**)

3. To compare the assessment of superb microvascular imaging and conventional power Doppler in knee OA and determine its added clinical value (**Chapter Six**)

4. To examine the association of MSKUS pathologies in thumb-base OA with pain, function, muscle strength and radiographic findings (**Chapter Seven**)

CHAPTER TWO

This chapter includes the following published literature review:

Oo W.M., Linklater J.M., and Hunter D.J., Imaging in knee *osteoarthritis*.

Current Opinion in Rheumatology, 2017. 29(1): p. 86-95.

Chapter 2

Imaging in Knee Osteoarthritis

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Statement from co-authors confirming authorship contribution of the PhD candidate

The co-authors of the paper: “Imaging in knee Osteoarthritis”, confirm that Win Min Oo has made the following contributions:

1. Conception and design of the research
2. Analysis and interpretation of the findings
3. Writing of the manuscript and critical appraisal of the content

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Win Min Oo Date: 15th August 2019

As supervisor for the candidature upon which this Thesis is based, I can confirm that the authorship attribution statements above are correct.

David Hunter Date: 15th August 2019

Chapter Two: Imaging in knee osteoarthritis

2.1 Abstract

Purpose of review

Osteoarthritis is the most prevalent and disabling disease still necessitating research in pathogenic mechanisms, predictors of disease progression and responsive techniques to detect the slow structural changes within a short time-frame. In this scenario, imaging modalities are essential. With recent advancements in technology and availability of large longitudinal datasets, tremendous advances are occurring. The present review discusses and summarizes recent original publications in this area.

Recent findings

MRI has been the most popular modality used to evaluate the different roles of structural pathologies in incident knee osteoarthritis, to compare the predictability of individual features of semi-quantitative scores for knee replacement, and to formulate different disease progression models. More ultrasound studies have been published, including the proposed semi-quantitative scoring system by the OMERACT group.

Summary

As more advanced emerging technologies are developed in imaging, there are great opportunities to formulate new incident and prediction OA models, and discovering tissue-targeted disease-modifying drugs.

Keywords

Plain radiography; x-rays; ultrasound; magnetic resonance imaging; MRI; osteoarthritis

2.2 Introduction

Knee osteoarthritis (OA) is a complex, multi-factorial, prevalent joint disease with multi-tissue alterations [12]. Therefore, a comprehensive assessment of the whole joint structure is required for advances in our knowledge of person-level and local risk factors, demonstration of pathologic changes and clarification of their relationship to symptoms and structural progression.

Whilst plain radiography still is the principal imaging tool for OA diagnosis, MRI has become the most widely utilized modality in the research community to evaluate OA risk factors, identify predictors of disease progression and assess treatment change due to its reliable clinimetrics. Recently, ultrasound is becoming popular in OA evaluation, taking advantage of its relatively low cost and easy accessibility.

2.3 Literature search

This narrative review, covering the period from the first of January 2015 until the 30th of April 2016, was based on PubMed database with search strategy focusing on but not limited to terms “Knee osteoarthritis”, “MRI”, “Magnetic Resonance Imaging”, “Ultrasonography”, “Ultrasound”, “Radiography”. Only original articles were included while excluding animal studies, review articles, publications focusing on surgery and publications ≤ 25 observations (usually patients or joints). This is a time of rapid change in knowledge as it relates to imaging use, application and interpretation in the context of knee OA and we have tried to focus on articles deemed to provide a purposeful increase in our knowledge base.

2.4 Plain radiography

Recognizing technical challenges and increased radiation exposure to measure conventional mechanical axis (hip-knee-ankle [HKA] angle), anatomical axis (femorotibial angle [FTA]) on short

knee posterior-anterior 20-30° fixed flexion weight-bearing radiographs was studied in 934 knees from Osteoarthritis Initiative (OAI) knees, and FTA was comparable with the HKA in predicting medial and lateral cartilage loss after adjusting the sex-specific varus shift [51]. Therefore, FTA measurements from fixed flexion radiographs, commonly used for staging radiographic joint-space narrowing during recruitment, might be used in future clinical trials.

Osteophyte formation is a typical radiographic sign of OA. Using incident cohort data (n=132) of the OAI with Kellgren-Lawrence (KL)[16] severity grade (0/1), hidden osteophyte formation at intra-condylar notch (IC) of femur detected by MRI was associated with an increased risk for incident radiographic OA by 48 months [52]. This study provoked some interest in using new radiographic views to increase the sensitivity of plain radiography in demonstrating IC notch osteophytes.

In 219 middle-aged OA patients, baseline JSN and osteophytes did not independently predict cartilage volume loss over ten years after adjusting for MRI-assessed co-pathologies [53]. This calls in to question the role of these radiographic parameters as a prognostic measure in early OA. MRI whole-organ magnetic resonance imaging score (WORMS) composite score [26] was used as a reference standard to assess the validity and sensitivity of the KL scale [16], OARSI joint space narrowing scale [54] and compartmental grading scale [55]. Although all three scoring methods were highly correlated to WORM composite score, scores changes over 30 months show just a moderate sensitivity to change in WORMS cartilage morphology [56], suggesting caution in using these tools for monitoring structural changes.

2.5 Magnetic Resonance Imaging

2.5.1 MRI Disorders

Symptomatic KOA patients often have multiple co-existent structural pathologies. Recent studies showed that **synovitis** on non-contrast MRI (**Figure 2.1**) could precede the development of radiographic OA, albeit that contrast-enhanced MRI (**Figure 2.2**) provided a superior demonstration of

synovitis in OA [57, 58]. In a nested case–control study over 4 years using OAI data, effusion-synovitis and Hoffa-synovitis on MRI OA Knee Score (MOAKS) system [29] strongly predicted development of incident radiographic OA with an odds ratio for synovitis being 1.56 at baseline, 3.23 at one year prior to incident OA and 4.7 at the time of incident OA respectively [57]. In a separate longitudinal case-control 84-month Multicenter Osteoarthritis Study (MOST) study, synovitis on WORMS system was an independent risk factor for incident KOA after adjusting for other structural pathologies, and the greater the synovitis score, the higher the risk [58]. These findings highlight the possible potential for developing targeted therapies towards inflammation to prevent incident KOA.

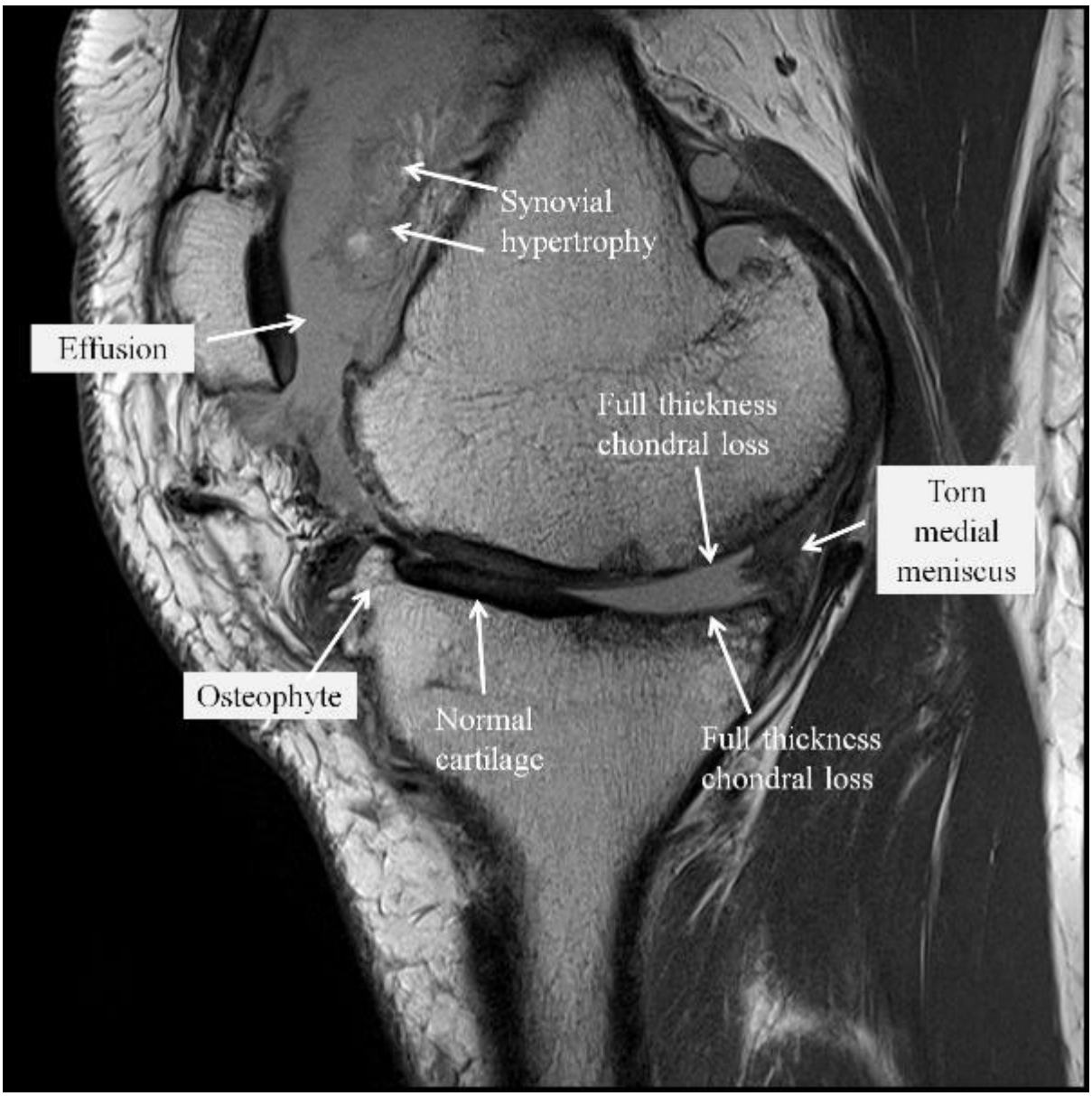
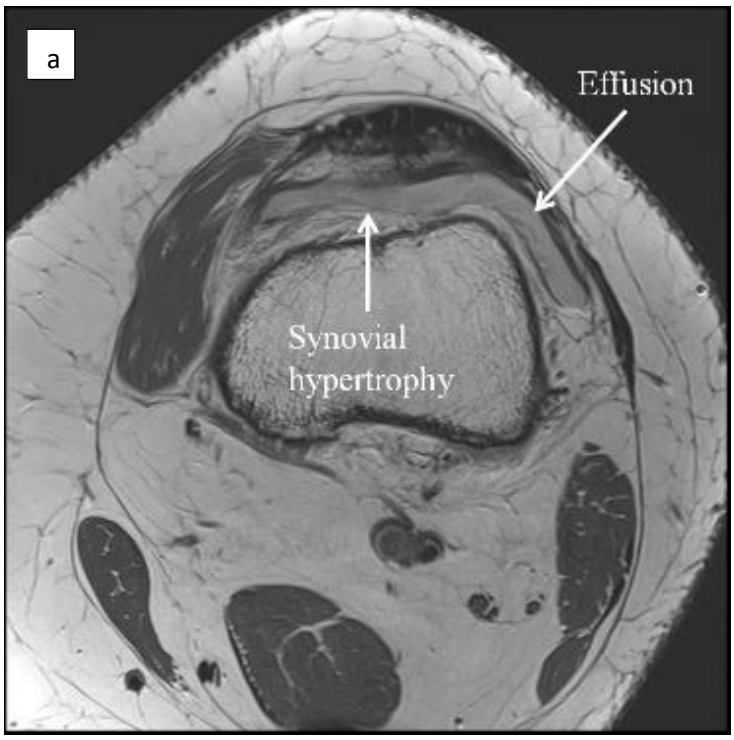


Figure 2.1. Sagittal proton density MRI showing advanced medial femorotibial compartment osteoarthritis, with full-thickness cartilage loss, large effusion and prominent synovial thickening. Note also the chronically torn medial meniscus and osteophyte formation.



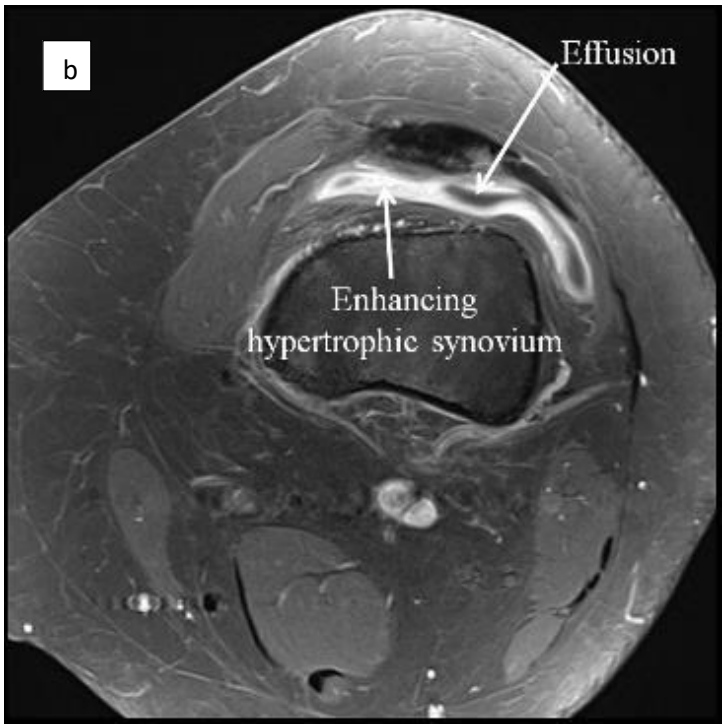


Figure 2.2. Axial proton density (a) and axial post-intravenous contrast fat-suppressed T1 (b) MRIs demonstrating synovial thickening and small effusion on the non-contrast PD image (a) and moderately intense enhancement of the thickened synovium, with a small non-enhancing simple fluid component on the contrast-enhanced image (b).

Quantification of chondral T2 relaxation times indirectly demonstrates reversible collagen matrix abnormalities in **articular cartilage** prior to the onset of changes on morphologic MRI. This technique shows promise in early OA assessment. The first reference database of normative T2 values for morphologically normal knee cartilage (KL 0/1 and WORMS 0/1) showed a weak trend towards higher T2 values with age and gender but the strongest trend with body mass index (BMI). However, these normal values can vary depending on the type of MRI scanner, field strength, radiofrequency coil, pulse sequence, artefacts such as magic angle and T2 fitting method used [59]. Another study demonstrated racial differences in T2 values in normal participants [60]. Baseline T2 values in all compartments except the medial tibia predicted later onset of radiographic tibiofemoral (TF) OA over 4 years in normal participants with a baseline KL grade= 0 and BMI <35 [61]. In another study, a decrease in BMI of ≥ 10% was related to a slower T2 progression over 4 years, highlighting a beneficial effect of weight loss on cartilage matrix integrity [62]. There was a 1.2 mm^3 reduction in the loss of medial tibial cartilage volume for every 1% of weight loss achieved in 2.3 years on average [63]. A significant association was observed between medial meniscal extrusion area and cartilage loss over 1 year [64]. A separate study reported the association of plasma phylloquinone (vitamin K1) with the progression of articular cartilage and meniscus damage [65], awaiting further studies to provide insights to the underlying mechanism.

Meniscal lesions may be one of the earliest changes in KOA causal pathway [66]. In an 8-year longitudinal study of mostly middle-aged adults (n=198), 16 % of the participants had an increase in their mean meniscal score which measured the meniscal tears and meniscal extrusion of each anterior, body and posterior meniscal horns separately from 0 to 2 [67]. Change in meniscal tears had an independent association with cartilage volume loss, change in bone marrow lesions (BMLs) and change in meniscal extrusion [67]. In a study (n=137) with pre-radiographic KOA, posterior root/horn radial tears in medial meniscus were independent factors which increased T1ρ values of medial femorotibial cartilage, suggesting its potential usefulness in screening very early-stage OA [68].

In a 6-year longitudinal study in an OAI sub-cohort (n=340) without KOA (KL grade=0), female sex, baseline extrusion ratio ([meniscus body extrusion]/[tibia width]×100) and incident

meniscal tear during follow-up were associated with increased meniscal body extrusion [69]. In a separate longitudinal 4-year study, greater medial meniscus extrusion predicted incident radiographic KOA. The earlier the onset of incident KOA, the greater meniscus extrusion was found at baseline [70]. In an 84-month study, different patterns of coexisting MRI lesions were identified for incident OA for TF and patellofemoral (PF) joints by using a latent class analysis. Therefore, meniscal damage seemed to play a different role in the development of incident OA in TF versus PF joints [71].

Most past epidemiological and clinical OA studies have focused only on the role of **BMLs** in TF compartment rather than the PF joint. In a recent study (n=904), patellar BMLs were associated with increased patellar cartilage defects, and decreased patellar cartilage volume both cross-sectionally and longitudinally, independent of TF BMLs [72]. This might suggest a site-specific association between BMLs and cartilage changes and supports the concept of possible cross-talk between subchondral bone and cartilage, with the resultant progression of chondral lesions [73]. BML quantification on intermediate-weighted fat-suppressed (IW FS) turbo spin-echo offered better validity and sensitivity to change than BML quantification on 3-dimensional dual echo steady state (3D DESS) sequences against knee pain both cross-sectionally and longitudinally [74], highlighting that DESS is far from an optimal sequence for depicting the BML to the maximal extent [75].

Greater JSW loss and cartilage volume loss were demonstrated when meniscal extrusion and BML were co-localized than when each existed separately [76]. This combined, cumulative negative impact on cartilage loss was 0.31 mm for radiographic JSW loss and 2.22% for MRI cartilage volume loss per additional co-localized factor. Both radiographic changes and MRI abnormalities such as cartilage damage and BMLs in both knees exhibited a more bilateral symmetric pattern than expected, supporting the presence of person-based risk factors for OA-related tissue changes [77].

The maximal cross-sectional area of the **infra-patella fat pad** (IPFP) was predominantly located in lateral (54.2 %), rather than medial tibiofemoral compartment (1.7 %) [78]. A large IPFP prevented knee cartilage loss mainly in the lateral compartment and development of knee pain in generalized KOA, suggesting its role in a local shock-absorbing mechanism [78] and favouring IPFP

preservation at total knee arthroplasty for reduced recurrent knee pain [79, 80]. Similar protective role of IPFP size was reported in other studies as well [81, 82]. One cm^3 greater IPFP volume was associated with 30 to 80 cm^3 greater knee cartilage volume [81]. In a 2.6 year longitudinal study, change in IPFP maximal area in women was beneficially had a significant association with change in tibial cartilage volume per annum (β: +1.56% per cm^2 at the medial site; +0.86% per cm^2 at the lateral site) [82].

In contrast, a recent cross-sectional study in PF OA patients (n=41) found that a larger IPFP volume explained 20.1 % of the variance in KOOS-pain and was associated with worse pain [83]. These findings suggest different impacts of IPFP on OA principally affecting PFJ versus TFJ. Healthy men in OAI normal control cohort showed a significantly greater ratio of IPFP volume/body weight than women, similar amounts of inter-muscular fat, and less subcutaneous fat in the thigh [84].

Studies on other **peri-articular structures** reported that concurrent presence of low vastus medialis (VM) area, high VM %Fat, and high BMI could identify a subgroup of patients with medial femur cartilage volume loss [85]. In a nested case-control study, loss of ACL integrity on MRI did not confer a significantly increased risk of incident radiographic OA in an older adult cohort with the average age of 60.1 ± 8.5 years [86], in contrast to findings in young adults mostly less than 30 years [87]. In another study, anterior cruciate ligament reconstruction using single-bundle hamstring tendon autograft was a risk factor for early PF OA [88]. Other studies awaiting future confirmation are the age-adjusted significant association of popliteal artery wall-thickness with medial tibial cartilage volume loss [89] and the relationship of increased DXA-assessed ipsilateral bone strength with KOA severity after age-adjustment [90].

Roemer et al [91] highlighted the importance of concomitant **structural MRI lesion load** (i.e. cartilage morphology, BMLs, meniscal status, meniscal extrusion, Hoffa synovitis, and effusion-synovitis) than the presence of any specific feature alone (**Figure 2.3**), reporting a 12-fold increased risk for presence of 5 or 6 concomitant features 1 year prior to diagnosis, compared to knees with only 1 feature or with no features. In addition, the incidence of new features over time might be more important than the presence of any given feature alone [91].

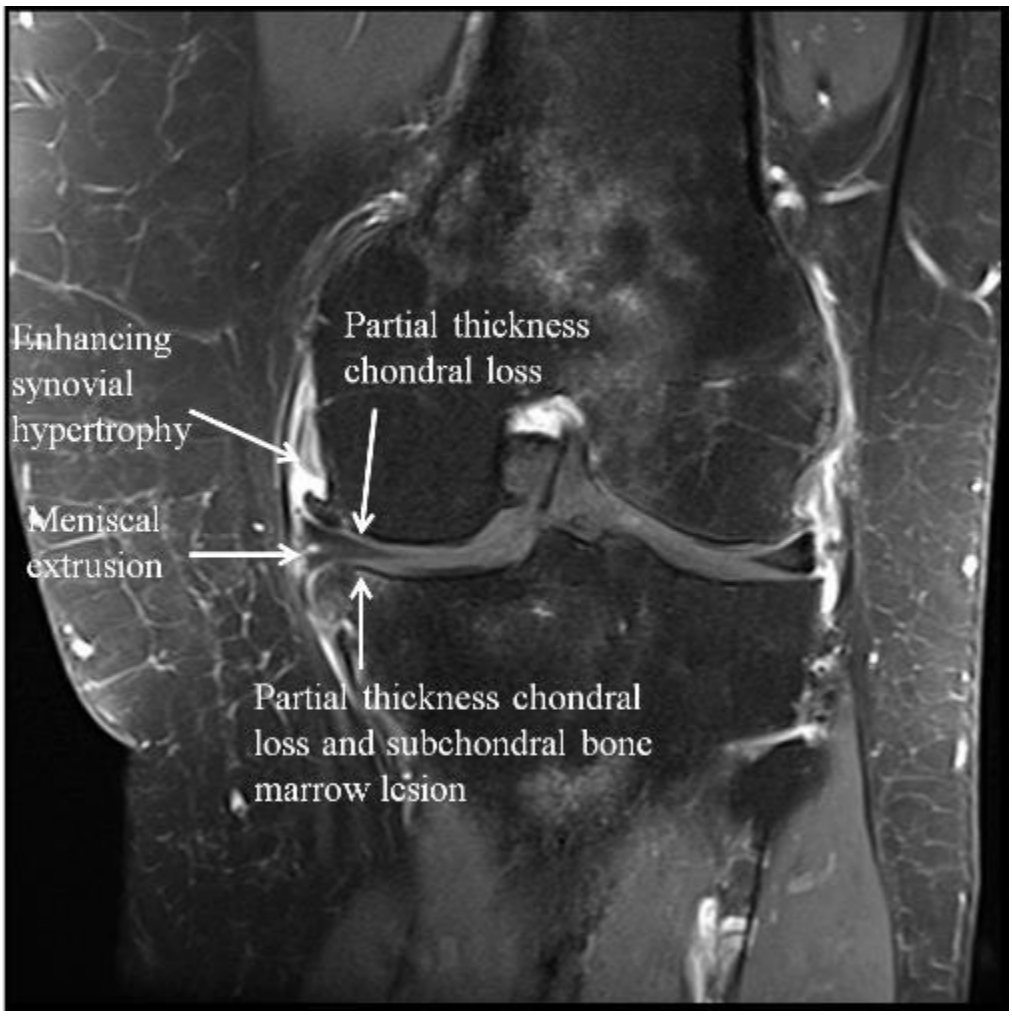


Figure 2.3. Coronal contrast-enhanced fat-suppressed T1 MRI of an osteoarthritic knee demonstrating partial thickness chondral loss towards the medial joint line involving the medial femoral condyle and medial tibial plateau, with small subchondral bone marrow lesions, moderate medial joint line osteophyte formation, meniscal extrusion and adjacent enhancing synovitis in the meniscofemoral recess.

2.5.2 MRI Scoring System

Although radiography is still used in grading KOA severity, MRI is now increasingly used in evaluating KOA due to several advantages [92]. In a 6.2 year longitudinal study to evaluate whether Boston-Leeds Osteoarthritis Knee Score (BLOKS) [28] [47] and WORMS [26] could predict knee replacement in the OAI database, a one-score increase in the average BLOKS full-thickness cartilage

score posed the greatest risk [HR:13.55(3.61–50.89)]. Both BLOKS and WORMS cartilage scores were independent predictors of subsequent KR while the BLOKS cartilage and meniscus scores, and WORMS BML score were superior to their counterparts (**Table 2.1**). However, there was no significant additional predictive value of follow-up MRI assessment at 24-month for KR [93].

Table 2.1. Significant risk of subsequent knee replacement with regard to one score increase in the average baseline BLOKS and WORMS scores of cartilage, BML and meniscus (as indicators of structural tissue damage)

	BLOKS	**Adjusted HR (95%CI)**	**WORMS**	**Adjusted HR (95%CI)**
1	Average cartilage score (full thickness)	13.55 (3.61–50.89)	Average cartilage score	2.60 (1.19–5.68)
2	Average cartilage score (lesion extent)	3.02 (1.07–8.52)	Average BML score	3.99 (1.25–12.77)
3	Average meniscal extrusion score	4.19 (1.08–16.19)		

Abbreviations: BLOKS=Boston Leeds Osteoarthritis Knee Score; CI: Confidence Interval; HR: Hazard Ratio; WORMS=Whole-Organ Magnetic Resonance Imaging Score

P-value≤ 0.05. Adjustment includes age, gender and BMI, maximum baseline radiographic KL score, Physical Activity Scale for the Elderly (PASE) and Western Ontario McMaster Questionnaire (WOMAC) (Modified and reprinted with permission from Springer)[88]

2.5.3 Uses in Clinical Trial

In a prospective **pharmacological** trial, the presence of meniscal extrusion had a significant association with more JSW loss and cartilage volume loss independent of NSAID treatment [94]. In a

meniscal extrusion-positive subgroup without analgesics/NSAIDs, those taking glucosamine/chondroitin had significantly less cartilage volume loss than those not taking glucosamine/chondroitin while no significant difference was seen in JSW [94]. Quantitative MRI seems to be a more sensitive and reliable method to evaluate disease-modifying agents than x-ray.

In a large 2-year trial, vitamin D supplementation did not provide any MRI structural benefits [95]. In a phase III trial, strontium ranelate (2g/day) had protective effects on medial cartilage volume at 36 months in OA patients with meniscal extrusion as well as when both meniscal extrusion and BML were co-localized [76]. Another clinical trial demonstrated poor effectiveness of percutaneous calcium phosphate injection in symptomatic BMLs of the knee [96].

Among three **non-pharmacological** studies, one study (n=112) showed a significant negative association of every 1% weight change with 1.2 mm^3 change in medial tibial cartilage volume over 2.3 years [63]. Another study reported no significant difference in structural progression between intensive weight loss (10% of baseline) through diet, with and without exercise and exercise alone over 18-month [97] probably due to cancelling benefit of the dietary arm by benefit of exercise arm. The beneficial compartment-specific effects of a patella brace were found in decreasing BML volume in PF OA over 6-weeks [98].

2.5.4 Predictors for Disease Progression

In the past year, more studies have focused more on the prediction of structural progression than symptomatic progression. In a 4-year nested case-control OAI study (n=600), loss of medial femorotibial cartilage thickness over 24 and 12 months was associated with a combination of radiographic and pain progression in knee OA over 48 months, confirming MRI cartilage thickness change as a robust imaging biomarker for KOA progression. In this study, the medial TF radiographic joint space loss (≥0.7 mm) was used for radiographic progression and a persistent increase in the WOMAC score (≥9 on a 0-100 scale) for pain progression [99].

In middle-aged KOA patients, baseline TF cartilage volume predicted greater absolute cartilage volume loss over 10 years independent of other co-pathologies [53]. One cross-sectional study in PF OA from MOST (n=1137) and Framingham OA (n=934) database, knee pain risk and severity was associated with cartilage loss in lateral PF joint and large BMLs in either the medial or lateral PFJ [100].

The 3-year Strontium Ranelate Efficacy in Knee Osteoarthritis Trial (SEKOIA) study reported that the presence of BML, but not other MRI abnormalities at baseline, could predict change in JSW per year of follow-up. Average annualized JSW was reduced by 0.18 mm in men and by 0.13 mm in women. However, the limitation is the lack of assessing meniscal extrusion and synovitis as other potential confounders [101]. Cartilage damage, bone marrow lesions, medial meniscal damage, and synovitis and effusion measured with MOAKS [29] could predict knee replacement in the following year, with severe cartilage damage having the highest association (odds ratio, 16.5; 3.96-68.76) [102].

Additional studies reported a positive association of thigh adipose tissue with structural progression of KOA over 2 years [103], predictability of vastus medialis fat content for cartilage volume loss and BMLs progression [85] and an independent association of meniscal tear score with pain and structural progression over 8 years [67]. A latent class cluster analysis (LCA) determined the existence of distinct subtypes of KOA with different structural progression and symptoms using baseline radiographic scores, quantitative MRI measures of cartilage quantity and denuded bone, and self-reported clinical scores. The first cluster represented no areas of denuded bone and limited progression. Cluster 2 included small areas of denuded bone. The third and fourth clusters showed larger areas of denuded bone with increasing OA severity [104] but the study was limited by not including other important MRI lesions.

2.5.5 Novel MRI Methods

A cross-sectional study showed that dynamic contrast-enhanced MRI (DCE-MRI) analytic approaches (heuristic and pharmacokinetic) were highly reproducible and might provide novel insights into the role of synovial inflammation and vascularity in KOA [105].

Longitudinal active appearance models (AAM)-determined 3D bone area changes (total area of subchondral bone [tAB]) were more responsive than radiographic medial joint space width and MRI cartilage thickness for assessing structural progression [106]. In the femur, medial femur/medial trochlear femur (MF/MedPF) and lateral femur/lateral trochlear femur (LF/LatPF) boundary was defined as a line on bone corresponding to the anterior edge of medial or lateral meniscus, and extended smoothly to the edge of the tAB. The MedPF/LatPF boundary was defined as the centre of the trochlear groove. In their methodology, auto-segmentation of these regions with AAMs was used for measurement of tAB, and spatial distribution of change greater than measurement error was shown with a colour scale.

A 0.25 T rotating open-configuration MRI scanner was used to scan while lying supine (clinostatic position) or while standing in a true weight-bearing position (orthostatic position) in 26 KOA patients. MME (clinostatic MME, orthostatic MME and ΔMME) were correlated with WORMS and KL score. In univariate analyses, ΔMME significantly correlated with TF cartilage loss, meniscal damage, osteophytes, global WORMS and radiographic KL score while significant correlation existed only between orthostatic MME and osteophyte WORMS sub-score. In multivariate analysis, ΔMME was independently correlated with cartilage loss [107].

2.6 Ultrasonography

2.6.1 Ultrasound disorder

Ultrasound is traditionally labelled somewhat disparagingly as being highly operator-dependent. However, for dichotomous scales, a recent study (n=80) demonstrated excellent inter-observer agreement for femoral cartilage thinning (k=0.99), osteophytes (k=0.94), synovial effusion (k=0.98), synovial thickening (k=0.96), popliteal cyst (k=1.00), and meniscal protrusion (k=0.86) (**Figure 2.4 and 2.5**) [108]. Authors determined a better assessment of ultrasound for TF osteophytes, medial meniscal extrusion (**Figure 2.6**) and medial femoral cartilage changes, in comparison to

radiography, using MRI as a reference standard. Ultrasound can serve as a complementary modality to radiography, providing a cost-effective tool in depicting relevant soft tissue pathology [109].

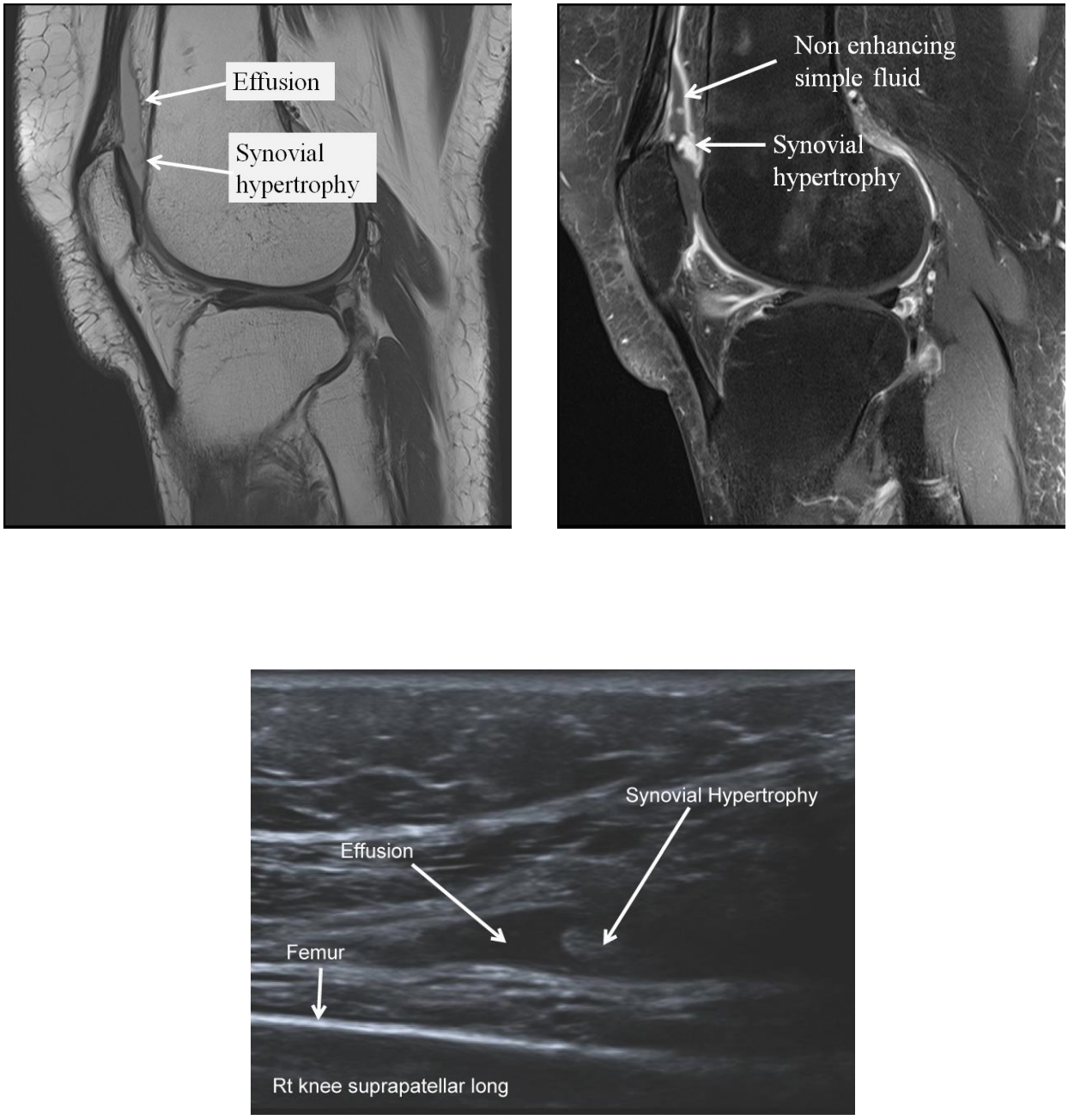


Figure 2.4. Sagittal fat-suppressed proton density (a), post-intravenous contrast sagittal fat-suppressed T1(b) MRIs and transverse ultrasound image (c) demonstrating synovial hypertrophy and effusion in the suprapatellar bursa of a knee in which there was moderate osteoarthritis in the medial femorotibial compartment.

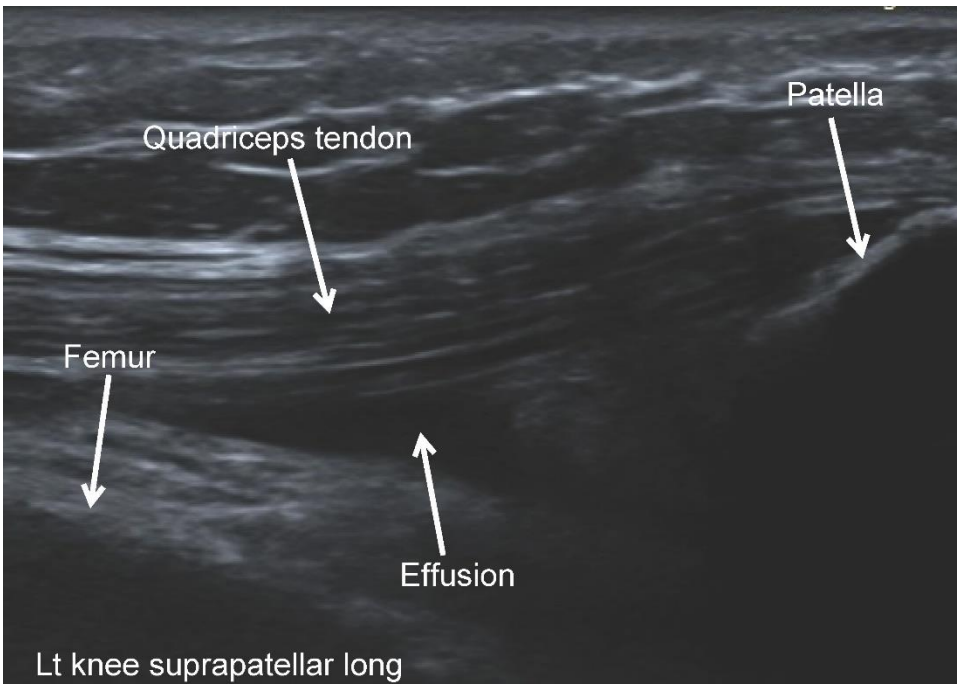


Figure 2.5. Longitudinal ultrasound image of the suprapatellar bursa in an osteoarthritic knee demonstrating a small effusion and synovial hypertrophy.

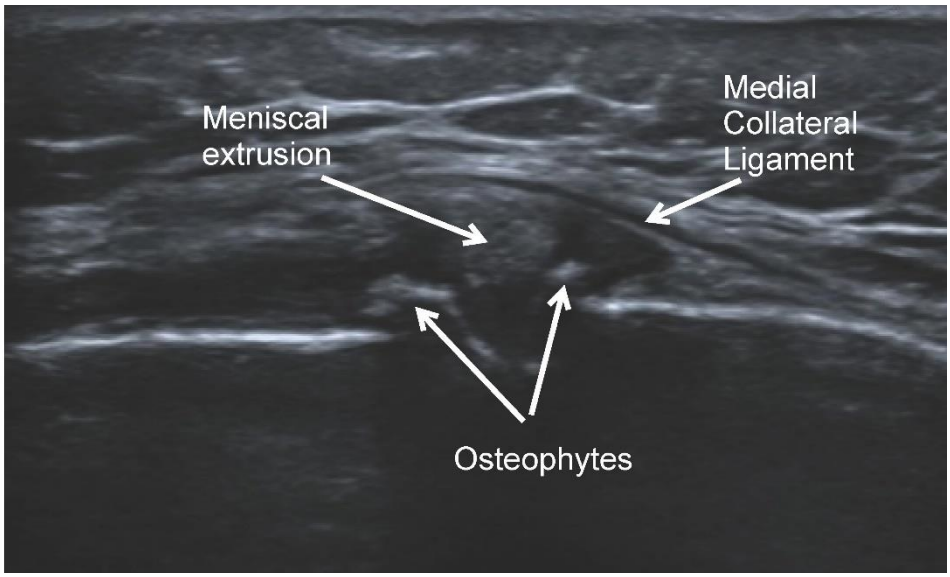


Figure 2.6. Longitudinal ultrasound image at the medial joint line of the knee demonstrating osteophytes and medial meniscal extrusion in a patient with osteoarthritis.

Variations in quality and quantity (muscle thickness and echogenicity) of lower limb muscles with varying severity of KOA were reported recently [110]. Another study (n=85) demonstrated a relatively high prevalence of pes anserine bursitis (20%) with a positive correlation of OA grade with bursitis size and area [111].

2.6.2 Ultrasonography Grading System

The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Ultrasound group developed scoring systems for inflammatory and structural changes in KOA by a consensus process [42]. The scoring scale is shown in **Table 2.2**. Intra- and inter-observer reliability scores were moderate to good for synovitis and global synovitis, fair to good for cartilage damage, medial meniscal damage and osteophytes. Limitations included small sample size (n=13) and lack of validation of this score with other constructs such as clinical scores or MRI [112].

Table.2.2. The OMERACT Ultrasound Scoring system

Scoring US pathology	**Range**	**Location**	**Patient Position**	**Scanning Plane**
Synovitis	0-3	Suprapatellar recess	Supine with the knee flexed 30º	longitudinal
		Medial and lateral parapatellar recess	Supine with the knee in a neutral position	transverse
Synovial hypertrophy	Each for 0-1	Suprapatellar recess	Supine with the knee flexed 30º	longitudinal
Effusion		Medial and lateral parapatellar recess	Supine with the knee in a neutral position	transverse
Synovial PD signal				
Cartilage damage	0-3	Trochlear cartilage	Supine with full flexion of the knee.	transverse
Meniscal damage	0-2	Anterior horn of the medial meniscus	supine with the knee flexed 10º	longitudinal
Osteophytes	0-3	Medial and lateral femorotibial space	supine with the knee flexed 10º	longitudinal

Abbreviation: PD=Power Doppler; US=Ultrasound

(Modified and reprinted with permission from the BMJ group)[41]

2.6.3 Ultrasonography as an Outcome Measure in Clinical Trials

In recent years, pharmacological trials for KOA have incorporated ultrasound into outcome measures. Ultrasound demonstrated a reduction in synovial thickness, effusion and power Doppler flow 1 week after intra-articular steroid injection (80mg), reflecting the anti-inflammatory effects of steroid on synovium. In one study, power Doppler flow in synovium was more sensitive and more strongly associated with pain than synovial thickening and effusion [113]. In contrast, a different KOA study reported no significant effects of an intra-articular steroid injection (40mg) on synovial hypertrophy, synovial Doppler flow, or Baker's cyst presence at 3 months. The difference may be due to different end-points (1 week vs. 3 months), highlighting transient benefits of intra-articular steroid for KOA, or reduced steroid dosage (80mg vs. 40 mg) or using dichotomous scales for power Doppler and Baker's cyst [114].

In a longitudinal study to evaluate intra-articular platelet-rich plasma in severe KOA patients (KL grade=3-4), quantitative ultrasonographic cartilage thickness, measured as a distance perpendicular to the articular surface of medial condyle at the level of which the cartilage was well-differentiated, was sensitive to treatment change [115].

2.6.4 Ultrasonography as Predictors of Disease Progression

In a 2-year longitudinal study in KOA (n=125), a strong consistent association with clinical and radiographic progression was found for the presence of Baker's cyst (found in 26% of participants in their study), and to a lesser extent for synovial hypertrophy, suggesting the potential role of ultrasound to define patients at risk of more rapid progression in clinical practice [116]. Cartilage changes, osteophytes, and synovial thickening in dichotomous scale were associated with higher WOMAC index and worse clinical symptoms in their cross-sectional study [108]. Another study reported the significant association of a semi-quantitative ultrasonographic grading system of femoral cartilage with the VAS, WOMAC, and Lequesne index [117].

2.7 Conclusion

MRI remains the dominant imaging modality in the OA research community. Many research efforts are focusing on tissue-targeted pathologies and on the prediction model for disease progression. New imaging techniques continue to be developed to identify more specific and responsive measure for assessing treatment change. The ready availability of large datasets such as OAI has facilitated activity within the research community formulating different models for risk factors and fast progressors. Additionally, the use of ultrasound is also increasingly being deployed for imaging of KOA. The future potential of KOA imaging will offer exciting opportunities to examine targeted structure-modifying therapies.

Key Points:

1) Hidden osteophyte formation at intra-condylar notch (IC) of femur, detected by MRI, identifies persons at risk for incident radiographic OA.

2) The greater amount of structural lesion load than the presence of any specific feature alone posed a higher risk of incident OA.

3) Individual sub-scores of WORMS, BLOKS and MOAKS have respective advantages in predicting knee replacement.

4) The OMERACT Ultrasound scoring system has substantial reliability in KOA and should be studied for validity and sensitivity to treatment change.

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None

Conflicts of interest

Prof David Hunter-consultant to Nestle, Merck Serono and Flexion Therapeutics. Dr. James Linklater and Dr. Win Min Oo do not have any conflict of interest.

CHAPTER THREE

This chapter includes the following published literature review

Oo W.M. and Bo M.T., *Role of Ultrasonography in Knee Osteoarthritis*. Journal of Clinical Rheumatology, 2016. 22(6): p. 324-9.

Chapter 3

Role of Ultrasonography in Knee Osteoarthritis

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Statement from co-authors confirming authorship contribution of the PhD candidate

The co-authors of the paper: "Role of Ultrasonography in Knee Osteoarthritis", confirm that Win Min Oo has made the following contributions:

1. Conception and design of the research
2. Analysis and interpretation of the findings
3. Writing of the manuscript and critical appraisal of the content

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Win Min Oo Date: 15th August 2019

As supervisor for the candidature upon which this Thesis is based, I can confirm that the authorship attribution statements above are correct.

David Hunter Date: 15th August 2019

Chapter Three: Role of Ultrasonography in Knee Osteoarthritis

3.1. Abstract

Ultrasound has become popular among rheumatologists as the first-choice imaging investigation for the evaluation and monitoring of osteoarthritis (OA). Because of recent improvement in technology, ultrasound has the ability to demonstrate and assess the minimal structural abnormalities, which relate to the pathophysiology and progression of OA, such as abnormalities involving articular cartilage, synovial tissue, bony cortex, and other soft tissue. Ultrasonography is a promising technique for assessing soft tissue abnormalities such as joint effusion, synovial hypertrophy, Baker's cyst, and other structural changes including the decrease in cartilage thickness, meniscus extrusion, and osteophyte formation. Ultrasonography not only possesses diagnostic potential in knee OA but also is useful as an imaging biomarker to predict long-term disease progress. Ultrasonography has also been proven as a useful tool in guiding therapeutic interventions and monitoring treatment effectiveness. This review addresses the utility, reliability, and potential utilization of ultrasonography as an imaging technique in knee OA.

3.2. Introduction

Osteoarthritis (OA) is the most common rheumatic disorder and a frequent health problem in the community where symptomatic knee OA has a prevalence of 6% to 10% in the adult population. Traditionally, OA has been defined as degenerative changes in bone, cartilage, and the soft tissues of the joints. More recently, OA has been regarded as a failure of the joint as an organ, much like renal or cardiac failure [118, 119]. Non-destructive synovial proliferation, joint effusions, popliteal cysts, tendonitis, and bursitis are frequent findings in OA [120]. Adequate assessment of the various structures within and around the joint and measurement of a variety of the pathological aspects of OA is best provided by diagnostic imaging [121].

As a criterion standard, radiological imaging has been used to diagnose and classify the severity of knee OA such as the Kellgren and Lawrence system [16]. However, radiographs have several limitations, such as the inability to evaluate soft tissue structures and their related inflammation [122]. In addition, radiographic features of OA do not correlate with the symptoms of OA [123].

In recent years, imaging techniques such as ultrasonography (US) have been used to assess the pathology associated with a number of different musculoskeletal diseases. Ultrasonography allows multiplanar imaging of the joint, providing a "one-stop" assessment of many rheumatic problems, which may not be provided by clinical examination alone. Ultrasonography has the advantage of not using ionizing radiation and can provide unlimited multiplanar assessments. It can also visualize soft tissue abnormalities such as the meniscal extrusion and cartilage thinning, which involve the pathophysiology and progression of OA [124, 125]. This relatively inexpensive technology with the added advantages of portability and real-time dynamic examination can lend itself to diagnostic service in the community [126]. Modern US systems can use beam steering and compound imaging technologies to allow wider fields of view. High-resolution probes with frequencies of up to 20 MHz are being applied in routine joint assessment [127].

3.3. Literature search

To address the utility, reliability, and potential uses of US as an imaging technique in knee OA, we searched articles in MEDLINE (34), EMBASE (65), EBM Reviews (29), AMED (3), Scopus (63), Web of Science (76), and the Cochrane Central Registers for Controlled Trials from their conception up to September 2015. These databases were looked up individually for all possible terms and combination of terms to accommodate differences in their search engines. Hand searches were also performed in addition to additional searches through Google Scholar and Reference Manager Search engines. The keywords used in combination (OR) are knee osteoarthritis, knee osteoarthrosis, osteoarthritis, ultrasonography, and ultrasound. The combination (AND) is used between knee osteoarthritis/knee osteoarthritis and ultrasonography/ultrasound. All key terms are limited to title/abstract. Then the duplicate terms are removed, and among the maximum 105 full texts, articles concerning therapeutic ultrasound or animal studies are excluded for narrative review.

3.4. Cartilaginous Changes

Cartilage thickness ranges from 0.1 mm on the articular surface of the head of the proximal phalanx to 2.6 mm on the lateral femoral condyle of the knee joint [128]. In 1984, ultrasound was used to determine the thickness of articular cartilage, as well as to detect changes in it's surface and internal characteristics such as the ratings of clarity and sharpness [129]. Loss of clarity of the cartilaginous layer and loss of the normal sharpness of the synovial space-cartilage interface are the earlier features of cartilage damage [125].

The weight-bearing surfaces of the femoral cartilage can be assessed by transverse suprapatellar scan plane with the knee in maximal flexion (Figure 3.1) or with an infrapatellar transverse scan with the leg fully extended. Cartilage is characterized in early OA by loss of the sharp contour and the heterogeneous echogenicity of the cartilage matrix on ultrasound. An asymmetric narrowing of the cartilaginous band follows later in the disease process. It was reported that multiple sonographers demonstrated good reproducibility and high levels of agreement between US and histology in

assessing the normal to moderately damaged cartilage [130]. In addition, the measurement of cartilage thickness is rapid (several seconds), painless, and non-invasive.

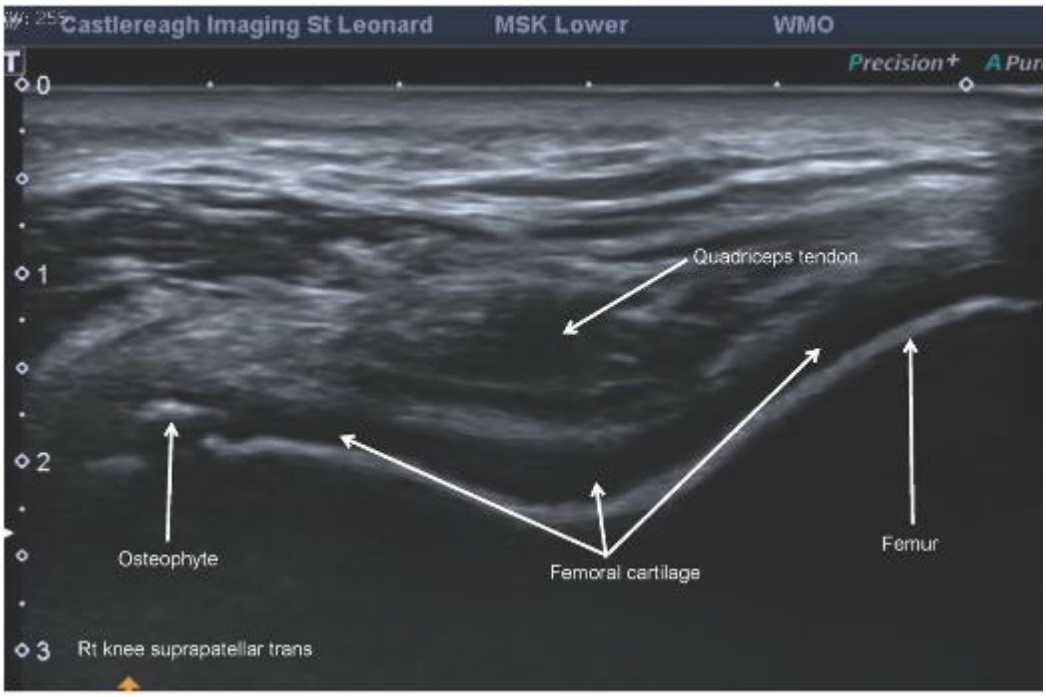

Figure 3.1 Suprapatellar transverse scan showing femoral cartilage of knee OA joint.

It has been demonstrated that the ultrasonographic grading (in vitro) of femoral cartilage correlated well with the histologic grading (OARSI Osteoarthritis Cartilage Histopathology Assessment System)[131] of anterior and middle areas of femoral articular cartilage ([rho] = 0.78, 0.89, both $P < 0.001$) [132]. According to this ultrasonographic grading, grade 1 showed a homogenously anechoic cartilage band with sharp anterior and posterior margins; grade 2 showed blurring or obliteration of the margin of the cartilage band; grade 3 included blurring, obliteration of the margin, and narrowing of the cartilage band; grade 4 was coded if the cartilage band could not be visualized.

Recently, it was reported that the semiquantitative ultrasonographic grading system was significantly corelated with the clinical symptoms and functions in knee OA on evaluation against the visual analogue scale, Western Ontario and McMaster Universities Arthritis Index, and Lequesne

index[133, 134]. The US grading system for femoral cartilage has been proposed after validation against the arthroscopic Noyes grading[135] for cartilage degeneration, and this outcome score includes assessment of local reduction of thickness, loss of the normal sharpness of cartilage interfaces, and increased echogenicity. The cartilage was evaluated as grade 0 if they showed a monotonous anechoic band with sharp hyperechoic anterior and posterior interfaces. Grade 1 changes include loss of the normal sharpness of cartilage interfaces and/or increased echogenicity of the cartilage. Grade 2A changes were as follows: in addition to the previously mentioned changes, clear local thinning (<50%) of the cartilage. Grade 2B changes showed local thinning of the cartilage of more than 50% but less than 100%. Grade 3 changes included 100% local loss of the cartilage tissue (**Figure 3.2**). The sum of cartilage grades in all 3 sites of the femoral cartilage at the medial and lateral femoral condyles, as well as at the intercondylar notch area (sulcus) had the highest correlation between US and arthroscopy ($r_s = 0.655$, $P < 0.001$). However, it still needs further validation studies, which might include, for example, quantitative magnetic resonance imaging or histology as references. Non-invasive knee US is a promising technique for screening and evaluating degenerative changes of articular cartilage[136].

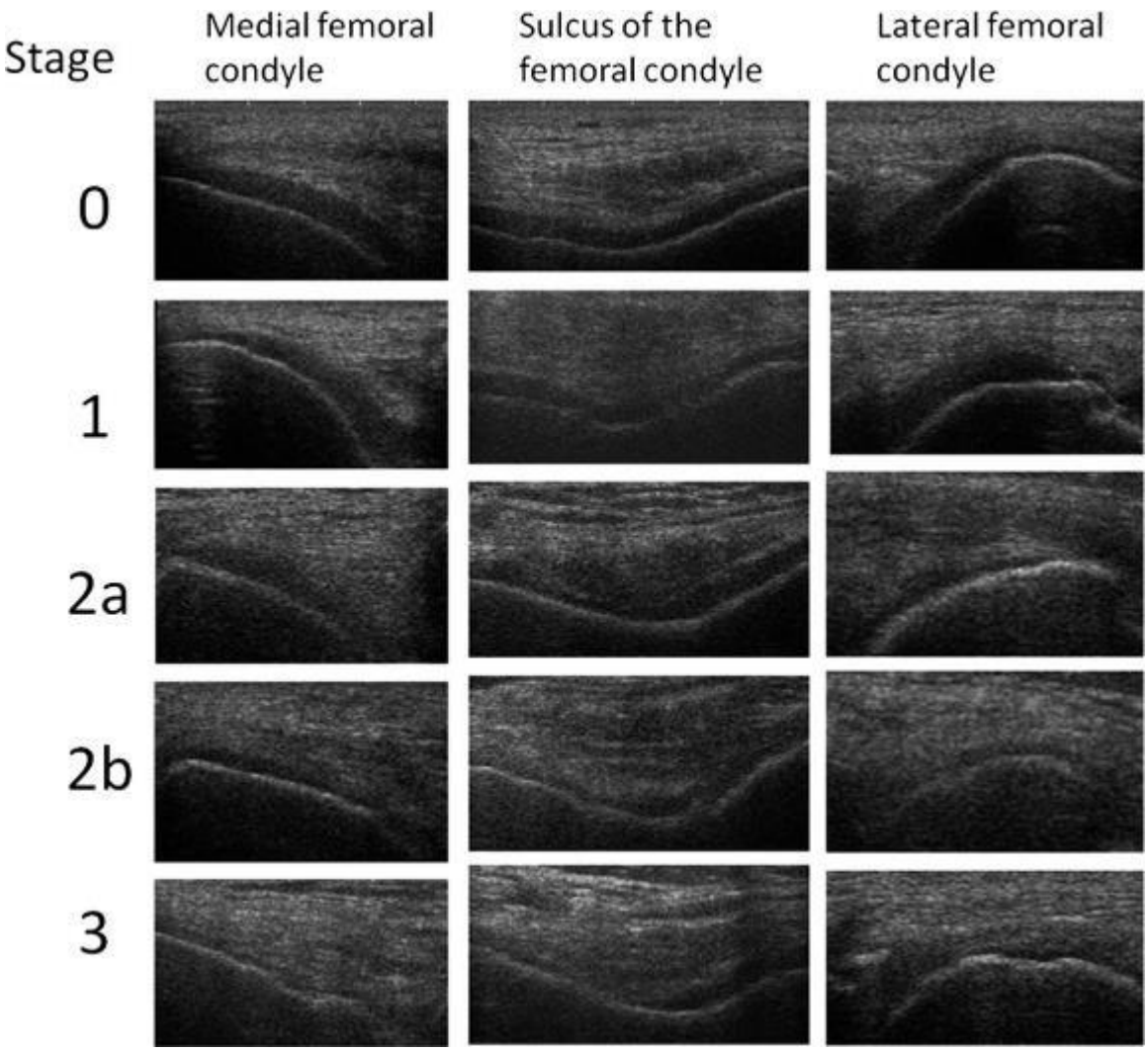

Figure 3.2 Typical examples of different cartilage degenerative US grades (0, 1, 2A, 2B, 3) in the knee joint.[131] Grade 0 for a monotonous anechoic band with sharp hyperechoic anterior and posterior interfaces; Grade 1 changes for loss of the normal sharpness of cartilage interfaces and/or increased echogenicity of the cartilage; Grade 2A for the previously mentioned changes plus clear local thinning (<50%) of the cartilage; Grade 2B for local thinning of the cartilage of more than 50% but less than 100%; Grade 3 changes for 100% local loss of the cartilage tissue

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3.5. Bony Changes

The early bone changes in the OA joint are characterized by hyperechoic signal at the site of the attachment of the joint capsule to the bony cartilaginous margin, which will eventually form as osteophytes on conventional radiography. In advanced disease, the bony profile of the osteophytes is evident [137]. Moderate to substantial validity was reported in comparing ultrasonographic osteophytes to those seen on radiographs [138].

A novel atlas for scoring osteophytes in the tibiofemoral joint was used to prove that the US was more sensitive in detecting osteophytes than plain radiographs at the medial compartment of the tibiofemoral joint (**Figure 3.3)**. Furthermore, osteophyte size detected with US, compared with only their presence, is a better predictor of articular cartilage degeneration as there is a significant correlation between osteophyte size (summed US grade) and the arthroscopic grade of degenerative changes of the articular cartilage at the medial compartment [139]. The grading of osteophyte size was as follows: grade 0 included no osteophytes, that is, a smooth cortical surface; grade 1 demonstrated small and distinct cortical protrusion(s) of the bony surface; grade 2 showed larger protrusion(s) of the bony surface; grade 3 included very large protrusion(s) of the bony surface. However, it should be noted that this result is based on a small trial of 26 patients.

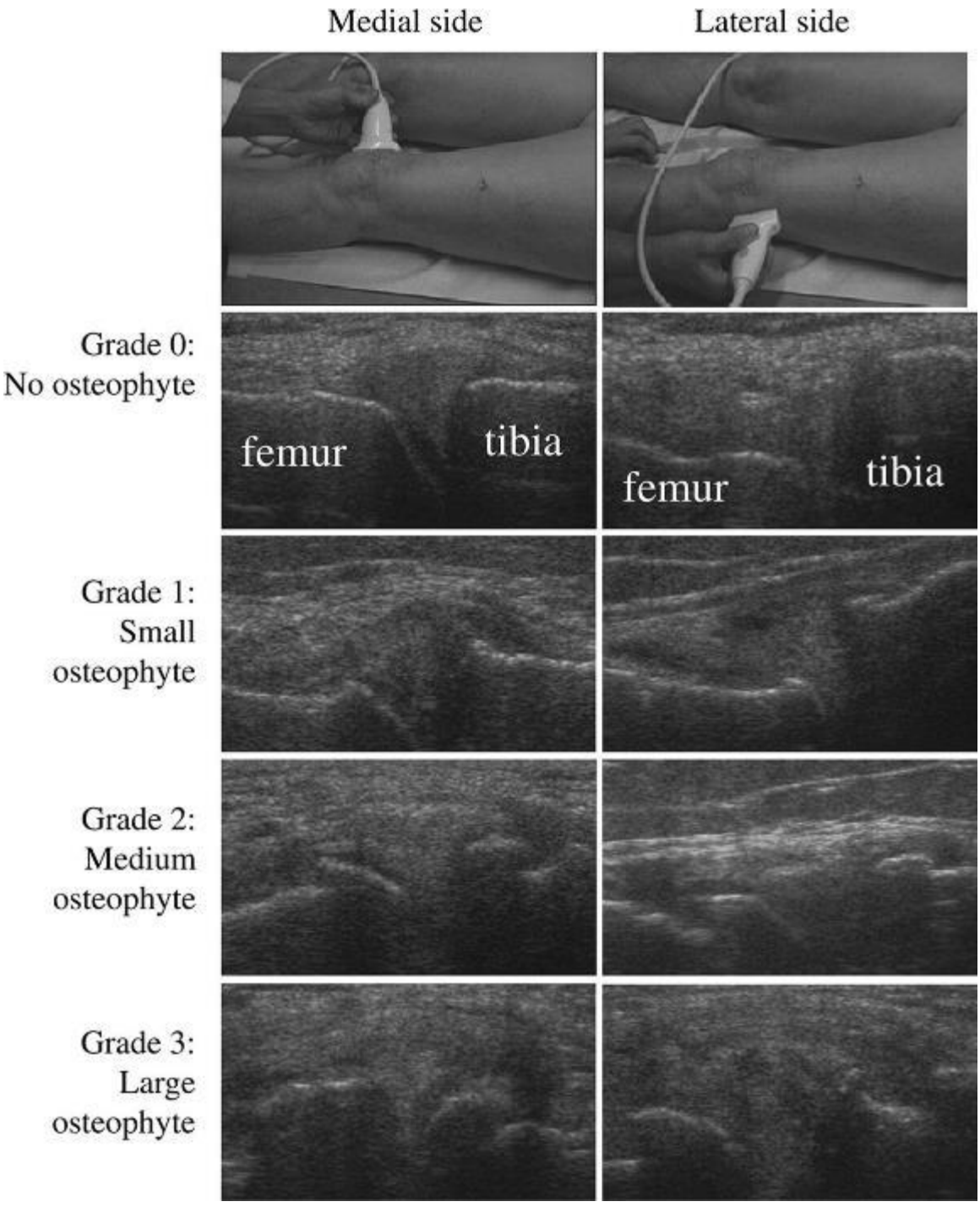

Figure 3.3 The US atlas for knee osteophyte detection.[134] Reprinted with permission from Taylor & Francis.

Recently, the US score was developed in knee OA and includes relevant domains measuring (1) morphological changes in the medial and lateral compartments such as osteophyte and meniscus extrusion, (2) inflammatory markers in the medial and lateral compartments such as synovial hypertrophy and Doppler activity, and (3) effusion. Bony changes demonstrated a strong correlation between the morphological changes in the medial and lateral compartments and the corresponding Kellgren-Lawrence score. Total ultrasound score displayed substantial reliability and reproducibility, with interclass correlations coefficients ranging from 0.75 to 0.97. Construct validity was confirmed with statistically significant correlation coefficients (0.47-0.81, $P < 0.01$). However, the relevance for longitudinal studies remains to be demonstrated, for example, during treatment [140].

3.6. Soft Tissue Changes

It has been increasingly recognized that synovitis plays a more important role in the pathogenesis of OA than previously thought. A small to moderate amount of synovitis and effusion is commonly detected in patients with knee OA (Figure 3.4). Depending on the study, between 47% and 100% of patients were noted to have synovitis and/or effusion of the symptomatic knee [141, 142]. A large European League Against Rheumatism study of 600 people with knee OA demonstrated synovial hypertrophy or effusion in 46%. Synovial hypertrophy was defined as synovial thickening of >=4 mm and effusion recorded as present or absent based on the depth of fluid of more than 4 mm or less than 4 mm in the suprapatellar recess [142]. Ultrasonography is more sensitive than clinical examination in detecting synovitis[143] and correlates well with magnetic resonance imaging and arthroscopic findings. Synovitis or joint effusion detected by US also shows a relationship with pain in knee OA [144-146].

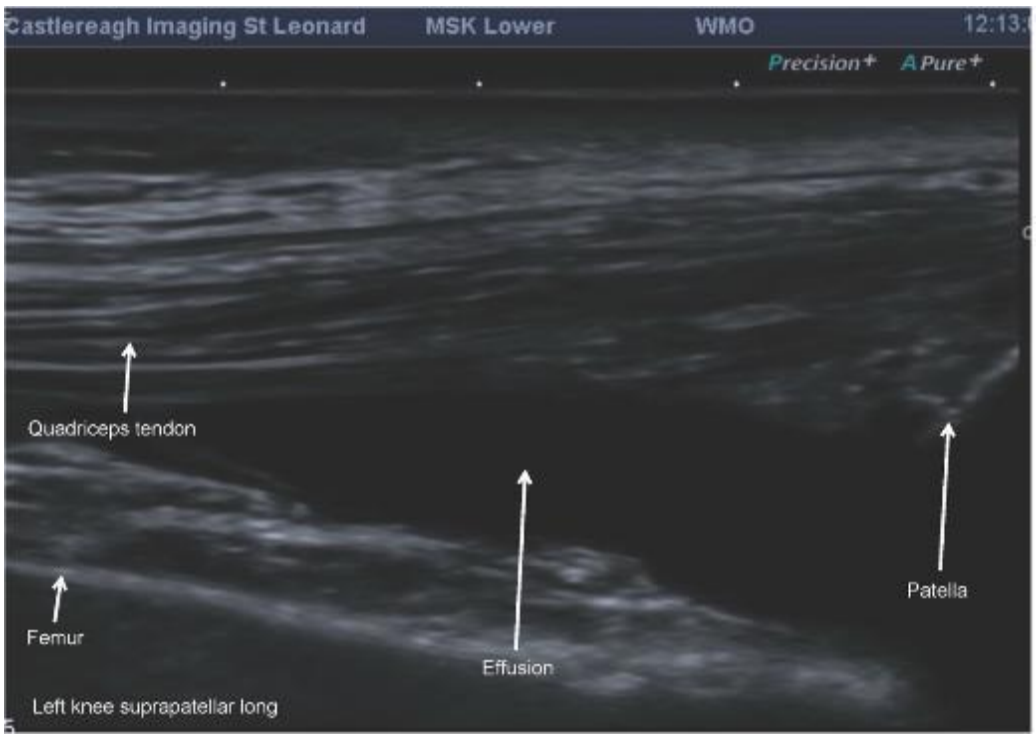

Figure 3.4. Large effusion in the suprapatellar recess of knee joint in a longitudinal scan on sagittal plane.

The serial arthroscopies performed on knees with symptomatic but pre-radiographic OA revealed a clear association between the presence of synovitis and the future development of medial cartilage loss (an odds ratio for progression of the arthroscopic chondropathy score of 3.11 [1.07-5.69]), suggesting that, at its earliest stages, before visible cartilage degeneration has occurred, ultrasonographic synovitis has a potential role in predicting the structural progression of knee OA [147].

Power Doppler can be utilized to assess synovial flow, which denotes increased synovial vascularization (**Figure 3.5**) [148]. Increased Doppler signal correlates with increased vascularity seen on histologic examination of synovial tissue of knee OA [149]. In a study that used a novel technique of digital synovial vascularization quantification with contrast enhancement for detecting synovitis in patients with knee OA, US of the superior recess revealed an effusion or synovial

thickening in 58% in B-mode, 63% in power Doppler sonography, and 95% with contrast medium enhancement [150].

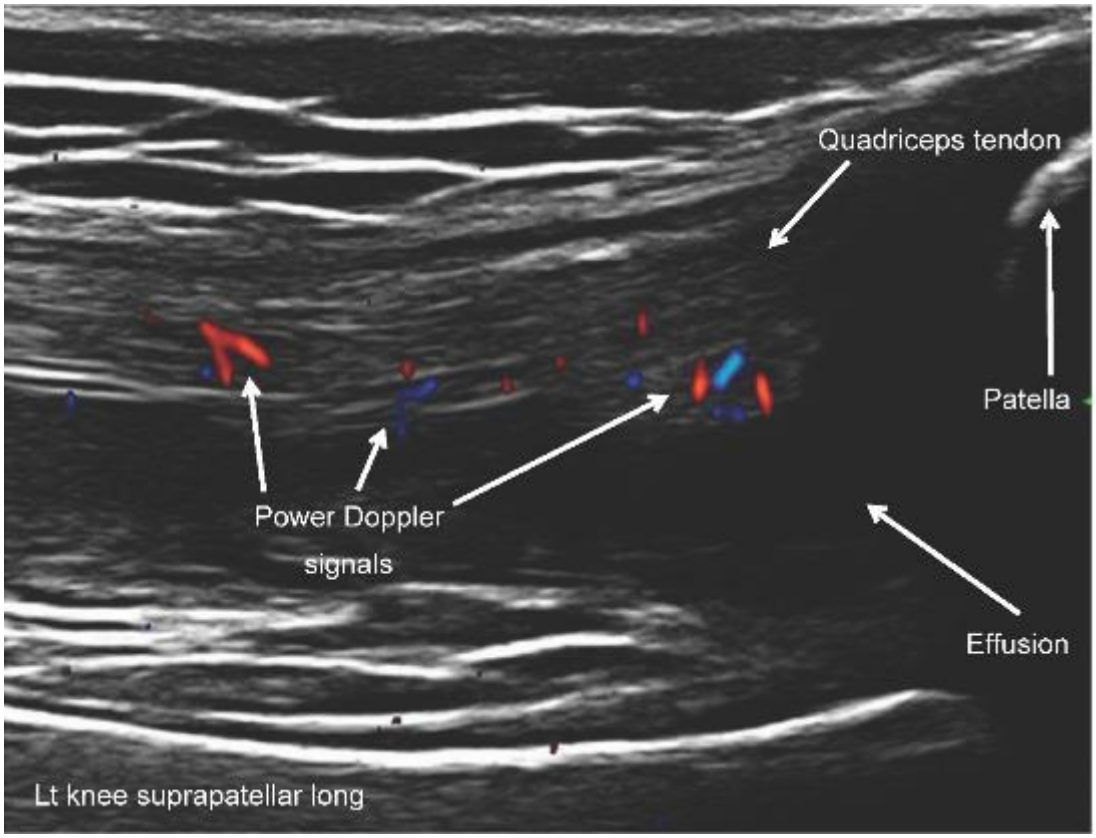

Figure 3.5. Increased bidirectional Power Doppler signals in the suprapatellar fat pad and quadriceps tendon around the suprapatellar recess in a longitudinal scan on sagittal plane

On the other hand, there were reports that no association between US features and the degree of knee pain was detected after 1-year follow-up[151], and further studies are still warranted to answer which part of pain in knee OA is explained by soft tissue pathology and whether US is the imaging method of choice to measure this pathology. In a systemic review in 2009, a paucity of reliability data was highlighted with regard to inter-reader and intrareader reliability in image acquisition and the scoring of stored images [121].

3.7. Monitoring and intervention

In clinical trials in knee OA, outcome measures usually include structural assessment, functional status, and the level of pain. Serological markers are unavailable for monitoring disease progression in OA, and imaging markers using US abnormalities will be valuable in this scenario. Studies are still lacking to identify and precisely determine a population in which OA progresses more rapidly [152].

Recently, US prediction in the long-term progress of knee OA is reported. After 1-year follow-up, meniscal protrusion (**Figure 3.6**) and Baker's cyst (**Figure 3.7**) might be useful for long-term prediction of clinical or radiological outcome, although effusion, synovial hypertrophy, and infrapatellar bursitis seem to be more temporary phenomena [151]. A longitudinal association between Baker's cyst at baseline and radiological and clinical progression was found after 2-year follow-up [153].

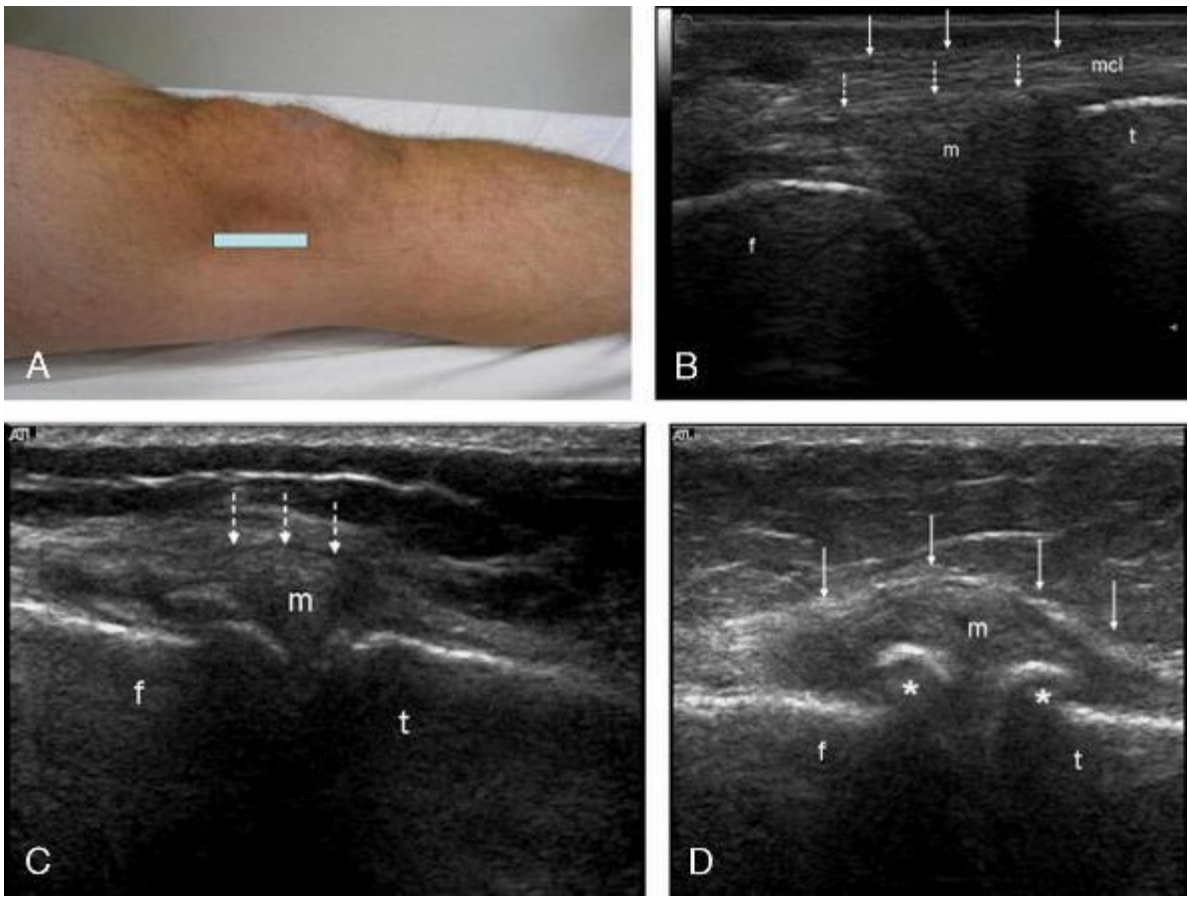

Figure 3.6. Longitudinal ultrasonographic images of the medial joint line (in black and white). A, Position of probe footprint. B, Ultrasonographic image of a normal knee shows distal femur (f), proximal tibia (t), triangular outline of the medial meniscus (m, dashed arrows), and the linear echoes produced by the medial collateral ligament (mcl, solid arrows). C, Ultrasonographic image shows medial meniscal extrusion (m, dashed arrows). D, Ultrasonographic image in knee OA demonstrates medial meniscal extrusion (m) with resulting displacement of the medial collateral ligament (arrows) and obvious osteophytes (*) proximal and distal to the joint line.[148] Reprinted with permission from Elsevier.

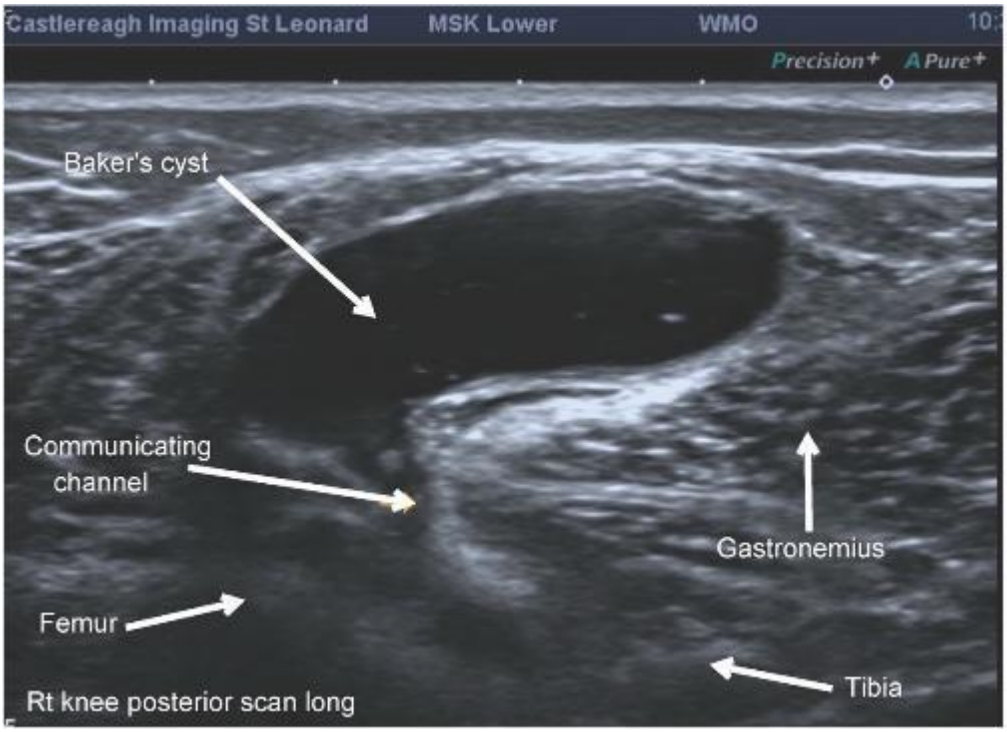

Figure 3.7. Baker's cyst in a longitudinal scan on the sagittal plane.

In another study, increased meniscal bulging and presence of Baker's cyst/joint effusion were correlated with worse pain or poorer function [154]. A 3-year multi-center European League Against Rheumatism prospective study examined the predictors for joint replacement in more than 500 subjects with knee OA. The multivariate analysis demonstrated that the presence of a joint effusion (>=4 vs. <4 mm) at baseline was a significant independent predictor of joint replacement at 3 years (hazard ratio, 2.63 [95% confidence interval, 1.70-4.06]) [155].

Ultrasonography has proved to be an effective and safe imaging method for guiding intra-articular injections because of the advantage of visualizing the proper needle positioning inside the joint cavity. In a study of 62 patients with symptomatic knee OA to investigate the predictive value of US characteristics by defining responders as patients with numeric rating pain scale of 4 or less at 4 weeks after glucocorticoid injection, no US characteristic of inflammation has the ability to reliably predict those who respond to intra-articular glucocorticoids, requiring further study in a large-scale trial[156]. Given the disagreement between radiographic morphological changes and symptoms in

OA, further studies should establish the usefulness and value of US-detected changes in terms of the effectiveness of therapeutic interventions [126].

3.8. Limitations

Application of ultrasound to assess large joints seems still challenging because of the inherent inability of ultrasound to pass through bony structures and scan deeper portions of the joint [157, 158]. Thus, US visualization of articular cartilage is limited by the width of the acoustic windows that depend on the anatomy of the joint. Even with advances in the resolution of the transducers, deeper structures are difficult to visualize as the higher-frequency transducers have lower tissue penetration.

Moreover, US has been regarded as a highly operator-dependent imaging method with poor reproducibility, partly due to the intrinsic real-time nature of US image acquisition [127]. However, its usage is reassured by recent studies that have established moderate to good interobserver reliability [159-161].

Acquisition of US skills takes time depending on the trainee's hand-eye coordination skills. A long learning curve may be an important limiting factor in the widespread use of US. In addition, the examination of multiple scanning planes in the clinical setting can be time-consuming. Focused examination is proposed with concentration on a small number of scanning planes to reduce examination time [162].

3.9. Conclusion

US provides a safe, cost-effective, and reliable technique to assess knee OA. Ultrasonography is more sensitive than clinical examination and plain radiography in recognition of important abnormalities prevalent in knee OA. It is an excellent tool not only to recognize the bony profile but also to visualize the soft tissues, helping the rheumatologist to determine the type and extent of these structural damages. The semiquantitative ultrasonographic grading system has been validated and will be valuable in monitoring disease progression. Ultrasonography also has the potential to further

clarify the role of soft tissues and provide new insights into disease genesis, pathology, progression, and prediction of OA. However, the long learning curve is still an important limitation to be overcome for widespread application of US in routine clinical practice.

CHAPTER FOUR

This chapter includes the following published literature review

Oo W.M., Linklater J.M., Daniel M., Saarakkala S., Samuels J., Conaghan P.G., Keen H.I., Deveza L.A., and Hunter D.J., Clinimetrics of ultrasound pathologies in osteoarthritis: systematic literature review and meta-analysis. Osteoarthritis and Cartilage, 2018. 26(5): p. 601-611.

Chapter 4

Clinimetrics of ultrasound pathologies in osteoarthritis: systematic literature review and meta-analysis.

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Statement from co-authors confirming authorship contribution of the PhD candidate

The co-authors of the paper: "Clinimetrics of ultrasound pathologies in osteoarthritis: systematic literature review and meta-analysis", confirm that Win Min Oo has made the following contributions:

1. Conception and design of the research
2. Analysis and interpretation of the findings
3. Writing of the manuscript and critical appraisal of the content

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Win Min Oo Date: 15th August 2019

As supervisor for the candidature upon which this Thesis is based, I can confirm that the authorship attribution statements above are correct.

David Hunter Date: 15th August 2019

Chapter Four: Clinimetrics of ultrasound pathologies in osteoarthritis: systematic literature review and meta-analysis.

4.1. Abstract

Objective: The aims of this study were to systematically review the clinimetrics of commonly assessed ultrasound pathologies in knee, hip and hand osteoarthritis (OA), and to conduct a meta-analysis for each clinimetric property.

Methods: MEDLINE, EMBASE, and Cochrane Library databases were searched from their inceptions to September 2016. According to the OMERACT Instrument Selection Algorithm, data extraction focused on ultrasound technical features and performance metrics. Methodological quality was assessed with modified 19-item Downs and Black score and 11-item Quality Appraisal of Diagnostic Reliability (QAREL) score. Separate meta-analyses were performed for the following clinimetrics: 1)inter-rater/intra-rater reliability; 2)construct validity; 3)criteria validity; and 4)internal/external responsiveness. SPSS, Excel and Comprehensive Meta-analysis were used.

Result: Our search identified 1126 records; of these, 100 were eligible, including a total of 8542 patients and 32373 joints. The average Downs and Black score was 13.01, and average QAREL was 5.93. The stratified meta-analysis was performed only for knee OA, which demonstrated moderate to substantial reliability [minimum kappa>0.44(0.15,0.74), minimum ICC>0.82(0.73-0.89)], weak construct validity against pain(r=0.12 to 0.27), function(r=0.15 to 0.23), and blood biomarkers(r=0.01 to 0.21), but weak to strong correlation with plain radiography(r=0.13 to 0.60), strong association with MRI [minimum r=0.60(0.52,0.67)] and strong discrimination against symptomatic patients(OR=3.08 to 7.46). There was strong criterion validity against cartilage histology [r=0.66(-0.05,0.93), and small to moderate internal(SMD=0.20 to 0.58) and external(r=0.35 to 0.43) responsiveness to interventions.

Conclusion: Ultrasound demonstrated strong criterion validity with cartilage histology, poor to strong correlation with patient findings and MRI, moderate reliability, and low responsiveness to

interventions.

PROSPERO Registration No.CRD42016039954

4.2. Introduction

Osteoarthritis (OA) is a ubiquitous joint disease, predisposing to severe disability and resulting in a significant economic burden on the community [1], with its prevalence surging worldwide due to an increase in an ageing population [163]. The pathophysiology of OA is complex and involves multiple tissue pathologies. There is currently no consensus on which manifestations should be measured in OA clinical studies. In attempting to objectively evaluate OA structural components, X-ray and MRI have been commonly employed as they visualize constructs related to cartilage. Ultrasound has been less well studied, but does provide certain advantages such as real-time assessment of multiple joints, sensitive visualisation of synovitis without the need for contrast agents [153, 164, 165], its detection of pathologies such as meniscus extrusion [166-169], osteophytes [170-172], degeneration of femoral trochlear cartilage [136, 173-175], and effusions (which might be missed on clinical examination or plain radiography) [165, 176-178]. As a result of these attributes, and likely because of widespread uptake in the rheumatology community, ultrasound has increasingly been applied as an outcome tool in OA clinical studies over the last decade.

Since Keen *et al.* reported its clinimetrics, mainly with a focus on validity, in a systematic review in 2009, based on PubMed and Medline database searches [179], many ultrasound OA studies have been published according to recent narrative reviews [13, 35], with most papers having sound methodology, utilizing more advanced technology such as high-frequency probes, and use of definitions and techniques from Outcome Measures in Rheumatology (OMERACT) [33] and European League Against Rheumatism (EULAR) Ultrasound Working Groups [142]. The increase in the knowledge base in this area, therefore, warrants an update of the previous review in terms of clinimetrics (clinical measurement) such as reliability, validity, responsiveness [41]. Moreover, there is no published meta-analysis on these clinimetric of commonly assessed ultrasound pathologies in OA.

Therefore, the purposes of this study were: (1) to systematically review the performance metrics of ultrasound as applied to the detection of commonly assessed pathologies in people with OA

with a focus on knee, hand and hip joints and (2) to conduct a meta-analysis of each clinimetric property for the ultrasound findings if feasible.

4.3. Methodology

4.3.1. Selection criteria

Manuscripts were included if 1) they reported clinimetrics of commonly assessed ultrasound pathologies in knee or hand or hip OA in adults, and 2) separate clinimetrics for OA were recorded if the sample included different rheumatic diseases. Articles were excluded if 1) they were not related to the use of B-mode or colour/power Doppler ultrasound, 2) they utilized ultrasound only for injection guidance, 3) they did not provide any ultrasound clinimetrics, or 4) they were a review or editorial articles, non-human or non-English publications. The study protocol was registered in PROSPERO database with CRD42016039954.

4.3.2. Information source and selection process

One reviewer (WMO) searched MEDLINE via Ovid, EMBASE, and Cochrane Library databases from their respective inception to September 2016. The search strategy for each database was developed in consultation with an experienced librarian (**Appendix 1**). The same reviewer implemented the secondary searching in reference lists of included articles, ultrasound chapters in reference books, and conference abstracts of Osteoarthritis Research Society International (OARSI), EULAR and American College of Rheumatology (ACR) from 2014 to 2016.

The retrieved articles were imported into Covidence systematic review software [180], and two reviewers (WMO and MD) screened the titles and abstracts independently. Subsequently, the full texts of the selected articles were retrieved and judged against the inclusion and exclusion criteria. Any disagreement was resolved with a third reviewer (DJH). When the included studies referred to a

previous paper for methodology or reliability, it was obtained, and appraised if it met the selection criteria.

4.3.3. Data extraction and quality assessment

According to the OMERACT Instrument Selection Algorithm [181], the same two reviewers conducted data extraction with a standardized excel template including: 1) characteristics of studies such as study design, setting, sample size, participants selection and diagnostic criteria; 2) technical features such as ultrasound mode (*i.e.* B-mode, Power Doppler), machine settings, scanning methods, the particular joints and structures scanned; 3) pathological findings such as ultrasound definitions of pathologies and scoring methods; 4) types of clinimetrics.

For reliability, imaging and operator characteristics were recorded. Construct validity was defined if the study correlated ultrasound findings with clinical assessment, plain radiography or MRI. Criterion/predictive validity was defined when ultrasound findings were concurrently or predictively compared with the gold standard, *i.e.* histopathology, arthroscopy. Discriminative validity was also assessed in two aspects: internal responsiveness (the ability of ultrasound measure to change over a pre-specified time frame) or external responsiveness (the extent to which changes in ultrasound measure relate to corresponding changes in a reference measure of health status) for interventional studies. Feasibility was calculated in scanning time required for the whole ultrasound examination. One reviewer (WMO) appraised the methodological quality, using the modified 19-item version (**Table 4.1**) derived from Downs and Black score system [182, 183] for all included papers, and 11-item Quality Appraisal of Diagnostic Reliability (QAREL) score for reliability papers [184].

Table 4.1. Quality Assessment Tool modified and derived from Downs and Black score system

Domain/Item	Questions
Patients/selection bias	1) Is the hypothesis/aim/objective of the study clearly described? 2) Are the characteristics of the patients included in the study clearly described? 3) Is the patient sample representative of patients treated in routine clinical practice? 4) Is there information on the possibility of selection bias present in the study?
Interventions	5) Are the interventions of interest clearly described? Treatments should be clearly described. In non-treatment related observational studies, the characteristics under study should be clearly described.
Comparison	6) Was a comparison group identified and clearly defined?
Blinding	7) Blinding of the main outcome measured was reported?
Outcomes	8) Are the main outcomes to be measured clearly described in the Introduction or Methods section? If the main outcomes are first mentioned in the Results section, the question should be answered no. 9) Were the main outcome measures used accurate (valid and reliable)? For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes. 10) Have all important adverse events that may be a consequence of the intervention been reported? This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).
Reported findings/statistical analysis	11) Are the main findings of the study clearly described? Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below) 12) Does the study provide estimates of the random variability in the data for the main outcomes? In non-normally distributed data the inter-quartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes. 13) Were the statistical tests used to assess the main outcomes appropriate? The statistical techniques used must be appropriate to the data. For example, nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.
Confounding	14) Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided. 15) Was there adequate adjustment for confounding in the analyses from which the

	main findings were drawn?
Losses to follow-up	16) Were losses of patients to follow-up reported? 17) Were losses of patients to follow-up taken into account? If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.
Power	18) Was a sample size calculation reported? 19) Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? Sample sizes have been calculated to detect a difference of x% and y%.

4.3.4. Pooling Criteria for Meta-analysis

For the meta-analysis, data were pooled if the paper reported sufficient data to calculate 1) kappa or ICC for reliability, 2) Pearson and Spearman correlation coefficients for validity, 3) standardized mean difference for internal responsiveness, 4) correlation coefficient for external responsiveness. For validity, all types of regression coefficients (β) were omitted from pooling due to controversy in combining them [185].

4.4. Statistical analysis.

4.4.1. Qualitative analysis

Frequencies and percentages were computed for categorical variables of included papers.

4.4.2. Quantitative analysis

4.4.2.1. Meta-analysis and Meta-regression

Unit of analysis: Each sample of subjects from studies was assumed as one unit of analysis. When two or more articles documented reliability/correlation coefficients, using the same sample, the coefficient was included only once as the unit of analysis. When one article reported more than one reliability/correlation coefficients of the same clinimetric measurement from the same sample, the

mean coefficient was calculated, and then analyzed in the meta-analysis. If the study comprised independent subgroups, the subgroups were pooled as a separate unit of analysis [186].

Pooling data: Separate meta-analyses were performed for each type of clinimetrics: 1) kappa or ICC for inter-rater or intra-rater reliability 2) construct validity against healthy control, pain, functional assessment, conventional X-rays, MRI, or biomarkers, 3) internal or external responsiveness. These data were pooled, based on each ultrasound pathology (synovitis/effusion/ osteophyte/etc.) to be clinically meaningful. For reliability statistics, pooling was stratified for each grading method (binary/semi-quantitative/quantitative) of the same ultrasound pathology.

For the weighted meta-analysis of kappa estimates, when the standard error (SE) was unavailable, it was calculated from 95% confidence interval (CI) bounds [187]. If both SEs and CIs were not reported, the largest observed SE from the included studies was used. For ICC statistics of reliability and Pearson or Spearman correlation coefficients of validity, effect sizes were first obtained through the z-transformations, and then the resulting pooled effect sizes were back-transformed (z to r transformation) to the level of original coefficients for easier interpretation [188]. For merging odds ratios in validity studies, the log odds ratio and the standard error of the log odds ratio were determined [175]. The standardized mean difference (SMD), using Hedges' g due to the inclusion of small studies (<30 patients/joints), was calculated for internal responsiveness [189], and correlation coefficients were pooled for external responsiveness through the z-transformations [190].

For the assessment of heterogeneity, Cochran Q test was computed [188]. The I^2 was used to quantify how much of the total variability can be attributed to heterogeneity [191]. To scrutinize possible publication bias, it was intended to evaluate with funnel plot techniques [192], Begg's rank test [193] and Egger's regression test [194], as appropriate, given the known limitations of these methods, if the minimum number of studies could be pooled. All analyses for calculating the estimates from primary studies, and for pooling data were carried out by using the SPSS, Excel and Comprehensive Meta-analysis software.

4.5. Results

4.5.1. Identification of included studies

Our search identified 1246 records (468 Medline, 774 Embase and 4 Cochrane library) with 120 duplicates. After screening the titles and abstracts, 195 articles remained. Furthermore, 9 articles were retrieved from the reference lists, totalling 204 articles eligible for full-text review. Of these, 100 articles were selected as shown in the PRISMA flow diagram (**Figure. 4.1**).

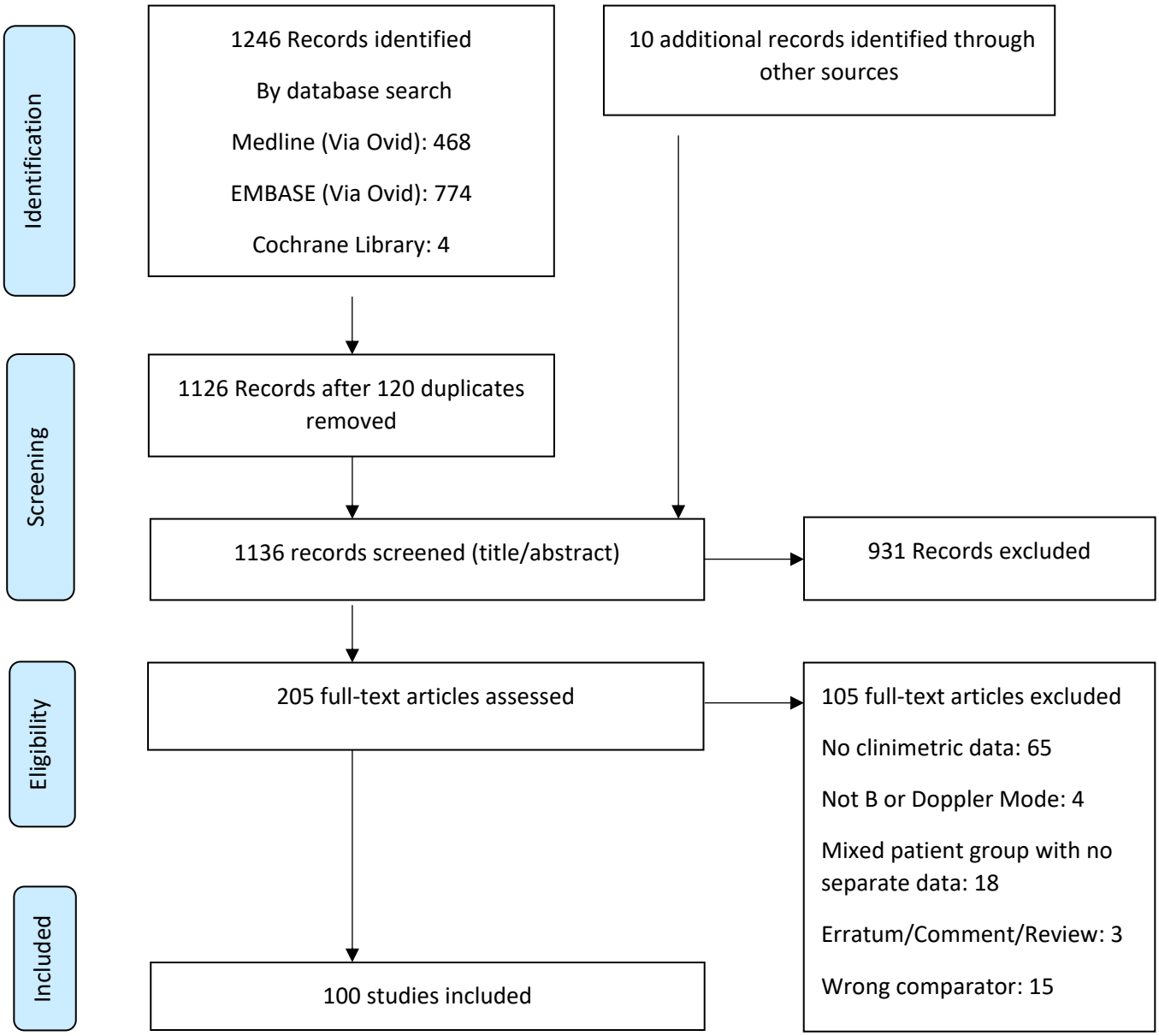

Figure 4.1. PRISMA Flow diagram of included studies.

4.5.2. Study characteristics

One hundred articles (listed in **Appendix 2**), having a total of 8542 patients and 32373 OA joints, and published between 1982 and 2016, were included in the systematic review. The studies' characteristics were summarized in **Table 4.2**. Majority of studies (79%) were documented after 2008. Knee OA was the most widely investigated (n=64), followed by hand OA (n=28), and hip OA (n=8).

Table 4.2. Characteristics of included studies in knee, hand and hip OA

No.	Authors	Year	Country	Study Design	Setting	Patient selection method	OA diagnostic criteria	No. of patients	No. of joints	Site	Quality	Quality (% of total score)
1	Abraham	2011	UK	cross-sectional study	General Practice	random	NR	18	36	knee	11	79
2	Acebes	2006	Spain	cohort study	outpatient rheumatology clinic	consecutive	ACR	30	30	knee	12	60
3	Acebes	2013	Spain	case-control observational study	outpatient rheumatology clinic	consecutive	ACR	33	46	knee	15	88
4	Iagnocco	2012	Italy	cross-sectional study	outpatient rheumatology clinic	consecutive	ACR	8	32	hand	13	68
5	Keen	2008	UK	cross-sectional study	outpatient rheumatology clinic	not reported	ACR	37	1106	hand	11	69
6	Arrestier	2011	France	case-control observational study	outpatient rheumatology clinic	not reported	ACR	101	1616	hand	15	79
7	Atchia	2011	UK	RCT	outpatient rheumatology clinic	not reported	ACR	77	77	hip	19	95
8	Bagnato	2012	Italy	RCT	outpatient rheumatology clinic	not reported	ACR	60	60	knee	18	90
9	Bandinelli	2012	Italy	cohort study	outpatient rheumatology clinic	consecutive	ACR	40	40	knee	15	79
10	Bansal	2014	India	RCT	not reported	not reported	ACR	93	93	knee	11	55
11	Bansal	2015	India	cohort study	not reported	not reported	Brandt Grading	43	43	knee	8	40
12	Bevers	2014	Netherlands	cohort study	specialized hip and knee outpatient clinic	not reported	ACR	62	62	knee	16	80
13	Beitinger	2014	Germany	cross-sectional study	not reported	not reported	ACR	106	111	knee	10	63
14	Bevers	2012	Netherlands	cross-sectional study	outpatient rheumatology clinic	consecutive	ACR	60	60	knee	13	87

15	Bevers	2014	Netherlands	cross-sectional study	specialized hip and knee outpatient clinic	consecutive	ACR	180	180	knee	12	80
16	Bevers	2015	Netherlands	cohort study	specialized hip and knee outpatient clinic	consecutive	ACR	125	125	knee	14	78
17	Iagnocco	2012	Italy	cross-sectional study	outpatient rheumatology clinic	consecutive	ACR	9	17	knee	13	81
18	Birn	2014	USA	Retrospective case-control study	not reported	convenience	NR	89	94	hip	12	75
19	Keen	2008	UK	case-control observational study	outpatient rheumatology clinic	not reported	ACR	55	55	hand	12	75
20	Bruyn	2016	Europe	cross-sectional study	outpatient rheumatology clinic	not reported	ACR	13	13	knee	10	77
21	Çalis	2015	Turkey	cohort study	outpatient rheumatology clinic	consecutive	Kellgren &Lawrence	82	103	knee	13	65
22	Chan	2014	Hong Kong	Retrospective case-control study	multicentre study	convenience	ACR	193	193	knee	12	80
23	Chatzopoulos	2009	Greece	cohort study	outpatient rheumatology clinic	consecutive	ACR	90	90	knee	17	85
24	Chen	2015	Taiwan	cross-sectional study	outpatient rehabilitation clinic	consecutive	knee pain	101	202	knee	16	84
25	Iagnocco	2012	Italy	cross-sectional study	multicentre study	consecutive	ACR	75	150	hip	13	81
26	Conaghan	2010	EUROPE	cohort study	multicentre study	not reported	ACR	531	531	knee	14	74
27	D'Agostino	2005	EUROPE	cross-sectional study	outpatient knee clinic	not reported	ACR	600	600	knee	17	89
28	Damman	2016	Netherlands	cohort study	outpatient rheumatology clinic	consecutive	ACR	56	56	hand	14	74
29	Darweesh	2010	Egypt	cross-sectional study	outpatient rheumatology and rehabilitation clinic	not reported	ACR	42	42	knee	11	69
30	de Miguel Mendieta	2006	Spain	case-control observational study	outpatient rheumatology clinic	not reported	ACR	101	101	knee	17	85

31	Di Sante	2010	Italy	cohort study	outpatient rheumatology clinic	consecutive	ACR	26	26	knee	13	65
32	Dundar	2016	Turkey	RCT	outpatient rehabilitation clinic	not reported	ACR	40	40	knee	16	80
33	Elsaman	2016	Germany	RCT	not reported	not reported	ACR	200	200	knee	16	80
34	Esen	2013	Turkey	case-control observational study	outpatient rheumatology clinic	consecutive	ACR	100	100	knee	13	81
35	Fam	1982	Canada	cross-sectional study	outpatient rheumatology clinic	consecutive	ACR	75	150	knee	11	69
36	Hall	2014	UK	case-control observational study	general practice	not reported	NR	243	243	knee	16	84
37	Hammer	2016	Norway	cross-sectional study	outpatient rheumatology clinic	not reported	ACR	10	300	hand	11	69
38	Hassan	2015	Egypt	cohort study	outpatient rheumatology and rehabilitation clinic	not reported	ACR	20	20	knee	12	60
39	Henricsdotter	2016	Denmark	RCT	outpatient OA clinic	not reported	ACR	100	100	knee	15	75
40	Henrotin	2012	Belgium	cohort study	outpatient rheumatology clinic	not reported	ACR	30	30	knee	12	60
41	Iagnocco	2005	Italy	case-control observational study	outpatient rheumatology clinic	consecutive	ACR	110	110	hand	12	75
42	Iagnocco	2010	Italy	cross-sectional study	outpatient rheumatology clinic	consecutive	ACR	82	164	knee	12	75
43	Jan	2006	Taiwan	cohort study	outpatient orthopedic clinic	convenience	Kellgren &Lawrence	30	44	knee	14	70
44	Jung	2006	South Korea	cross-sectional study	not reported	consecutive	ACR	51	51	knee	13	72
45	Keen	2010	UK	cohort study	outpatient rheumatology clinic	not reported	ACR	36	540	hand	10	63
46	Keen	2015	UK	cohort study	outpatient rheumatology clinic	consecutive	ACR	35	35	knee	15	75
47	Kim	2008	Korea	cross-sectional study	not reported	not reported	ACR	30	30	knee	14	70
48	Kim	2016	Korea	cross-sectional study	outpatient rheumatology clinic	not reported	ACR	34	34	knee	15	79

49	Klauser	2012	Austria	cohort study	not reported	not reported	ACR	33	78	hand	7	35
50	Köroglu	2012	Turkey	cohort study	not reported	consecutive	ACR	32	32	knee	11	55
51	Kortekaas	2010	Netherlands	cross-sectional study	outpatient rheumatology clinic	consecutive	ACR	55	1650	hand	16	84
52	Kortekaas	2011	Netherlands	case-control observational study	outpatient rheumatology clinic	consecutive	ACR	55	1649	hand	16	84
53	Kortekaas	2013	Netherlands	cohort study	outpatient rheumatology clinic	consecutive	ACR	55	990	hand	16	84
54	Kortekaas	2014	Netherlands	cross-sectional study	outpatient rheumatology clinic	consecutive	ACR	25	750	hand	15	79
55	Kortekaas	2015	Netherlands	cohort study	outpatient rheumatology clinic	consecutive	ACR	56	1680	hand	16	84
56	Kortekaas	2016	Netherlands	cohort study	outpatient rheumatology clinic	consecutive	ACR	56	1680	hand	16	84
57	Koski	2016	Finland	cross-sectional study	outpatient rheumatology clinic	random	ACR	40	40	knee	12	75
58	Koutroumpas	2010	Greece	cross-sectional study	outpatient rheumatology clinic	not reported	ACR	18	540	hand	11	69
59	Kristoffersen	2006	Denmark	case-control observational study	general practice	consecutive	ACR	71	71	knee	11	69
60	Lee	2008	Taiwan	cross-sectional study	not reported	not reported	ACR	95	172	knee	11	69
61	Malas	2013	Turkey	RCT	not reported	not reported	ACR	61	122	knee	12	60
62	Malas	2014	Turkey	case-control observational study	not reported	not reported	ACR	61	122	knee	11	69
63	Mallinson	2013	UK	cohort study	outpatient rheumatology clinic and general practice	consecutive	NR	68	68	hand	13	65
64	Mancarella	2010	Italy	case-control observational study	outpatient rheumatology clinic	consecutive	ACR	35	576	hand	19	100
65	Mancarella	2015	Italy	cohort study	outpatient rheumatology clinic	consecutive	ACR	35	576	hand	17	89
66	Martino	1993	Italy	case-control	not reported	not reported	NR	18	18	knee	9	56

				observational study								
67	Mathiessen	2013	Norway	cross-sectional study	outpatient rheumatology clinic	not reported	ACR	127	3810	hand	12	67
68	Mathiessen	2016	Norway	cohort study	outpatient rheumatology clinic	not reported	ACR	78	2340	hand	14	74
69	Mermerci	2011	Turkey	case-control observational study	outpatient rheumatology clinic	not reported	ACR	143	143	knee	13	81
70	Micu	2010	Romania	cohort study	outpatient rheumatology clinic	convenience	ACR	61	66	hip	13	76
71	Mortada	2016	Egypt	cross-sectional study	outpatient rheumatology and rehabilitation clinic	random	ACR	160	160	knee	15	83
72	Naguib	2011	Egypt	case-control observational study	not reported	not reported	NR	45	1350	hand	11	69
73	Naredo	2005	Spain	case-control observational study	outpatient rheumatology clinic	consecutive	ACR	50	50	knee	14	88
74	Nogueira-Barbosa	2015	Brazil	cross-sectional study	Department of Radiology	consecutive	NR	93	93	knee	12	86
75	Pendleton	2008	UK	cohort study	not reported	not reported	ACR	86	86	knee	7	35
76	Podlipská	2013	Finland	cross-sectional study	not reported	random	NR	39	39	knee	13	76
77	Podlipská	2016	Finland	cross-sectional study	Department of Radiology	consecutive	NR	159	159	knee	14	88
78	Qvistgaard	2006	Denmark	cross-sectional study	not reported	consecutive	ACR	100	100	hip	10	67
79	Razek and El-Basyouni	2016	Egypt	cross-sectional study	outpatient rheumatology and rehabilitation clinic	not reported	ACR	80	80	knee	11	79
80	Rennesson-Rey	2008	France	cohort study	not reported	not reported	ACR	55	55	hip	14	70
81	Riecke	2014	Denmark	cross-sectional study	Department of Radiology	consecutive	NR	45	90	knee	13	93
82	Robinson	2007	UK	cohort study	not reported	not reported	NR	120	120	hip	12	60

83	Saarakkala	2012	Finland	cross-sectional study	outpatient orthopedic clinic	random	NR	40	40	knee	13	87
84	Sampson	2010	USA	cohort study	not reported	not reported	NR	14	14	knee	13	65
85	Song	2008	Germany	case-control observational study	not reported	not reported	ACR	47	47	knee	10	53
86	Tarhan	2003	Turkey	case-control observational study	not reported	not reported	knee pain	58	58	knee	11	69
87	Toktas	2015	Turkey	case-control observational study	outpatient rehabilitation clinic	not reported	ACR	187	374	knee	16	84
88	Tormenta	2012	Italy	case-control observational study	not reported	not reported	ACR	860	860	hip	12	60
89	Traistaru	2013	Craiova	cross-sectional study	outpatient rehabilitation clinic	not reported	ACR	70	140	knee	10	50
90	Ulaşli	2014	Turkey	cross-sectional study	outpatient rehabilitation clinic	not reported	ACR	86	172	knee	12	75
91	Usón	2014	Spain	cross-sectional study	outpatient rheumatology clinic	not reported	ACR	20	100	hand	10	67
92	Uysal	2015	Turkey	cross-sectional study	outpatient rehabilitation clinic	convenience	ACR	85	170	knee	14	78
93	Vlychou	2009	Greece	cross-sectional study	outpatient rheumatology clinic	consecutive	ACR	22	660	hand	13	72
94	Vlychou	2013	Greece	case-control observational study	outpatient rheumatology clinic	consecutive	ACR	25	600	hand	15	94
95	Wittoek	2010	Belgium	cross-sectional study	not reported	consecutive	ACR	38	684	hand	12	67
96	Wittoek	2011	Belgium	case-control observational study	outpatient rheumatology clinic	not reported	ACR	14	252	hand	12	75
97	Wu	2012	Taiwan	cross-sectional study	outpatient orthopedic clinic	consecutive	ACR	156	156	knee	16	84
98	Yanagisawa	2014	Japan	cross-sectional study	outpatient Department of Orthopedic Surgery	not reported	NR	81	131	knee	10	71
99	Yoon	2008	South Korea	cross-sectional study	not reported	not reported	ACR	51	51	knee	11	69

100	Kortekaas	2015	Netherlands	cross-sectional study	outpatient rheumatology clinic	not reported	ACR	16	128	hand	15	79

Abbreviations: ACR= American College of Rheumatology; NR=Non-relevant; OA=Osteoarthritis, UK=United Kingdom;

According to the Oxford Centre for Evidence-Based Medicine guidelines (www.cebm.net/), 42 papers utilized a cross-sectional design (42%) and 28 papers applied a cohort design (28%). The participants were recruited from out-patient rheumatology clinics in 46 papers; the setting was not mentioned in 23 papers. The selection method was not described in half of the studies, followed by a consecutive method (n=40), convenience (n=5) and random methods (n=5). ACR criteria were employed for diagnosis in most of the studies (*n*=81); 14 papers did not disclose diagnostic criteria. The mean age of included studies ranged from 50.1±9.2 to 71.9±5.9 years; female participants varied from 37% to 100%; the mean BMI from 22.2±2.6 to 33.5±4.6 kg/m^2. Eight studies recruited mixed samples with different diseases but delineated separate clinimetrics of OA sub-group.

4.5.3. Ultrasound scanning techniques and definition

For simplicity, the EULAR scanning method [195] and OMERACT definitions [33] were assumed as the standard criteria to identify respective OA pathologies. Out of 100 papers, power Doppler was investigated in 31 (**Table 4.3).** Doppler specifications were detailed in 19 papers: Doppler frequency was reported in 9 (from 12 MHz to 6.3 MHz); pulse repetition frequency (PRF) in 10 (from 13.2KHz to 3 Hz); wall filter and gain in 17. One paper examined contrast ultrasound.

Table 4.3. Ultrasound Scanning Characteristics of Included Studies

Serial No,	Author	Year	Mode	B Freq	Doppler setting	Doppler Freq	PRF	Scanning method	Definition	Grading Score	Ultrasound scanner
1	Abraham	2011	B	10-18 MHz linear				EULAR	OMERACT	binary and quantitative	ultrasonographer
2	Acebes	2006	B	7.5 MHz linear				NR	other	quantitative	not specified
3	Acebes	2013	B	8-12 MHz linear				NR	other	quantitative	rheumatologist
4	Iagnocco	2012	B	6-18 MHz linear				other	OMERACT	binary	rheumatologist
5	Keen	2008	B	7-15 MHz hockey				other	other	binary	physician
6	Arrestier	2011	B+D	10–13MHz linear	yes	8.3	750Hz	EULAR	OMERACT	semi-quantitative (0-3)	rheumatologist
7	Atchia	2011	B	NR				NR	other	binary	not specified
8	Bagnato	2012	B	8 MHz				other	NR	binary	not reported
9	Bandinelli	2012	B	7.5–12 MHz linear				other	other	quantitative	rheumatologist
10	Bansal	2014	B	NR				NR	NR	quantitative	not reported
11	Bansal	2015	B	NR				NR	NR	quantitative	not reported
12	Beitinger	2014	B+D	5-14 MHz linear	yes	6.7		NR	other	semi-quantitative (0-3)	ultrasonographer
13	Bevers	2012	B	8-15 MHz				EULAR	OMERACT	Binary/quantitative	rheumatologist
14	Bevers	2014	B	8-15 MHz linear				EULAR	OMERACT	Binary/quantitative	rheumatologist
15	Bevers	2014	B	8-15 MHz linear				EULAR	OMERACT	Binary/quantitative	rheumatologist
16	Bevers	2015	B	6-18 MHz linear				EULAR	OMERACT	Binary/quantitative	rheumatologist

17	Iagnocco	2012	B+D	4-13 MHz at 13 MHz	yes	6.3	750 Hz	EULAR	OMERACT	Binary	rheumatologist
18	Birn	2014	B	NR				NR	NR	semi-quantitative (0-2)	fellow in training
19	Keen	2008	B+D	7-15 MHz hockey	yes		750 Hz	Other	OMERACT	Binary/semi-quantitative (0-3)	physician
20	Bruyn	2016	B	6–18 MHz linear				Other	OMERACT	Binary/semi-quantitative (0-3)	rheumatologist
21	Çalis	2015	B	7.5 MHz linear				Other	other	Quantitative	radiologist
22	Chan	2014	B	12–18 MHz linear				Other	OMERACT	Quantitative	ultrasonographer
23	Chatzopoulos	2009	B	NR				Other	other	Binary	physician
24	Chen	2015	B	5-13 MHz linear				Other	other	semi-quantitative (0-6)	not specified
25	Iagnocco	2012	B+D	9 MHz linear	yes	7.5	750 Hz	EULAR	OMERACT	Binary	rheumatologist
26	Conaghan	2010	B	NR				EULAR	other	binary	combined R and R
27	D'Agostino	2005	B	10 MHz				EULAR	other	Binary	combined R and R
28	Damman	2016	B+D	10-14 MHz linear				Other	OMERACT	semi-quantitative (0-3)	ultrasonographer
29	Darweesh	2010	B	13 MHZ linear				Other	other	quantitative	not reported
30	de Miguel Mendieta	2006	B	7-11 MHz linear				Van Holsbeeck technique	other	binary	rheumatologist
31	Di Sante	2010	B	7.5 MHz linear				Other	other	quantitative	physician
32	Dundar	2016	B	6-18 MHz linear				Other	OMERACT	Binary/semi-quantitative	physician

										(0-6)	
33	Elsaman	2016	B	8–12 MHz linear				EULAR	OMERACT	Quantitative	not reported
34	Esen	2013	B	5–10 MHz				EULAR	other	Binary	physician
35	Fam	1982	B	5-MHz				NR	other	Binary	not reported
36	Hall	2014	B+D	7-12 MHz linear				EULAR	OMERACT	Binary/semi-quantitative (0-3)	not reported
37	Hammer	2016	B	8–18 MHz hockey/6-15 MHz linear				other	OMERACT	semi-quantitative (0-3)	rheumatologist
38	Hassan	2015	B	5-12 MHz linear				other	OMERACT	semi-quantitative (0-3)	not reported
39	Henricsdotter	2016	B+D	15 MHz linear	yes	6.3	3 Hz	EULAR	other	Binary/quantitative	not specified
40	Henrotin	2012	B	10-15 MHz				other	NR	Binary/semi-quantitative (0-2)	not reported
41	Iagnocco	2005	B	8–16 MHz linear				other	other	Binary	rheumatologist
42	Iagnocco	2010	B+D	12 MHz	yes	7.5	500 Hz	EULAR	OMERACT	Binary/semi-quantitative (0-3)	not specified
43	Jan	2006	B	5-12 MHZ linear				Van Holsbeeck technique	NR	Quantitative	not reported
44	Jung	2006	B	12 MHz				other	other	Quantitative	rheumatologist
45	Keen	2010	B+D	7-15 MHz hockey	yes		750 Hz	other	other	semi-quantitative (0-3)	rheumatologist
46	Keen	2015	B+D	5-12 MHz linear	yes		750 Hz	EULAR	OMERACT	semi-quantitative (0-3) /quantitative	not reported

47	Kim	2008	B	7-12 MHz linear				EULAR	other	Quantitative	rheumatologist
48	Kim	2016	B	7–15 MHz linear				EULAR	OMERACT	Quantitative	rheumatologist
49	Klauser	2012	B+D	13–16 MHz	yes	12	750-1000 Hz	other	other	semi-quantitative (0-3) /quantitative	radiologist
50	Köroglu	2012	B	7.5 MHz linear				NR	other	Binary/quantitative	physician
51	Kortekaas	2010	B+D	10-14 MHz linear				other	OMERACT	semi-quantitative (0-3)	ultrasonographer
52	Kortekaas	2011	B+D	10-14 MHz linear				other	NR	semi-quantitative (0-3)	ultrasonographer
53	Kortekaas	2013	B+D	10-14 MHz linear				other	OMERACT	semi-quantitative (0-3)	ultrasonographer
54	Kortekaas	2014	B+D	10-14 MHz linear	yes		13.2KHz	other	OMERACT	semi-quantitative (0-3)	ultrasonographer
55	Kortekaas	2015	B+D	10-14 MHz linear	yes		13.2KHz	other	OMERACT	semi-quantitative (0-3)	ultrasonographer
56	Kortekaas	2016	B+D	10-14 MHz linear				other	OMERACT	semi-quantitative (0-3)	ultrasonographer
57	Koski	2016	B	13 MHz linear				other	other	semi-quantitative (0-3)	rheumatologist
58	Koutroumpas	2010	B+D	8–13 MHz linear				other	OMERACT	Binary	radiologist
59	Kristoffersen	2006	B+D	13 MHz (central)	yes	7	lowest PRF	other	other	Binary	not reported
60	Lee	2008	B	5-12 MHz linear				other	other	semi-quantitative (0-6)	not specified
61	Malas	2013	B	5-10 MHz linear				other	other	quantitative	physiatrist
62	Malas	2014	B	5–10 MHz linear				other	other	Binary/semi-quantitative (0-6) /quantitative	physiatrist
63	Mallinson	2013	B	8-15 MHz linear				other	other	semi-quantitative (0-3) /quantitative	radiologist

64	Mancarella	2010	B+D	5-13 MHz	yes	11.4		other	OMERACT	Binary/quantitative	ultrasonographer
65	Mancarella	2015	B	5-13 MHz				other	OMERACT	Binary	ultrasonographer
66	Martino	1993	B	7.5 MHz linear				other	NR	quantitative	not specified
67	Mathiessen	2013	B	5–13 MHz linear				EULAR	OMERACT	semi-quantitative (0-3)	ultrasonographer
68	Mathiessen	2016	B+D	5–13 MHz linear	yes	7.3	391 Hz	EULAR	OMERACT	Binary/semi-quantitative (0-3)	rheumatologist
69	Mermerci	2011	B	8–10 MHz linear				other	other	Binary/quantitative	radiologist
70	Micu	2010	B+D	5–7.5 MHz linear				NR	other	quantitative	not reported
71	Mortada	2016	B	5–12 MHz linear				other	OMERACT	semi-quantitative (0-4)	combined R and R
72	Naguib	2011	B	7.5–10 MHz				NR	NR	semi-quantitative (0-3)	not reported
73	Naredo	2005	B	7-12 MHz				EULAR	other	Binary	rheumatologist
74	Nogueira-Barbosa	2015	B	5-12 MHz linear				other	other	semi-quantitative (0-2)	radiologist
75	Pendleton	2008	B+D	5–12 MHz linear	yes		1100 Hz	EULAR	other	Binary	not reported
76	Podlipská	2013	B	13 MHz linear				other	other	quantitative	not reported
77	Podlipská	2016	B	15 MHz linear				other	other	semi-quantitative (0-3) /quantitative	ultrasonographer
78	Qvistgaard	2006	B	8–15 MHz				other	other	semi-quantitative (0-3)	combined R and R
79	Razek and El-Basyouni	2016	B	10-12 MHz linear				EULAR	OMERACT	Binary	combined R and R
80	Rennesson-	2008	B+D	5-12 MHz linear				other	other	binary	rheumatologist

	Rey										
81	Riecke	2014	B+D	14 MHz M12L linear	yes	7.5	900 Hz	other	other	semi-quantitative (0-3) /quantitative	physician
82	Robinson	2007	B+D	10–15 MHz linear				other	other	Binary/semi-quantitative (0-3) /quantitative	radiologist
83	Saarakkala	2012	B	13 MHz linear				other	other	semi-quantitative (0-3)	ultrasonographer
84	Sampson	2010	B	7.5 –13.0 MHz linear				other	NR	Quantitative	not reported
85	Song	2008	B+D	5-12 MHz linear for MUS, 8–4-MHz linear for CE-MUS	yes	6.3	500 Hz	EULAR	other	semi-quantitative (0-3)	rheumatologist
86	Tarhan	2003	B	5-10 MHz linear				other	NR	semi-quantitative (0-3) /quantitative	not reported
87	Toktas	2015	B	6-18 MHz linear				other	other	Binary/quantitative	not specified
88	Tormenta	2012	B	3.5–5 MHz convex/ 7.5–12 MHz linear				other	other	Binary	radiologist
89	Traistaru	2013	B	12.5 MHz linear				NR	other	Binary	not reported
90	Ulaşli	2014	B	6-18MHz linear				other	OMERACT	semi-quantitative (0-3)	not reported
91	Usón	2014	B	M12 linear				other	other	Binary	rheumatologist
92	Uysal	2015	B	12 MHz linear				other	other	Binary/quantitative	radiologist
93	Vlychou	2009	B+D	8-13 MHz linear				other	OMERACT	Binary	radiologist
94	Vlychou	2013	B	10–14 MHz linear/ 10–15 MHz hockey				other	OMERACT	Binary	radiologist
95	Wittoek	2010	B+D	10–18 MHz linear	yes	8.3	500 Hz	other	OMERACT	Binary	rheumatologist

96	Wittoek	2011	B	12–18 MHz				other	OMERACT	Binary	rheumatologist
97	Wu	2012	B	6-13 MHz linear				EULAR	OMERACT	Binary/semi-quantitative (0-3)	ultrasonographer
98	Yanagisawa	2014	B	12 MHz linear				other	other	quantitative	surgeon
99	Yoon	2008	B	12.5 MHz linear				EULAR	other	quantitative	rheumatologist
100	Kortekaas	2015	B+D	10-14 MHz linear				NR	NR	semi-quantitative	ultrasonographer

Abbreviation: B=B-mode; D= Doppler mode; EULAR= European League Against Rheumatism; NR= Non-relevant; OMERACT= Outcome Measure in Rheumatology

Eighty-eight papers defined ultrasound pathology; 26 papers referred to the EULAR scanning protocol; 59 papers administered their own methods or modification from previous papers; 13 papers did not delineate the specific scanning method. Thirty-nine studies applied the OMERACT definitions, which were found to be increasingly used across the years from 1 paper in 2008, and then 5 papers in 2012 to 10 papers in 2016 (**Figure 4.2**).

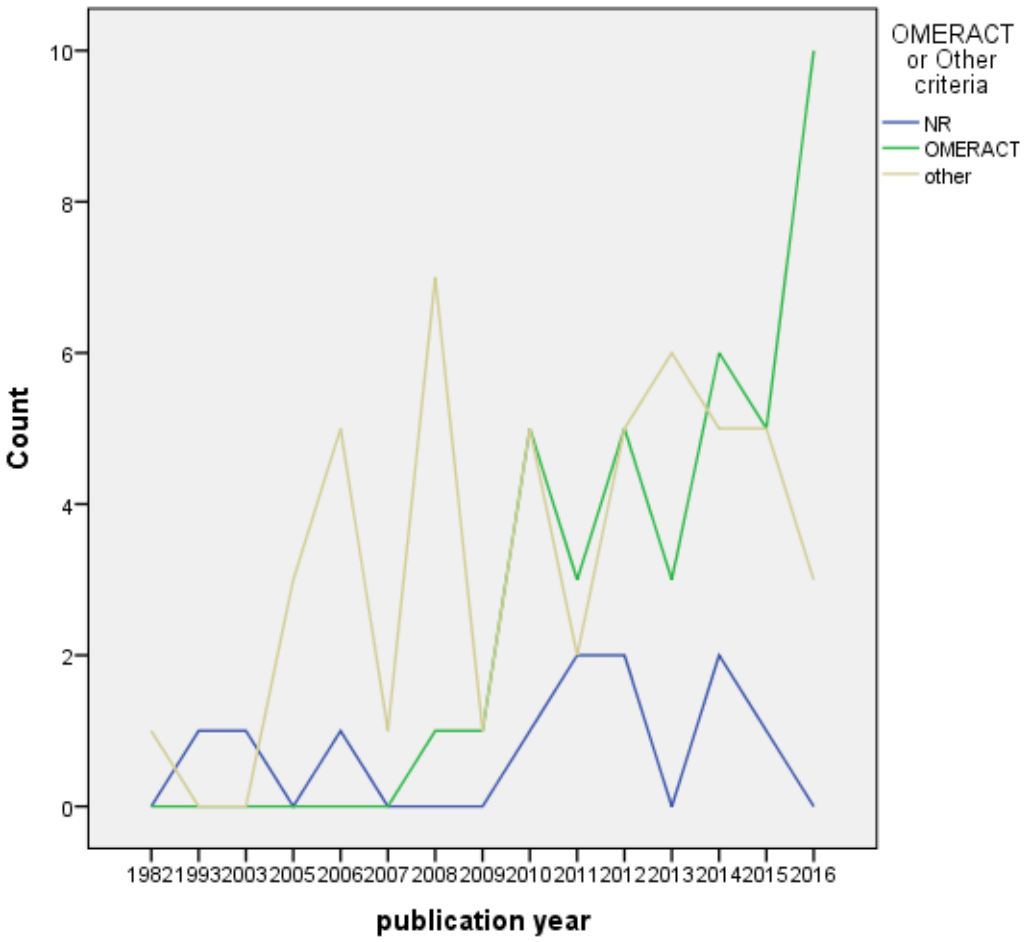

Figure 4.2. Utilization of OMERACT definitions in the included studies across the years in terms of number of publications in a specific year from 1982 to 2016.

Count=publication per year; NR= Non-relevant; OMERACT=Outcome measure in rheumatology; other= studies using other definitions

4.5.4. Ultrasound lesions and scoring system

Overall, synovial pathologies were more extensively examined, i.e, effusion (52%), synovial hypertrophy (37%), Doppler activity (31%), Baker's cyst (25%), compared to structural lesions, i.e, osteophyte (29%), cartilage thinning (28%). A variety of grading systems was evaluated [binary (*n*=49,49%), semi-quantitative (*n*=42, 42%), and quantitative (*n*=40,40%)].

4.5.5. Qualification of the ultrasound operator

Only twenty papers declared the number of operator's training years in musculoskeletal ultrasound, ranging from 3 months to 24 years. The operator/readers were also of diverse academic backgrounds: rheumatologist (27% of all papers), ultrasonographer (16%), radiologist (11%), others such as physiatrist, surgeon, fellow-in-training (26%), and no report (20%).

4.5.6. Methodological quality

The average quality score across the studies assessed with the modified Downs and Black instrument was 13.01 out of 19 items (taking into account the questions that were not applicable for certain studies). **Figure 4.3** outlined the proportion of the 100 studies that met each of the quality assessment items. The papers, in general, had a good rating (>60%) on the 13 items. However, most papers fell short severely on some items such as reporting of sample size calculation and sufficient power (10%).

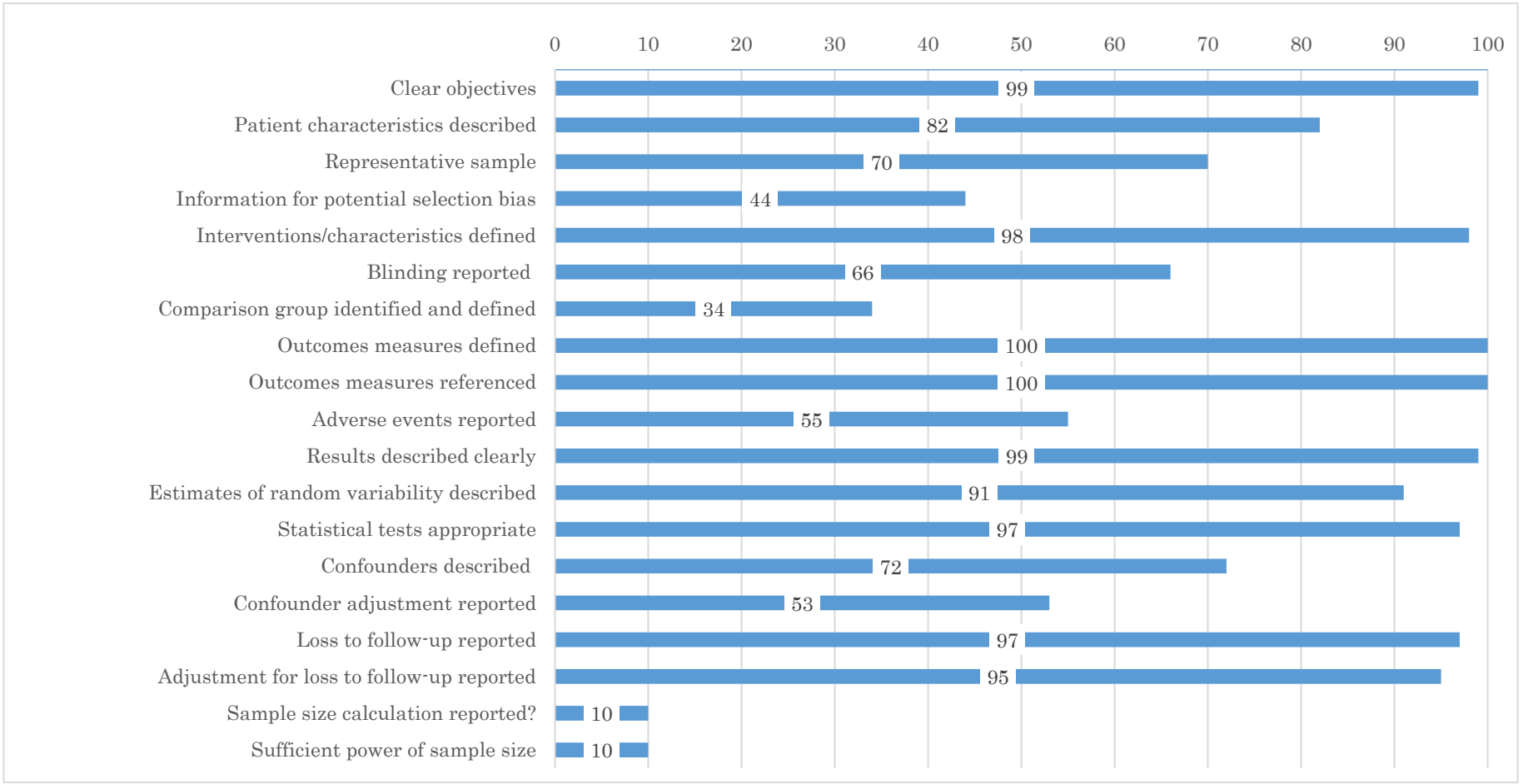

Figure 4.3. Methodological Quality of included studies in the systematic literature review

The average QAREL score was 5.93 out of 11 items across all reliability studies (n=43). Blindness to other raters, own prior findings, clinical information and non-clinical clues were described in 40% (*n*=17), 28% (*n*=12), 56% (*n*=24) and 5% (*n*=2), respectively (**Table 4.4**). Randomization of patients/raters was found only in 53% (*n*=23). As there was no definite consensus related to the time interval for the stability of ultrasound findings between repeated measurements, only evaluation of stored images was given as yes (*n*=17), and rating of the acquired image as unclear (*n*=26). Overall, the regression plot displayed the significant improvement of QAREL quality score across the years (β=0.40, P=0.01) (**Figure 4.4**).

Table 4.4. Quality Appraisal of Diagnostic Reliability (QAREL) score for included studies in the systematic literature review

	Author	Year	Representative Sample	Representative raters	Blinding (other raters)	Blinding (prior findings)	Blinding (reference)	Blinding (clinical info)	Blinding (Non-clinical data)	Order of exam	Time interval	Correct Test	Appropriate statistics
1	Abraham	2011	Unclear	Yes	Unclear	NA	NA	Unclear	Unclear	Unclear	Unclear	Yes	Yes
2	Acebes	2013	Yes	Yes	Yes	Yes	NA	Unclear	Unclear	Yes	Yes	Yes	Yes
3	Iagnocco	2012	Yes	Yes	Yes	Yes	NA	Unclear	Unclear	Unclear	Unclear	Yes	Yes
4	Keen	2008	Yes	Yes	NA	Unclear	NA	No	Unclear	Unclear	Unclear	Yes	Yes
5	Bandinelli	2012	Yes	Yes	Unclear	Unclear	NA	Unclear	Unclear	Unclear	Unclear	Yes	Yes
6	Bevers	2014	Yes	Yes	Yes	NA	NA	Yes	Unclear	Unclear	Unclear	Yes	Yes
7	Bevers	2012	Yes	Yes	Yes	NA	NA	Yes	Unclear	Unclear	Unclear	Yes	Yes
8	Iagnocco	2012	Yes	Yes	Yes	NA	NA	Yes	Unclear	Unclear	Unclear	Yes	Yes
9	Keen	2008	Yes	Yes	NA	Unclear	NA	Unclear	Unclear	Yes	Yes	Yes	Yes
10	Bruyn	2016	Yes	Yes	Yes	Yes	NA	Unclear	Unclear	Yes	Unclear	Yes	Yes
11	Damman	2016	Yes	Yes	Unclear	NA	NA	Unclear	Unclear	Unclear	Unclear	Yes	No
12	Hall	2014	Unclear	Yes	NA	Yes	NA	Unclear	Unclear	Unclear	Unclear	Yes	Yes
13	Hammer	2016	Yes	Yes	Unclear	Unclear	NA	Unclear	Unclear	Unclear	Unclear	Yes	Yes
14	Jung	2006	Yes	Yes	NA	Unclear	NA	Unclear	Unclear	Yes	Yes	Yes	Yes
15	Keen	2015	Yes	Yes	NA	Unclear	NA	Unclear	Unclear	Yes	Yes	Yes	Yes
16	Kortekaas	2010	Yes	Yes	NA	Unclear	NA	Yes	Unclear	Yes	Unclear	Yes	Yes

17	Kortekaas	2011	Yes	Yes	NA	Unclear	NA	Yes	Unclear	Yes	Unclear	Yes	Yes
18	Kortekaas	2015	Yes	Yes	NA	Unclear	NA	Yes	Unclear	Yes	Unclear	Yes	Yes
19	Kortekaas	2016	Yes	Yes	NA	Unclear	NA	Yes	Unclear	Unclear	Unclear	Yes	Yes
20	Koski	2016	Yes	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes
21	Koutroumpas	2010	Yes	Yes	NA	Unclear	NA	Yes	Unclear	Unclear	Unclear	Yes	Yes
22	Lee	2008	Yes	Yes	Unclear	NA	NA	Unclear	Unclear	Unclear	Unclear	Yes	Yes
23	Malas	2013	Yes	Yes	NA	Unclear	NA	Yes	Unclear	Unclear	Unclear	Yes	Yes
24	Mancarella	2010	Yes	Yes	NA	Unclear	NA	Yes	Unclear	Yes	Yes	Yes	Yes
25	Mancarella	2015	Yes	Yes	NA	Unclear	NA	Yes	Unclear	Yes	Unclear	Yes	Yes
26	Martino	1993	Unclear	Yes	Unclear	Unclear	NA	Unclear	Unclear	Unclear	Unclear	Yes	No
27	Mathiessen	2013	Yes	Yes	Yes	Yes	NA	Yes	Unclear	Yes	Yes	Yes	Yes
28	Mathiessen	2016	Yes	Yes	Yes	Yes	NA	Yes	Unclear	Yes	Yes	Yes	Yes
29	Mortada	2016	Yes	Yes	Yes	Yes	NA	Yes	Unclear	Unclear	Unclear	Yes	Yes
30	Nogueira-Barbosa	2015	Unclear	Yes	Yes	NA	NA	Yes	Unclear	Yes	Yes	Yes	Yes
31	Podlipská	2016	Unclear	Yes	NA	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes
32	Qvistgaard	2006	Yes	Yes	Yes	Yes	NA	Unclear	Unclear	Unclear	Unclear	Yes	No
33	Razek and El-Basyouni	2016	Yes	Yes	Yes	NA	NA	Yes	Unclear	Yes	Yes	Yes	Yes
34	Riecke	2014	Unclear	Yes	Unclear	Unclear	NA	Unclear	Unclear	Yes	Yes	Yes	Yes
35	Robinson	2007	Unclear	Yes	NA	Unclear	NA	Unclear	Unclear	Yes	Yes	Yes	No

36	Tormenta	2012	Yes	Yes	Yes	NA	NA	Unclear	Unclear	Yes	Yes	Yes	Yes
37	Usón	2014	Yes	Yes	NA	Unclear	NA	Yes	Unclear	Yes	Yes	Yes	Yes
38	Vlychou	2009	Yes	Yes	NA	Unclear	NA	No	Unclear	Unclear	Unclear	Yes	Yes
39	Wittoek	2010	Yes	Yes	Yes	NA	NA	Yes	Unclear	Yes	Yes	Yes	Yes
40	Wittoek	2011	Yes	Yes	Yes	NA	NA	Yes	Unclear	Unclear	Unclear	Yes	Yes
41	Wu	2012	Yes	Yes	Unclear	Yes	NA	Yes	Unclear	Yes	Unclear	Yes	Yes
42	Yanagisawa	2014	Unclear	Yes	NA	Unclear	NA	Yes	Unclear	Unclear	Unclear	Yes	Yes
43	Yoon	2008	Yes	Yes	Yes	Yes	NA	Yes	Unclear	Yes	Yes	Yes	Yes

Abbreviation: NA=Non-applicable

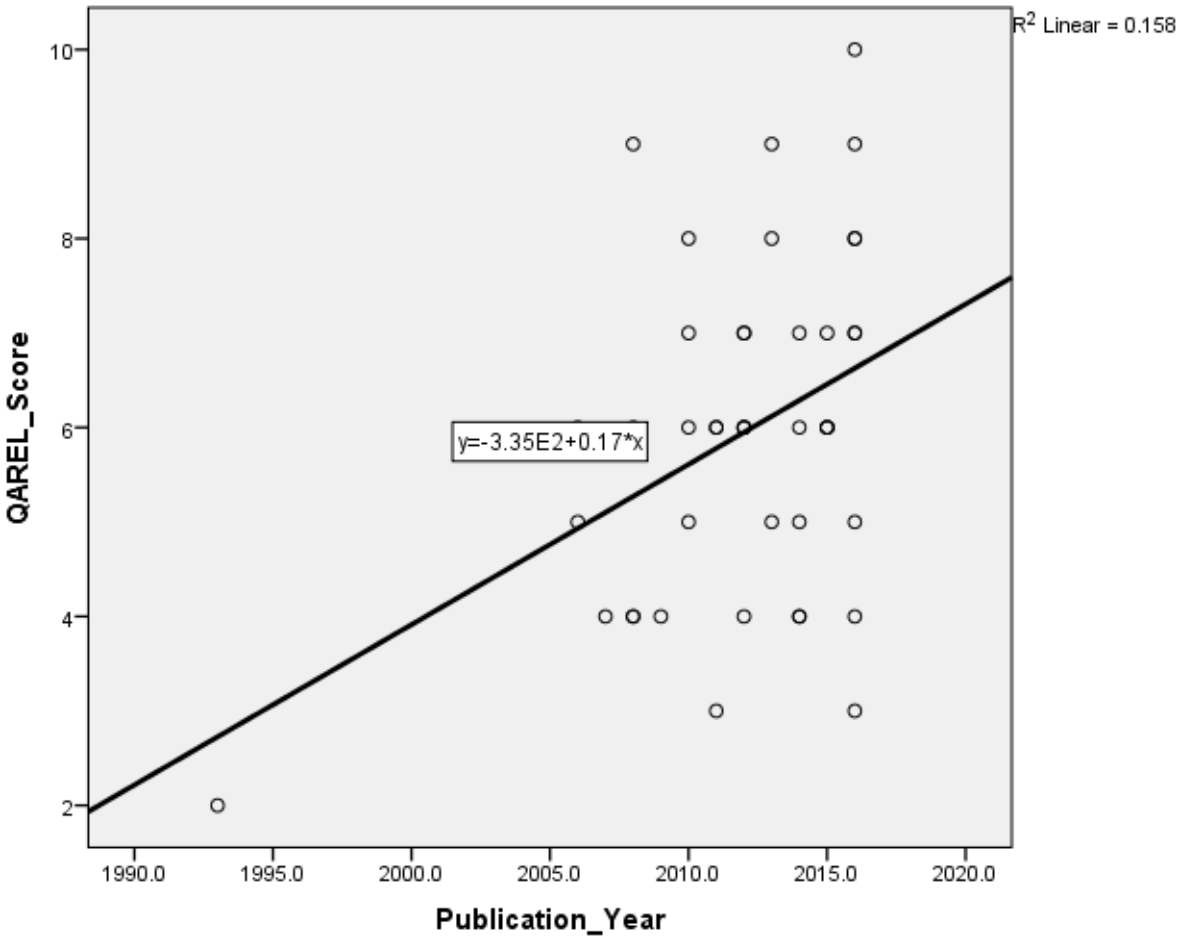

Figure 4.4. Scatter plot for improvement of QAREL Scores in reliability studies across the years

(QAREL=Quality Appraisal for Reliability Studies)

4.5.7. Clinimetric properties

Among the 100 studies, 32 papers were identified for the intra-rater reliability, 25 for inter-rater reliability, 57 for construct validity, 5 for criterion validity in the knee, 10 for clinical predictive validity, 6 for structural predictive validity, 21 for intrinsic responsiveness, 8 for extrinsic responsiveness and 7 for feasibility.

4.5.7.1. Quantitative meta-analysis in knee OA

The meta-analysis was conducted only for knee OA. Pooling could not be performed for hand and hip OA due to a paucity of reported clinimetric data for ultrasound, and so descriptive analysis was presented. Publication bias was not examined due to inadequate numbers of included papers for a specific OA pathology, which did not allow a proper assessment of funnel plots or more advanced regression-based assessments. All the forest plots are shown in **Appendix 3**.

4.5.7.2. Reliability:

Inter-rater reliability: According to the pooling criteria, **s**tratified kappa meta-analysis was conducted across 11 knee studies, including 38 kappa estimates and 556 joints of 506 patients. ICC estimates were pooled across 7 knee studies with a total of 19 ICC estimates in 340 joints of 308 participants. Kappa coefficients were interpreted according to Landis and Koch (0:poor; 0.01-0.20:slight; 0.21-0.40:fair; 0.41-0.60:moderate; 0.61-0.80:substantial; 0.81-1.00:almost perfect) [196].

The pooled kappa of the binary score *(***Table 4.5***)* was almost perfect for Baker's cyst [0.92(0.83-1)], and substantial for effusion [0.75(0.41,1)], with nearly all pathologies revealing considerable heterogeneity (I^2=70 to 99). For the semi-quantitative score, pooled kappa values were moderate for cartilage thinness [0.44(0.15-0.74)], and substantial for all pathologies, with high heterogeneity (I^2= 78-98). For quantitative scores, all pathologies provided almost perfect reliability for pooled ICC estimate.

Table 4.5. Stratified meta-analysis of ultrasound features for inter-rater reliability in knee OA

Stratified meta-analysis		No. of studies	No. of patients	No. of joints	Kappa (95% CI)		Heterogeneity		
Knee					Fixed	Random	P-value	I^2 (%)	Tau
Kappa (Binary)	Effusion	6	242	281	0.46(0.44-48)	0.75(0.41,1)	0.00	99	0.41
	Synovial Hypertrophy	5	224	245	0.37(0.34-0.40)	0.52(0.18,0.86)	0.00	98	0.38
	Osteophyte	3	107	133	0.89(0.83-0.95)	0.76(0.53,1)	0.00	83	0.19
	Cartilage thickness	2	89	97	0.98(0.95-1)	0.76(0.28,1)	0.00	95	0.34
	Meniscal extrusion	4	211	219	0.71(0.62-0.79)	0.66(0.49,0.83)	0.02	70	0.15
	Baker's cyst	4	211	219	0.92(0.83-1)	0.92(0.83,1)	0.58	0.00	0.00
Kappa (Semi-quantitative)	Synovitis	2	24	48	0.52(0.48-0.56)	0.63(0.36,0.90)	0.01	86	0.18
	Effusion	1	11	22	0.74(0.54-0.94)				
	Osteophyte	4	150	174	0.58(0.55-0.61)	0.66(0.50,0.82)	0.00	78	0.14
	Cartilage thickness	2	47	60	0.33(0.28-0.39)	0.44(0.15,0.74)	0.00	87	0.20
	Meniscal extrusion	3	117	141	0.84(0.81-0.87)	0.75(0.41,1)	0.00	98	0.30
ICC	Effusion	2	63	81	0.84(0.76-0.89)	0.84(0.74,0.90)	0.24	27	0.1
	Osteophyte	1	45	45	0.97(0.95-0.98)				
	Cartilage thickness	5	236	254	0.86(0.82-0.89)	0.86(0.53,0.97)	0.00	97	0.81

	Meniscal extrusion	3	137	151	**0.94(0.92-0.96)**	**0.95(0.79,0.99)**	**0.00**	**95**	**0.65**
	Baker's cyst	2	85	85	**0.95(0.92-0.97)**	**0.95(076,0.99)**	**0.00**	**93**	**0.60**

Abbreviation: ICC=Intra-class Correlation Coefficient; CI= Confidence Interval

Intra-rater reliability: Stratified kappa meta-analysis was performed from 8 knee studies, including a total of 23 kappa estimates for 502 joints of 465 patients. For ICC values, data were pooled from 9 knee studies with a total of 21 ICC estimates for 566 joints of 490 participants.

The pooled kappa of semi-quantitative score (**Table 4.6**) was varied from moderate for cartilage thinness [0.55(0.45-0.66)], substantial for synovitis [0.69(0.60-0.78)] and osteophyte [0.74(0.67-0.81)] to almost perfect for meniscal extrusion [0.81(0.66-0.96)], exhibiting low heterogeneity (I^2=7 to 51). For quantitative scores, reliability was almost perfect in all pathologies.

Table 4.6. Stratified meta-analysis of ultrasound features for intra-rater reliability in knee OA

Stratified meta-analysis		No. of studies	No. of patients	No. of joints	Kappa (95% CI)		Heterogeneity		
Knee					Fixed	Random	P-value	I^2	Tau
Kappa (Binary)	Effusion	1	13	26	**0.56(0.47-0.65)**				
	Synovial Hypertrophy	1	13	26	**0.49(0.34-0.64)**				
Kappa (Semi-quantitative)	Synovitis	2	24	48	**0.69(0.60-0.77)**	**0.69(0.60-0.78)**	**0.30**	**7**	**0.02**
	Effusion	1	11	22	**0.78(0.55-1)**				
	Doppler Activity	2	28	28	**0.88(0.72-1)**	**0.88(0.65-1)**	**0.15**	**51**	**0.12**
	Osteophyte	5	309	333	**0.74(0.68-0.79)**	**0.74(0.67-0.81)**	**0.30**	**18**	**0.03**
	Cartilage thickness	2	172	185	**0.55(0.45-0.66)**	**0.55(0.45-0.66)**	**0.91**	**0.00**	**0.00**
	Meniscal extrusion	3	117	141	**0.80(0.69-0.90)**	**0.81(0.66-0.96)**	**0.18**	**42**	**0.09**
ICC (reported ICC for semi scale in some papers)	Effusion	3	108	121	**0.89(0.85-0.92)**	**0.90(0.74-0.96)**	**0.00**	**86**	**0.41**
	Synovial hypertrophy	3	108	121	**0.82(0.75-0.87)**	**0.82(0.73-0.89)**	**0.20**	**37**	**0.13**
	Doppler activity	1	45	45	**0.75(0.59-0.86)**				
	Osteophyte	2	126	176	**0.93(0.91-0.95)**	**0.89(0.49-0.98)**	**0.00**	**96**	**0.64**
	Cartilage thickness	3	114	114	**0.88(0.83-0.92)**	**0.80(0.05-0.97)**	**0.00**	**96**	**0.90**
	Meniscal extrusion	4	318	381	**0.91(0.89-0.93)**	**0.91(0.78-0.96)**	**0.00**	**95**	**0.48**
	JSN	1	81	131	**0.93(0.90-0.95)**				

	Baker’s cyst	3	113	113	**0.90(0.86-0.93)**	**0.90(0.53-0.98)**	**0.00**	**95**	**0.75**

Abbreviation: ICC=Intra-class Correlation Coefficient; CI= Confidence nterval

4.5.7.3. Validity

Meta-analysis was stratified for each comparator such as asymptomatic controls, pain, function, X-rays, MRI or blood biomarkers or histology or arthroscopy. Correlation coefficients were interpreted according to the Evans' classification [197], <0.20:very weak; 0.20-0.39:weak; 0.40-0.59:moderate; 0.60-0.79;strong and >0.80:very strong.

Construct validity against asymptomatic controls: Six studies, including 643 joints from 582 participants, provided 23 odd ratios. In symptomatic patients (**Table 4.7**), the pooled odd ratio demonstrated a very strong association with effusion [7.46(2.56,21.70)], and a strong association with Baker's cyst [3.23(1.57,6.67)] and meniscal extrusion [3.08(1.06,8.92)]. Heterogeneity was generlly moderate (I^2=41 to 61).

Table 4.7. Stratified meta-analysis of ultrasound features for construct validity in people with knee OA comparing to asymptomatic controls.

Stratified meta-analysis	No. of studies	No. of patients	No. of joints	Odds ratio (95% CI)		Heterogeneity		
Knee				Fixed	Random	P-value	I^2	Tau
Synovitis	1	56	122	**10.53(3.42,32.44)**				
Effusion	5	421	598	**5.20(2.89,9.35)**	**7.46(2.56,21.70)**	**0.04**	**61**	**0.9**
Osteophyte	1	56	122	**3.23(0.20,53.47)**				
Meniscal extrusion	4	360	476	**2.38(1.21,4.69)**	**3.08(1.06,8.92)**	**0.14**	**45**	**0.70**
Infra-patella bursitis	1	101	101	**4.13(0.23,75.33)**				
Baker's cyst	5	421	598	**2.87(1.73,4.75)**	**3.23(1.57,6.67)**	**0.15**	**41**	**0.52**
Pes Anserine bursitis	1	101	101	**2.95(0.16,55.53)**				

Construct validity against pain: Pooling 37 estimates out of 16 studies, including 2577 joints from 2085 patients, revealed a weak correlation with trivial heterogeneity [I^2=0] *(***Table 4.8***)*.

Table 4.8. Stratified meta-analysis of ultrasound features for construct validity in knee OA (Pain)

Stratified meta-analysis	No. of studies	No. of patients	No. of joints	Correlation coefficient (95% CI)		Heterogeneity		
Knee				Fixed	Random	P-value	I^2	Tau
Synovitis	2	287	287	**0.27(0.16,0.38)**	**0.27(0.16,0.38)**	**0.72**	**0**	**0**
Effusion	7	1006	1092	**0.12(0.06,0.18)**	**0.12(0.06,0.18)**	**0.46**	**0**	**0**
Synovial hypertrophy	2	71	85	**0.20(0.07,0.32)**	**0.20(0.07,0.32)**	**0.43**	**0**	**0**
Power Doppler	1	41	41	**0.37(0.07,0.61)**				
Osteophyte	2	353	353	**0.15(0.05,0.25)**	**0.15(0.05,0.25)**	**0.83**	**0**	**0**
Meniscal extrusion	2	238	238	**0.17(0.04,0.29)**	**0.17(0.04,0.29)**	**0.99**	**0**	**0**
Cartilage thickness	4	287	295	**0.22(0.11,0.33)**	**0.22(0.11,0.33)**	**0.45**	**0**	**0**
Baker's cyst	3	264	264	**0.13(0.00,0.24)**	**0.13(0.00,0.24)**	**0.68**	**0**	**0**
Pes Anserine bursitis	2	257	414	**0.02(-0.08,0.12)**	**0.02(-0.08,0.12)**	**0.83**	**0**	**0**

Construct validity against function: Meta-analysis of 15 estimates out of 9 studies, including 1333 joints and 802 patients, resulted in weak correlation, and mild heterogeneity [I^2=20-38] *(***Table 4.9***)*. Six studies used WOMAC [198].

Table 4.9. Stratified Meta-analysis for Construct Validity (function)

Stratified meta-analysis	**No. of studies**	**No. of patients**	**No. of joints**	**Correlation coefficient (95% CI)**		**Heterogeneity**		
Knee				**Fixed**	**Random**	**P-value**	**I^2**	**Tau**
Effusion	3	171	257	**0.25(0.13,0.36)**	**0.23(0.08,0.37)**	**0.29**	**20**	**0.06**
Power Doppler	1	71	71	**0.23(-0.01,0.44)**				
Osteophyte	2	205	205	**0.18(0.04,0.31)**	**0.18(0.04,0.31)**	**0.43**	**0**	**0**
Meniscal protrusion	1	61	122	**0.22(-0.04,0.45)**				
Cartilage thickness	2	101	162	**0.14(-0.06,0.33)**	**0.15(-0.11,0.39)**	**0.20**	**38**	**0.12**
Baker's cyst	1	70	140	**0.35(0.12,0.54)**				
Pes Anserine bursitis	1	157	314	**0.18(0.07,0.29)**				

Construct validity against X-rays: Pooling across a total of 49 estimates from 11 studies (1956 joints, and 1530 patients) indicated strong correlation with osteophyte [0.60(0.45,0.71)], moderate correlation with effusion [0.54(0.37,0.68)] and meniscal extrusion [0.48(0.34,0.60)], and weak association with cartilage thickness [0.35(0.12,0.55)]. Heterogeneity was moderate [I^2=34-52] *(***Table 4.10***)*. Kellgren Lawrence score [16] was applied in 10 studies.

Table 4.10. Stratified meta-analysis of ultrasound features for construct validity in knee OA (X rays)

Stratified meta-analysis	**No. of studies**	**No. of patients**	**No. of joints**	**Correlation coefficient (95% CI)**		**Heterogeneity**		
Knee				**Fixed**	**Random**	**P-value**	**I^2**	**Tau**
Synovitis	1	45	45	**0.39(0.11,0.62)**				
Effusion	2	139	139	**0.55(0.42,0.66)**	**0.54(0.37,0.68)**	**0.21**	**35**	**0.10**
Synovial hypertrophy	1	94	94	**0.70(0.58,0.79)**				
Osteophyte	3	94	102	**0.60(0.45,0.71)**	**0.60(0.45,0.71)**	**0.43**	**0**	**0**
Meniscal protrusion	2	111	212	**0.48(0.37,0.58)**	**0.48(0.34,0.60)**	**0.22**	**34**	**0.07**
Cartilage thickness	2	60	68	**0.35(0.12,0.55)**	**0.35(0.12,0.55)**	**0.37**	**0**	**0**
Baker's cyst	1	94	94	**0.30(0.10,0.47)**				
Pes Anserine bursitis	2	242	484	**0.12(0.03,0.21)**	**0.13(0.00,0.26)**	**0.15**	**52**	**0.07**

Construct validity against MRI: Strong correlation (r>0.60) was detected on pooling 29 estimates across 4 studies examining 306 knee joints in 230 patients, using 0.2T to 1.5 T MRI with dedicated knee coils *(***Table 4.11***)*.

Table 4.11. Stratified Meta-analysis for Construct Validity (MRI)

Stratified meta-analysis	**No. of studies**	**No. of patients**	**No. of joints**	**Correlation coefficient (95% CI)**		**Heterogeneity**		
Knee				**Fixed**	**Random**	**P value**	**I^2**	**Tau**
Synovitis	1	41	41	**0.63(0.41,0.79)**				
Effusion	1	138	212	**0.63(0.54,0.70)**				
Synovial hypertrophy	1	138	212	**0.62(0.53,0.70)**				
Osteophyte								
Meniscal protrusion								
Cartilage thickness	2	189	265	**0.60(0.52,0.67)**	**0.60(0.52,0.67)**	**0.67**	**0**	**0**
Baker's cyst	1	138	212	**0.66(0.58,0.73)**				

Construct validity against biomarkers: Twenty-three estimates of serum cartilage oligomeric matrix protein (COMP) were pooled across 4 studies involving 95 knee joints from 95 patients, generating weak correlation [*r*=0.003 to 0.21] with trivial heterogeneity [I^2=0] *(***Table 4.12***)*.

Table 4.12. Stratified Meta-analysis for Construct Validity (biomarkers)

Stratified meta-analysis	**No. of studies**	**No. of patients**	**No. of joints**	**Correlation coefficient (95% CI)**		**Heterogeneity**		
Knee				**Fixed**	**Random**	**P-value**	**I^2**	**Tau**
Effusion	3	95	95	**0.003 (-0.206,0.211)**	**0.003 (-0.206,0.211)**	**0.085**	**0**	**0**
Capsular distension	3	95	95	**0.21(0.01,0.40)**	**0.21(0.01,0.40)**	**0.81**	**0**	**0**
Osteophyte	3	95	95	**0.19(-0.01,0.39)**	**0.19(-0.01,0.39)**	**0.50**	**0**	**0**
Cartilage thickness	3	95	95	**0.13(-0.08,0.33)**	**0.13(-0.08,0.33)**	**0.91**	**0**	**0**

Criteria validity against histology: Pooling of four estimates from 2 studies, evaluating histological cartilage thickness in 190 knee joints from 113 patients, produced a moderate correlation [*r*=0.66(-0.05-0.93)], and considerable heterogeneity [I^2=90] (**Table 4.13**).

Table 4.13. Stratified meta-analysis for Criteria validity of cartilage thickness with histology

Stratified meta-analysis	No. of studies	No. of patients	No. of joints	Correlation coefficient (95% CI)		Heterogeneity		
Knee				Fixed	Random	P-value	I^2	Tau
Cartilage thickness	2	113	190	**0.44(0.32,0.55)**	**0.66(-0.05,0.93)**	**0.001**	**90**	**0.59**

Criteria validity against arthroscopy: Ultrasound pathologies focused by three arthroscopic studies, using Noyes' grading scale [135], were not the same among the papers, and so pooling could not be executed. Generally, arthroscopic gradings correlated strongly with osteophyte [171], moderately with cartilage grading [136]and weakly with subchondral bone [199].

4.5.7.4. Responsiveness

According to Cohen [200], values of 0.0, 0.20, 0.50, and 0.80 or greater represented trivial, small, moderate, and large responsiveness, respectively.

Internal responsiveness: Pooling 31 estimates across 10 studies, comprising 480 joints from 393 patients, produced a moderate effect size for Baker's cyst [0.58(0.40,0.77)], and small effect size for synovial hypertrophy [0.30(0.05,0.56)], effusion [0.28(0.00,0.56)] and cartilage thickness [0.20(0.04,0.36)] (**Table 4.14 and 4.15**). The interventions included injections of different steroids (*n*=6), platelet rich plasma (*n*=2), glucosamine (*n*=1), and exercises (*n*=1). The study duration ranged from 2 weeks to 6 months.

Table 4.14. Stratified meta-analysis of ultrasound features for internal responsiveness in knee OA (paired sample)

Stratified meta-analysis	No. of studies	No. of patients	No. of joints	Correlation coefficient (95% CI)		Heterogeneity		
Knee				Fixed	Random	P-value	I^2	Tau
Effusion	2	73	73	**0.28(0.00,0.56)**	**0.28(0.00,0.56)**	**0.63**	**0**	**0**
Synovial hypertrophy	2	63	63	**0.30(0.05,0.56)**	**0.30(0.05,0.56)**	**0.61**	**0**	**0**
Cartilage thickness	3	136	157	**0.20(0.04,0.36)**	**0.20(0.04,0.36)**	**0.61**	**0**	**0**
Baker's cyst	4	128	128	**0.58(0.40,0.77)**	**0.58(0.40,0.77)**	**0.78**	**0**	**0**
Quadriceps thickness	1	66	132	**0.32(0.17,0.47)**				

Table 4.15. Stratified Meta-analysis for Internal Responsiveness (independent sample)

Stratified meta-analysis	No. of studies	No. of patients	No. of joints	Correlation coefficient (95% CI)		Heterogeneity		
Knee				Fixed	Random	P-value	I^2	Tau
Effusion	2	240	240	**0.64(0.42,0.85)**	**0.64(0.42,0.85)**	**0.38**	**0**	**0**
Synovial hypertrophy	1	20	20	**0.37(0.05,0.69)**				
Power Doppler	1	20	20	**0.28(-0.04,0.61)**				
Cartilage thickness	3	240	240	**0.29(0.04,0.55)**	**0.29(0.04,0.55)**	**0.80**	**0**	**0**

External responsiveness: Pooling 7 estimates across 4 studies with a total of 121 joints and 121patients, provided moderate correlation for synovial hypertrophy [0.43(-0.02,0.73)], and weak correlation for Baker's cyst [0.35(-0.11,0.69)]. Substantial heterogeneity was detected [I^2=68-74] *(***Table 4.16***)*. The interventions were intra-articular steroid injections (*n*=3), and shortwave diathermy (*n*=1).

Table 4.16. Stratified Meta-analysis for External Responsiveness

Stratified meta-analysis	**No. of studies**	**No. of patients**	**No. of joints**	**Correlation coefficient (95% CI)**		**Heterogeneity**		
Knee				**Fixed**	**Random**	**P-value**	**I^2**	**Tau**
Effusion	1	33	33	**0.05(-0.30,0.39)**				
Synovial hypertrophy	2	63	77	**0.45(0.25,0.62)**	**0.43(-0.02,0.73)**	**0.05**	**74**	**0.30**
Power Doppler	1	33	33	**0.36(0.02,0.63)**				
Baker's cyst	2	58	58	**0.37(0.12,0.58)**	**0.35(-0.11,0.69)**	**0.08**	**68**	**0.29**

4.5.7.5. Feasibility

Five studies reported the scanning time for a complete examination, which varied from 5 min to 15 min depending on how many pathologies were scanned *(***Table 4.17***)*.

Table 4.17. Feasibility of ultrasound scores in term of scanning time

	Author/Year	OA site	Pathologies	Grading Score	Scanning method	Scanning time
1	Bevers, 2012	knee	Effusion, synovial hypertrophy, meniscal lesion, cartilage thickness, Baker's cyst, bursitis	Binary/ quantitative	EULAR	5 min
2	Bevers, 2014	knee	Effusion, synovial hypertrophy, meniscal lesion, cartilage thickness, Baker's cyst, bursitis	Binary/ quantitative	EULAR	10 min
3	Bruyn, 2016	knee	Synovitis, Effusion, Synovial hypertrophy, Global synovitis, Meniscal damage, Cartilage damage, Osteophytes	Binary/ Semi-quantitative	EULAR	8 min
4	Riecke, 2014	Knee	Synovitis, Effusion, Synovial hypertrophy, Global synovitis, Meniscal damage, Cartilage damage, Osteophytes (61 items)	Binary/semi-quantitative	other	5 min (scanning) 10-15min (subsequent analysis)
5	Saarakkala, 2012	knee	cartilage thickness, grading	semi-quantitative	other	10 min

Abbreviation: EULAR= European League Against Rheumatism

4.5.8. Hand OA

4.5.8.1. Reliability

There were 4 inter-rater reliability studies for binary scores [201-204], 3 for semi-quantitative scores [165, 172, 202] and 1 for quantitative scores [205].The binary scoring system provided the kappa ranging from slight for cartilage thickness [202] to excellent for synovitis, effusion and osteophyte [203]. For the semi-quantitative score, the kappa values varied from slight for cartilage thickness [202] to substantial for osteophyte and synovitis [165, 172]. For the quantitative score, ICC was excellent for synovial hypertrophy [205].

Among intra-reliability studies, 7 studies applied binary scores [165, 170, 172, 201, 202, 206, 207]; five studies used semi-quantitative scores [165, 172, 202, 208, 209]; one study examined quantitative scores [210]. Similar findings of kappa values were reported for different pathologies but with higher actual kappa values.

4.5.8.2. Validity

Only two studies reported construct validity of ultrasound with pain, disclosing very weak correlation [208, 211]. Four studies documented ultrasound data for functional correlation which varied from very weak to weak for most pathologies [206, 208, 211, 212]. The validity of ultrasound with X-rays was investigated in two studies, providing very weak correlation [207, 211]. However, ultrasound provided moderate correlation with MRI for osteophyte (r=0.49) and synovitis (r=0.43) on a semi-quantitative scale [213].

4.5.8.3. Responsiveness

Two studies supplied sufficient information to calculate internal responsiveness. One study revealed trivial effect size for synovitis and power Doppler outcomes at 12 weeks after intramuscular methylprednisolone injection [214], and a small effect size was detected at 4 weeks for the same pathologies in another study, using intra-articular injections of hyaluronic acid as an intervention [215].

For external responsiveness, one study reported a strong correlation of synovial thickening and power Doppler with VAS pain at 4 weeks [215].

4.5.9. Hip OA

4.5.9.1. Reliability

Inter-rater reliability of binary score ranged from fair in effusion to moderate for osteophyte in one study [216] while another study recorded excellent reliability for the same pathologies [217].

Intra-rater reliability of binary score was moderate in joint effusion and substantial in osteophyte [216] while the other revealed the excellent kappa [217]. For semi-quantitative scores by radiologists, excellent kappa was reported for the synovial thickness [218].

4.5.9.2. Validity

Ultrasound synovitis and osteophyte scores demonstrated a strong association with pain on activity [216]. A weak correlation was documented between effusion and Lequesne index [219], and between osteophyte and KL grading (r=0.26) [216].

4.5.9.3. Responsiveness

One study applied ultrasound synovial hypertrophy and effusion as an outcome measure to evaluate internal responsiveness, providing moderate effect size (SMD=0.44) at 3 months after intra-articular injection of 8 mg betamethasone [220].

4.6. Discussion

Overall, the main findings of our meta-analysis suggest various (weak to very strong) construct validity with patients findings and other imaging modalities, depending on pathologies and comparators, moderate to substantial reliability, strong criterion validity with cartilage histology, and small to moderate responsiveness to interventions. On qualitative analysis, this systematic review

revealed substantial clinical, technical and methodological heterogeneity of ultrasound within OA literature, requiring caution in interpreting these meta-analytic results. However, on quantitative analysis, I^2, which denotes statistical heterogeneity, was only low or moderate for most of the clinimetrics.

Although ultrasound possesses promising potential in OA clinical trials, fewer studies in hand and hip joints were detected in the literature, compared to the knee. Although utilization/reporting of OMERACT definitions has gained a significantly positive trend over last decade, a marked variability of ultrasound scanning characteristics was noted, highlighting the necessity of following/reporting international consensus protocols in future studies.

In the context of methodological quality, a modified Downs and Black quality assessment score [182] was administered to identify the potential bias and display the summary of these bias. All studies, which documented the clinimetric data for each pathology, were pooled without applying exclusion on the basis of study quality scale because the threshold for exclusion reduced the precision [221], and was necessarily subjective [222]. According to Detsky *et al*, it seemed highly unlikely that these quality scores would generate a linear or monotonically increasing association with true quality, and no objective reference standard simply existed for determining the "true" scientific rigour of a trial [223]. Moreover, due to a limited number of papers which documented clinimetric data for each ultrasound pathology, the sensitivity analysis, based on study quality score, could not be examined (i.e. there were some pathologies for each of which only one paper existed as a unit of analysis.). Moreover, validity research in OA is difficult due to the diversed definitions and diagnostic criteria for OA (radiographic or symptomatic).

Our meta-analysis results indicated moderate to substantial reliability [minimum kappa≥0.44(0.15,0.74) and minimum ICC≥0.82(0.73-0.89)] for ultrasound pathologies of knee OA. Generally, the binary and quantitative scores produced higher reliability statistics than semi-quantitative scores. Some papers calibrated the semi-quantitative scores by utilizing the atlas-based grading methods [171, 224] while some defined the grading by quantitative cut-offs [166]. The

reliability of Baker's cyst, meniscal extrusion, osteophyte, synovitis and effusion were at least substantial for the semi-quantitative scores.

The musculoskeletal experience of ultrasound operators ranged from those with short-course training to very experienced specialist, and so the meta-analysis results represented the generalizability of reliability statistics across different levels of ultrasound experience. However, it should be noted that the operator-dependent nature of ultrasound measurement and quality of US machines could largely influence on the performance of the reliability statistics, especially when smaller joints are addressed.

The limited data for the criterion validity of OA ultrasound features focused predominantly on cartilage histology, with an overall strong correlation. Conflicting reports were found for correlations of synovitis/Doppler signals with synovial vascularity in a mixed sample of inflammatory arthritis and osteoarthritis [148, 149, 225, 226]. Semi-quantitative grading scores currently applied for OA synovitis were adopted from those validated for inflammatory rheumatoid arthritis, assuming that synovitis was only quantitatively but not qualitatively different between inflammatory arthritis and osteoarthritis [227]. However, replication of these semi-quantitative scoring systems in OA might require consideration due to the low degree of inflammation, sustained in osteoarthritis compared to rheumatoid arthritis [177], which is likely to contribute to floor effects, and thereby impairs the capability to detect improvement changes in interventional studies.

Pooling construct validity of ultrasound findings in case-control studies (OA versus healthy population) exhibited strong discrimination in some pathologies, suggesting that ultrasound might be a potential tool for developing ultrasonographic OA propositions, similar to preliminary OA propositions with MRI [228]. Furthermore, ultrasound demonstrated a strong correlation with MRI in principal OA features, indicating the promising usefulness of ultrasound in clinical care where MRI is not readily accessible.

Generally, ultrasound, as expected, had a very weak association with pain, function and blood biomarker [*e.g.* Cartilage Oligomeric Matrix Protein (COMP)]. Almost all individual studies

incorporated in the meta-analysis consistently denoted a weak correlation between ultrasound features and pain ($r \leq 0.40$). This finding may be attributed to a number of reasons such as complex causes of symptoms in OA, multi-factorial subjective experience of pain (biopsychosocial factors), and that the ultrasound outcomes used in individual studies might not capture the multi-dimensional nature of pain (measurement issues) [229]. In contrast, the relationship of ultrasound with X rays produced various values ranging from weak to strong correlation, depending on ultrasound pathologies.

At least small effect size (SMD≥0.2) was documented in most interventional studies, and the low I^2 in pooled meta-analysis was detected. Generally, the inflammatory features such as Baker's cyst, synovial hypertrophy provides greater internal responsiveness, compared to cartilage changes, perhaps due to short follow-up duration (maximum 24 weeks). However, this result should be interpreted with caution as the included studies for sensitivity to change were all small studies with some limitations. Combining external responsiveness of inflammatory pathologies revealed a moderate correlation with pain while no studies examined external responsiveness for structural pathologies.

Ultrasound scanning duration largely depended on the number of joints and pathologies assessed and the scoring systems employed, which were varied across studies. Development of international consensus guidelines for feasible composite scoring methods is essential and still ongoing.

It should be noted that several papers included in the validity assessment of previous systematic review [179] had to be excluded as our inclusion criteria was focused only on knee, hand and hip, not other joints such as foot, shoulder, cervical spine, etc and some papers did not publish the comparator for validity assessment, clinimetric data, etc. However, more than 60 new papers were included in this updated review.

4.7. Limitations

Our review had several potential limitations. The first was the considerable clinical and methodological heterogeneity of included studies, requiring caution in interpreting the pooled results. However, I^2 was low for validity and responsiveness measures. The second limitation was that we could not rule out some publication bias, although a thorough literature search was attempted. The third limitation is the application of SMD for internal responsiveness instead of calculating standardized response mean (SRM), as most interventional studies did not describe the standard deviation of mean change [230]. However, in the literature, the best statistics for treatment responsiveness and interpretation is still controversial, and according to mathematical formulae proposed by Norman *et al.*[189], SRMs tend to be higher than SMDs. The fourth limitation is that we could not appropriately analyze the confounding effects over technology changes over the years because there were numerous confounders such as machine model, probe frequency, operator's clinical background, qualification, training period, the severity of the sample, the sensitivity of comparator machine models in examining construct validity against X rays and MRI, while a limited number of papers with clinimetric data for each pathology existed, causing a lack of power to examine the impact of these confounders on the clinimetrics by regression analysis.

4.8. Conclusion

To our knowledge, this is the first meta-analytic systematic review comprehensively examining the clinimetrics of ultrasound utilized to evaluate common features of OA, covering the original OMERACT filter components. A stratified meta-analysis demonstrated moderate to substantial reliability, various construct validity with several clinical and imaging comparators, strong criterion validity with cartilage histology and small to moderate responsiveness. Future studies should improve the conduct and reporting of clinimetric studies, especially for the areas of several poor quality-items. As most of the individual studies were of small sample size and just focused on some

individual pathologies, larger studies with comprehensive ultrasound outcomes in future would provide more clear insight into the clinimetrics of commonly assessed ultrasound pathologies in OA.

Contributions: WMO and DJH conceived and designed the study. JML, PGC, HK, SS, JS and LAD were also involved in the design of the study. WMO, MD and DJH contributed to acquisition of the main clinimetric data of included papers. WMO had full access to all the data and analysis, drafted the manuscript and takes responsibility for the integrity of the work from inception to the finished article. All authors critically revised the manuscript and gave final approval of the article for submission.

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Conflict of interest: None

CHAPTER FIVE

This chapter includes the following submitted paper:

Oo W.M., Linklater J., Bennell K.L., Pryke D., Yu S., Wang X., Duong V., and Hunter D.J, Are OMERACT knee osteoarthritis ultrasound scores associated with pain severity, other symptoms, radiographic and MRI findings? Rheumatology. Revision submitted on 7th March 2020

Chapter 5

Are OMERACT knee osteoarthritis ultrasound scores associated with pain severity, other symptoms, radiographic and MRI findings?

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Statement from co-authors confirming authorship contribution of the PhD candidate

The co-authors of the paper: "Are OMERACT knee osteoarthritis ultrasound scores associated with pain severity, other symptoms, radiographic and MRI findings?", confirm that Win Min Oo has made the following contributions:

1. Conception and design of the research
2. Analysis and interpretation of the findings
3. Writing of the manuscript and critical appraisal of the content

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Win Min Oo Date: 15th August 2019

As supervisor for the candidature upon which this Thesis is based, I can confirm that the authorship attribution statements above are correct.

David Hunter Date: 15th August 2019

Chapter Five: Are OMERACT knee osteoarthritis ultrasound scores associated with pain severity, other symptoms, radiographic and MRI findings?

Abstract

Objectives

To investigate the associations of Outcome Measures in Rheumatology (OMERACT) ultrasound scores for knee osteoarthritis (OA) with pain severity, other symptoms, and OA severity on radiographs and magnetic resonance imaging (MRI).

Methods

Participants with symptomatic and mild-moderate radiographic knee OA underwent baseline dynamic ultrasound assessment according to standardized OMERACT scanning protocol. Using the published ultrasound image atlas, a physician operator obtained semi-quantitative or binary scores for ultrasound pathologies. Clinical severity was measured on Numerical Rating Score (NRS) and Knee Injury and Osteoarthritis Outcome Score (KOOS) symptoms and pain sub-scores. OA severity was assessed using the Kellgren-Lawrence grade (KLG) on X-rays and MRI osteoarthritis knee score (MOAKS) on non-contrast-enhanced MRI. Separate linear regression models were used to determine associations of ultrasound OA pathologies with pain and KOOS sub-scores, and Spearman's correlations were used for ultrasound scores with KLG and MOAKS.

Results

Eighty-nine participants were included. Greater synovial hypertrophy, power Doppler (PD) and meniscal extrusion scores were associated with worse NRS pain (B=0.92,95% confidence interval CI 0.25,1.58); B=0.73(95% CI 0.11,1.35) and B=1.01(95% CI 0.22,1.80). All greater ultrasound scores except for cartilage grade demonstrated significant associations with worse KOOS symptoms while only PD and meniscal extrusion were associated with worse KOOS pain. All ultrasound scores except

for PD were significantly correlated with KLG. Ultrasound pathologies except for cartilage revealed moderate to good correlation with their MOAKS counterparts with ultrasound synovitis having the greatest correlation {0.69(95% CI 0.60, 0.78}c.

Conclusion

OMERACT ultrasound scores revealed significant associations with pain severity, KLG and MOAKS.

Keywords

Osteoarthritis; Musculoskeletal ultrasound; Imaging; Association

5.2. Introduction

Osteoarthritis (OA) is one of the most prevalent chronic health conditions causing pain and disability among elderly adults [1]. Approximately 15.4% of the adult population have symptomatic OA [2]. By 2030, OA is predicted to be the single greatest cause of disability globally, with an estimated 35% prevalence [4].

The pathophysiology of knee OA is complex and involves multiple-tissue pathologies affecting the whole joint structure [13]. Pathologies include synovitis, synovial hypertrophy, effusion, power Doppler (PD) signals, meniscal damage, cartilage loss and bony osteophyte [23, 228]. Imaging tools are used to visualize the severity of these pathologies, but each has its own limitations [231]. The plain radiograph involves radiation and can view only the bony structure while MRI is expensive and not readily accessible in clinical practice [13]. Ultrasound is a non-invasive imaging tool that can detect soft tissues as well as the bony cortex including osteophytes in OA [23].

One concern expressed about ultrasound has been observer-dependence. As such, the Outcome Measures in Rheumatology (OMERACT) group [42] used international consensus and reliability testing to develop standardized knee ultrasound scanning methods and grading scores for synovitis, synovial hypertrophy, effusion, power Doppler (PD), cartilage thinning, osteophyte and meniscal extrusion; however, the validity of these grading scores has not been tested. Therefore, the objective of this study is to examine the associations of the OMERACT knee OA ultrasound grading scores by testing their relationship with pain severity, clinical symptoms, and severity on plain radiograph and MRI findings.

5.3. Methods

5.3.1. Study design and participant selection

This is a cross-sectional analysis using baseline data from the Sydney, Australia site of the ongoing RESTORE (platelet-Rich plasma as a symptom- and disEaSe-modifying Treatment fOR

knee ostEoarthritis) clinical trial (Trial registration No: ACTRN12617000853347) [232]. Inclusion and exclusion criteria were the same as for the RESTORE study [232]. Briefly, eligible participants met the following inclusion criteria.

(i) aged>50 years;

(ii) knee pain on most days in the last month;

(iii) osteophytes on x-ray; and

(iv) A minimum pain score of 4 on an 11-point numeric rating scale (NRS) for the last week

The exclusion criteria included (i) Kellgren and Lawrence (KL) grade 1 or grade 4; (ii) predominant lateral tibiofemoral disease; (iii) systemic or inflammatory joint disease; (iv) history of crystalline or neuropathic arthropathy; (v) be unwilling to discontinue NSAID and other analgesic usage for knee pain, except for paracetamol for rescue pain relief, from 2 weeks prior to baseline assessment.

For those participants with bilaterally eligible knees, the most symptomatic knee was deemed the study knee. The cohort included here is a convenience sample recruited from the baseline visit, and all participants available for an ultrasound visit between September 2017 and February 2019 were included.

Participants' demographic data such as age, gender, height, weight and symptom duration were collected as previously described [232]. Body mass index (BMI) was calculated using height and weight (kg/m2). This study was approved by the Northern Sydney Local Health Districts Human Research Ethics Committee (HREC/16/HAWKE/430).

5.3.2. Clinical assessment

On the same day of the ultrasound scan, average overall knee pain severity over the last week was measured using an 11-point NRS with terminal descriptors 'no pain' (score 0) and 'worst pain possible' (score 10), with the highest scrores denoting the worst pain, and this outcome measure is recommended to be included in knee OA clinical trials by the Osteoarthritis Research Society

International [233]. The Knee Injury and Osteoarthritis Outcome Score (KOOS) pain and other symptoms sub-scores were collected. The KOOS is a knee-specific self-report outcome measure with high test-retest reliability, internally consistent and face and content validity [12]. Likert responses range from None to Extreme, and scores range from 0 to 100, with lower scores indicating worse symptoms. The KOOS pain subscale is scored from 9 questions about knee pain frequency experienced in the last week, and the amount of knee pain experienced during specific activities such as twisting, bending and walking. The KOOS other symptoms subscale is scored from 7 questions regarding other symptoms experienced in the last week, such as swelling, restricted range of motion and mechanical symptoms.

5.3.3. Radiological Assessment

Participants underwent bilateral weight-bearing posteroanterior radiography ([Model R-20 J] Shimadzu Corporation, Nakagyo-ku, Kyoto, Japan) before ultrasound and MRI examinations. Kellgren and Lawrence grade was assessed by a rheumatologist (SY, 7 years of experience in grading radiograph of knee OA) who was blinded to clinical, ultrasound and MRI scores.

5.3.4. Ultrasound evaluation

A physician operator (WMO, 6 years of musculoskeletal ultrasound experience and certified with musculoskeletal ultrasound in rheumatology (RhMSUS) by the American College of Rheumatology) blinded to clinical, radiograph and MRI findings, performed and scored the ultrasound scans of the study knee [234]. These were done dynamically and extensively in a wide area with a multi-frequency linear 14L5 transducer (using 10MHz) of Aplio Platinum 500 machine, Toshiba, Japan, according to the standardized OMERACT scanning protocol [42]. The ultrasound scores for seven disease manifestations were then graded by the same operator using the OMERACT knee ultrasound OA atlas: semi-quantitative scores for (i) synovitis (0-3) (combined synovial hypertrophy and effusion), binary scores (0-1) for (ii) synovial hypertrophy ≥ 4mm, (iii) effusion ≥ 4mm [142], and (iv) PD signals separately from suprapatellar recess in a longitudinal plane, medial

and lateral para-patella recesses in a transverse plane, semi-quantitative scores for (v) osteophytes (0-3) from the medial and lateral joint aspects in a longitudinal plane and (vi) meniscal extrusion (0-2) (only the medial joint aspects) in longitudinal plane, and for (vii) cartilage abnormalities (0-3) in transverse plane on a maximally flexed knee (**Appendix 4, supplementary file 1**). The application specialist from Toshiba machine settings optimised the machine setting, providing grey scale gain=85%, probe frequency=10 MHz, doppler frequency=6Mhz, doppler gain=40%, pulse repetition frequency=14.8kHz and wall filter=5. The ultrasound operator was not allowed to change these, except for depth and focus, through the study.

The maximum score approach (i.e, the highest score of the same ultrasound features such as synovitis, osteophyte, etc from different scanned sites was taken as the final score of the whole knee) [29] was then used to correlate with clinical and radiographic and MRI data of the study knee. For the whole knee scan for these seven disease manifestations, it took around 8 minutes for scanning and about 13 minutes for scoring.

5.2.4.1. Inter-rater and intra-rater reliability

Testing of inter-rater reliability testing was limited to supra-patellar synovitis and PD, medial osteophyte and medial meniscal extrusion. A second trained reader (DP, 8 years of musculoskeletal ultrasound experience) independently performed the ultrasound scans of the study knee in 20 patients after the first ultrasound operator finished scanning, and provided the independent grading. To evaluate intra-rater reliability of all seven ultrasound OA manifestations, the same operator (WMO) re-scanned 10 patients one week later and calculated ultrasound scores whilst blinded to the previous scores.

5.3.5. MRI evaluation

On the same day as the ultrasound scanning, the study knee was imaged with a 3T MRI scanner (Siemens Skyra, Siemens Healthcare, Erlangen, Germany) using a 15-channel transmit/ receive knee coil. The following 5 MRI sequences were performed:

1) sagittal T2-weighted dual-echo steady-state

2) sagittal proton-density-weighted fat-suppressed non-contrast turbo spin-echo (TSE)

3) coronal proton-density-weighted TSE

4) coronal proton-density-weighted fat-suppressed TSE

5) axial proton-density-weighted fat-suppressed TSE.

Technical details of the sequences can be found in **Appendix 4, supplementary file 2.**

The semiquantitative MOAKS grading involves evaluation of the cartilage loss (any or full-thickness) from patellofemoral, medial and lateral tibiofemoral compartments, osteophyte from 12 different sites, medial meniscal extrusion, effusion-synovitis over the supra-patellar and parapatellar areas, and Hoffa's synovitis over the Hoffa's fat pad at the infra-patellar area as described by Hunter *et al* [29]. The maximum score of the same MRI features such as cartilage loss (any or full-thickness), and osteophyte from all sites was taken as the whole knee score for that MRI feature.

5.3.5.1. Inter-rater and intra-rater reliability of MRI

Scoring of the MOAKS was performed by W.M.O., who obtained imaging training from an experienced musculoskeletal radiologist (J.M.L., 25 y of experience in musculoskeletal MRI). Both readers independently scored the MRI images of 10 consecutive participants. The readers were blinded to clinical features and symptoms and radiograph and ultrasound scores. WMO also performed the second reading of all MRI images one month apart to obtain the intra-rater reliability.

5.4. Statistics

Descriptive statistics of categorical variables were expressed as frequencies and percentages. Descriptive statistics of continuous variables were calculated as mean and standard deviation (SD) for normally distributed data, and median and range for non-normally distributed data. Although it might seem that "the OMERACT US scoring system" is 1 single scoring system, in fact, it consists of 7 US scoring systems, covering both structural and inflammatory features present in knee OA. For all these scoring systems, relationship has to be assessed separately. To investigate whether these ultrasound

features were associated with pain and other symptoms, separate linear regression models were fit with each ultrasound feature as predictor, adjusting for age, gender, BMI, duration of disease and radiographic KLG. Spearman's correlations were calculated to determine the relationship of ultrasound features with radiographic KLG and MRI MOAKS scores. Correlation coefficients were interpreted according to the Evans' classification [197], <0.20:very weak; 0.20-0.39:weak; 0.40-0.59:moderate; 0.60-0.79;strong and >0.80:very strong. The study was powered for the association of the seven ultrasound pathologies with VAS joint pain. With 7 potential predictors, testing at the 5% significance level with 80% power, and assuming a minimum R^2 of 0.3, 42 patients were required to show that the ultrasound scores explain a statistically significant amount of the variation in joint pain. All statistics were conducted with SPSS version 23 and a significant association/correlation was defined as a p-value less than 0.05.

5.5. Results

5.5.1. Demographic, clinical characteristics, ultrasound and MRI findings

Eighty-nine participants were included in this study with 48 (53.9%) females, BMI of 27.5±6.4), pain of 5.8±1.5 on an NRS scale, 59.6% of participants having KLG III, and 95.5% and 47.0% showing ultrasound synovitis grade ≥1 and PD signals respectively. However, synovial hypertrophy and effusion on ultrasound were present in 47.2% and 59.6% of the participants using quantitative cut-offs of 4 mm. All participants had osteophytes and meniscal extrusion on ultrasound, with 95.5% having cartilage abnormalities. **Table 5.1.** demonstrates the other characteristics in detail.

Table 5.1. Baseline clinical, radiographic, ultrasound and MRI data of study participants

	Number (%)	**Mean (SD)/Median (Range)**
Population	89	
Age, years		61.5±6.9
Female	48(53.9)	
BMI		27.5±6.4
Disease duration, years		8.9±9.4
NRS pain		5.8±1.5
KOOS Symptom		49.5±16.4
KOOS Pain		51.3±14.5
Radiological scores		
Kellgren and Lawrence grade		3(2-3)
II	36(40.4)	
III	53(59.6)	
Ultrasound OMERACT Scores		
Synovitis grade		2(0-3)
0	4(4.5)	
I	18(20.2)	
II	33(37.1)	
III	34(38.2)	
Effusion (+)	53(59.6)	
Synovial Hypertrophy (+)	42(47.2)	
PD (+)	42(47.2)	
Cartilage grade		2(0-3)
0	4(4.5)	
I	21(23.6)	
II	41(46.1)	
III	23(25.8)	
Osteophyte grade		2(1-3)
0	0	
I	11(12.4)	
II	41(46.1)	
III	37(41.6)	
Meniscal Extrusion grade		2(1-2)
0	0	
I	23(25.8)	
II	66(4.2)	
MRI MOAKS Scores		
Effusion-synovitis grade		2(0-3)
0	6(6.7)	
I	24(27)	
II	26(29.2)	
III	33(37.1)	
Hoffa's synovitis grade		1(0-3)
0	5(5.6)	
I	40(44.9)	
II	32(36)	
III	12(13.5)	
Cartilage Any Loss grade		3(2-3)
0	0	

I	0	
II	12(13.5)	
III	77(86.5)	
Cartilage Full Loss grade		2(0-3)
0	2(2.2)	
I	15(16.9)	
II	37(41.6)	
III	35(39.3)	
Osteophyte grade		3(1-3)
0	0	
I	1(1.1)	
II	8(9)	
III	80(89.9)	
Meniscal Extrusion grade		3(0-3)
0	3(3.4)	
I	10(11.2)	
II	31(34.8)	
III	45(50.6)	

KOOS= Knee Injury and Osteoarthritis Outcome Score; MRI= Magnetic Resonance Imaging; MOAKS= MRI Osteoarthritis Knee Score; NRS =Numerical Rating Scale; OMERACT= Outcome Measure in Rheumatology; PD= Power Doppler

5.5.2. Reliability for ultrasound scores

The kappa statistics for inter-rater reliability ranged from 0.55 to 0.88 indicating moderate to excellent agreement and the kappa statistics for intra-rater reliability ranged from 0.63 to 1.00 indicating good to excellent reliability (**Table 5.2**).

Table 5.2. Intra-rater and inter-rater reliability of OMERACT ultrasound scores in knee OA

Ultrasound pathologies	Intra-rater reliability (Kappa/ Weighted Kappa)	Percent agreement	Inter-rater reliability	Percent agreement
Synovitis (Supra-patella)	0.81(0.58 to 1.00)#	80	0.55 (0.36 to 0.75)	55
Synovitis (Medial parapatella)	0.63(0.22 to 1.00)#	70		
Synovitis (Lateral Parapatella)	0.75(0.43 to 1.00)#	80		
Effusion	1.00	100		
Synovial hypertrophy	0.80(0.44,1.00)	90		
PD (Supra-patella)	0.80(0.44,1.00)	90	0.62(0.15 to 0.87)	90
Med Osteophyte grade	0.67(0.32 to 1.00)#	80	0.88(0.72to 1.00)	90
Lateral osteophyte grade	0.74(0.40 to 1.00)#	80		
Medial Meniscal Extrusion grade	0.74(0.26 to 1.00)#	90	0.55(0.25 to 0.84)	70
Medial Cartilage grade	0.64(0.04 to 1.00)#	70		
Lateral cartilage grade	0.7540.51 to 0.99)#	70		

# indicates weighted kappa; OA=Osteoarthritis

5.5.3. Reliability for MOAKS score

The kappa statistics for the inter-rater reliability ranged from 0.42 to 0.90 indicating moderate to excellent agreement for individual MRI lesions while intra-rater reliability was mostly good to excellent as shown by kappa statistics ranging from 0.62 to 0.92 (**Appendix 4, supplementary file 3**).

5.5.4. Association of ultrasound findings with clinical symptoms

After adjusting for the confounders, only OMERACT scores of synovial hypertrophy, PD signals and meniscal extrusion scores were significantly associated with pain severity on NRS (Table 3). For example, when power Doppler was present (0-1), the pain NRS increased by 0.54 units (Beta coefficient 0.54, 95% CI [0.11, 0.96]).

All OMERACT scores except for cartilage grade demonstrated significant associations with KOOS other symptoms (**Table 5.3**). For example, when PD signals were present (0-1), the KOOS other symptoms score decreased (worsened) by 6.1 units (Beta coefficient -6.12, 95% CI [-10.93, -1.31]). Only meniscal extrusion and PD signals were significantly associated with KOOS pain (Table 3). For example, for a one unit increase on meniscal extrusion grade (0 to 2 on a semi-quantitative score), knee pain on the KOOS score decreased (worsened) by 10.8 units (Beta coefficient -10.84, 95% CI [-18.57, -3.10]).

Table 5.3. The association of OMERACT ultrasound KOA scores with NRS pain, KOOS symptoms and KOOS pain

Ultrasound pathologies	Grading score	Unadjusted Beta (95% CI)	Adjusted Beta (95% CI)	Unadjusted Beta (95% CI)	Adjusted Beta (95% CI)	Unadjusted Beta (95% CI)	Adjusted Beta (95% CI)
		NRS		KOOS Symptoms		KOOS pain	
Synovitis	0-3	0.06 (-0.30,0.41)	0.23 (-0.17,0.62)	-1.22 (-2.66,0.22)	**-7.00 (-11.09,-2.90)**	-1.12 (-4.64,2.40)	-3.00 (-6.85,0.87)
Synovial hypertrophy	0-1	0.49 (-0.12,1.10)	**0.92 (0.25,1.58)**	-4.47 (-11.39,2.44)	**-10.81 (-18.10,-3.51)**	-0.29 (-1.37,0.79)	-6.82 (-13.53,-0.12)
Effusion	0-1	0.16 (-0.47,0.78)	0.50 (-0.23,1.23)	-4.19 (-11.23,2.85)	**-10.74 (-18.54,-2.94)**	-1.84 (-8.08,4.40)	-5.29 (-12.49,1.90)
Power Doppler	0-1	**0.54 (0.11,0.96)**	**0.73 (0.11,1.35)**	**-6.12 (-10.93,-1.31)**	**-12.66 (-19.20,-6.12)**	**-4.73 (-9.01,-0.45)**	**-8.39 (-14.47,-2.30)**
Meniscal extrusion	0-2	**0.71 (0.02,1.40)**	**1.01 (0.22,1.80)**	-5.42 (-13.29,2.46)	**-9.88 (-18.60,-1.10)**	**-8.11 (-14.90,-1.31)**	**-10.84 (-18.57,-3.10)**
Osteophyte	0-3	0.21 (-0.25,0.67)	0.25 (-0.28,0.77)	**-6.46 (-11.45,-1.48)**	**-7.79 (-13.35,-2.24)**	-3.58 (-8.07,0.91)	-0.28 (-7.96,2.37)
Cartilage thickness	0-3	-0.11 (-0.48,0.27)	-0.22 (-0.61,0.18)	2.30 (-1.93,6.53)	2.27 (-2.11,6.64)	3.10 (-0.59,6.80)	3.52 (-0.35,7.38)

CI=Confidence Interval; KOA= Knee Osteoarthritis; KOOS= Knee Injury and Osteoarthritis Outcome Score; NRS =Numerical Rating Scale; OMERACT= Outcome Measure in Rheumatology; PD= Power Doppler

Significant results with p value <0.05 are denoted in bold. Adjustment included age, gender, BMI, duration of disease and radiographic Kellgren and Lawrence grade

5.5.5. Association of ultrasound findings with radiographic KLG

The ultrasonographic synovitis, synovial hypertrophy, effusion, osteophyte and meniscal extrusion were significantly correlated with KLG except for PD signals and cartilage scores (**Figure 5.1, and Appendix 4, supplementary file 4**).

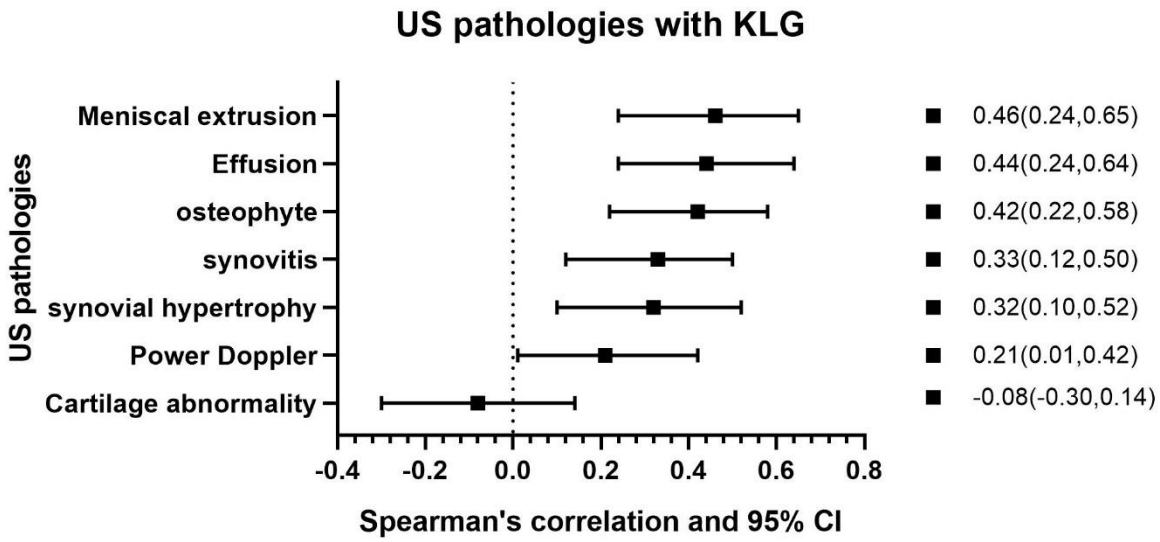

Figure 5.1. The association of OMERACT ultrasound OA scores with KLG on the radiograph

5.5.6. Association of ultrasound findings with MOAKS scores

The associations between ultrasound features and their MRI counterparts are presented in **figure 5.2, and Appendix 4, supplementary file 5.** Synovitis, synovial hypertrophy, effusion, PD signals, osteophyte and meniscal extrusion on ultrasound were significantly associated with their respective MRI counterparts with the largest correlation for ultrasound synovitis (**Figure 5.3**). Measures of osteophytes and meniscal extrusion showed significant associations between the two imaging modalities while ultrasound cartilage thickness showed a significant but weak relationship with MRI cartilage thickness (any or full) on MRI.

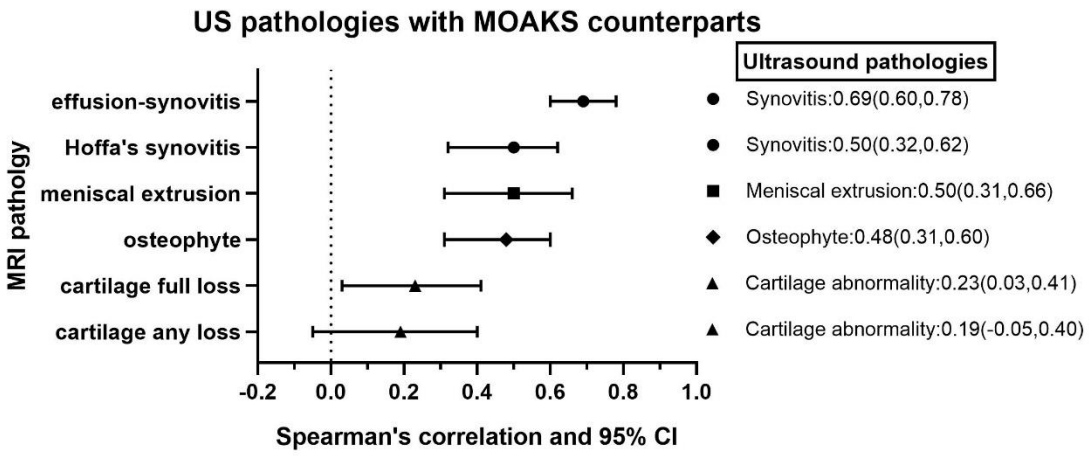

Figure 5.2. The association of OMERACT ultrasound OA scores with MOAKS on magnetic resonance imaging

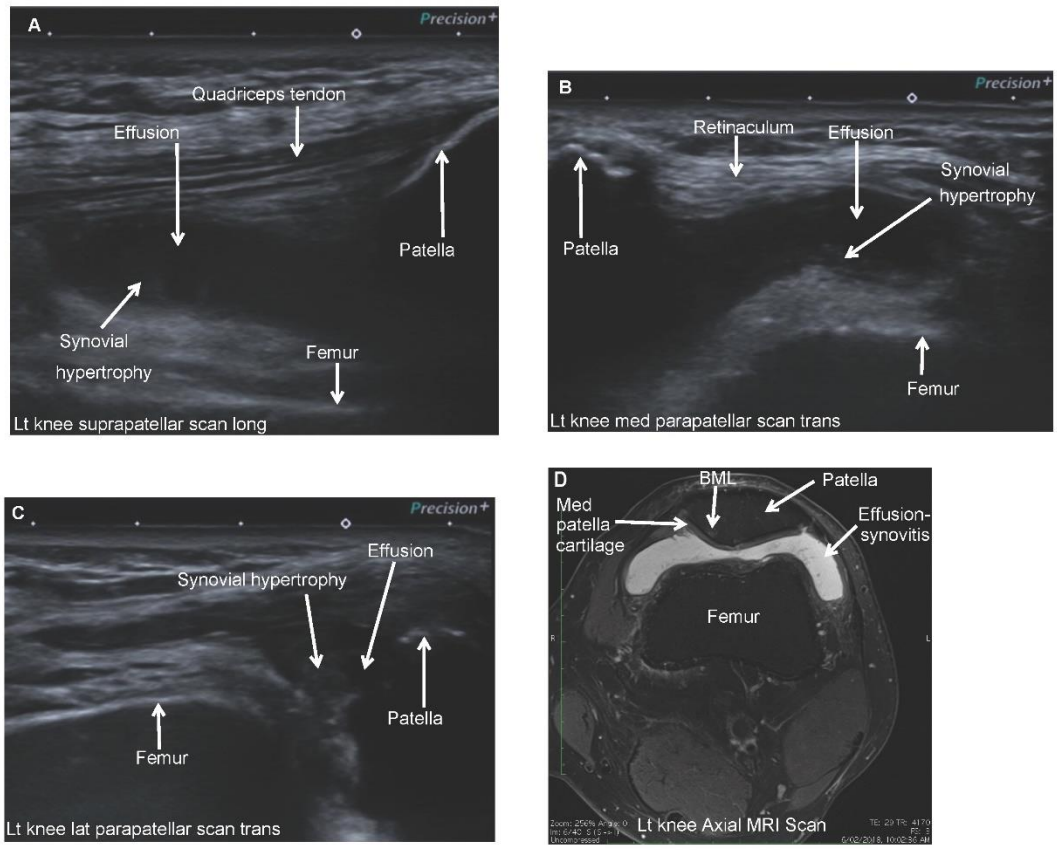

Figure 5.4. **The demonstration of ultrasound and MRI synovitis from three synovial recesses of the knee in the same patient**. **A.** OMERACT Grade 3 synovitis at the suprapatellar recess on a longitudinal scan. **B.** OMERACT Grade 3 synovitis at the medial parapatellar recess on a transverse scan **C.** OMERACT Grade 3 synovitis at the lateral parapatellar recess on a transverse scan **D.** MOAKS grade 3 effusion-synovitis on the axial non-contrast-enhanced MRI scan

5.6. Discussion

This is the first study examining the associations of OMERACT knee ultrasound scores against pain severity and other symptoms using well-validated self-reported questionnaires, and standard imaging tools widely used in the OA clinical and research setting. We found significant associations of ultrasound scores such as PD signal, synovial hypertrophy and meniscal extrusion with NRS pain and KOOS pain sub-score as well as KOOS symptoms. Significant associations with

radiographic severity were detected in all ultrasound pathologies except for PD signals and cartilage grades, with meniscal extrusion showing the highest associations. Ultrasound synovial and structural disorders had significant associations with their MRI counterparts with moderate to strong correlation for synovitis, synovial hypertrophy, PD signals, meniscal extrusion and osteophyte. Thus, our findings further support the use of the OMERACT ultrasound scores in the knee OA research setting. The OMERACT scanning protocol involved scanning over a wide area as well as multiple sites instead of a single predefined location. This can increase the chance of detecting more pathologies, if present, compared to a single predefined scan, due to the capability of scanning the entire joint. In addition, the maximum score of a certain ultrasound pathology from different scanning sites was used as a single final score in our study instead of adding them because the semi-quantitative score is an ordinal and not an interval scale [235]. This method is commonly used in MRI research [29, 236]. It might provide better coverage of pathologies present in the whole knee compared to single location-specific score. As an example, out of 16 patients with grade 0 synovitis in supra-patella recess in our study, 8 people demonstrated ≥ grade 1 synovitis in medial parapatellar recess. This is also supported by the fact that the prevalence of MRI effusion-synovitis which takes into account synovitis in all synovial recesses on axial MRI scan is almost the same in our study (93.3%).

5.6.1. Reliability of ultrasound scores

The reliability was done in medial compartment because our study participants had predominant medial OA. On comparison with OMERACT reliability exercises which reported moderate to good agreement across two rounds (kappa= 0.52 and 0.51 for synovitis, kappa=0.54 and 0.58 for meniscal extrusion, and kappa=57 and 0.62 for osteophyte), our results were comparable for synovitis (kappa=0.55) and meniscal extrusion (kappa=0.55) while we have better agreement for osteophyte (kappa=0.88). In addition, in this study, we have recruited the sonographer to perform and score the ultrasound scan independently in 20 patients (only 22% of the whole study sample). In order to get away from the conception of operator-dependency in ultrasound, it would be helpful in future

studies to also have an uninvolved reader assess the US images and determine the agreement between those two US readers, which could support the lack of operator-dependency.

5.6.2. Association of ultrasound synovitis grade with clinical and other imaging score

The prevalence of synovitis, when assessed using the OMERACT atlas maximum score approach [42], is high (more than 95%). However, for synovial hypertrophy and effusion which used the strict criteria of 4mm cut-offs (for which there is no published atlas), the prevalence of these synovial disorders reduces to about 50%, in agreement with a meta-analysis report in knee OA {49% (95% CI 30.5,67.6)} [48]. This may indicate that OMERACT atlas for grade 1 synovitis might include people with normal physiological fluid which can be up to 3mm thick as the semi-quantitative grading score is visually based on the amount of distension of knee recesses using the standardized atlas [142].

The association of synovial pathologies with pain and symptoms did not show consistent results in the literature. Some authors reported significant associations [150, 237-239] while others determined no association [176, 240-242]. This may be due to using different cut-offs (4mm in vs 2mm for synovial hypertrophy), different grading methods (semi-quantitative or qualitative), and application of varying case-definitions and inclusion of different disease severity in the study protocols. The utilisation of standardized OMERACT ultrasound knee score in future studies will help minimise heterogeneity of such scanning protocols and grading methods. Our study using the OMERACT synovitis atlas and quantitative cut-off (4 mm) for synovial hypertrophy demonstrated significant correlation.

Ultrasound synovitis is strongly correlated with MRI effusion-synovitis. This finding further supports the symptom-structure discordance widely recognized in the OA imaging literature [243]. This is due to the fact that pain is a very subjective phenomenon [244], and psychosocial factors and neurobiological mechanism such as pain sensitization [245] can influence the association. Although synovial hypertrophy has significant correlations with NRS pain, KOOS symptoms and KOOS pain,

it had only a moderate correlation with MRI synovitis. As a note, MRI is not contrast-enhanced in our study and so not optimal for detecting the synovial hypertrophy [246], thereby placing MRI at a disadvantage on the level of association. Our magnitude of association is consistent with the report by two studies [150, 247] although they utilized different ultrasound scanning methods and grading definitions (different quantitative cut-offs for semi-quantitative scores) for both MRI and ultrasound scores.

5.6.3. Association of ultrasound power Doppler grade with clinical and other imaging scores

Only PD signals and meniscal extrusion are important predictors for NRS pain. This finding is reinforced by the significant associations of these ultrasound pathologies with KOOS pain, a different composite measure of pain characteristics involving pain frequency and amount of pain during specific activities. Although PD signals had been a focus of interest in rheumatoid arthritis [248], there is a paucity of publications which reported the isolated association of PD signals with pain severity due to very low prevalence of PD observations in the studies [176, 238, 249] or because the extent of association was based on total inflammatory score combining synovitis and PD signals [49, 140] or the scanning protocol did not include evaluation of PD signals. Iagnocco *et al* [249] observe PD signals in only one patient in their sample (n=17) while Hall *et al* obtain 10 observations in 62 patients with symptomatic knee OA [176], leading to lack of power to detect any significant associations. Song *et al* reported that PD signals revealed the significant association of PD signals with pain (r=0.37,p=0.02) [150], which is confirmed by our study.

As expected, PD is not a significant predictor of KL grade perhaps due to the fact that PD is a sensitive and reliable marker only for acute and active inflammatory phase of arthritis [35, 250]. However, knee OA is recognized as off-and-on disease with exacerbation and remission [244] while KLG reflects the collective structural outcome accumulated over long-term disease process and focused on change in the bone [251, 252].

5.6.4. Association of ultrasound meniscal extrusion grade with clinical and other imaging scores

Discordant results were reported for the association of meniscal extrusion with pain; some with significant results [240, 253] and other with negative results [154, 239, 254]. Chan *et al* [240] reported that medial meniscal extrusion measured in mm showed significant association with extent of pain during stair-climbing while the degree of meniscal extrusion was significantly increased in painful knee OA compared with painless knee [253]. On the other hand, significant association was not detected between presence of meniscal extrusion (cut-off >3mm) with pain severity in a case-control design [154, 254]. In a recent study, Kijima *et al* reported that meniscal extrusion >4.3mm cut-off provided high sensitivity (85%) and specificity (85%) for presence of knee pain in the general population[255]. In MRI studies, meniscal extrusion plays a crucial role in OA pathogenesis, progression and symptom genesis [256, 257].

The meniscal extrusion showed the strongest association with KLG perhaps due to the fact that our sample was limited only to KLG 2 and 3 the difference of which is only joint space narrowing (JSN). Hunter *et al* reported that the meniscus accounts for a substantial proportion of the variance explained in JSN [258].

5.6.5. Association of ultrasound cartilage grade with clinical and other imaging scores

Unexpectedly, cartilage grade did not reveal a significant association with KLG. Several reasons might contribute to this: 1) the location where cartilage ultrasound measures were taken might not exactly represent the actual maximal weight-bearing area on standing and 2) cartilage thinning might be on the tibial cartilage which is inaccessible to ultrasound. However, further analysis after dichotomising the cartilage (cartilage thinning present or not by combining grade 0 and 1, and grade 2 and 3 respectively) is non-significant. The authors of the OMERACT ultrasound OA atlas discussed that ultrasound cartilage grade needs further research due to assessment problems [42]. Ultrasound cartilage grade also failed to show a significant association with all other outcome measures except

for MRI cartilage loss which revealed a significant but weak association. In the MRI literature, the associations between cartilage abnormalities and symptoms are not consistent [259, 260].

While it is important to standardize outcome tools in clinical trials, and this study does provide the usefulness of OMERACT ultrasound knee OA protocol as a scoring system, the utility of this US scoring tool for a meaningful clinical practice needs further research for several reasons. Cartilage loss correlated with nothing but MRI, PD did correlate with NRS pain, but as yet, anti-synovial/ anti-inflammatory therapies haven't been very promising in knee OA, and baseline inflammation hasn't consistently been shown to predict response to anti-inflammatory/anti synovial therapies [10, 11]

5.6.6. Limitations of the study

We did not include psychosocial factors which can have an impact on the level of symptom-structure association. However, the important known confounders are adjusted in our analysis. Another limitation is that the anatomical site of ultrasound scoring might take place in a different location from measurements on an MRI in the absence of invasive marker as in the cartilage and osteophyte scores. Similarly, the x-rays were obtained in weight-bearing position while the ultrasound and MRI were obtained with a person lying supine. The last limitation is that the study relies mainly on results of linear regression and correlation analyses. Therefore, the lack of correlation between variables may not necessarily represent a lack of a relationship as some relationships may be non-linear.

5.7. Conclusion

In conclusion, most of OMERACT ultrasound OA scores had a significant but modest association with symptoms and imaging scores from radiographs and MRI. These results support the construct validity of the OMERACT ultrasound scores and their use in future ultrasound studies as a

useful outcome. As this is a cross-sectional study, longitudinal studies are required to determine its responsiveness to change to further determine its value as an outcome measure in interventional studies.

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Conflict of Interest: DJH provides consulting services to Pfizer, Lilly, Merck Serono, TLC bio. Other authors declared no conflict of interest.

Data Availability: Data are available from the corresponding author on reasonable request.

Author contributions

WMO, DJH and JML conceived and designed the study. WMO, DJH, JML, KLB, DP and SY contributed to acquisition of clinical data of this study. WMO had full access to all the data and analysis and drafted the first manuscript. All authors revised the manuscript and gave final approval of the article for submission.

CHAPTER SIX

This chapter includes the following submitted paper:

Oo W.M., Linklater J., Bennell K.L., Yu S., Wang X., Duong V., and Hunter D.J, Superb Microvascular Imaging in low-grade inflammation of knee osteoarthritis compared with power Doppler: Clinical, radiographic and MRI relationship. Ultrasound in Medicine and Biology. 2020 Mar;46(3):566-574.

Chapter 6

Superb Microvascular Imaging in low-grade inflammation of knee osteoarthritis compared with power Doppler: Clinical, radiographic and MRI relationship

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Statement from co-authors confirming authorship contribution of the PhD candidate

The co-authors of the paper: "Superb Microvascular Imaging in low-grade inflammation of knee osteoarthritis compared with power Doppler: Clinical, radiographic and MRI relationship", confirm that Win Min Oo has made the following contributions:

1. Conception and design of the research
2. Analysis and interpretation of the findings
3. Writing of the manuscript and critical appraisal of the content

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Win Min Oo Date: 15th August 2019

As supervisor for the candidature upon which this Thesis is based, I can confirm that the authorship attribution statements above are correct.

David Hunter Date: 15th August 2019

Chapter Six: Superb Microvascular Imaging in low-grade inflammation of knee osteoarthritis compared with power Doppler: Clinical, radiographic and MRI relationship

6.1. Abstract

We compared assessment of active synovitis in knee osteoarthritis (OA) by utilising Superb Microvascular Imaging (SMI) and conventional power Doppler (cPD) and correlate with symptoms, radiographic features, and magnetic resonance imaging (MRI)-detected synovitis. A subgroup of participants with symptomatic knee OA underwent dynamic ultrasound assessment for semi-quantitative scores for SMI and cPD in the suprapatellar, medial and lateral parapatellar knee recesses. Knee pain and other symptoms were evaluated with Knee Injury and Osteoarthritis Outcome Score (KOOS). OA severity was assessed using the Kellgren and Lawrence grade (KLG) on radiograph and effusion-synovitis and Hoffa's synovitis score of MRI Osteoarthritis Knee Score (MOAKS) on non-contrast-enhanced MRI sequences. Chi-square test and kappa statistics were conducted to compare detectability of SMI and cPD for low-grade inflammation, and Spearman's correlation and Fisher's r to z transformation to compare correlations of both techniques with symptoms and imaging severity. Eighty-nine participants were included in analyses. SMI increased detection rate by 25.5% for grade 0 cPD, by 35.4% for grade 1 cPD and by 9% for grade 2 cPD. SMI showed significant correlations with KOOS symptoms, KLG, MRI effusion-synovitis and Hoffa's synovitis scores {r=-0.24(-0.45,-0.01), r=0.31(0.10,0.50), r=0.49(0.33,0.63) and r=0.54(0.37,0.68). cPD was significantly correlated with KOOS pain, other symptoms, MRI effusion-synovitis and Hoffa's synovitis {r=-0.23(-0.44,-0.01), r=-0.29(-0.49,-0.06), r=0.46(0.28,61), r=0.46(0.25,0.63}. However, no significant differences were detected in their extent of correlations. SMI can detect low-grade inflammation implicated in OA disease better than cPD and reveal a significant correlation with symptoms, radiographic features and MRI synovitis. The added clinical value of SMI over cPD is still not clear.

Keywords: Ultrasound; Osteoarthritis; Power Doppler; SMI; Inflammation

6.2. Introduction

Osteoarthritis (OA) is one of most prevalent joint diseases, leading to severe disability and economic burden globally. In spite of being assumed to be a degenerative disease of cartilage, recent evidence indicates that it is a complex, multi-factorial disease with multiple tissue alterations within the whole joint [1]. An emerging and important research interest has been the implication of synovial inflammation (i.e. synovitis) in the pathogenesis and progression of OA disease process over the last decade [13].

Musculoskeletal ultrasound is a safe, non-invasive imaging modality which can assess the elements of synovitis of the joints using sound waves [32]. On a basic ultrasound machine, the B mode and power Doppler mode are used to detect grey scale pathologies and slow blood flow of inflammatory process. The conventional power Doppler (cPD) can detect slow blood flow rates and small vessels in the region of interest [35, 261], so it is often used to visualise the site of active synovitis which represented by the angiogenesis and increased blood flow in the synovium tissue [262]. cPD was demonstrated to be reliable in the detection of the vascularity of histologic synovial inflammation of knee arthritis in a mixed sample of rheumatoid arthritis (RA) and OA patients [149].

However, cPD technology has many limitations. The ability of Doppler, especially power or color Doppler imaging, depends on settings and optimization. In addition, its slow flow detection may be impaired by the noise sources of PD images such as thermal noises and clutter [263]. Slow moving signals could appear as flash artifacts. Flow in small vessels may be problematic because flow is slow and noise.

Koski *et al.* determined that a negative cPD finding in the synovium could not exclude the presence of synovitis seen on histopathological specimens in patients with inflammatory arthritis (r= = 0.239, non-significant) [226]. Osteoarthritis is believed to involve chronic low-grade patchy inflammation unlike the high-grade diffuse synovitis of

rheumatoid arthritis, the prototypical inflammatory arthritis [10, 149]. However, several studies reported that cPD signal is not very common in OA populations [23, 176] which might be due to low-grade inflammation which cPD cannot pick up [226]. Several studies have highlighted the crucial role of such low-grade inflammation in the disease pathogenesis, being a risk-factor for developing radiographic OA [57] as well as imaging markers for structural progression of OA [13].

Superb Microvascular Imaging (SMI) is an innovative Doppler technology specifically designed for detecting low-velocity blood flow states [45] as it can utilise a specialised algorithm with a novel wall filter to distinguish true very slow blood flow from clutter artefacts traditionally experienced in cPD signal [264, 265]. The advantages include the effective separation of flow signals from overlying tissue motion artifacts, preserving subtle low-flow components, high resolution of the image, minimal motion artefact and high frame rates [266]. SMI is superior to cPD in detecting synovial vessel signals in inflammatory arthritis conditions such as RA [46, 267], and well associated with clinical outcomes such as disease activity score (DAS) 28-C-reactive protein [264].

Based on these preliminary data of SMI and importance of detection of low-grade inflammation in OA described above, we aimed to examine whether SMI can be used to detect low-grade inflammation of OA compared to cPD. The primary objectives of this study were (1) assessing the potential of SMI to detect inflammatory flow and compare it with cPD and (2) comparing these modalities to other symptom scoring schemes and modalities such as Knee Injury and Osteoarthritis Outcome Score (KOOS) pain and other symptoms subscores [268], Kellgren and Lawrence grade (KLG) [16] on plain radiograph and MRI Osteoarthritis Knee Score (MOAKS) effusion-synovitis and Hoffa's synovitis [29].

6.3. Materials and methods

6.3.1. Study design and selection criteria

We used a cross-sectional analysis using baseline data of a sub-sample from the Sydney, Australia site of the ongoing RESTORE (platelet-Rich plasma as a symptom- and disEaSe-modifying Treatment fOR knee ostEoarthritis) clinical trial. Selection criteria were the same as for the RESTORE study (Trial registration No: ACTRN12617000853347) [232]. Briefly, eligible subjects met the following inclusion criteria:

(i) aged>50 years;

(ii) knee pain on most days in the last month;

(iii) osteophytes on x-ray; and

(iv) A minimum pain score of 4 on an 11-point numeric rating scale (NRS) in the last week

The exclusion criteria included (i) Kellgren and Lawrence (KL) grade 1 or grade 4; (ii) predominant lateral tibiofemoral disease; (iii) inflammatory or systemic joint disease; (iv) history of neuropathic or crystalline arthropathy; (v) be unwilling to stop NSAID and other analgesic usage for knee pain, except for paracetamol for rescue pain relief, from 2 weeks prior to baseline assessment.

For those participants with bilaterally eligible knees, the most symptomatic knee was taken as the study knee. Data from those who attended for a baseline ultrasound examination between September 2017 and February 2019 were analysed.

Demographic data including age, gender, weight, height and duration of knee symptoms were recored as previously described [232]. Body mass index (BMI) was calculated using height and weight (kg/m^2).

This study was approved by the Northern Sydney Local Health Districts Human Research Ethics Committee (HREC/16/HAWKE/430). We received informed consent from each participant in the study.

6.3.2. Knee symptoms

KOOS pain and other symptoms scores were collected. KOOS is a knee-specific self-reported outcome measure with high test-retest reliability, internal consistency and face and content validity [269]. Likert responses range from None to Extreme, and scores are measured from 0 to 100, with lower scores denoting worse symptoms, function or quality of life.

(a) The KOOS Pain is scored from nine questions regarding knee pain frequency which occurred in the last week, and the amount of knee pain encountered during specific activities such as twisting, bending and walking.

(b) KOOS other symptoms is measured from seven questions for other symptoms experienced in the last week, such as swelling, restricted range of motion and mechanical symptoms.

6.3.3. Radiological assessment

Participants underwent bilateral weight-bearing postero-anterior radiography (Model R-20J, Shimadzu, Japan) before ultrasound and MRI examinations. Radiographs were independently assessed for KLG by a rheumatologist (SLY) who was unaware of clinical, ultrasound and MRI scores.

6.3.4. Ultrasound evaluation

At the baseline assessment, following the MRI scan, a physician operator {WMO, 6 years of musculoskeletal ultrasound experience and certified with RhMSUS (Musculoskeletal

Ultrasound in Rheumatology) by the American College of Rheumatology} who was blinded to clinical, radiograph and MRI findings, performed the dynamic ultrasound scan of the study knee with a multi-frequency linear transducer (using 10MHz with 14L5 MHz probe) of Aplio Platinum 500 machine (Toshiba, Japan). To be able to detect synovial blood flow to the level just below random noise, SMI and cPD settings were optimized by an application specialist from Toshiba by adjusting color gain, pulse repetition frequency, wall filter and Doppler frequency (SMI parameters: color map=5, color frequency=SMI6, color gain=40%, PRF=11.6k, Filter=2; cPD parameters: color map=6, color frequency=6,color gain=40%, PRF=14.8k, filter=5) . The settings remained consistent for the duration of the study, the only settings changed were the depth and focus of the images.

During PDI and SMI evaluation, the transducer was placed lightly on the skin surface with the minimum pressure to prevent the collapse of blood vessels. Scanning gel should be visible in the image as a sign of light transducer pressure while excessive transducer pressure can be seen as abnormal compression of tissue planes and obliteration of blood vessels. Once maximum colour flow signals were found, the transducer was held in the same scan position to observe colour flow signals by the SMI technique in the background of synovial hypertrophy (abnormal hypoechoic intraarticular tissue that is non displaceable and poorly compressible). The colour grading 0-3 was used in PDUS and SMI image respectively : Grade 0: no color in the synovium; Grade 1: single color signals (up to 3) in the synovium; Grade 2: confluent color signals in less than half of the area of the synovium; Grade 3: more than 50% of the synovium covered by color signals [270]. The ultrasound scores were obtained for cPD and SMI from suprapatellar recess, medial and lateral para-patella recesses respectively according to standardized scanning protocol [42] (**Figure 6.1**) (**Appendix 5, supplementary file 1**). Then, the maximum score of three synovial recesses was used as the

score of the whole knee for the comparison with clinical and radiographic and MRI data of the study knee.

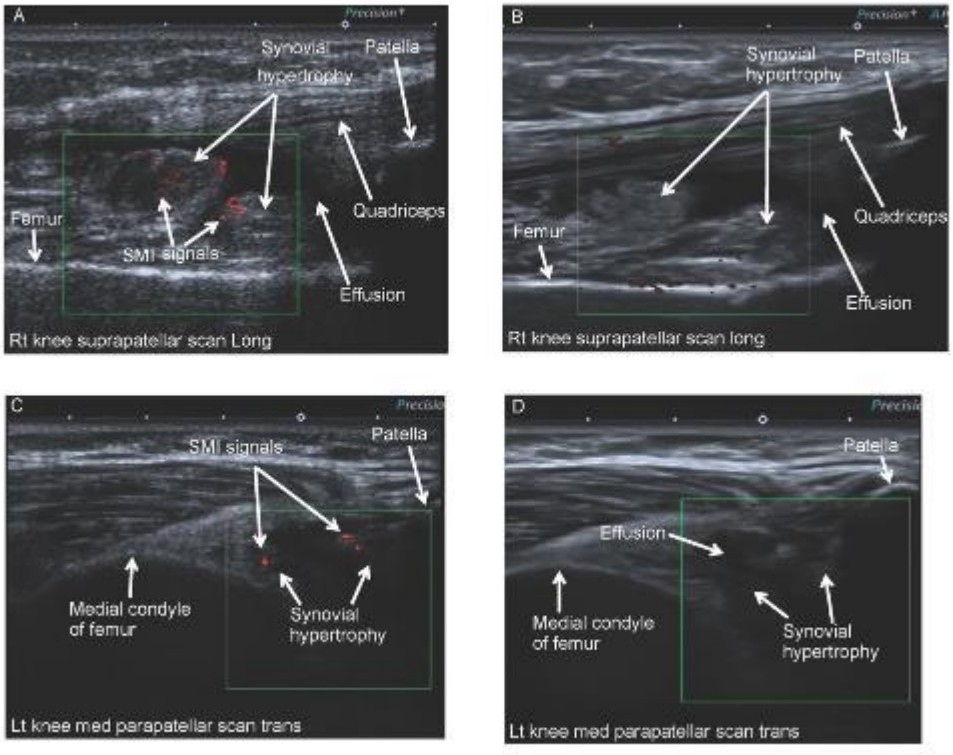

Figure 6.1. **The demonstration of SMI and cPD from three synovial recesses of the knee.** A and B come from the same patient, and C and D from the same patient. A. Grade 2 SMI signals at the suprapatellar recess on a longitudinal scan. B. Grade 0 cPD signals at the same site of suprapatellar recess C. Grade 1 SMI signals at the medial parapatellar recess on a transverse scan D. Grade 0 cPD signals at the same site of the medial parapatellar recess. Synovial hypertrophy (abnormal hypoechoic intraarticular tissue that is non displaceable and poorly compressible)

6.3.4.1. Intra-rater reliability

To evaluate intra-rater reliability, the same operator re-scanned 10 patients one week later and calculated the intra-rater reliability, being unaware of the previous scores. The kappa statistics ranged from 0.63 to 1.00 indicating good to excellent results (**Appendix 5, supplementary file 2**).

6.3.5. MRI evaluation

All of the participants underwent MRI scan on their index knee with a 3T whole-body magnetic resonance unit (Siemens Healthcare, Germany) and a 15-channel transmit/ receive knee coil. Two MRI sequences were used including a sagittal proton-density-weighted fat-suppressed non-contrast turbo spin-echo (TSE) and an axial proton-density-weighted fat-suppressed TSE. Technical details of sequences can be found in **Appendix 5, supplementary file 3**.

Knee effusion-synovitis and Hoffa's synovitis were assessed using validated semi-quantitative criteria, MOAKS [29]. Hoffa-synovitis is defined as the degree of hyperintense signal in Hoffa's fat pad on midsagittal fluid-sensitive sequences (0: normal, 1: mild, 2: moderate, 3: severe). Effusion-synovitis is the combination of effusion and synovitis defined as the hyperintense signal in the suprapatellar recess on fluid sensitive sequences (0: physiological amount; 1: small – fluid continuous with the retropatellar space; 2: medium – with slight convexity of the suprapatellar recess; 3: large evidence of capsular distension). The maximum score was then calculated for getting the whole knee score.

6.3.5.1. Inter-rater and intra-rater reliability of MRI

Scoring of MOAKS was performed by WMO who underwent training and calibration by an experienced musculoskeletal radiologist (JML, 25 years of experience in musculoskeletal MRI). Both readers independently scored the MRI images of ten consecutive

participants. The kappa statistics ranged from 0.42 to 0.90 indicating moderate to excellent agreement for individual MRI lesions (**Appendix 5, supplementary file 4**)). The readers were blinded to clinical features, symptoms, radiographic and ultrasound scores.

WMO also performed the second reading of all MRI images one month later, intra-rater reliability was good to excellent as shown by kappa statistics ranging from 0.52 to 0.91 ((**Appendix 5, supplementary file 4**)).

6.4. Statistics

Descriptive analysis of categorical data were described as frequencies and percentages while continuous variables were expressed as mean and standard deviation (SD). To investigate whether SMI can detect more vascular signals than cPD, the cross-tabulation and Chi-square test were conducted for the presence of SMI or cPD, and kappa statistics for semi-quantitative scores of both techniques. Spearman correlations were conducted to determine the association of SMI and cPD with symptoms, KLG and MOAKS synovitis scores, and the correlation coefficients of both techniques for symptoms and imaging findings were compared to investigate any significant difference. All statistics were analysed using SPSS version 23 and a p-value <0.05 denotes a significant association or correlation. The difference in correlations was calculated by Fisher's r to z transformation using Medcalc version 18.

6.5. Results

6.5.1. Demographic, clinical characteristics, ultrasound and MRI findings

The current study included 89 participants with 48 (53.9%) females, mean BMI of 27.5 ±6.4, and 59.6% of participants having a KLG of 3. Other detailed characteristics were demonstrated in **Table 6.1**.

Table 6.1. Baseline clinical, radiographic, ultrasound and MRI data of study participants

Population, N	89
Age, years, mean (SD)	61.5±6.9
Female, N (%)	48(53.9)
BMI, kg/m^2, mean (SD)	27.5±6.4
Disease duration, years, mean (SD)	8.9±9.4
KOOS Symptom, mean (SD)	49.5±16.4
KOOS Pain, mean (SD)	51.3±14.5
Radiological scores	
Kellgren and Lawrence grade, N (%)	
II	36(40.4)
III	53(59.6)
Ultrasound OMERACT Scores (Maximum score of the whole knee)	
PD grade, N (%)	
0	47(52.8)
I	31(34.8)
II	11(12.4)
III	0
SMI grade, N (%)	
0	36(40.4)
I	31(34.8)
II	21(23.6)
III	1(1.1)
MRI MOAKS Scores (Maximum score of the whole knee)	
Effusion-synovitis grade, N (%)	
0	6(6.7)
I	24(27)
II	26(29.2)
III	33(37.1)

Hoffa synovitis grade, N (%)	
0	5(5.6)
I	40(44.9)
II	32(36)
III	12(13.5)

BMI = Body mass index; KOOS= Knee Injury and Osteoarthritis Outcome Score; MRI= Magnetic Resonance Imaging; MOAKS= MRI Osteoarthritis Knee Score; OMERACT= Outcome Measure in Rheumatology; cPD= Conventional Power Doppler; SMI= Superb Micro-vascular Imaging

6.5.2. Comparison of the grades by SMI and cPD

Forty-one knee joints revealed blood flow signals with both cPD and SMI while either technique detected no flow signal in 35 cases. Flow signals were detected only with SMI in 12 joints but not with cPD while vascularity was found only with cPD in one joint but not with SMI. These data are summarised in **Table 6.2**. SMI could visualize the presence of synovial flow signals in a significantly greater number of joints compared with cPD (60% vs. 47%, $P < 0.001$).

Table 6.2. Comparison of presence of SMI and cPD

	SMI grade -	**SMI grade +**	**Total**
PD grade -	35	12	47
PD grade +	1	41	42
Total	36	53	89

cPD= Conventional Power Doppler; SMI= Superb Micro-vascular Imaging

Chi Square value, 47.85 and P-value<0.001

Table 6.3 demonstrates the comparison of the semi-quantitative grades (0-3) of flow signals detected by both techniques. Using SMI, 25.5 % of the cPD flow signals raised grade 0 to 1, while 35.4% increased from grade 1 to 2 and 9% from grade 2 to 3. In addition, one joint determined as Grade 1 using cPD was determined as 0 using SMI. SMI visualize more signals than cPD when using semi-quantitative score (Kappa Statistic: 0.56 (95% CI: 0.41, 0.71). There were significant linear associations between cPD and SMI (Spearman's r= 0.82, 95% CI 0.74,0.89), demonstrating that one consistently scores higher than the other.

Table 6.3. Comparison of semi-quantitative grades of SMI and cPD

	SMI grade 0	**SMI grade 1**	**SMI grade 2**	**SMI grade 3**	**Total**
PD grade 0	35	12	0	0	47
PD grade 1	1	19	11	0	31
PD grade 2	0	0	10	1	11
PD grade 3	0	0	0	0	0
Total	36	31	21	1	89

cPD= Conventional Power Doppler; SMI= Superb Microvascular Imaging

Chi Square value, 80.91 and P-value<0.001

6.5.3. Spearman's correlation of SMI and cPD with symptoms and imaging scores

Except for KOOS pain, SMI showed significant (weak to moderate) correlation with KOOS symptoms, KLG, MRI effusion-synovitis and MRI Hoffa's synovitis scores. The strongest correlation was between SMI and MRI Hoffa's synovitis (r=0.54; 95% CI 0.37,0.68) while cPD is significantly correlated with other scores except for KLG (**Figure 2**).

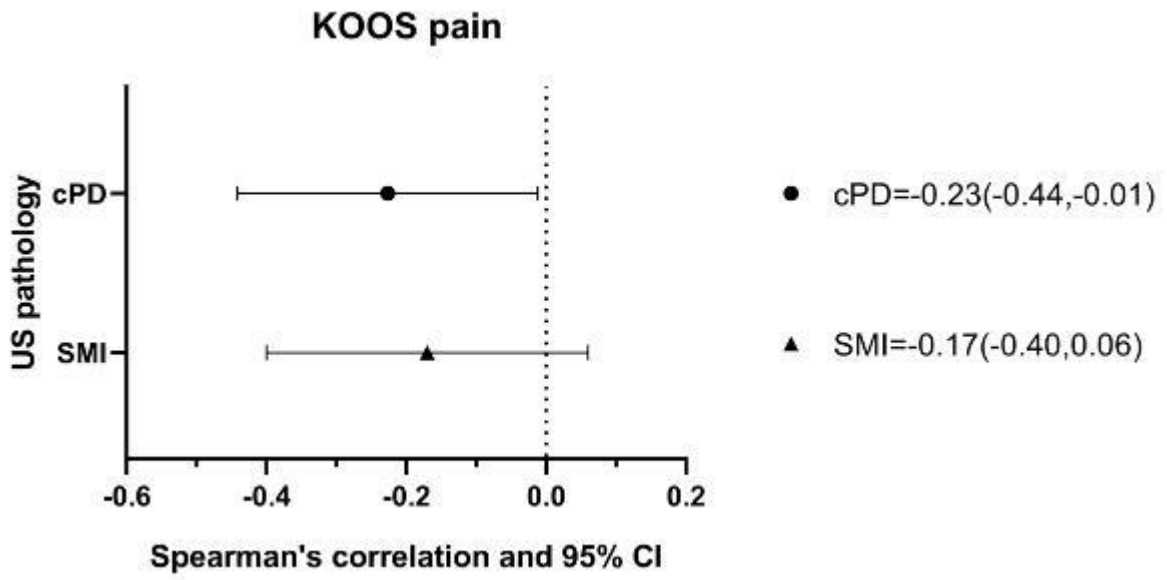

Figure 6.2A. The association of SMI and cPD scores with KOOS pain

CI=Confidence interval; cPD=Conventional power Doppler; KOOS = Knee Injury and Osteoarthritis Outcome Score; SMI= Superb Microvascular imaging,

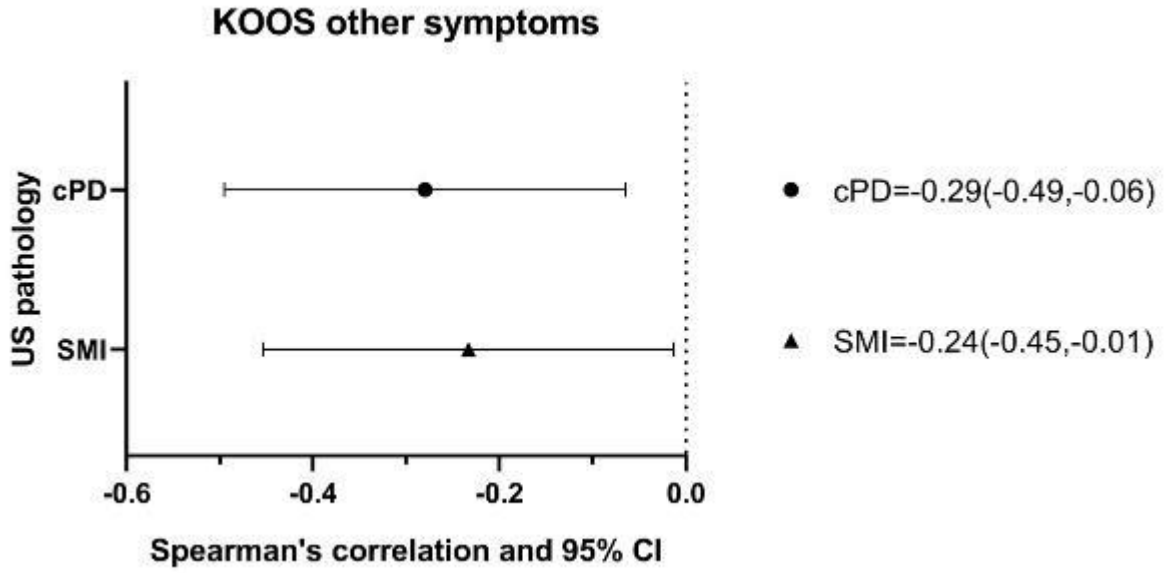

Figure 6.2B. The association of SMI and cPD scores with KOOS other symptoms

CI=Confidence interval; cPD=Conventional power Doppler; KOOS= Knee Injury and Osteoarthritis Outcome Score; SMI= Superb Microvascular imaging

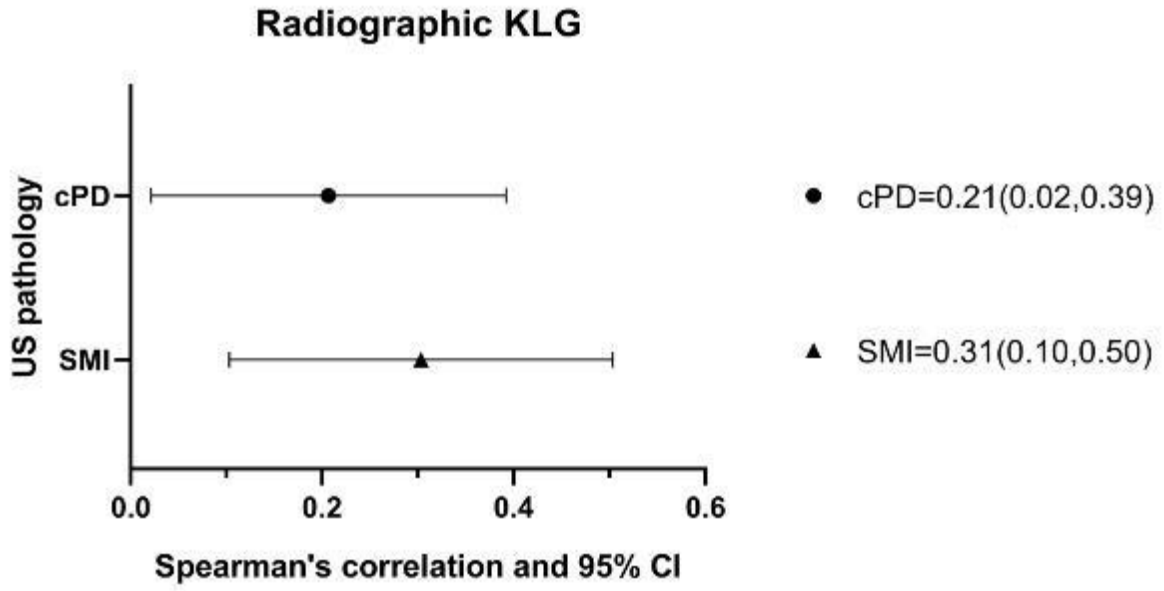

Figure 6.2C. The association of SMI and cPD scores with KLG on the radiograph

CI=Confidence interval; cPD=Conventional power Doppler; KLG= Kellgren and Lawrence grade; SMI= Superb Microvascular imaging

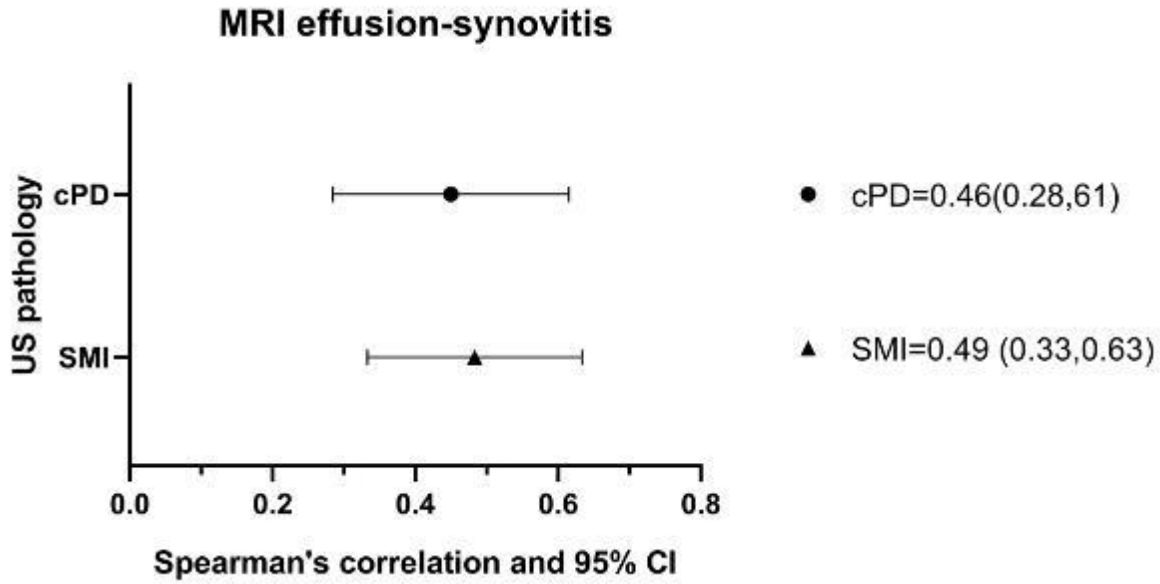

Figure 6.2D. The association of SMI and cPD scores with MRI effusion-synovitis

CI=Confidence interval; cPD=Conventional power Doppler; MRI= Magnetic Resonance Imaging; SMI= Superb Microvascular imaging

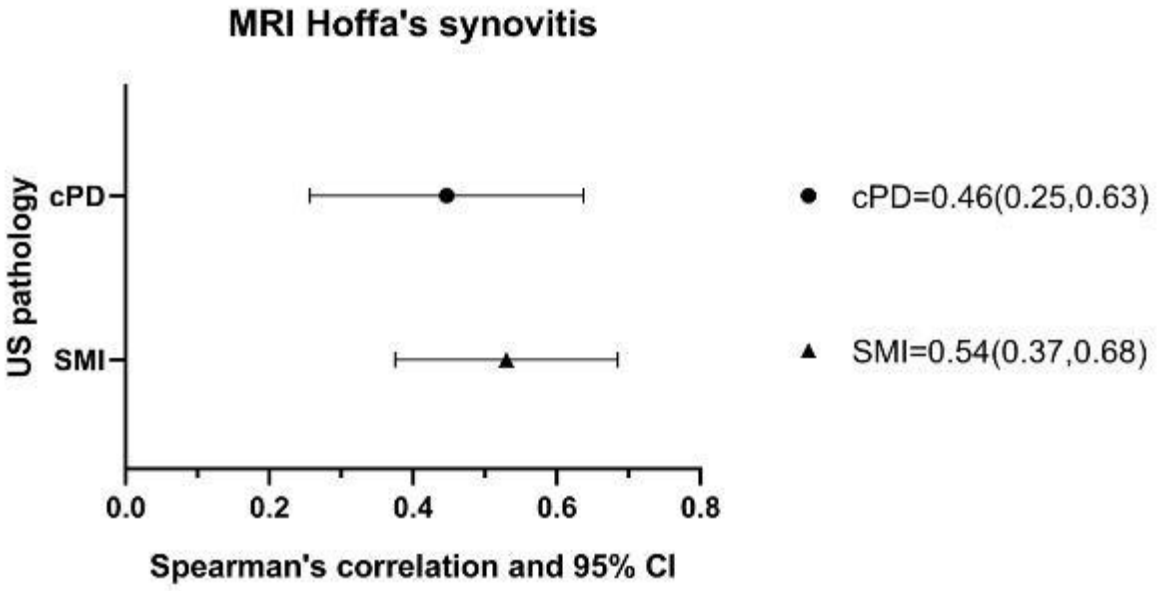

Figure 6.2E. The association of SMI and cPD scores with Hoffa's synovitis on MRI

CI=Confidence interval; cPD=Conventional power Doppler; MRI= Magnetic Resonance Imaging; SMI= Superb Microvascular imaging

When comparing these correlation coefficients of SMI and cPD, a weaker correlation was found between SMI and symptoms, and a stronger correlation was found between SMI and imaging measures. However, no significant differences in the extent of correlation were detected (**Table 4**).

Table 6.4. Spearman's correlation of SMI and cPD with KOOS pain and symptoms sub scores, radiographic KL grading and MRI effusion-synovitis and Hoffa's synovitis scores (Whole knee)

Spearman's correlation	SMI	cPD	Comparison of correlation
KOOS Symptoms	-0.24(-0.45,-0.01) **P=0.02**	-0.29(-0.49,-0.06) **P=0.01**	Z statistics=0.35 P=0.72
KOOS Pain	-0.17(-0.40,0.06) P=0.11	-0.23(-0.44,-0.01) **P=0.03**	Z statistics=0.41 P=0.68
KL Grade	0.31(0.10,0.50) **P=0.004**	0.21(0.02,0.39) P=0.05	Z statistics=0.70 P=0.48
MRI effusion-synovitis	0.49 (0.33,0.63) **P<0.001**	0.46(0.28,61) **P<0.001**	Z statistics=0.25 P=0.80
MRI Hoffa's synovitis	0.54(0.37,0.68) **P<0.001**	0.46(0.25,0.63) **P<0.001**	Z statistics=0.70 P=0.48

CI= Confidence Interval; KL =Kellgren-Lawrence grade; KOOS= Knee Injury and Osteoarthritis Outcome Score; MRI= Magnetic Resonance Imaging; cPD= Conventional Power Doppler; SMI= Superb Microvascular Imaging

6.6. Discussion

Our study is the first to compare the detectability of SMI with cPD in detecting low-grade inflammation and examine their relationships with symptoms, features on radiograph and MRI in a knee OA population. We demonstrated several interesting findings. Firstly, SMI can detect increased blood flow signals compared to cPD. Secondly, both techniques showed significant and mild to moderate associations with validated self-reported clinical outcomes, radiographic and MRI assessment criteria for synovitis in knee OA. Thirdly, Even

though SMI was able to detect a higher proportion of low-grade blood flow, the clinical preference/relevance of SMI over cPD is still questionable at least in the OA population.

Both blood flow and tissue motion can generate Doppler activity. There is overlapping of strong clutter signals with the components of slow blood flow. cPD utilized a wall filter to discard clutter and motion artefacts, leading to a loss of slow flow signals. However, SMI utilized a novel algorithm for removing tissue motion artefacts while showing true flow signals. It allows detection of fine vessels [261]. Therefore, it was assumed that SMI would be useful to detect low-grade inflammation of OA synovium.

Our study showed that SMI displayed a 25% increase in detection rate of vascularisation compared with cPD, suggesting that SMI visualizes low-grade, inflammatory activity that cannot be detected by cPD. Our results are in agreement with the RA study which reported a 60% increase in the detection rate of vascularization [271]. There are also several studies which showed that SMI can increase the detection rate of minute blood flows compared to cPD in RA patients [46, 264, 265, 267].

Although SMI could make up for the deficiency of cPD in visualizing minute blood vessels in low-grade inflammation, there was a weaker correlation of SMI with symptom measures. This may suggest that higher sensitivity of SMI to very low flows seems to have no association with symptoms severity. In addition, there are conflicting reports related to the clinical relevance of SMI's better sensitivity compared with cPD when both techniques were correlated with clinical measures such as DAS, and health assessment questionnaire disability index (HAQ-DI) in RA population [46, 264].

On the other hand, SMI did reveal a higher correlation with KL grade as well as MRI effusion-synovitis and Hoffa-synovitis than cPD. However, the extent of correlation is not significant. This might suggest that the increased blood flow signals picked up by SMI seems to be a true flow. However, there is no such earlier study in either RA or OA population.

These findings put forward some interesting points for consideration. Firstly, the added clinical usefulness of SMI over PDI is still controversial in OA patients given poorer performance in its relationship to symptoms. It might be assumed that SMI could misinterpret the normal vascularization as positive signals due to its higher sensitivity, leading to a weaker correlation with symptoms. However, its higher correlation with MRI synovitis and Hoffa's synovitis seems to dispute it. Therefore, the clinical relevance of positive finding in SMI vascularization warrants further research.

Low-grade inflammation detected by MRI up to 4 years prior to OA incidence is implicated in the development of radiographic knee OA [57, 272]. Therefore, it would be interesting to see whether patients with SMI positivity but who were negative on cPD progress faster or have higher odds of developing OA as a distinct OA phenotype in a future study.

6.7. Limitations

One of the limitations is that the present study did not include an age-matched control group with normal knees. Another limitation is that the MRI sequence used in our study was not contrast-enhanced and not optimal for detecting synovial hypertrophy. Lastly, we did not obtain a synovial biopsy to confirm the vascularization. However, synovial biopsy is very unusual for people with mild-moderate knee OA.

6.8. Conclusion

SMI can detect low-grade inflammation implicated in OA disease process compared to cPD and revealed a significant correlation with symptoms and features on radiograph and MRI synovitis. However, there is no difference in the extent of such correlations. Therefore,

the clinical utility of SMI in knee OA is still unclear and further research is required to establish its validity.

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Conflict of Interest: DJH provides consulting services to Pfizer, Lilly, Merck Serono, TLC bio.

CHAPTER SEVEN

This chapter includes the following published paper:

Oo W.M., Deveza L.A., Duong V., Fu K., Linklater J.M., Riordan E.A., Robbins S.R., and Hunter D.J., Musculoskeletal ultrasound in symptomatic thumb-base osteoarthritis: clinical, functional, radiological and muscle strength associations. BMC Musculoskeletal Disorders, 2019. 20(1): p. 220.

Chapter 7

Musculoskeletal ultrasound in symptomatic thumb-base osteoarthritis: clinical, functional, radiological and muscle strength association

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Statement from co-authors confirming authorship contribution of the PhD candidate

The co-authors of the paper: "Musculoskeletal ultrasound in symptomatic thumb-base osteoarthritis: clinical, functional, radiological and muscle strength associations", confirm that Win Min Oo has made the following contributions:

1. Conception and design of the research
2. Analysis and interpretation of the findings
3. Writing of the manuscript and critical appraisal of the content

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Win Min Oo Date: 15th August 2019

As supervisor for the candidature upon which this Thesis is based, I can confirm that the authorship attribution statements above are correct.

David Hunter Date: 15th August 2019

Chapter Seven: Musculoskeletal ultrasound in symptomatic thumb-base osteoarthritis: clinical, functional, radiological and muscle strength association

7.1. Abstract

Background: Thumb-base osteoarthritis (OA) is a common cause of pain and disability This study aimed to investigate the associations of musculoskeletal ultrasound OA pathologies with the extent of pain, function, radiographic scores, and muscle strength in symptomatic thumb-base osteoarthritis.

Methods: This is a cross-sectional study of an ongoing clinical trial with eligibility criteria including thumb-base pain on Visual Analogue Scale (VAS) ≥40 (0 to 100mm), Functional Index for Hand OA (FIHOA) ≥ 6 (0 to 30) and Kellgren Lawrence (KL) grade ≥ 2. The most symptomatic side was scanned to measure synovitis and osteophyte severity using a 0-3 semi-quantitative score, power Doppler and erosion in binary score. A linear regression model was used for associations of ultrasound findings with VAS pain, FIHOA and hand grip and pinch strength tests after adjusting for age, gender, body mass index, disease duration and KL grade as appropriate. For correlation of ultrasound features with KL grade, OARSI ((Osteoarthritis Research Society International) osteophyte and JSN scores, Eaton grades, Spearman coefficients were calculated, and a significant test defined as a p-value less than 0.05.

Results: The study included 93 participants (mean age of 67.04 years, 78.5% females). Presence of power Doppler has a significant association with VAS pain [adjusted β coefficient = 11.29, P=0.02] while other ultrasound pathologies revealed no significant associations with all clinical outcomes.

In comparison to radiograph, ultrasonographic osteophyte score was significantly associated with KL grade [r_s=0.44 (P<0.001)], OARSI osteophyte grade [r_s=0.35 (P=0.001)], OARSI JSN grade [r_s=0.43 (P<0.001)] and Eaton grade [r_s=0.30 (P<0.01)]. Ultrasonographic erosion was significantly related with radiographic erosion [r_s=-0.49 (P=0.001)].

Conclusion: From a clinical perspective the significant relationship of power Doppler with pain severity in thumb base OA suggests this might be a useful tool in understanding pain aetiology. It is important to recognise that power Doppler activity was only detected in 14% of the study so this might be an important subgroup of persons to monitor more closely.

Clinical Trial No: Registered at Australian New Zealand Clinical Trials Registry (ANZCTR), http://www.anzctr.org.au/, ACTRN12616000353493

Keyword: Ultrasonography; Hand Osteoarthritis; Arthritis; Inflammation

7.2. Background

Thumb-base osteoarthritis (OA) denotes structural alteration of the thumb carpometacarpal joint with a female predominance up to 6:1 [273]. It is a common cause of pain and disability, restricting the ability to perform simple tasks of daily living, and is characterized by hand weakness and radiographic abnormalities [274]. The lifetime prevalence is nearly 10%, with the epidemiological radiographic prevalence varying from 4% to 33% for middle-aged and elderly populations [275].

OA is traditionally imaged with plain radiograph which has several limitations, such as inability to visualize soft tissue pathologies which can contribute to pain and symptoms [18]. Ultrasound may afford some advantages including higher sensitivity for detecting osteophytes than plain radiographs [22, 207]. In addition, the use of ultrasound would permit the study of OA phenotypes with respect to inflammatory and structural changes that cannot be visualized with a plain radiograph [276].

A number of studies have examined the association of ultrasound findings with symptoms, function and radiographic findings in multifocal hand OA [211, 276] and other large joints such as knee and hip [13, 35, 277, 278]; however, only three studies utilized ultrasound specifically for thumb-base OA, pinpointing on comparative prevalence of ultrasound-detected effusion (31 OA vs 37 controls) [279], the relationship of ultrasound features with disability (n=57) [280] and the association of inflammatory ultrasound features with presence of pain on palpation (n=87) [281]. As a diagnostic tool to be used in clinical research and practice, the validity of the tool should be determined using comparators such as disease symptoms, functional status in daily living activities, strength and other routine imaging. As yet, there is a lack of ultrasound studies focusing on its construct validity using all relevant symptomatic and structural outcomes as comparators in thumb-base OA.

This study aimed to determine the associations of ultrasound features of OA with the extent of pain at the thumb-base joint, grip and pinch strength, functional score and radiographic findings.

7.3. Method

7.3.1. Study Design and participant selection

This is a cross-sectional analysis from baseline assessment of the ongoing COMBO (Effect of Combined Conservative Therapies on Clinical Outcomes in Patients with Thumb-base Osteoarthritis) clinical trial starting from May 2016 (Trial registration No: ACTRN12616000353493) [282]. Approval for this study was obtained from the local research ethics committee (HREC/15/HAWKE/479).

Participants were recruited from the community and our research volunteer database by using the recruitment strategies such as affixation of posters/flyers on notice boards of waiting rooms of medical practices and community areas; advertisement in newsletters, radio, and local and major newspapers and advertisements on social media networks. Firstly, a preliminary screening was conducted by phone/internet, and then if the participant passed this initial screening, a face-to-face visit was arranged to confirm their eligibility. The inclusion criteria were: 1) age ≥40 years; 2) thumb-base pain at least half of the days in the past month; 3) average pain ≥40 on a 100 mm Visual Analogue Scale (VAS) [283] over the 48 hours prior to the study enrollment; 4) Functional Index for Hand Osteoarthritis scores ≥6 (FIHOA, range 0–30) [284]; 5) Kellgren Lawrence grade (KLG) [16] ≥2 in the index thumb-base joint.

Exclusion criteria were: 1) known diagnosis of crystal-related arthritis (e.g., gout); 2) autoimmune arthritis (e.g., rheumatoid arthritis); 3) hemochromatosis 4) fibromyalgia; 5) significant injury to the index joint in the past 6 months; 6) any other self-reported hand condition that is likely to cause pain at the thumb base (e.g., scaphoid fracture). All participants provided informed consent.

The most symptomatic hand, as defined by pain on VAS score or worst function over the prior 48 hours if the same VAS score in both hands, was included in cases of bilateral symptomatic thumb-base OA.

The cohort included here is a convenience sample recruited from the baseline visit of the COMBO clinical trial, and all participants available for an ultrasound visit between May 2016 and August 2017 were included. One hundred and seventy-two potential participants were screened to get the current sample size.

7.3.2. Clinical, functional and radiological assessment

Demographic data such as age, gender, height, weight and symptom duration were collected. Pain at the thumb base was scored on a 100 mm VAS. Bilateral grip and tip-pinch strength measured in kilogram-force (Kg-F), using the hand dynamometer (Jamar Hand Dynamometer, Model: A7291, Patterson Medical) and pinch gauge (Model: PG-30, B&L Engineering), respectively. Participants were seated with both feet flat on the ground and the elbow flexed at 90 degrees and were instructed to use their maximum force; the average score of the three trials was used in the analysis.

Hand function was assessed by FIHOA questionnaire, which includes ten self-reported items scored on a 4-point Likert scale of 0 (possible without difficulty) to 3 (impossible). The outcomes measures were validated instruments recommended to be measured in hand OA clinical trials [285].

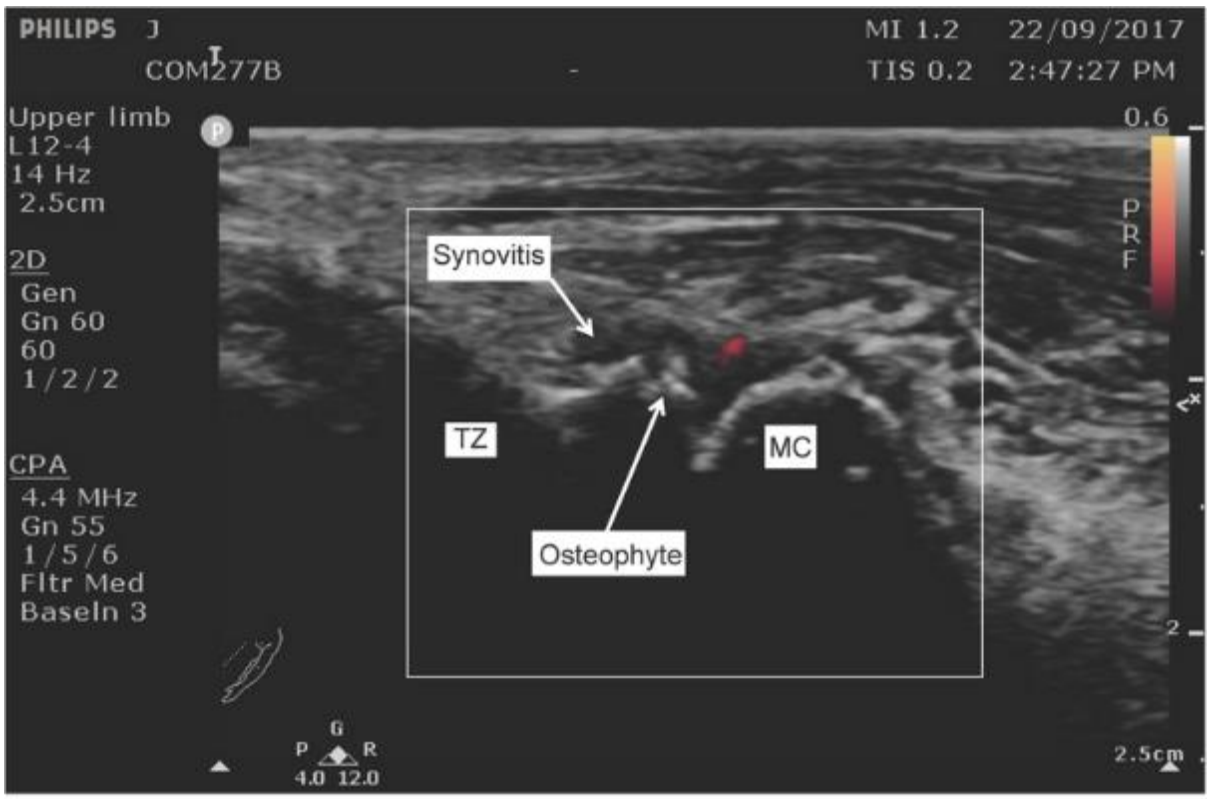
Bilateral hand radiograph (posteroanterior view) was used to score KLG [16], osteophyte and joint space narrowing (JSN) scores of the Osteoarthritis Research Society International (OARSI) atlas [17], and Eaton classification [286]. Radiographic KLG, OARSI osteophyte and JSN were graded by a rheumatologist (LD), and Eaton grades by a physician (ER), respectively. The intra-rater reliability was assessed using 20 radiographs with a 6-month interval between two sessions, providing the weighted kappa of (0.76, 0.72, 0.78, and 0.82) for KLG, OARSI osteophyte, OARSI JSN and Eaton grade, respectively.

7.3.3. Ultrasound examination

The physician sonographer (WMO, four years of musculoskeletal ultrasound experience, designated with a RhMSUS certification by American College of Rheumatology and having attended EULAR ultrasound courses) performed the ultrasound on the index hand in the air-conditioned

radiological setting, being unaware of the other clinical and radiographic outcomes. The thumb-base joint was scanned on the longitudinal and transverse plane of the palmar and dorsal aspect according to the OMERACT ultrasound definitions and scanning methods of published papers [33, 50]. A 12 MHz linear probe (L12-4, Philips Sparq Model) was used with fixed ultrasound parameters throughout the study. Power Doppler was assessed with a frequency of 4.4 MHz and medium wall filter, using minimal pressure during the scanning. The gain was adjusted until the background signal was removed.

Effusion was defined as hypoechoic or anechoic fully compressible material, synovial hypertrophy as echogenic or hypoechoic slightly compressible or non-compressible intra-articular tissue[287]. Synovial hypertrophy and effusion were considered together as a single domain ‘‘synovitis’’ which was graded on a 0-3 scale (absent, mild, moderate and severe) as suggested by Keen *et al.* [50]. Doppler signal as a pulsating colour spot found within the synovial structure [33], and graded in the binary score (present/absent) (**Figure 7.1**). Osteophytes were defined as cortical protrusions at the joint margin seen in two planes [33], and severity of osteophytes was scored semi-quantitatively (0-3) using the atlas by Mathiessen *et al.* [288], based on the largest osteophyte independently of the number, size and location of other osteophytes (**Figure 7.2**). Erosion was defined as an intra-articular discontinuity of the bone surface that is visible in two perpendicular planes [33] and scored on a binary scale. An evaluation sheet form was used for documenting the ultrasonographic findings.



TZ= Trapezium; MC= Metacarpal

Figure 7.1. Power Doppler activity in thumb-base osteoarthritis

Legends: TZ=Trapezium; MC=Metacarpal

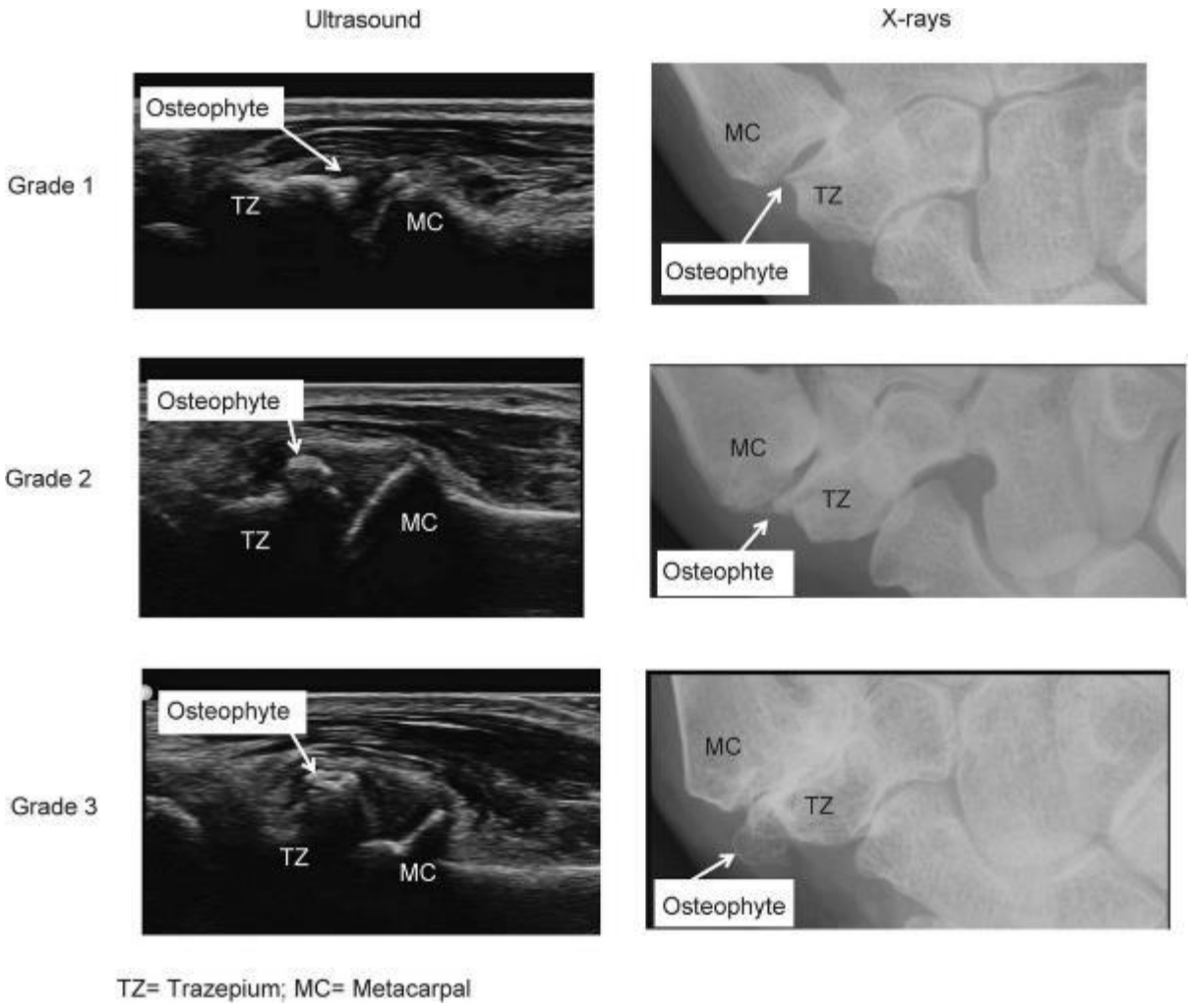


Figure 7.2. Atlas for Osteophyte grading of ultrasound and plain radiograph in our sample

Legends: Grade 1=mild; Grade 2=moderate; Grade 3=severe; TZ= Trapezium; MC=metacarpal

7.3.3.1. Intra-rater reliability

Utilizing still images of 40 randomly selected cases, the intra-rater reliability was examined 6 months after the first session, with a K_W value of 0.77 (0.60 to 0.94) for synovitis, 0.79 (0.63 to 0.96) for osteophyte, and unweighted kappa of 0.89 (0.69 to 1.00) for power Doppler.

7.3.3.2. Inter-machine reliability

To evaluate the inter-machine reliability, the same scanning procedures and scoring system were performed in 40 patients, using a latest high-end ultrasound machine (Aplio Platinum 500, Toshiba, Japan) equipped with multi-frequency linear transducers (6-18MHz). The B-mode and power Doppler settings of the machine were optimized by the application specialist from Toshiba. Due to the low prevalence of some ultrasound pathologies, prevalence-adjusted bias-adjusted kappa (PABAK) was calculated, giving rise to a PABAK value of 0.81(0.65, 0.97) and percentage agreement of 87.5% for synovitis, 0.78(0.60, 0.95) and percentage agreement of 85% for osteophyte, 0.60(0.34,0.86) and percentage agreement 80% for power Doppler.

7.4. Statistics

To investigate whether US features were independently associated with pain, function and strength tests, linear regression analyses were conducted for synovitis and power Doppler, adjusting for age, sex, body mass index (BMI), duration of disease and KLG. Adjustments for age, sex, body mass index (BMI), duration of disease were performed for regressing structural ultrasound features such as osteophyte, erosion. Spearman correlations were calculated to calculate the relationship of ultrasound features with radiographic gradings. Correlation coefficients were interpreted according to the Evans' classification [197], <0.20:very weak; 0.20-0.39:weak; 0.40-0.59:moderate; 0.60-0.79;strong and >0.80:very strong. All statistics were conducted with SPSS version 23 and a significant association/correlation was defined as a p-value less than 0.05.

7.5. Results

7.5.1. Demographic and clinical characteristics.

A total of 93 participants were included in this study, with 73 females. The demographics of the participants are shown in **Table 7.1**.

Table 7.1. Baseline, clinical and radiographic data of study participants

Population, n	93
Age, mean (S.D.); years	67.04 ±6.95
Female, n (%)	73 (78.5%)
BMI, mean (S.D.); kg/m2	29.35±6.73
Disease duration, mean (S.D.), years	3.06±1.10
VAS pain, mean (S.D.)	61.61±14.37
Pinch Strength, mean (S.D.), Kg-F	3.21±1.16
Grip Strength, mean (S.D.), Kg-F	20.06±8.16
FIHOA, mean (S.D.)	11.33±3.91
Kellgren and Lawrence grade, n (%)	
0	0
I	0
II	27 (29.0)
III	48(51.6)
IV	18 (19.4)
OARSI osteophyte, n (%)	
0	6 (6.5)
I	37 (39.8)
II	21 (22.6)
III	29 (31.2)
OARSI JSN, n (%)	
0	13 (14.0)
I	28 (30.1)
II	33 (35.5)
III	19 (20.4)
Eaton grade, n (%)	
0	2 (2.2)
I	22 (23.7)
II	18 (19.4)

III	47 (50.5)
Radiographic erosion on X-rays, n (%)	2 (2.2)

BMI=Body mass index; FIHOA=Functional index for hand osteoarthritis; JSN= Joint space narrowing; OARSI=Osteoarthritis research society international; VAS=Visual analogue scale

7.5.2. Radiographic findings

According to KLG, grade 3 was found in more than half of the participants (n=48,51.6%), grade 2 in 27 (29.0%) and grade 4 in 18 (19.4%). Osteophytes were not detected in 6 (6.5%) of participants, respectively, using the OARSI atlas. Radiographic erosion was present in 2 participants. The distribution of all radiographic findings is outlined in **Table 7.1.**

7.5.3. Distribution of ultrasound-detected pathologies

On ultrasound, synovitis and power Doppler was detected in 52 (55.9%) and 13 (14.0%), respectively. No participants showed severe synovitis (grade 3) on ultrasound. The majority of participants (n= 65, 69.9%) demonstrated large osteophytes on ultrasound. Ultrasound-detected erosion was found in 2 patients. The frequency of different ultrasound findings is shown in **Table 7.2**.

There were significant associations synovitis vs erosion (r_s=0.23 (P=0.026).

Table 7.2. Ultrasonographic findings in study participants

Population, n	93
Synovitis, n (%) 0 I II III	 41(44.1) 36(38.7) 16(17.2) 0
Power Doppler, n (%)	13 (14.0)
Osteophyte, n (%) 0 I II III	 0 3 (3.2) 25 (26.9) 65 (69.9)
Erosion on ultrasound, n (%)	2(2.2)

7.5.4. Association of ultrasound findings with pain, strength and function

The presence of power Doppler was significantly associated with the degree of VAS pain [β coefficient = 11.29, P=0.02] after adjusting the confounders. The synovitis and osteophyte were not significantly associated with pain, pinch and grip strength, and FIHOA score (**Table 7.3**).

Table 7.3. Association between ultrasound-detected pathologies and clinical and functional measures

	Synovitis†	Power Doppler†	Osteophyte‡	Erosion‡
VAS pain				
Adjusted β	0.60	11.29	0.24	-12.91
(95% CI)	(-3.91- 5.12)	(2.47- 20.12)	(-6.12-6.61)	(-33.88-8.07)
P (2-tailed)	0.79	**0.02**	0.94	0.22
Pinch strength				
Adjusted β	0.120	-0.01	-0.16	0.85
(95% CI)	(-0.22-0.46)	(-0.63-0.66)	(-0.64-0.33)	(-0.76-2.46)
P (2-tailed)	0.48	0.97	0.53	0.30
Grip Strength				
Adjusted β	0.82	-0.71	1.27	1.84
(95% CI)	(-1.17-2.81)	(-4.56-3.13)	(-1.50-4.04)	(-7.28-10.97)
P (2-tailed)	0.42	0.71	0.36	0.69
FIHOA				
Adjusted β	-.35	0.40	0.21	-2.84
(95% CI)	(-1.47- 0.78)	(-1.93- 2.72)	(-1.52-1.94)	(-8.53-2.86)
P (2-tailed)	0.54	0.74	0.81	0.32

B= β coefficient; FIHOA=Functional index for hand osteoarthritis; VAS=Visual analogue scale; 95% CI=95% confidence interval.

† Adjusted for age, sex, and body mass index, disease duration and KL grade

‡ Adjusted for age, sex, body mass index, and disease duration

7.5.5. Association of ultrasound findings with radiographic findings

The ultrasonographic osteophyte scores were significantly correlated with KLG [r_s=0.44 (P<0.001)], OARSI osteophyte grade [r_s=0.35 (P=0.001)], OARSI JSN grade [r_s=0.43 (P<0.001)] and Eaton grade [r_s=0.30 (P<0.01)] as shown in **Table 7.4**. Erosion detected on ultrasound had a correlation of 0.49 with radiographic erosion as ultrasound could not visualize the radiographic erosion in one patient with florid osteophytes. In addition, in 6 patients, ultrasound could detect osteophytes which the plain radiograph could not.

Table 7.4. Relationship between ultrasound-detected pathologies and radiological findings

	Synovitis	Power Doppler	Osteophyte	Erosion
KL score				
r_s	-0.09	-0.03	**0.44**	-0.09
P (2-tailed)	0.41	0.76	**0.001**	0.41
OARSI OST				
r_s	-0.13	-0.14	**0.35**	-0.13
P (2-tailed)	0.21	0.19	**0.001**	0.22
OARSI JSN				
r_s	-0.03	-0.06	**0.43**	-0.08
P (2-tailed)	0.75	0.57	**0.001**	0.43
Eaton SUB				
r_s	-0.11	-0.01	**0.30**	-0.03
P (2-tailed)	0.29	0.98	**0.01**	0.75
Erosion				
r_s	0.15	0.15	0.10	**0.49**
P (2-tailed)	0.14	0.14	0.36	**0.001**

KL= Kellgren Lawrence; OARSI=Osteoarthritis research society international; OST=Osteophyte; rs= Spearman's correlation; SUB= Subluxation

7.6. Discussion

The current study revealed the frequent finding of some ultrasound pathologies, the significant association of the presence of power Doppler with the severity of pain, and significant correlations of ultrasound-detected osteophyte with radiographic scores in thumb-base OA. However, the study could not detect any significant correlation of ultrasound pathologies with strength and functional measures.

This study showed that synovitis, when present, were mostly scored toward the lower end of the semi-quantitative scale as these grading scores were adopted from the scoring system created originally for rheumatoid arthritis [33], which is quantitatively different in inflammatory severity from OA [289]. Recent papers questioned the use or relevance of semi-quantitative scores in OA as it can lead to unequal distribution of the scores [290] and floor effects causing less sensitivity to detect an improvement in interventional trials [23].

Our participants had worse grades of osteophyte compared to the counterparts of thumb-base joint recorded in multifocal hand OA study by Naguib *et al.* [211]. This discordant result might be accounted for by the older age in our study population and different study selection criteria (American College of Rheumatology criteria vs radiological criteria), the number of joints involvement (multifocal vs mono-articular OA) and severity of the disease. Structural changes of the hand joints tend to be more commonly found with increasing age. About 6% of adults aged > 30 years [291] and 13% of persons aged 60 and over [292] had radiographic OA features. Such demographic and selection criteria differences might lead to our study population having more participants with fully established OA features.

A poor correlation between clinical symptoms and radiographic findings has previously been demonstrated in knee OA [293], and a similar discordance was suggested by our findings which revealed a significant association of only power Doppler with VAS pain, and no significant association with other ultrasound features. The finding of a significant correlation of power Doppler signal is in agreement with increasing evidence of MRI literature, which implied that active synovial

inflammation plays a critical role as pain generator of OA [294, 295]. This result is also consistent with meta-analytic reports in knee OA ultrasound [23].

However, the lack of significant correlation of grey-scale synovitis with pain raised several questions about its role in pain generation in OA. Hall *et al.* [176] postulated that perhaps synovial hypertrophy as seen on grey-scale ultrasound might not be inflammatory as grey-scale ultrasound cannot differentiate between active and indolent synovitis, tissue debris and fibrosis. Synovial hypertrophy and effusion could be the results of altered joint biomechanics [296] and reduction in lymphatic vessels [297]. In addition, pain in OA can be partly due to bone marrow oedema (BMOs) [298], which ultrasound cannot detect as sound waves cannot penetrate the bone, reducing the strength of correlation between grey-scale synovitis and VAS pain. The other reason might be a measurement issue. Pain is a subjective phenomenon, and inter-individual differences may modify the pain experience and intensity [259]. Subjects sustaining the same degree of structural damage experienced widely different degrees of pain, a phenomenon that is poorly elucidated [299]. Kroon *et al.* reported no significant association between inflammatory OA features of ultrasound and presence of pain on palpation although MRI synovitis and BMOs showed a significant relationship with pain in a different cohort [281]. In multifocal hand OA as well, conflicting results were reported in this aspect as Keen *et al.* [276] reported no significant association of synovitis, power Doppler, osteophyte and joint space width (JSW) with pain whilst Naguib *et al.*[211] documented a significant relationship of osteophyte, JSW and cartilage thinning with pain.

The relationship of grip and pinch strength with OA imaging features are broadly discordant in the radiological literature [300]. We found no correlation between ultrasound features and grip or pinch strength, which was contradictory with those of Naguib *et al.* [211], which found that significant associations existed between the grip strength and osteophyte in multifocal hand OA (n=30). However, Naguib *et al.* [211] did not find a significant correlation between strength and JSW, which was comparable with our findings. This disparity might be perhaps due to demographic differences such as greater strength (19.3 Kg-F vs 15.0 Kg-F) and older age (67.3 vs 60.0 years) in our study. Baron *et al.*[301] did not find a correlation between hand function, grip strength, and

radiographic features of hand OA, and postulated that hand function and strength were related more to neuromuscular condition than to the articular damage.

Regarding the correlation between ultrasound features and functional measures, the current study was consistent with most of the multifocal hand OA reports in the literature [276, 280, 302]. In multifocal hand OA, Keen *et al*. [276] demonstrated that synovitis, power Doppler and osteophyte had no significant correlation with functional impairments, utilizing the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) while Koutroumpas *et al.* [302] reported no correlation of synovitis and power Doppler with FIHOA score. In thumb-base OA, most ultrasound features had no correlation with Disabilities of the Arm Shoulder and Hand (DASH) score [280]; the only difference being that they found a correlation of osteophyte with function while we did not. However, contrary to these findings, Naguib *et al.*[211] determined a significant correlation of the structural features of ultrasound such as osteophyte with AUSCAN questionnaire in multifocal hand OA. It should be noted that the measures of hand function depend on multiple joints acting in concert, whereas our study looked at only one of those joints and so we could not exclude the impact of other finger joints OA on the associations. A recent meta-analysis in clinimetrics of ultrasound in knee OA reported that functional impairments are significantly but weakly correlated with effusion [r=0.23 (0.08, 0.37)] and osteophyte [r=0.18 (0.04, 0.31)] [23]. The reason for this discrepancy was unclear.

Our study found that ultrasound had the ability to detect osteophytes which plain radiographs failed to visualize. These findings are in agreement with those of Mathiessen *et al.* [288], Keen *et al.* [22] and Vlychou *et al.* [207], which demonstrated more osteophytes on ultrasound than on plain radiograph in multifocal hand OA. This can be explained by the capability of ultrasound to perform dynamic multiplanar imaging both longitudinally and transversely, and two-dimensional nature of plain radiograph which is likely to miss the small osteophyte localized to either palmar or dorsal aspect of the joint on standard PA view. However, the current radiographs are single-viewed and this may position radiography at a disadvantage.

Although Vlychou *et al.* [207] reported that ultrasound could reveal more erosions than plain radiograph in erosive multifocal hand OA, our study could not detect more erosions on ultrasound than plain radiograph perhaps due to higher prevalence of osteophyte (100% vs 41%) and reduced number of erosive OA (2% vs 100%) in our study. In one patient, erosion was near the central joint area with the overhanging osteophyte, which could not be visualized on ultrasound due to the limited acoustic window. Our finding was consistent with Keen *et al.* [22] who reported 6 erosions on plain radiograph (3 DIP, 2 PIP and 1 MCP); 2 joints were normal on ultrasound while the other 4 had marked osteophytosis. The similar conclusion was documented in another study [303] which implied that ultrasound could not detect 27.3% of erosions seen on plain radiograph. In small joints having severe osteophytes, deformities and subluxation, ultrasound was distinctly cumbersome due to acoustic artefacts and small acoustic window. Ultrasound appears to be more useful for detection of non-radiographic phase of erosive OA before the appearance of frank erosion which plain radiograph can visualize at this stage.

Naguib *et al.* [211] demonstrated the significant correlation of osteophyte with KLG, which is concordant with the current study. However, the correlation is just moderate probably due to different measurement methods of plain radiograph and ultrasound in scoring the grades of severity (each grades of ultrasound osteophyte atlas was not standardized exactly with the same grade of OARSI radiographic atlas; this might lead to over- or under-estimation of ultrasound severity score), more scanning planes for ultrasound and the fact that the comparison was not site-specific.

7.7. Limitation

As this was a cross-sectional study, we cannot establish a cause-effect relationship and determine the clinical importance of variability of the power Doppler with longitudinal changes in pain. Another limitation was the lack of a reference method such as MRI in detecting synovial and bony pathologies, and so we are not able to comment on the percentage of false positive and false negative ultrasound features. Ideally, the inter-rater reliability data should be conducted but only one

ultrasound operator was available for this study. In addition, the ultrasound machine used in our study is not the optimal high-end machine equipped with the latest high-frequency probe. In an ideal world, we would also have included a cohort of healthy individuals for comparison of ultrasound pathologies. Another important study limitation was that the ultrasound operator was not blinded to diagnosis; however, in practice, blinding a sonographer to joint deformities and joint tenderness is not feasible.

7.8. Conclusion

From a clinical perspective, the significant association of power Doppler with pain severity in thumb base OA suggests that ultrasound might be a useful tool in understanding pain aetiology. It is important to recognise that power Doppler activity was only detected in 14% of the study so this might be an important subgroup of persons to monitor more closely. In addition, the lack of association of other ultrasound structural features with hand function and strength reinforces the complex biopsychosocial origins of pain and function and the ongoing challenge of pain and structure dissociation in osteoarthritis. Further study with longitudinal follow-up may contribute to more clarification.

Declarations

Ethics approval and consent to participate: The informed consent obtained from study participants was written. Approval for this study was obtained from the Human Research Ethics Committee (HREC) of the University of Sydney and by Northern Sydney Local Health District HREC - reference number HREC/15/HAWKE/479.

Consent for publication: Non-applicable

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: None

Funding Source: None

Author Contributions

WMO, DJH and JML conceived and designed the study. LAD, VD and SRR were also involved in the design of the study. WMO, LAD, VD, KF, JML, EAR, SRR, DJH contributed to acquisition of clinical data of the study. WMO had full access to all the data and analysis and drafted the first manuscript. All authors critically revised the manuscript and gave final approval of the article for submission.

CHAPTER EIGHT

Chapter Eight: Thesis discussion and future directions

8.1. Overview

The overarching aim of this thesis was to examine the clinimetrics of MSKSU in knee and thumb-base OA. In order to fulfil this, we started with a broad literature review which involves two narrative reviews and a systematic review. The first narrative review described the role of different imaging tools, including plain radiographs, MRI and MSKUS in the OA pathogenic mechanisms and clinical utilities; and the second discussed a variety of pathophysiological manifestation of OA visualised by MSKUS and relevant clinical utilities of MSKUS. Finally, the systematic review and meta-analysis elaborated the clinimetrics of each MSKUS-detected abnormalities implicated in OA disease process. These reviews identified the limitations and deficiencies of the imaging modalities in OA diagnosis and monitoring such as difficulty to reproduce joint space narrowing and invisibility of hidden osteophyte in plain radiograph, the presence of different grading ultrasound scores and their respective clinimetrics, highlighting the need of further studies in this area.

Based on the literature review, the OMERACT MSKUS knee score was selected to examine its reliability and validity in knee OA as this was the most updated grading system based on international consensus. Validation study is a pre-requisite for the outcome instrument to be widely used in clinical practice; for this OMERACT scoring system, our study is the first such verification study. In addition, we examine the added clinical value of the innovative ultrasound technology, known as SMI, in the detection of low-grade inflammation, using a cross-sectional design. The role of MSKUS in thumb-base OA was examined using well-validated clinical and radiographic outcomes in a cross-sectional design, suggesting that OA phenotypes demonstrating synovial vascularity on power Doppler may benefit from close monitoring of disease. These ultrasound data utilised in this thesis were obtained by the candidate while he was working in the RESTORE knee OA and COMBO thumb-base OA studies conducted at the rheumatology department of Royal North Shore Hospital, Sydney.

8.1.1. **Summary of Thesis findings**

Chapter One demonstrated the burden of OA as highly prevalent and disabling disease with immense financial costs. It increased all-cause mortality and there were no disease-modifying drugs approved by regulatory bodies. It is a whole-joint disease involving multiple tissues, such as cartilage, synovium, subchondral bone etc. Each imagining modality commonly used in OA was discussed in terms of the advantages and disadvantages, semi-quantitative scoring systems and technical problems. We then briefly reported the OMERACT filter for outcome instrument selection such as truth, validity and discrimination and explained the OMERACT MSKUS knee scores, novel technology known as SMI and ultrasound scores in thumb-base OA.

In **Chapter Two**, we described the importance of hidden osteophyte formation at the intercondylar notch of the femur, detected by MRI. Then, we discussed the identification of persons at risk for incident radiographic OA, suggesting a greater amount of combined structural lesion load than the presence of any specific feature alone posing a higher risk of incident OA. We also discussed respective advantages of individual sub-scores of WORMS, BLOKS and MOAKS for predicting knee replacement. We updated the literature, reporting the deficiencies of plain radiograph in OA diagnosis and monitoring as well as evaluating the values of major MRI staging scores to be used in clinical trials. The newly developed OMERACT Ultrasound scoring system for knee OA was discussed highlighting the need of validation study [13].

Chapter Three described clinimetrics such as reliability, validity, and potential clinical utilization of ultrasonography as an imaging technique in knee OA. Clinical roles included the ability to demonstrate and assess the multiple soft tissue and structural abnormalities, which involved in the initiation and progression of OA, including joint effusion, synovial hypertrophy, Baker's cyst, cartilage thickness, meniscal extrusion, and formation of osteophyte. It can also be used to guide therapeutic interventions and monitoring treatment effectiveness. This chapter Three updated the state of the art of ultrasound for detecting the OA pathologies around knee joints, respective ultrasound

scoring systems, their values in correlating with the clinical and imaging outcomes, and we identified a recent ultrasound scoring system developed by internal consensus for further validation [35].

Chapter Four reported a systematic review and meta-analysis including 100 papers which demonstrated moderate to substantial reliability [minimum kappa > 0.44 (0.15,0.74), minimum intraclass correlation coefficient (ICC) > 0.82(0.73-0.89)], weak construct validity against pain (r = 0.12 to 0.27), function (r = 0.15 to 0.23), and blood biomarkers (r = 0.01 to 0.21), but weak to strong correlation with plain radiography (r = 0.13 to 0.60), strong association with MRI [minimum r = 0.60 (0.52,0.67)] and strong discrimination of symptomatic patients (OR = 3.08 to 7.46). There was strong criterion validity with cartilage histology [r = 0.66 (0.05,0.93)], and small to moderate internal [standardized mean difference (SMD) = 0.20 to 0.58] and external (r = 0.35 to 0.43) responsiveness to interventions. This chapter updated the ultrasound literature assessing its clinimetric values in OA population, reporting the reliability issues due to lack of standardized definition and scanning methods, varied validity across different ultrasound pathologies with different clinical and imaging outcomes, identifying the area which needed further research and validation as well as paucity of studies for responsiveness [23].

Chapter Five reported the construct validity of the OMERACT MSKUS knee score in 89 symptomatic knee OA participants using severity of pain on NRS and KOOS symptoms and pain sub-scores, Kellgren-Lawrence grade (KLG) on plain radiograph MRI osteoarthritis knee score (MOAKS) on non-contrast-enhanced MRI sequences as constructs for comparison. Synovial hypertrophy, power Doppler (PD) signals and meniscal extrusion scores were associated with increased pain severity. All ultrasound scores, except for cartilage grade, demonstrated associations with KOOS symptoms while only PD signals and meniscal extrusion were associated with KOOS pain. All ultrasound scores, except for PD signals, were significantly correlated with KLG; and most ultrasound pathologies revealed moderate to good correlation with their MRI counterparts with ultrasound synovitis having the greatest correlation. This validation study provided evidence to support its use as a standardized tool for determining ultrasound OA phenotypes.

In **Chapter Six**, we investigated the sensitivity of SMI vs cPD in low-grade inflammation of OA and compared their correlations with clinical and imaging tools. SMI has better sensitivity to detect flow signals, especially for low grades of cPD. SMI and cPD both showed significant correlations with KOOS symptoms, KLG, MRI effusion-synovitis and Hoffa's synovitis scores while only SMI was significantly correlated with KLG. However, there were no significant differences to the extent of correlations. SMI can detect low-grade inflammation implicated in OA disease better than cPD and reveal a significant correlation with symptoms, radiographic features and MRI synovitis. The added clinical value of SMI over cPD is still not clear.

Chapter Seven described the associations of MSKUS ultrasound scores in 93 patients with thumb-base OA using pain on VAS, FIHOA and KLG on plain radiography. Presence of power Doppler has a significant association with VAS pain, while other ultrasound pathologies revealed no significant associations with all clinical outcomes. In comparison to radiography, ultrasonographic osteophyte score was significantly associated with radiographic scores for osteophyte, JSN, subluxation and erosion. From a clinical perspective, the significant relationship of power Doppler with pain severity in thumb base OA suggests this might be a useful tool in understanding pain aetiology. However, power Doppler activity was only detected in 14% of the study participants so this might be an important subgroup of persons to be monitored more closely.

8.2. Strengths and limitations of this Thesis

8.2.1 Literature Reviews

We included two narrative reviews [13, 35] and one systematic review [23] to broadly investigate the clinimetrics of OA imaging tools with a focus on MSKUS. In the first narrative review [13], we synthesised from the recent publications that OA is represented by multi-tissue involvement, the utilities of imaging tools in clinical trials as outcome measures and prognostic markers or predictors of disease progression and briefly discussed semi-quantitative grading scoring systems. In the second review [35], we updated clinical utilities of MSKUS focusing on a variety of MSKUS

pathologies detected in osteoarthritis and their implications in relation to pain, function, other imaging outcomes, prognostic use, imaging-guidance and its limitations for clinical practice.

The shortcoming for the first review is that we conducted the database search only in PubMed to retrieve all potential studies and limited publication years to papers published after January 2015 [13]. However, our aim was to update the current state of evidence for identification of the gaps in the literature as this is a time of rapid change in knowledge as it relates to imaging use, application and interpretation in the context of knee osteoarthritis with a focus on articles deemed to provide a purposeful increase in our knowledge base. Another shortcoming is that only one reviewer performed the database search and the selection process for inclusion of potential papers in the narrative reviews [13, 35], and so selection bias cannot be excluded. However, these were narrative reviews to broaden our depth of knowledge, not a systematic review where, ideally, at least two reviewers will conduct the selection process of included papers and then choose the papers depending on the consensus [304].

For the systematic review [23], one of the strengths was the prospective registration with the International Prospective Register of Systematic Reviews (PROSPERO) [305] which is a highly sensitive search strategy to find the best available evidence. Another strength is that it also follows the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) [306]. We conducted a stratified meta-analysis for each ultrasound pathological manifestations using the OMERACT filter [41], which utilises a comprehensive conceptual framework to validate or refine the outcome tools in research for rheumatic diseases. In addition, this is the first meta-analytic systematic review comprehensively examining the clinimetrics of ultrasound utilized to evaluate common features of OA. As ultrasound is notorious for being operator-dependent and our appraisal of reliability studies revrealed average score of 5.93 out of 11 items in QAREL scores , it is crucial to stringent adherence to a consensual agreed protocol that clearly describes probe positions and definitions of elementary lesions and pathology. Limitations included the small sample sizes of included papers for some MSKUS pathologies, the considerable clinical and methodological heterogeneity of included studies, and most of the included studies just focusing on some individual

pathologies (not comprehensive), requiring caution in interpreting the pooled results. Moreover, we could not appropriately analyse the confounding effects of technology changes over the years which can have an impact on the psychometric properties of the scoring system.

8.2.2 **Reliability Study**

To be able to recommend utilisation of MSKUS as a validated modality, the OMERACT filter states that an outcome measure must be truthful, feasible, and discriminatory [39]. The latter includes reliability which posed a key concern for MSKUS which is known as highly operator-dependent [307]. Therefore, we evaluated a number of reliability testings of ultrasound scores in the thesis (**Chapter Five, Six and Seven**). In all these studies, we evaluated both components of obtaining final MSKUS scores, image acquisition and imaging interpretation [308]. Assessment of only stored images can inflate reliability values as ultrasound is a dynamic imaging tool and consistency of readings largely depends on how images are acquired [309].

Reliability of OMERACT ultrasound knee score was tested only among the experts involved in the development process of the scoring system [224]. In clinimetrics, replication of the results in an additional sample is crucial before its use in clinical trials [310]. Therefore, it is relevant as well as essential to assess examine its reliability statistics outside the group of score developers before the potential outcome tool can be widely used in the clinical practice. Reliability forms the precursor of validity studies as validity without reliability will not be meaningful for the widespread utilisation of grading scores from the perspective of psychometric principles [311]. Therefore, our validation study and replication of reliability results in another sample is timely and appropriate.

Our reliability statistics examining both intra-rater and inter-rater reliability (**Chapter Five**) are comparable to those of the OMERACT publication [224], supporting the evidence of the consistency of the grading scores and the possibility of using this score in multi-centre trials. The sessions for calibration and discussion among the raters with the published atlas reinforced the reliability of the scores. The weakness of this reliability study is that the inter-rater reliability assessment was only limited to the medial tibiofemoral compartment due to limited availability of

another rater and the higher likelihood of inclusion of medial type knee OA due to the study protocol's inclusion criteria [232].

Inter-rater reliability of SMI has been examined in rheumatoid arthritis providing weighted kappa statistics ranging from 0.46 [265] to 0.82 [46] in rheumatoid arthritis. No available studies reported intra-rater reliability values. Our SMI study (**Chapter Six**) showed good intra-rater reliability with weighted kappa being 0.78 (0.52 to 1.00).

In thumb base OA (**Chapter Seven**), intra-rater reliability was carried out to evaluate the ultrasound scoring system and demonstrated good reliability (minimum weighted kappa value >0.77). We also compared medium and high-end ultrasound machines in 40 patients and demonstrated good reliability except for Power Doppler which revealed only moderate reliability [312]. This supports the findings in rheumatoid arthritis that ultrasound devices and transducers differ in showing slow flow and that the instrument settings have a marked effect on the sensitivity of the ultrasound machine [313]. This finding highlights the importance of not only the consensus of the ultrasound raters for the scores used but also for calibration of ultrasound machines in multicentre clinical trials. The limitation is the lack of inter-rater reliability data for thumb-base scoring methods.

8.2.3 **Validity Studies**

Though reliability forms an important contributor to the validity of a grading score, it is not a sufficient condition for its validity [314]. OMERACT MSKUS knee scores have proved reliable, though validity needed to be examined [224], leading to the first validation study included in the thesis (**Chapter Five**). The strength of our validation study is that the association of the ultrasound scores with a variety of common clinical and imaging constructs in OA research such as pain, function, plain radiograph and MRI which are well-validated scores and recommended by OARSI guideline [233]. Therefore, it is believed that the validation results represent the true relationship with other constructs. The main shortcomings were the absence of invasive marker and difference of patient's position for imaging correlation which can cause measurement in different sites.

Chapter Six reported the first study in knee OA which compare SMI and cPD for relative clinical value using patient-reported outcomes, plain radiographs and MRI synovitis. Due to the limitation of conventional power Doppler such as clutter effects, insensitivity to slow flow as well as the development of advanced technology such as SMI which showed the effective separation of flow signals from overlying tissue motion artefacts, preserving subtle low-flow components, high resolution of the image, minimal motion artefact and high frame rates, it was hypothesized that SMI would be a useful innovative technology in the setting of low-grade inflammation of OA disease process [13]. Although our study revealed that SMI has a better correlation than cPD with imaging scores, we could not determine its added clinical value. In addition, histological correlation was not conducted to confirm the presence of low-grade inflammation visualised by SMI.

We investigated the construct validity of MSKUS in thumb-base OA in **Chapter Seven.** This is the first study examining the comprehensive MSKUS pathologies with a variety of outcomes such as pain, functions, muscle strengths and plain radiographs, demonstrating that only power Doppler proved a significant association with pain and confirmed symptom-structure discordance for other pathologies. In the literature, there are some inconsistencies regarding the association of ultrasound features with pain [209, 276, 315] . These might be due to the difference in demographic parameters of the study population, difference in inclusion criteria, the difference in ultrasound machines especially for power doppler sensitivity, etc. The main limitations were the small sample size, and the absence of a gold standard method such as MRI or histology synovitis to confirm positive doppler signals.

In all these validity studies, the main strength was the inclusion of multiple relevant constructs in OA to find the associations with MSKUS scores. However, we used a cross-sectional study design, and so the longitudinal variations of MSKUS with changes on other constructs could not be evaluated. In addition, our study sample did not include healthy controls as a definition of what is normal joint causes difficulty for validation research. Furthermore, we did not include histological biopsy for confirming the true positive or negative findings of MSKUS pathologies, and there was no analysis of synovial fluid to assess for inflammatory markers.

8.3. Implications and recommendations for future research

OA has been well-recognised as a heterogeneous disease involving a variety of joint tissues [13]. With the advancement of technology, imaging modalities are crucial tools for understanding the pathophysiological manifestations implicated in OA. As described in the introduction chapter of the thesis, the MRI expense for a given joint is almost fourfold higher than an ultrasound scan which has easy availability and point-of-care usability. The thesis demonstrated that MSKUS possesses a multitude of clinical values including detection of soft-tissue pathologies [35], reliable consistency and validity [23, 312], usefulness as a monitoring tool or as imaging guidance [35], prediction for disease progression [13], etc. However, further studies using cost-effectiveness analysis are warranted to determine whether it is economically feasible as an imaging tool in this context, taking into account the expense of MRI and plain radiograph in a clinical setting.

Although ultrasound has been popular during this decade due to portability, easy accessibility, low costs and safety [32], our systematic review showed a paucity of validation research using the histology or MRI [23]. Although our current knee OA studies included MRI as one of the comparative measures, we could not include the histological samples of cartilage or synovium. Therefore, criterion validity of MSKUS synovitis and cartilage could not be examined. This seems to be more relevant in the future studies given that cartilage ultrasound measure assessed with OMERACT score failed to show significant associations with semi-quantitative MRI cartilage score. In a recent study using the quantitative measurement of cartilage thickness on ultrasound and MRI, a significant correlation was obtained in 19 healthy individuals ($r = .67$, $P \leq .05$) [316]. Therefore, the value of MSKUS in the quantitative assessment of cartilage should be examined in the OA population. The evidence of good correlation of MSKUS pathologies with histological specimens will provide further insight into the diagnosis and relevance of existing staging scores.

We did not include contrast-enhanced (CE) MRI which is optimal for evaluation of active synovitis [317]. The correlation between PD or SMI and CE MRI will validate the value of the ultrasound in OA. In addition, the MOAKS does not take into account intercondylar synovitis

posterior to the PCL which is the commonest site of definite synovitis [318]. Therefore, future study should examine whether the inclusion of intercondylar synovitis viewed on MRI can change the extent of correlation between MRI and ultrasound. It is also interesting whether the presence of SMI in patients without PD signals can predispose to the progression of knee OA disease process or increase the incidence of knee OA in a pre-radiographic population with high risks for knee OA in future studies.

Few ultrasound studies existed for thumb-base OA highlighting the knowledge gap for these OA joints. However, PD signals were present in a small subset of our thumb-base OA sample. As the machine we used was not high-end, further study utilising such high-end machine or including SMI for visualising low-grade inflammation will support its clinical value.

For the outcome tool to be used in clinical trials, the natural disease process visualised on MSKUS and the sensitivity of MSKUS pathologies to changes by treatment should be determined. In addition, the association of MSKUS changes with changes in pain, function and other imaging outcomes in a longitudinal study will provide the fulfilment of OMERACT Filter as an outcome instrument in OA.

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Appendices

Appendix 1: Search strategy in databases

I.Cochrane data search for clinimetrics of ultrasound on 1/9/2016

4. [mh osteoarthritis]
5. osteoarthritis .ti.ab.kw
6. osteoarthrosis.ti.ab.kw
4. osteoarthropathy.ti.ab.kw
5. degenerative joint disease*.ti.ab.kw.
6. [mh osteophyte]
7. osteophyte.ti.ab.kw
8. joint space narrowing.ti.ab.kw
9. [3-#8]
10. [mh ultrasonography]
11. ultrasonography.ti.ab.kw
12. ultrasonog*.ti.ab.kw
13. sonograph*.ti.ab.kw
14. ultrasound.ti.ab.kw
15. [mh“ultrasonography, doppler”]
16.doppler ultrasonography.ti.ab.kw
17. musculoskeletal ultrasound.ti.ab.kw
18. ultrasonic*.ti.ab.kw
19.{or #10-#18}
20. #9 and #15
21. [mh “sensitivity and specificity”]
22. sensitivity and specificity.ti.ab.kw
23. [mh diagnosis]
24. diagnos*.ti.ab.kw
25. predictive value.ti.ab.kw
26. likelihood ratio.ti.ab.kw
27. performance.ti.ab.kw
28 [mh“validity and reliability”]

29. validity and reliability.ti.ab.kw

30. reproducibility.ti.ab.kw

31. responsiveness.ti.ab.kw

32. [mh“feasibility study”]

33. feasibility.ti.ab.kw

34. [224-#32]

35. #20 and #33

II.EMBASE data search for clinimetrics of ultrasound on 1/9/2016

1. exp osteoarthritis/ or osteoarthritis.mp.

2. osteoarthrosis.mp.

3. exposteoarthropathy/ or osteoarthropathy.mp.

4. degenerative joint disease$.mp.

5. osteophyte.mp. orexp osteophyte/

6. joint space narrowing.mp.

7. 1 or 2 or 3 or 4 or 5 or 6

8. ultrasonography.mp. orexp echography/

9. ultrasonog$.mp.

10. sonograph$.mp.

11. ultrasound.mp. orexp ultrasound/

12. doppler.mp. orexp tissue Doppler imaging/

13. musculoskeletal ultrasound.mp.

14. ultrasonic$.mp.

15. 8 or 9 or 10 or 11 or 12 or 13 or 14

16. 7 and 15

17. exp "sensitivity and specificity"/ or sensitivity.mp.

18. specificity.mp. orexp "sensitivity and specificity"/

19. exp diagnosis/ or diagnosis.mp.

20. diagnos$.mp.

21. predictive value.mp. orexp predictive value/

22. likelihood ratio.mp.

23. performance.mp. orexp performance/

24. exp validity/ or validity.mp.

25. reproducibility.mp. orexp reproducibility/

26. reliability.mp. orexp reliability/

27. responsiveness.mp.

28. exp feasibility study/ or feasibility.mp.

29. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28

30. 16 and 29

31. limit 30 to English language

32. limit 31 to human

33. limit 32 to adult <18 to 64 years>

III.Medline data search for clinimetrics of ultrasound on 1/9/2016

1. osteoarthritis.mp. orexp Osteoarthritis/

2. osteoarthrosis.mp.

3. expOsteoarthropathy, Secondary Hypertrophic/ or expOsteoarthropathy, Primary Hypertrophic/ or osteoarthropathy.mp.

4. degenerative joint disease$.mp.

5. osteophyte.mp. orexp Osteophyte/

6. joint space narrowing.mp.

7. 1 or 2 or 3 or 4 or 5 or 6

8. exp Ultrasonography/ or ultrasonography.mp.

9. ultrasonog$.mp.

10. sonograph$.mp.

11. ultrasound.mp.

12. exp Ultrasonography, Doppler, Color/ or doppler.mp. orexp Ultrasonography, Doppler/

13. musculoskeletal ultrasound.mp.

14. ultrasonic$.mp. orUltrasonics/

15. 8 or 9 or 10 or 11 or 12 or 13 or 14

16. 7 and 15

17. sensitivity.mp. orexp "Sensitivity and Specificity"/

18. specificity.mp. orexp "Sensitivity and Specificity"/

19. diagnosis.mp. orexp Diagnosis/
20. diagnos$.mp.
21. exp "Predictive Value of Tests"/ or predictive value.mp.
22. likelihood ratio.mp.
23. performance.mp.
24. validity.mp.
25. exp "Reproducibility of Results"/ or reproducibility.mp.
26. reliability.mp.
27. responsiveness.mp.
28. exp Feasibility Studies/ or feasibility.mp.
29. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 16 and 29
31. limit 30 to English language
32. limit 31 to humans
33. limit 32 to "all adult (19 plus years)"

Appendix 2: List of studies included in the systematic review

1. Abraham, A.M., et al., Reliability and validity of ultrasound imaging of features of knee osteoarthritis in the community. BMC Musculoskeletal Disorders, 2011. 12.
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3. Acebes, C., et al., Dynamic ultrasound assessment of medial meniscal subluxation in knee osteoarthritis. Rheumatology (United Kingdom), 2013. 52(8): p. 1443-1447.
4. Iagnocco, A., et al., The reliability of musculoskeletal ultrasound in the detection of cartilage abnormalities at the metacarpo-phalangeal joints. Osteoarthritis & Cartilage, 2012. 20(10): p. 1142-6.
5. Keen, H.I., et al., Can ultrasonography improve on radiographic assessment in osteoarthritis of the hands? A comparison between radiographic and ultrasonographic detected pathology. Annals of the Rheumatic Diseases, 2008. 67(8): p. 1116-20.
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10. Bansal, H., et al., Chondroprotection using naturally occurring mineral supplementation formula in degenerative Osteoarthritis of the knees. Journal of Stem Cells, 2014. 9(1): p. 65-76.
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14. Bevers, K., et al., Ultrasonographic analysis in knee osteoarthritis: evaluation of inter-observer reliability. Clinical & Experimental Rheumatology, 2012. 30(5): p. 673-8.
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20. Bruyn, G.A., et al., An OMERACT reliability exercise of inflammatory and structural abnormalities in patients with knee osteoarthritis using ultrasound assessment. Ann Rheum Dis, 2016. 75(5): p. 842-6.

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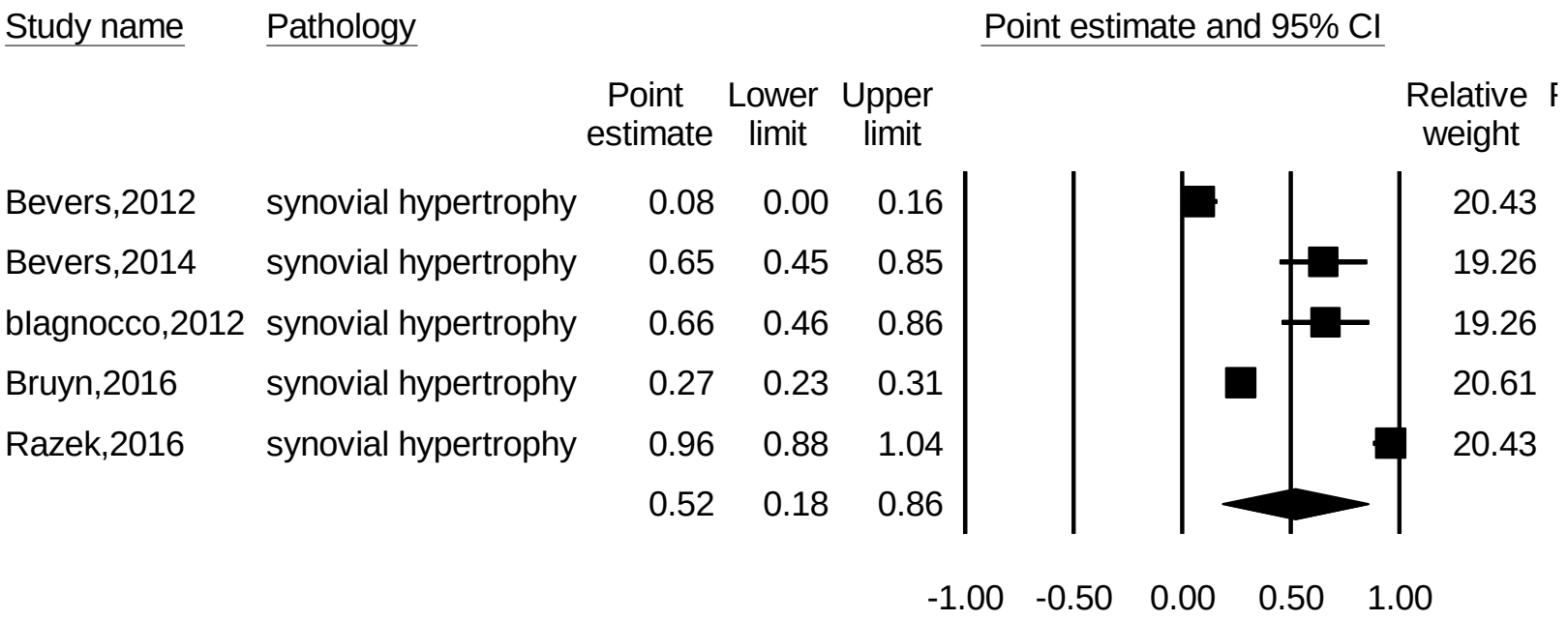
Appendix 3: Forest plots

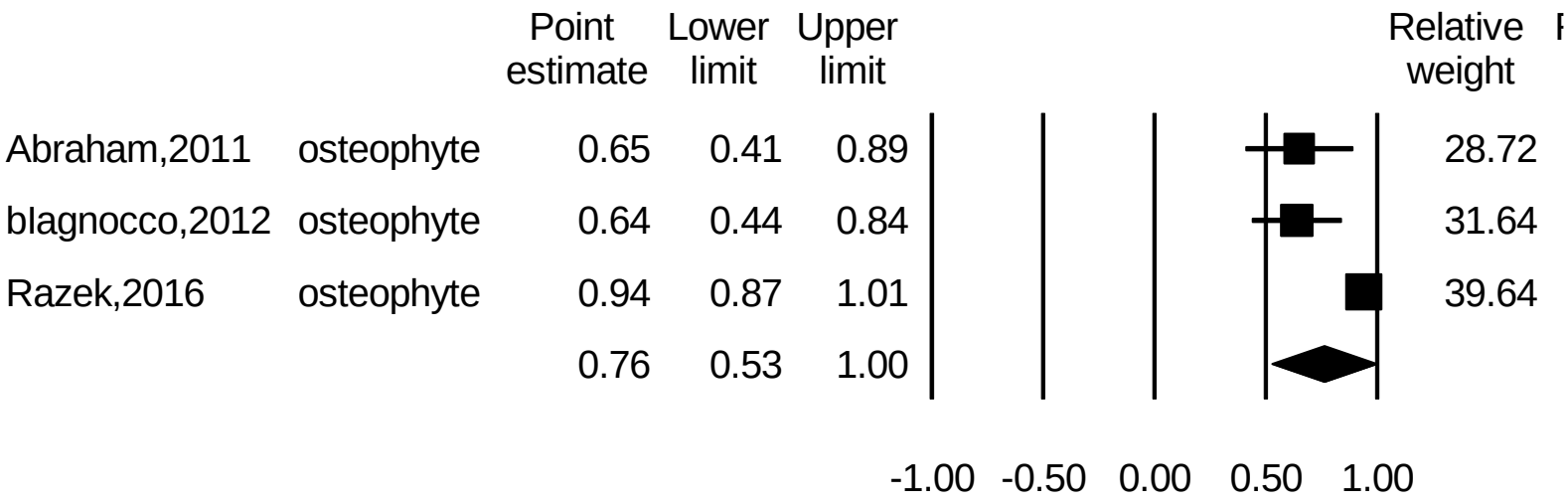
A. Reliability

I. Inter-rater reliability of ultrasound features for knee OA (binary score)

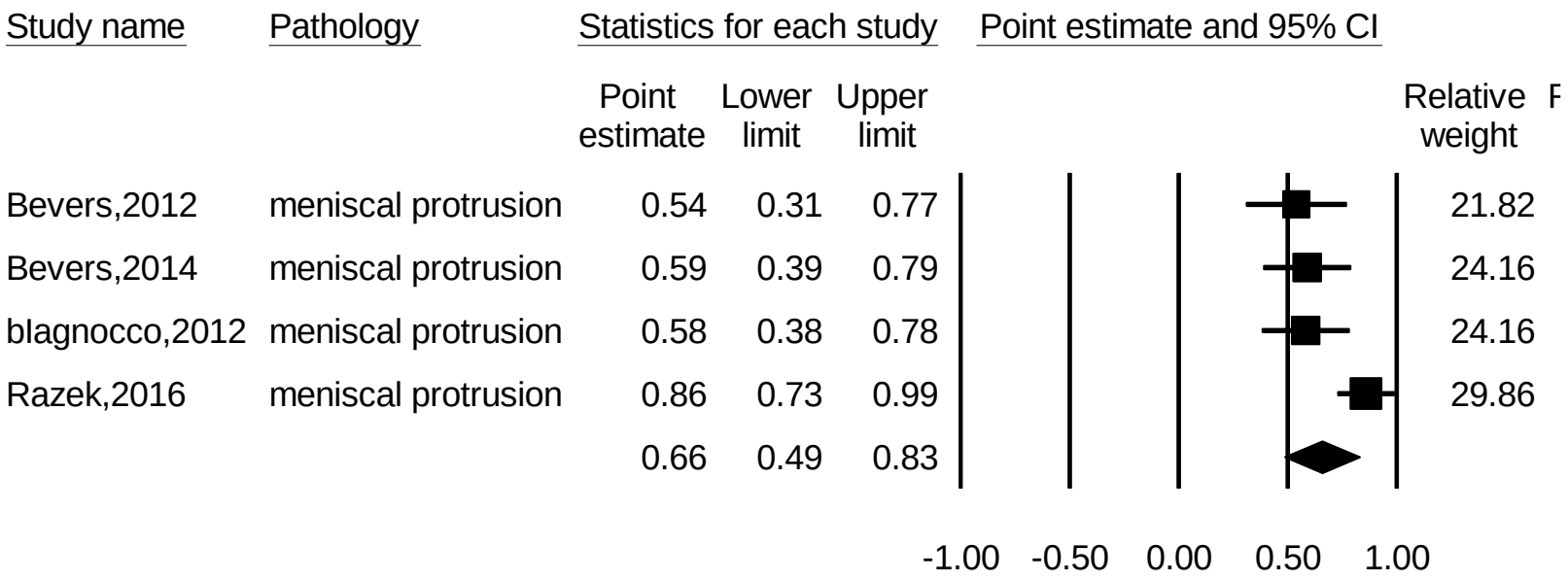
1. Forest plot for meta-analysis of synovial hypertrophy in knee OA



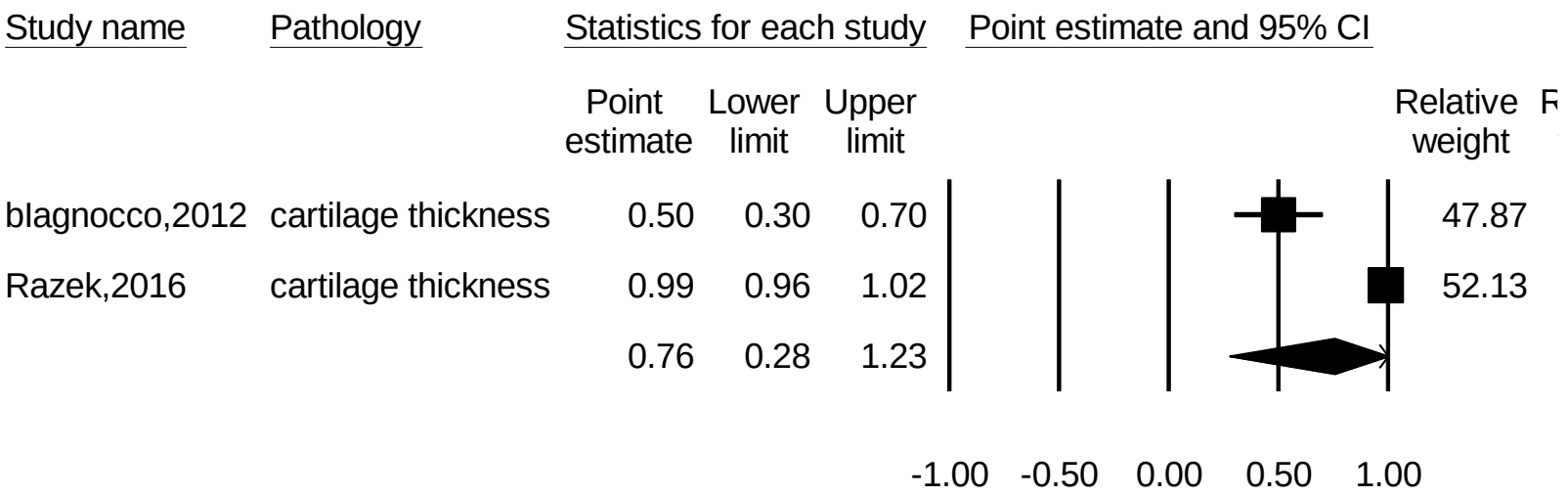
2. Forest plot for meta-analysis of osteophyte in knee OA



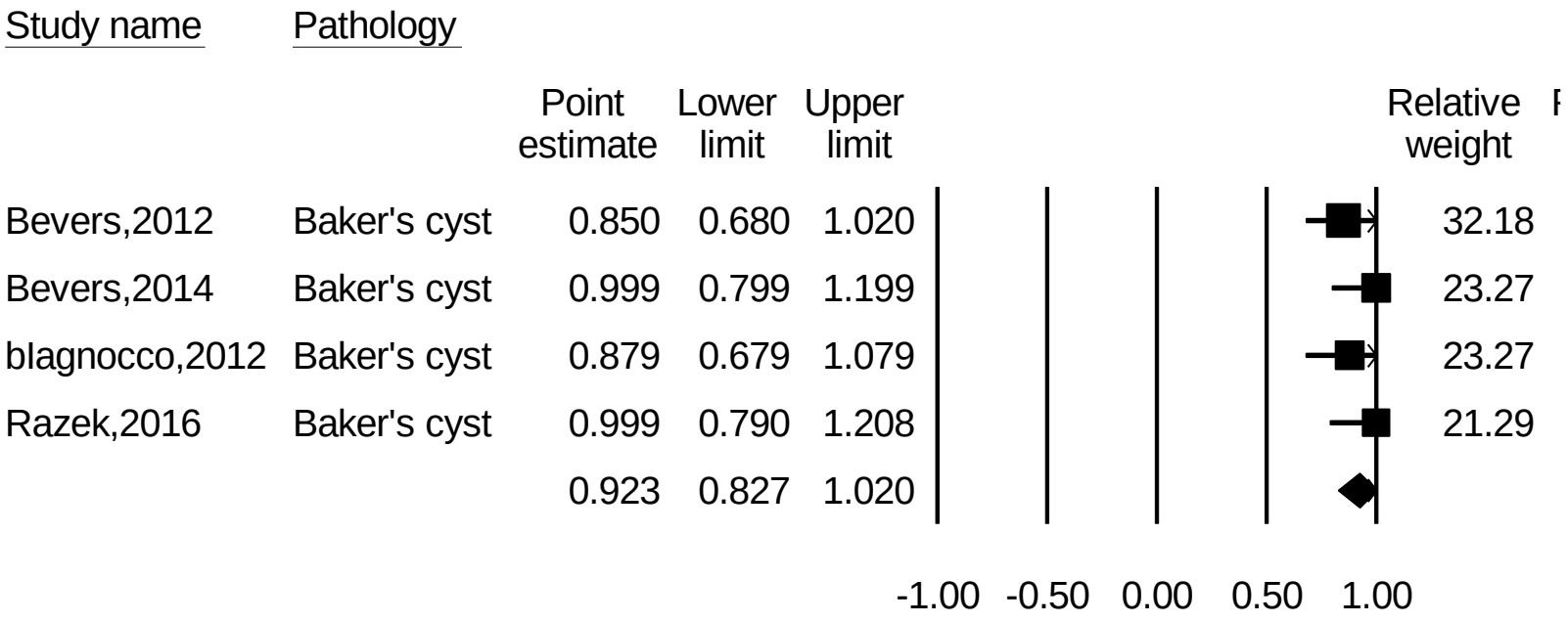
3. Forest plot for meta-analysis of meniscal extrusion in knee OA



7. Forest plot for meta-analysis of cartilage thickness in knee OA

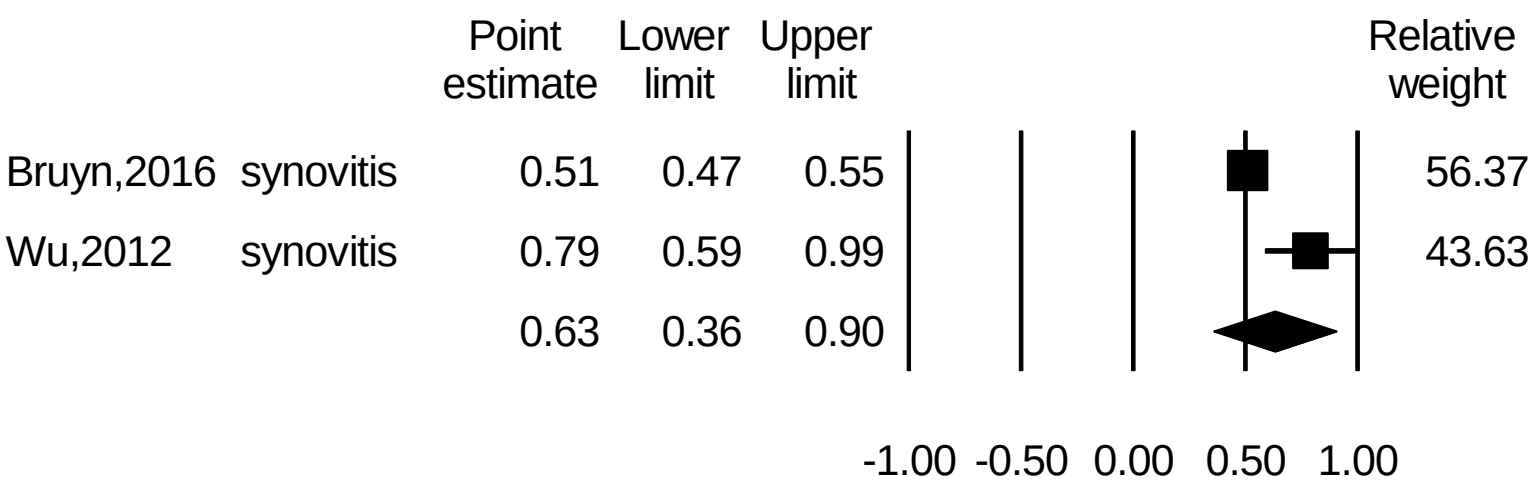


8. Forest plot for meta-analysis of Baker's cyst in knee OA

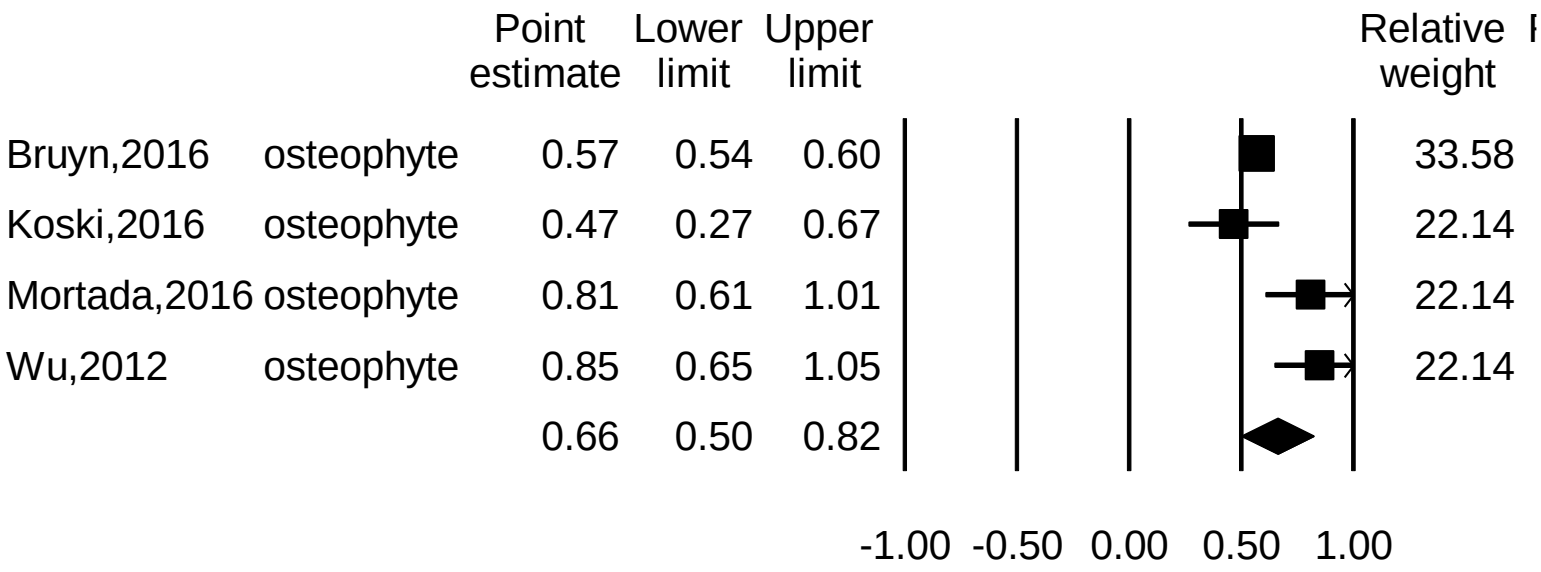


II. Inter-rater reliability for ultrasound features in knee OA (semi-quantitative score)

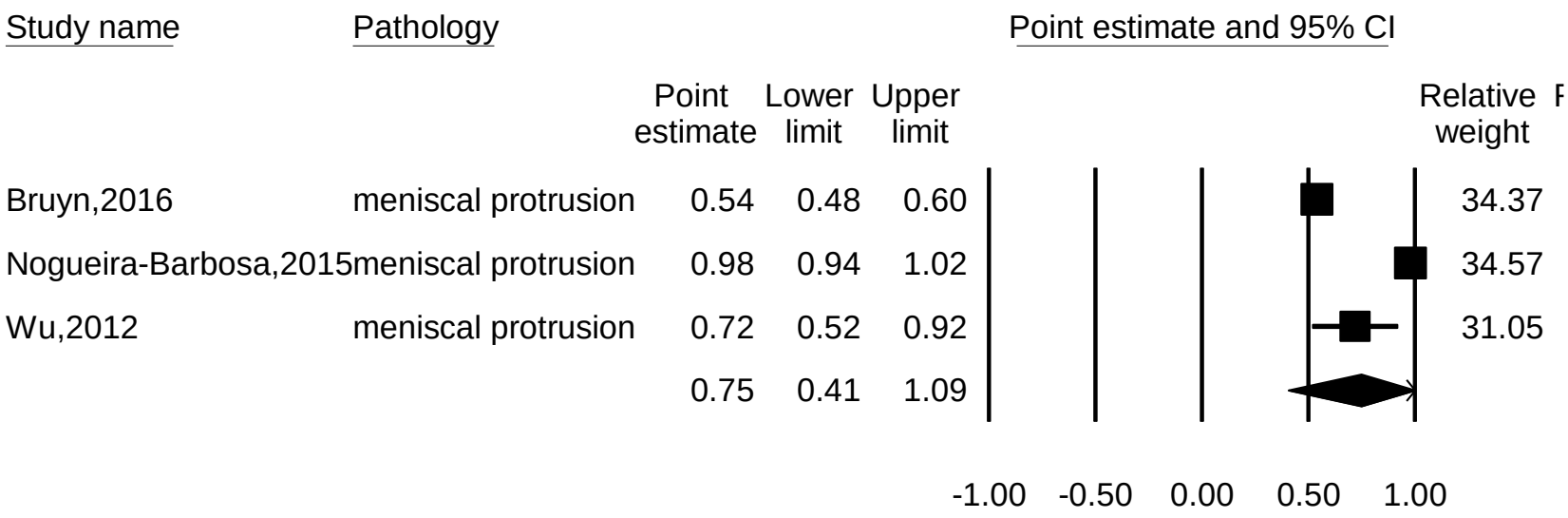
1. Forest plot for meta-analysis of synovitis in knee OA



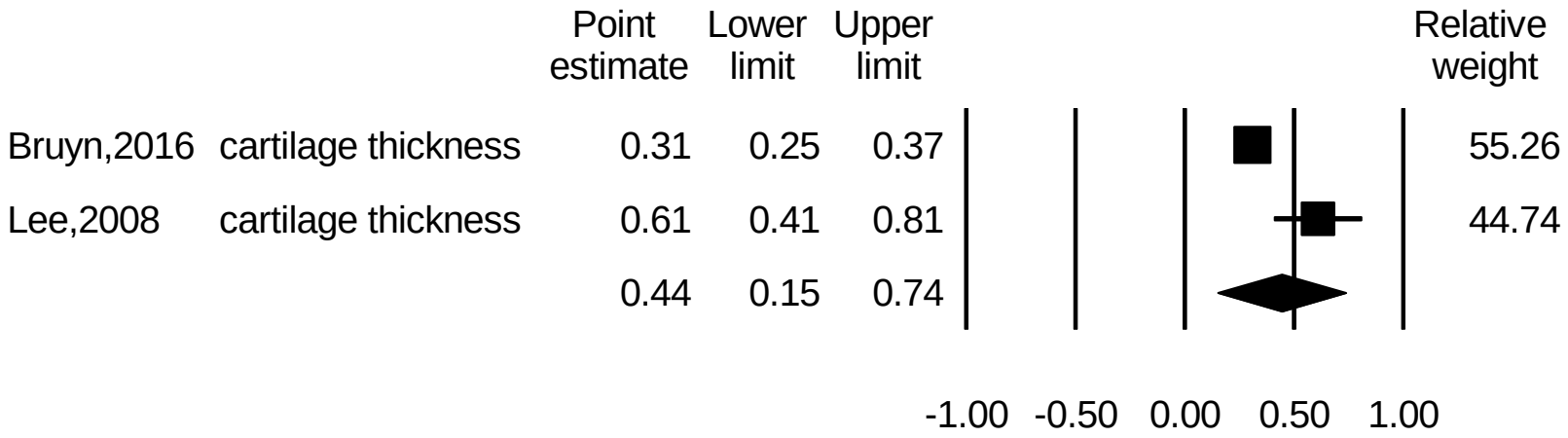
2. Forest plot for meta-analysis of osteohyte in knee OA



3. Forest plot for meta-analysis of meniscal extrusion in knee OA

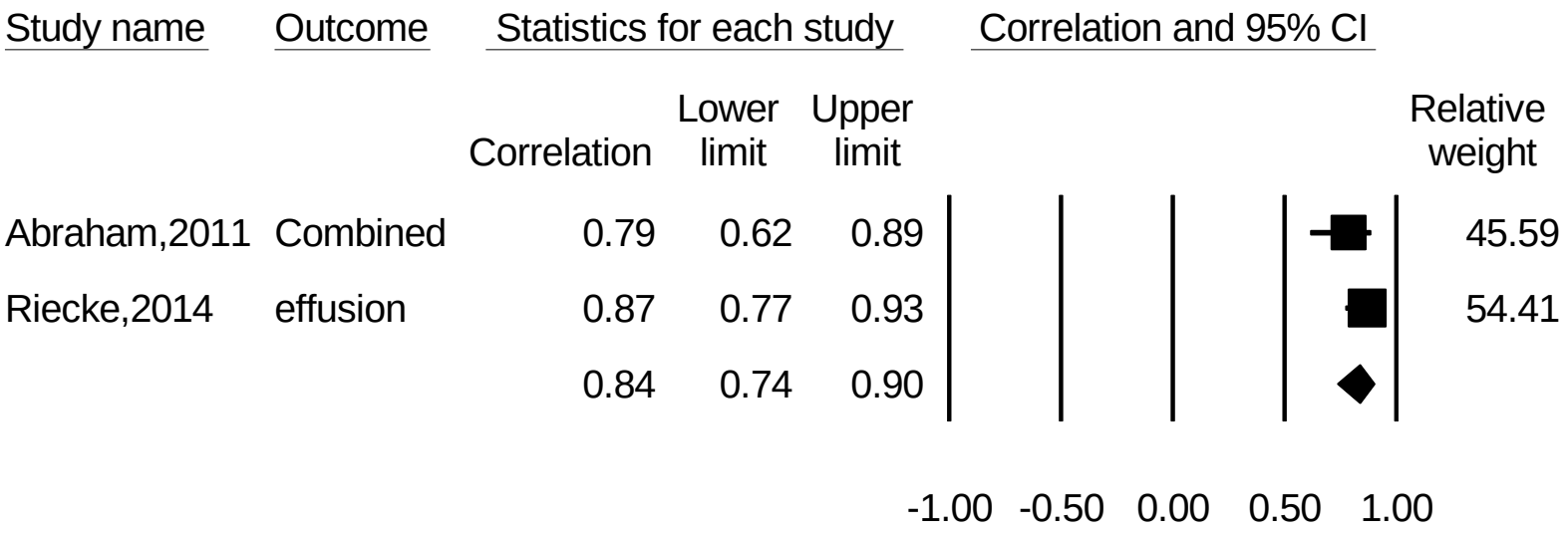


4. Forest plot for meta-analysis of cartilage thickness in knee OA

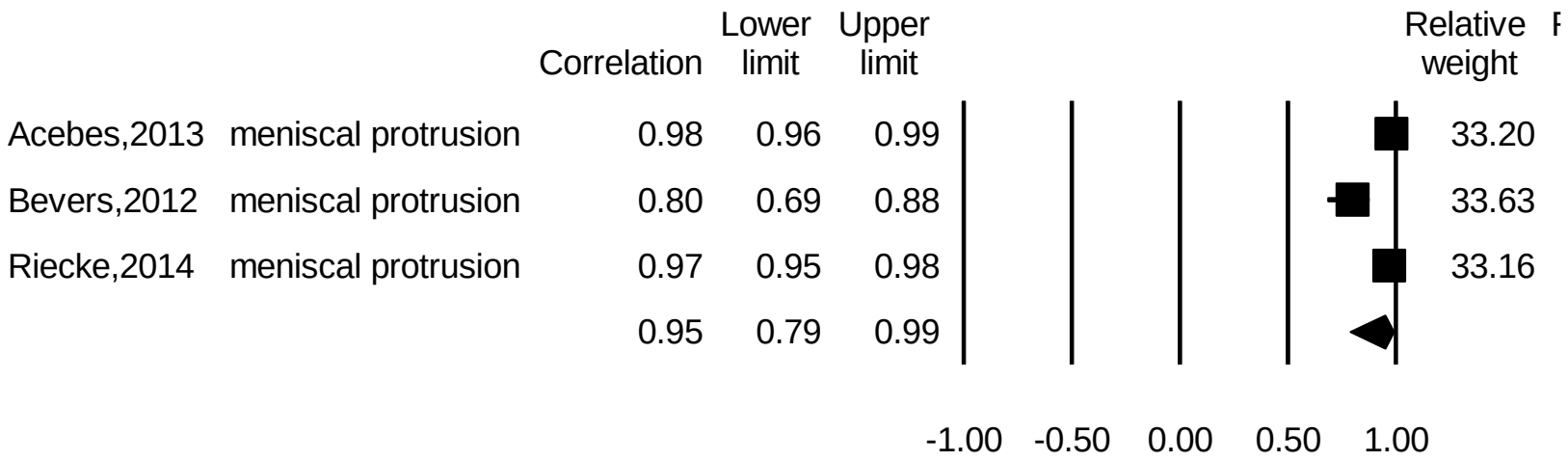


III. Inter-rater reliability for knee OA (Quantitative score)

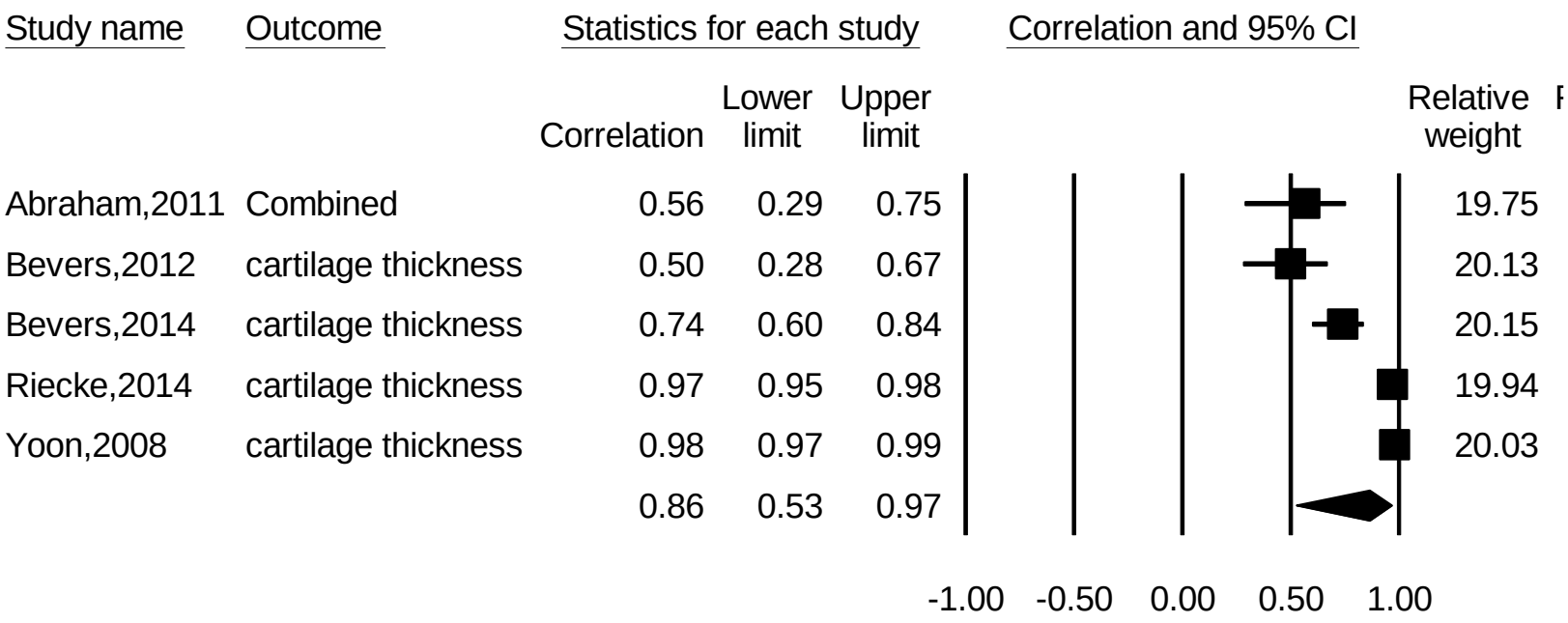
1. Forest plot for meta-analysis of effusion in knee OA



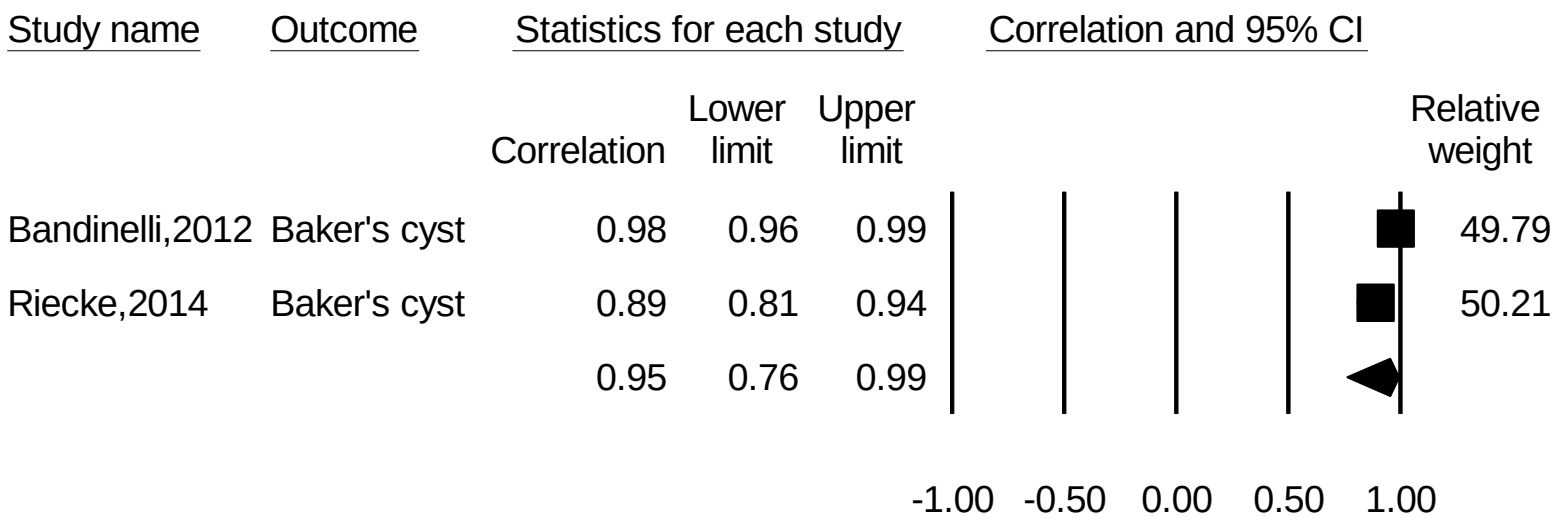
2. Forest plot for meta-analysis of meniscal protrusion in knee OA



3. Forest plot for meta-analysis of cartilage thickness in knee OA

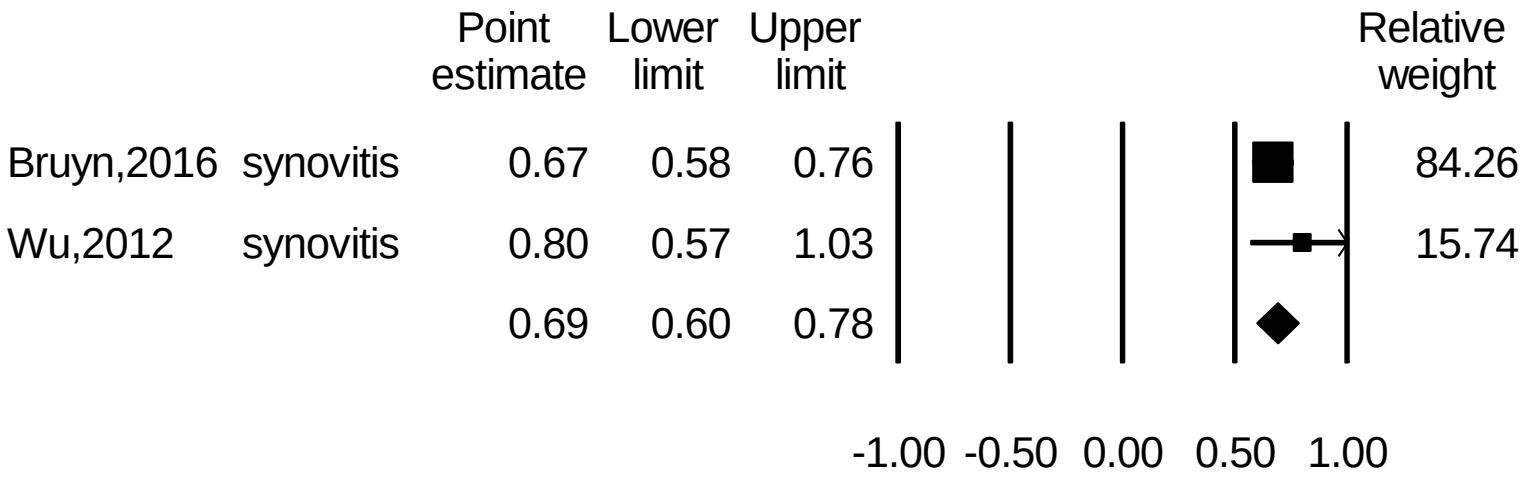


4. Forest plot for meta-analysis of Baker's cyst in knee OA

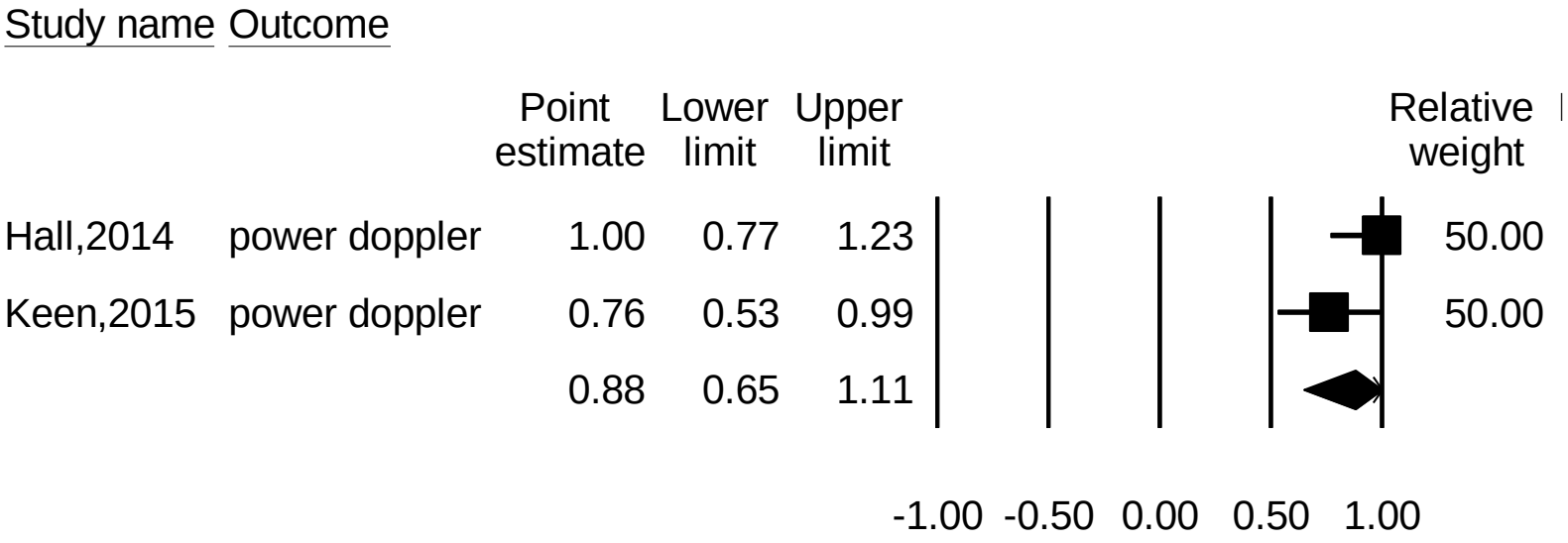


IV. Intra-rater reliability for knee OA (semi-quantitative score)

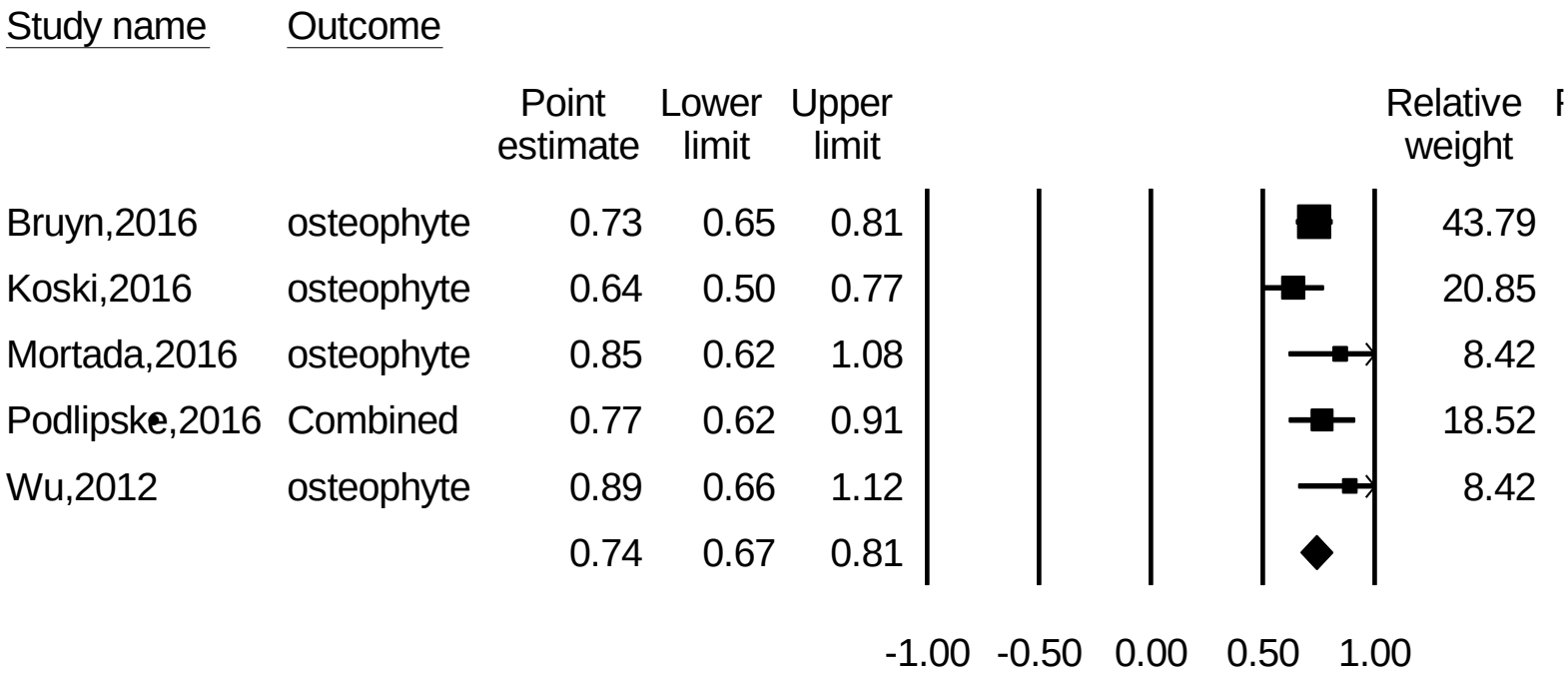
1. Forest plot for meta-analysis of synovitis in knee OA



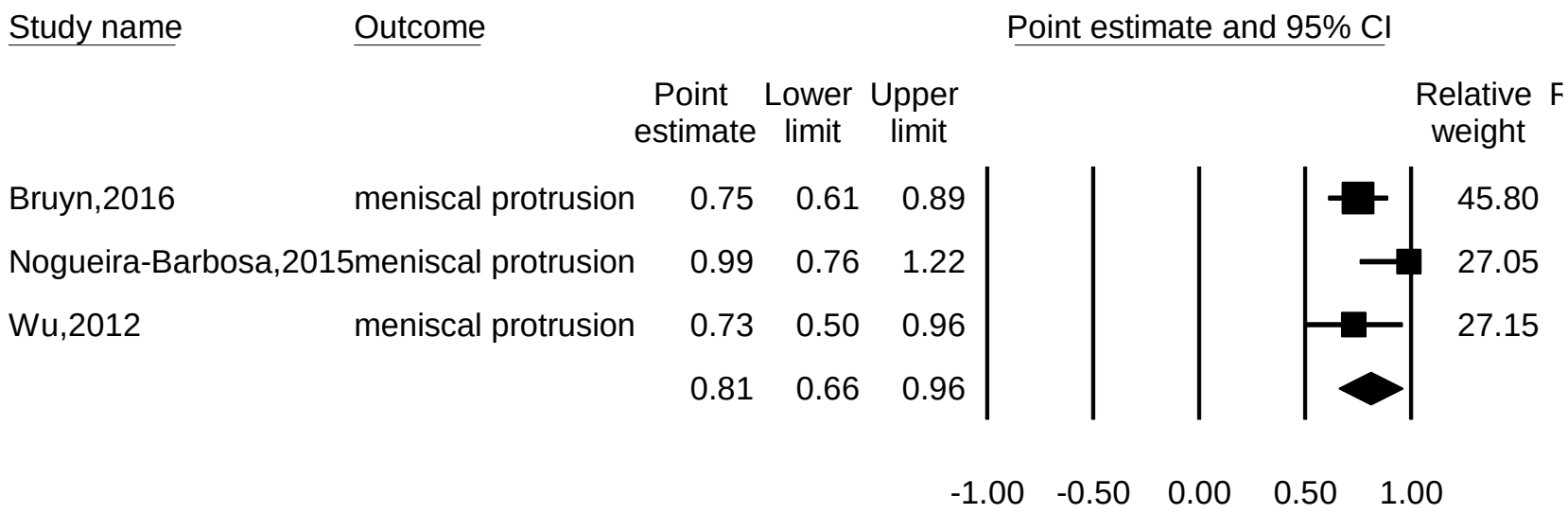
2. Forest plot for meta-analysis of power Doppler in knee OA



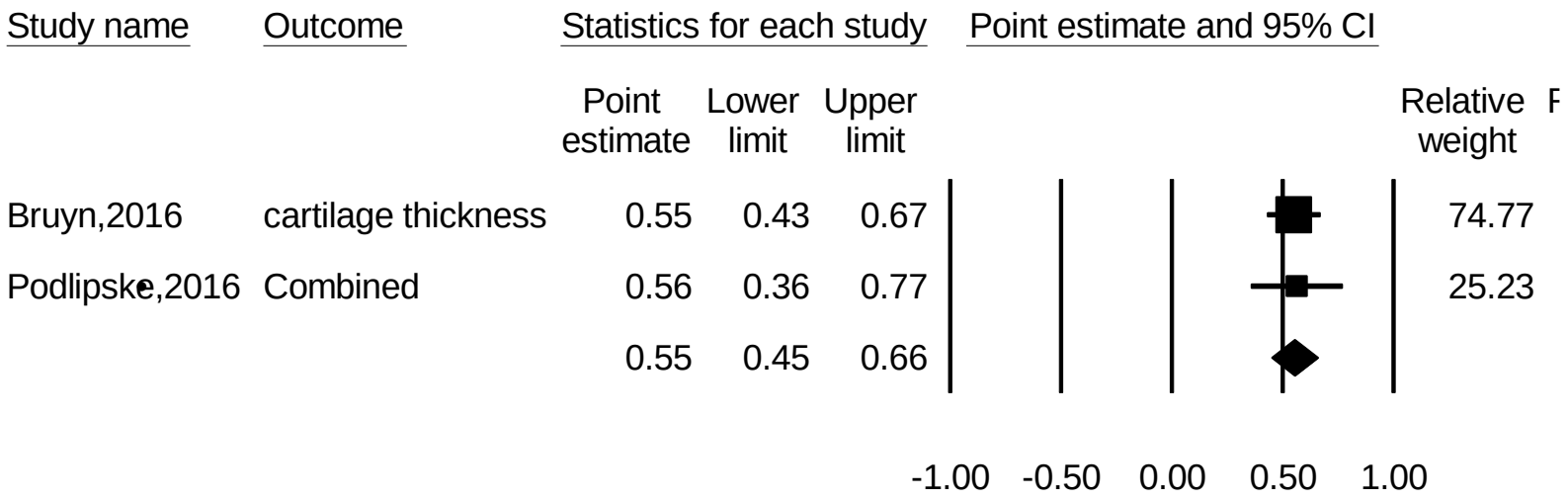
3. Forest plot for meta-analysis of osteophyte in knee OA



4. Forest plot for meta-analysis of meniscal protrusion in knee OA



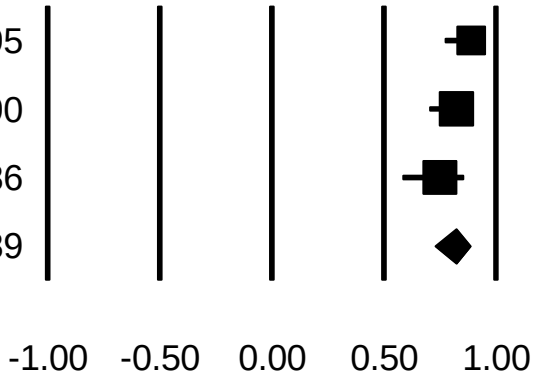
5. Forest plot for meta-analysis of cartilage thickness in knee OA



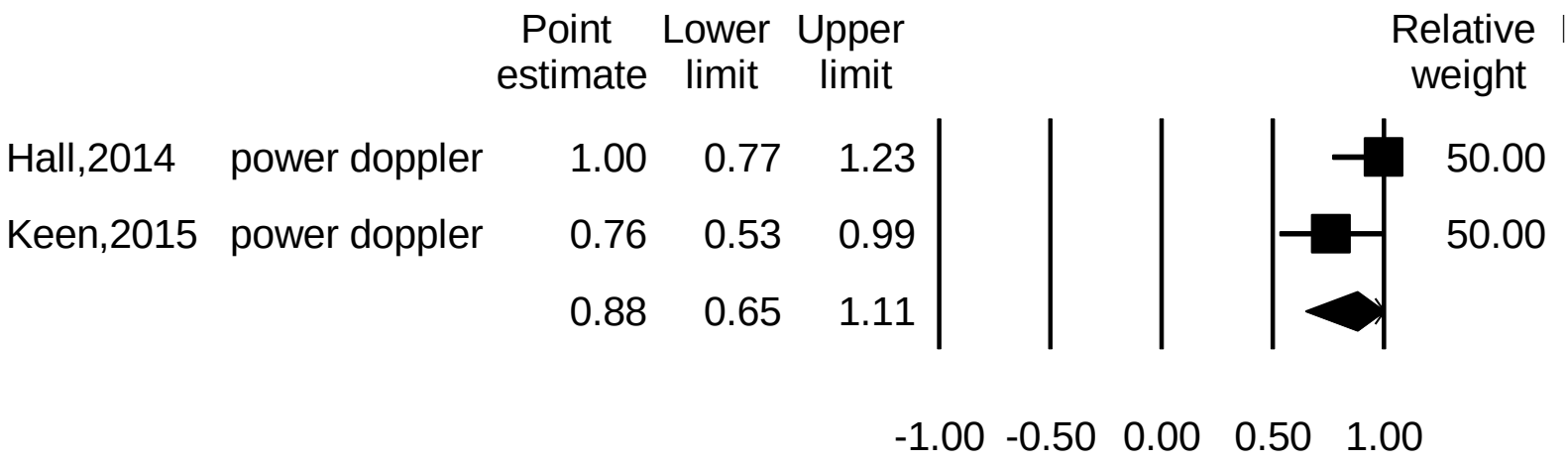
V. Intra-rater reliability for knee OA (Quantitative score)

1. Forest plot for meta-analysis of synovial hypertrophy in knee OA

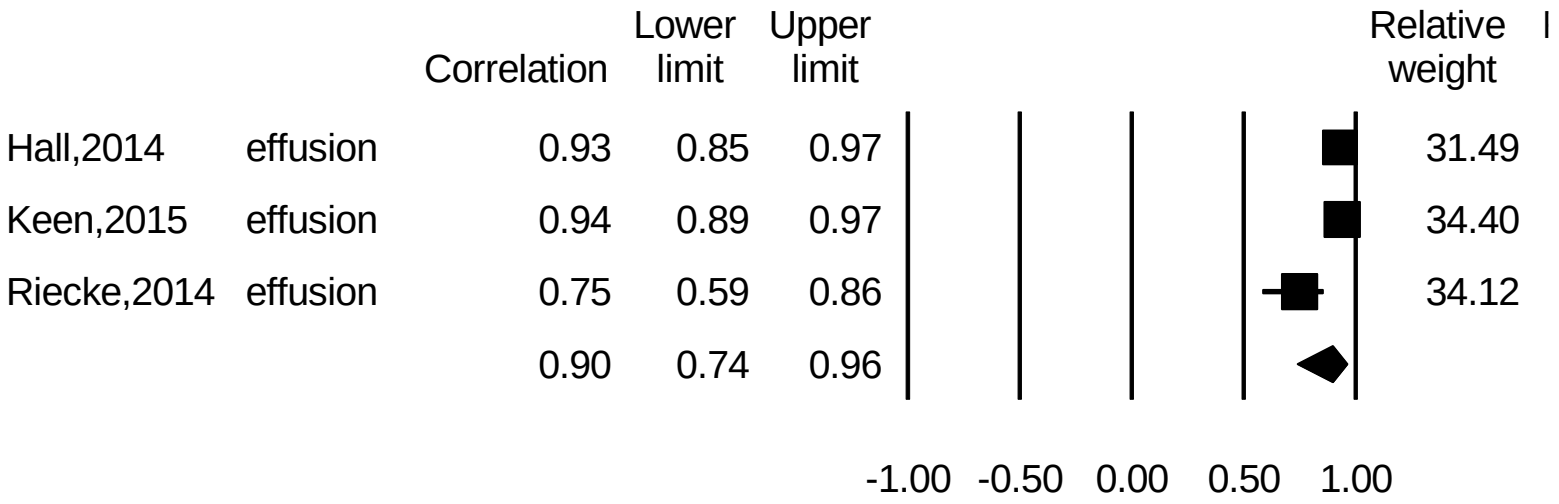
Study name	Outcome	Statistics for each study			Correlation and 95% CI	
		Correlation	Lower limit	Upper limit		Relative weight
Hall,2014	synovial hypertrophy	0.89	0.77	0.95		25.87
Keen,2015	synovial hypertrophy	0.82	0.70	0.90		37.81
Riecke,2014	synovial hypertrophy	0.75	0.59	0.86		36.32
		0.82	0.73	0.89		



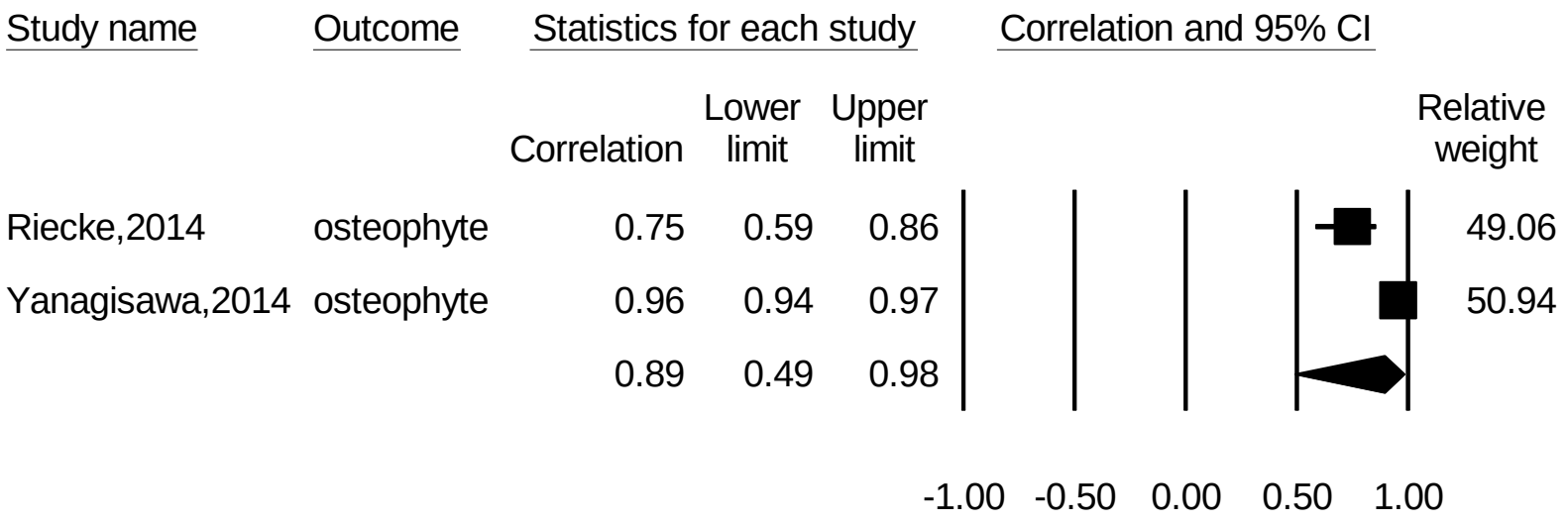
2. Forest plot for meta-analysis of power Doppler in knee OA



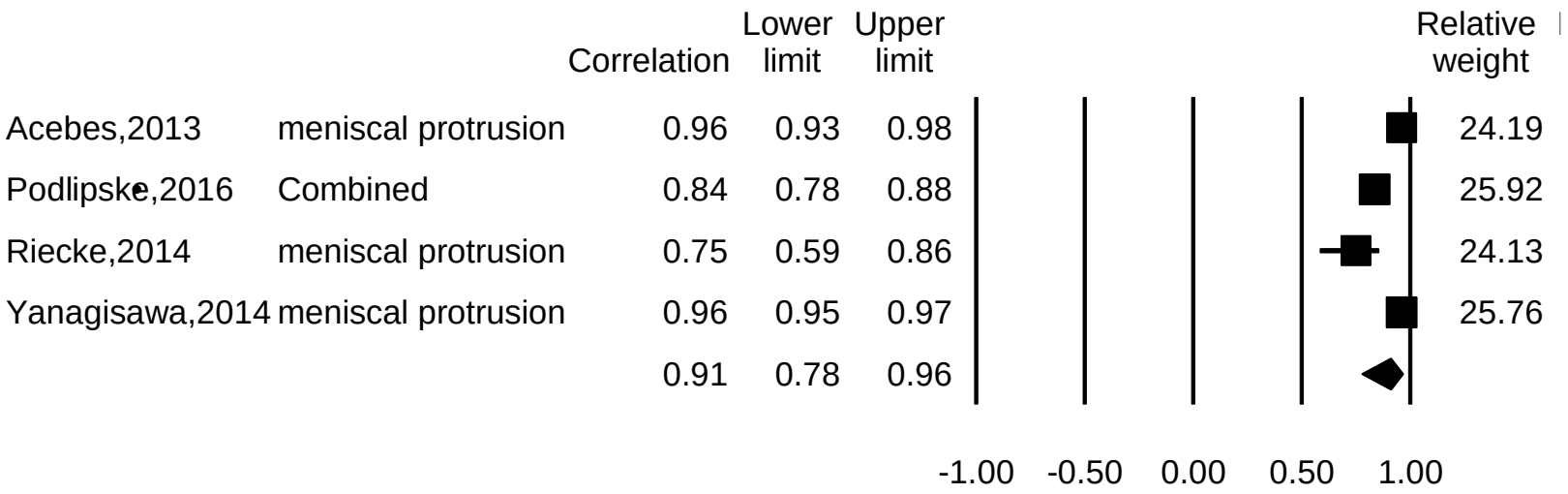
3. Forest plot for meta-analysis of effusion in knee OA



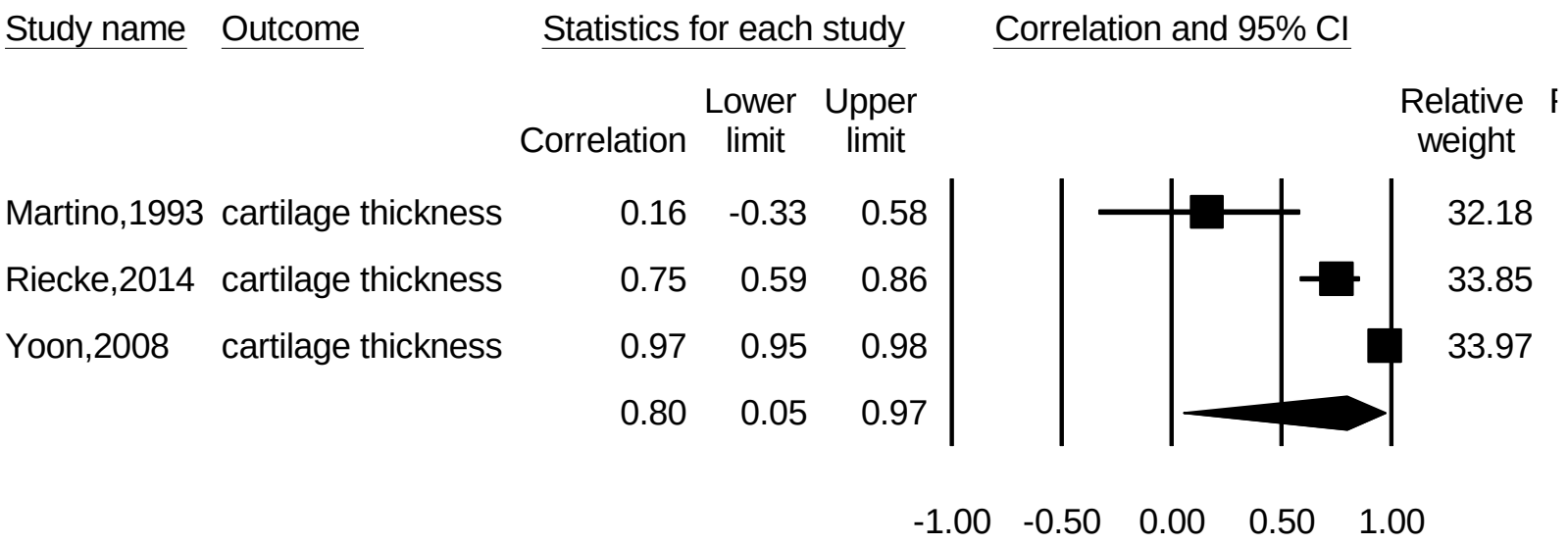
4. Forest plot for meta-analysis of osteophyte in knee OA



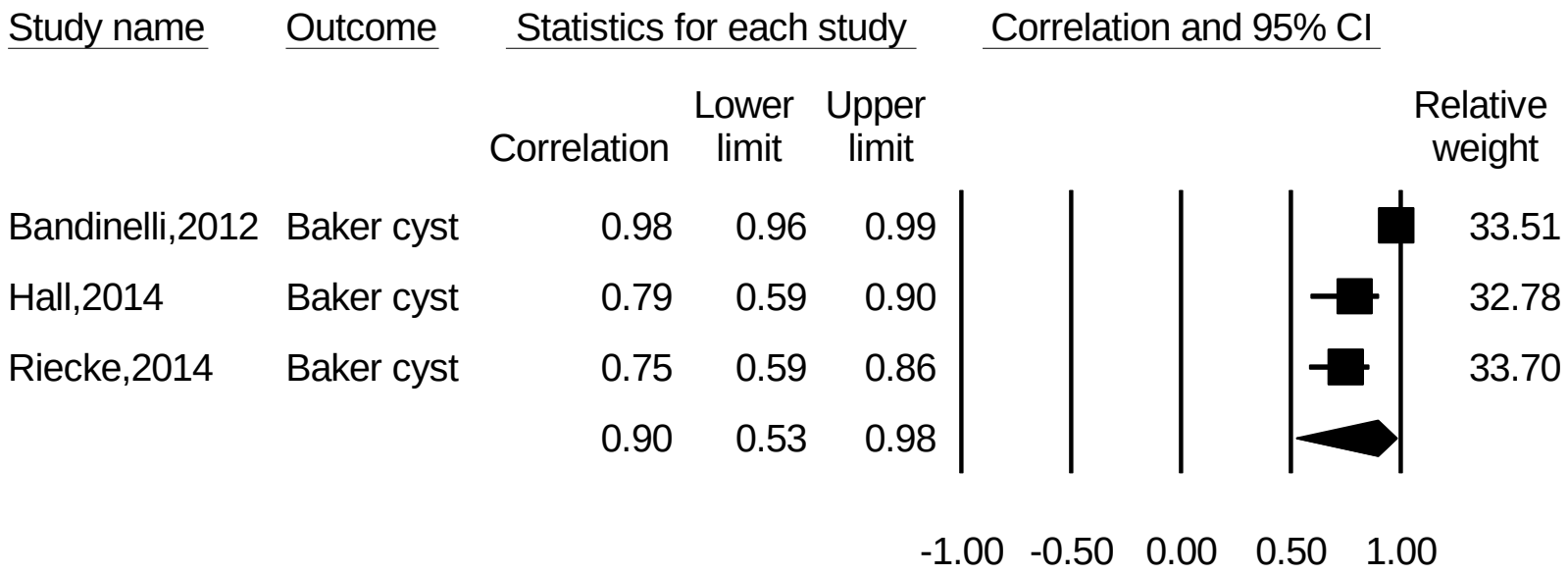
5. Forest plot for meta-analysis of meniscal protrusion in knee OA



6. Forest plot for meta-analysis of cartilage thickness in knee OA



7. Forest plot for meta-analysis of Baker's cyst in knee OA

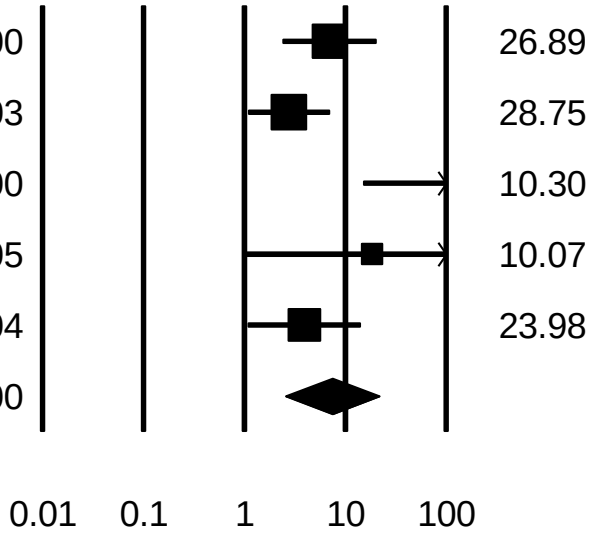


B. Construct validity

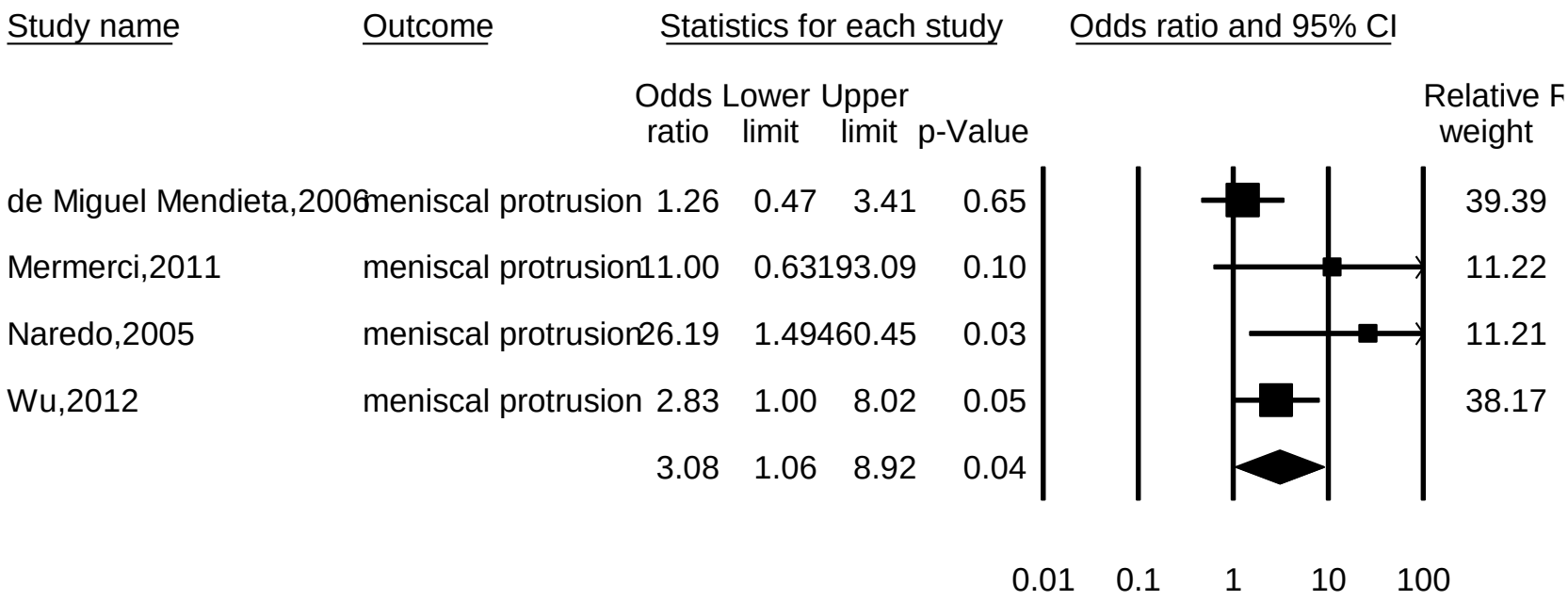
I. Construct validity of ultrasound features with symptomatic patients against healthy control

1. Forest plot for meta-analysis of effusion in knee OA

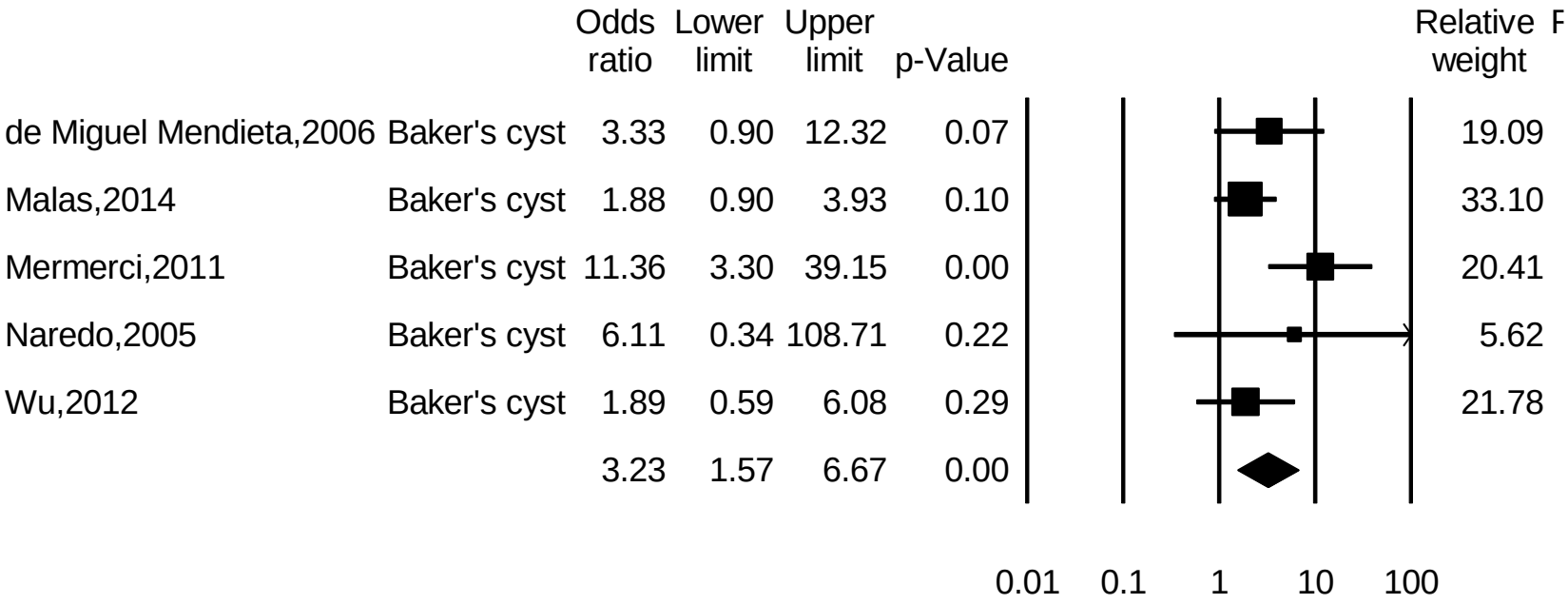
Study name	Outcome	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
de Miguel Mendieta,2006	effusion	6.99	2.41	20.24	0.00	26.89
Malas,2014	effusion	2.77	1.10	6.99	0.03	28.75
Mermerci,2011	effusion	255.91	15.23	4300.27	0.00	10.30
Naredo,2005	effusion	18.40	1.05	323.51	0.05	10.07
Wu,2012	effusion	3.93	1.09	14.17	0.04	23.98
		7.46	2.56	21.70	0.00	



2. Forest plot for meta-analysis of meniscal protrusion in knee OA

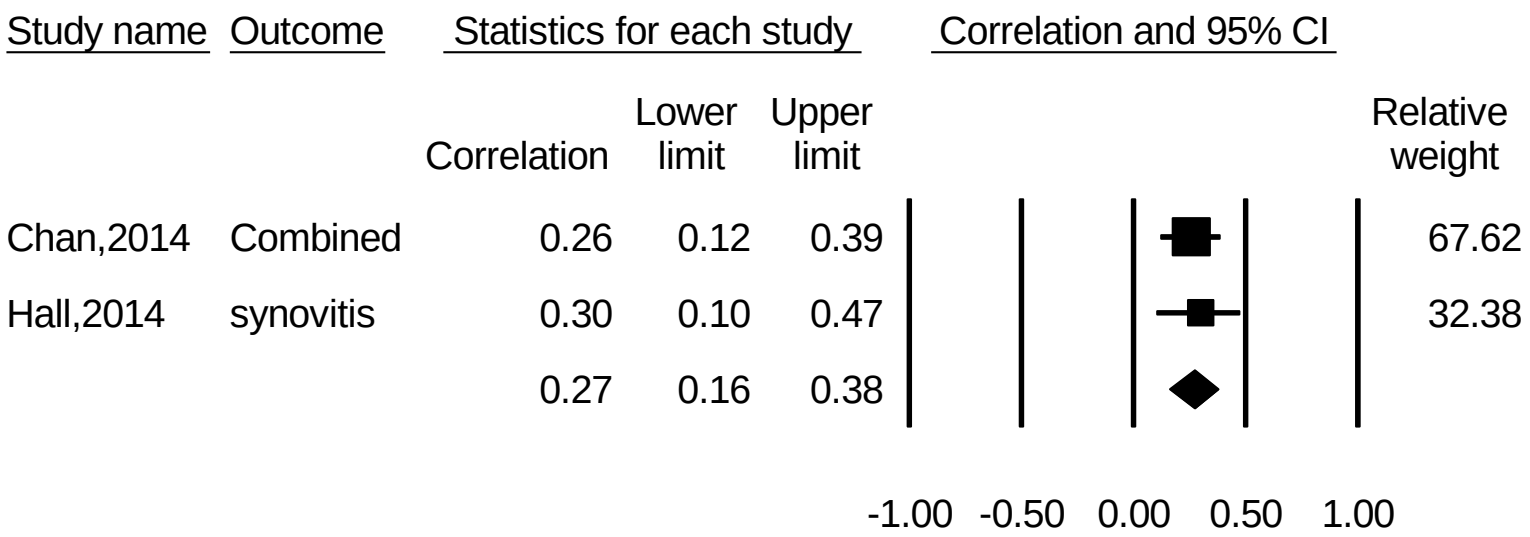


3. Forest plot for meta-analysis of Baker's cyst in knee OA

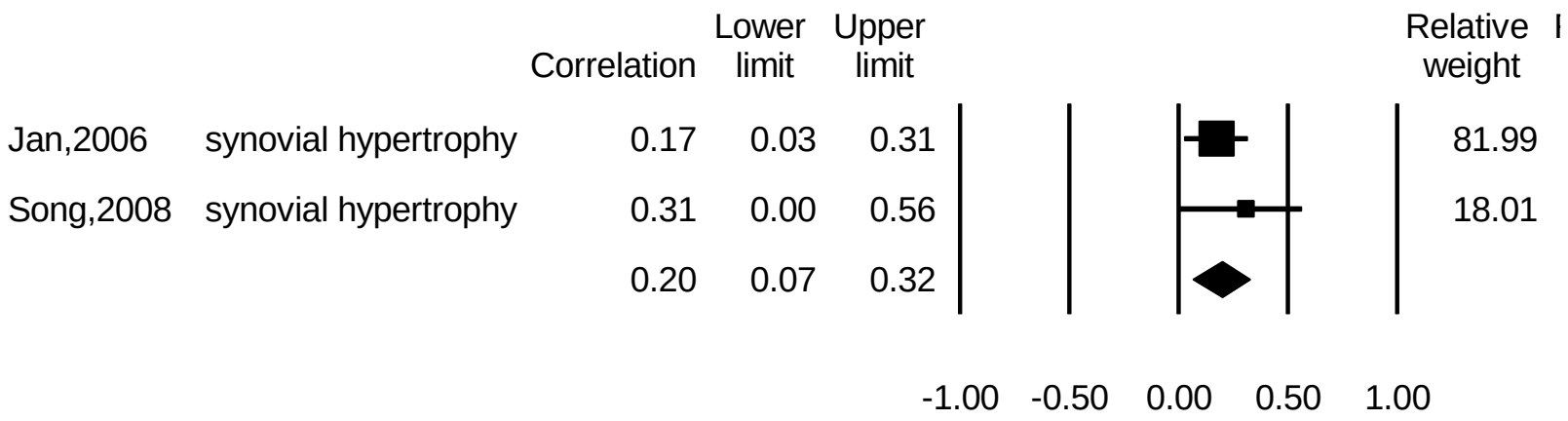


II. Construct validity of ultrasound features with pain

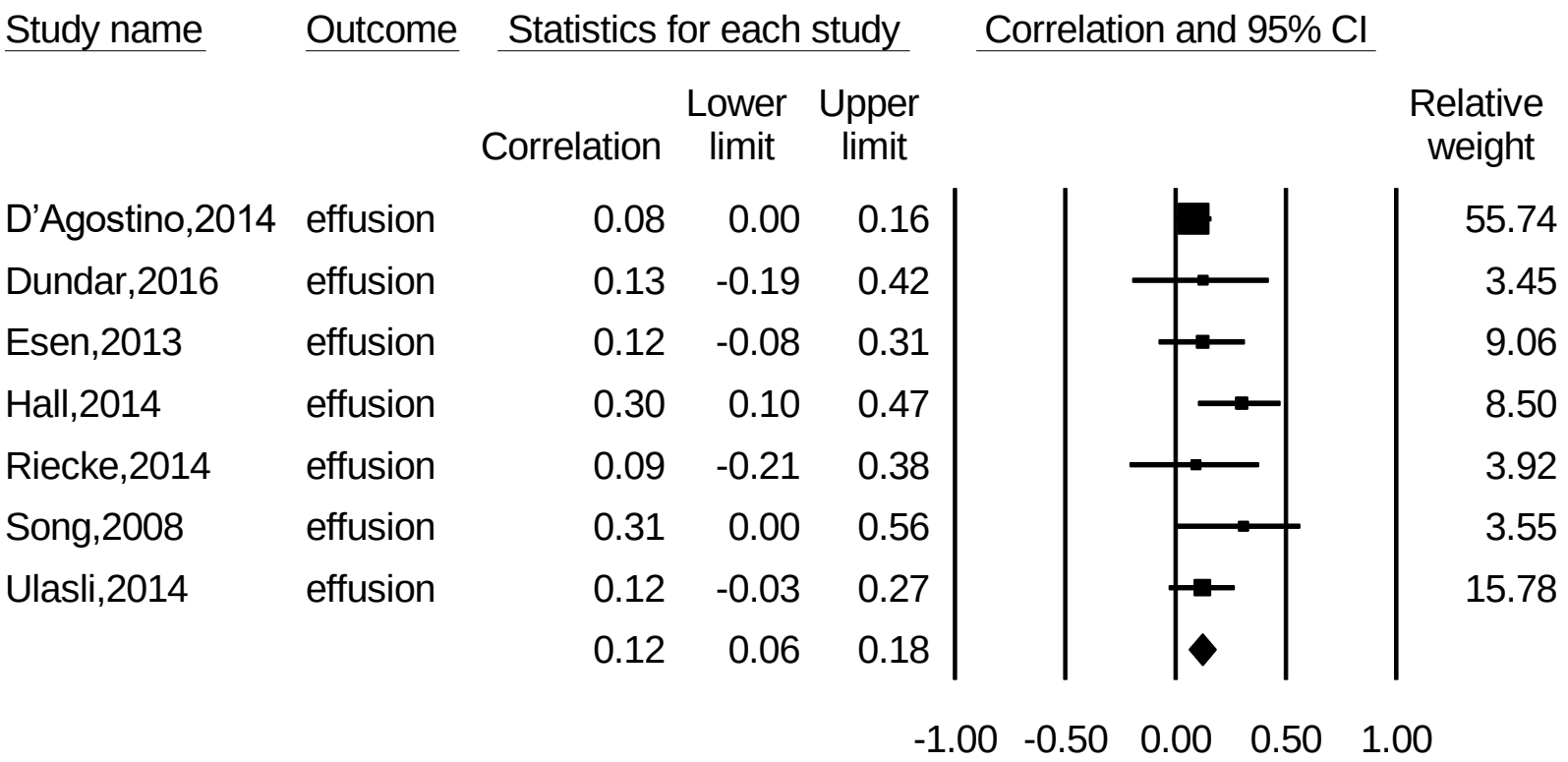
1. Forest plot for meta-analysis of synovitis in knee OA



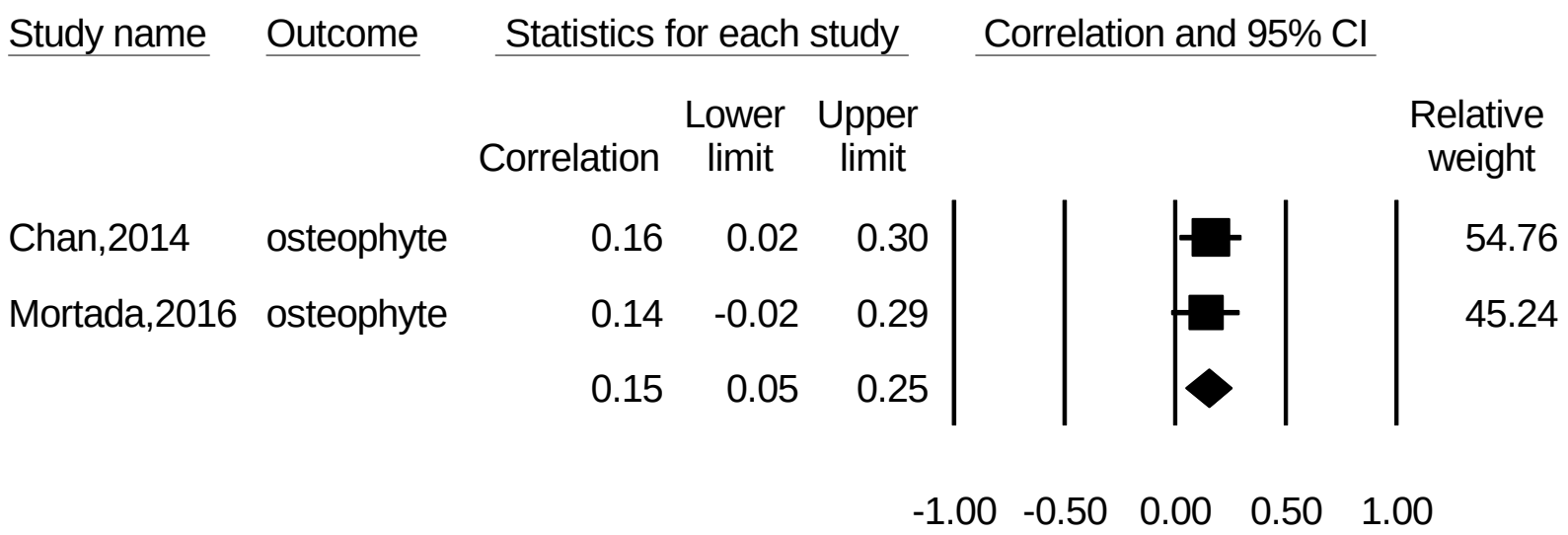
2. Forest plot for meta-analysis of synovial hypertrophy in knee OA



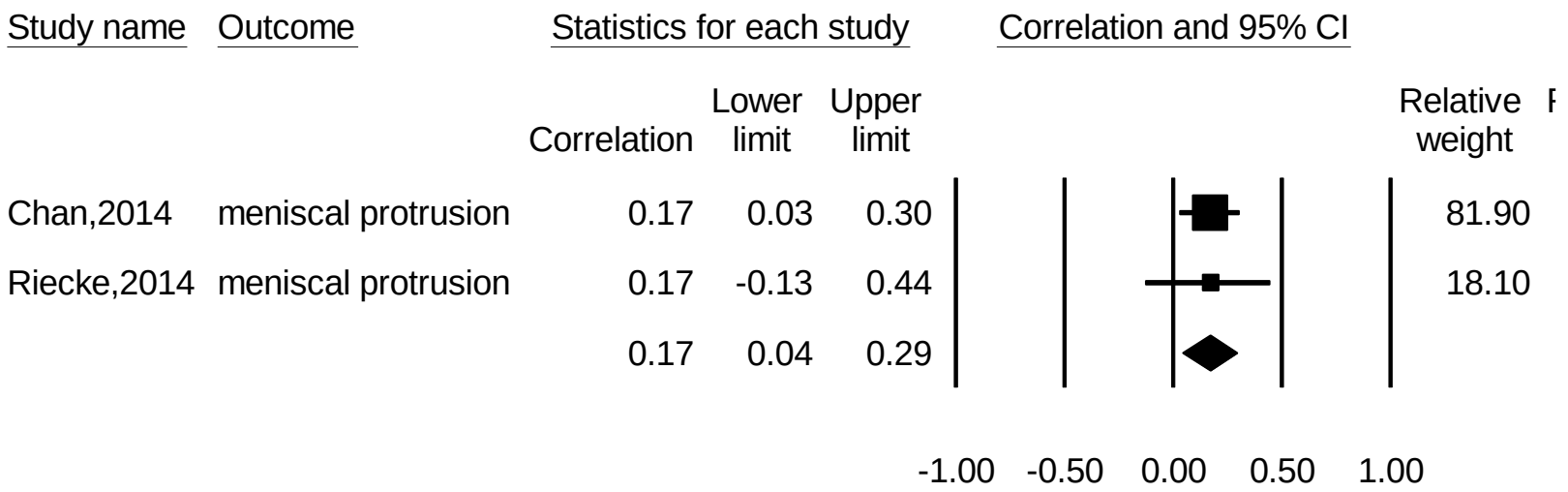
3. Forest plot for meta-analysis of effusion in knee OA



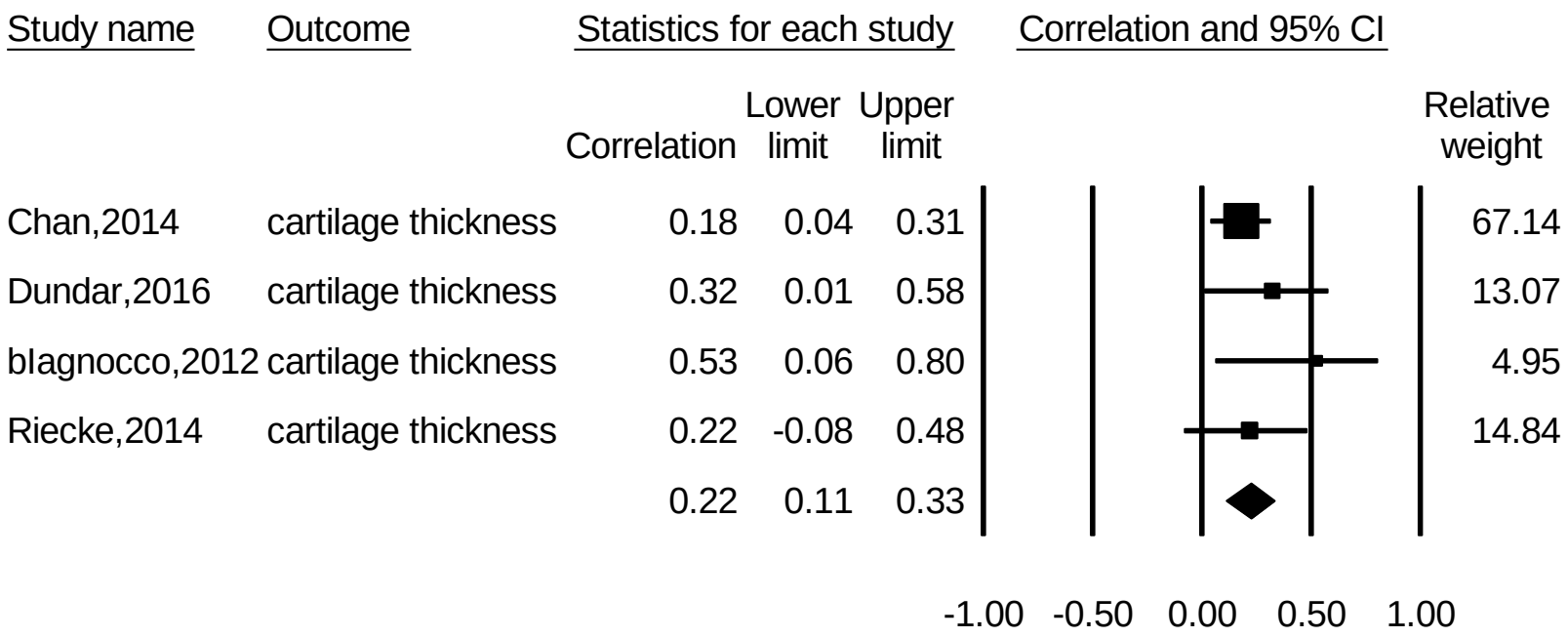
4. Forest plot for meta-analysis of osteophyte in knee OA



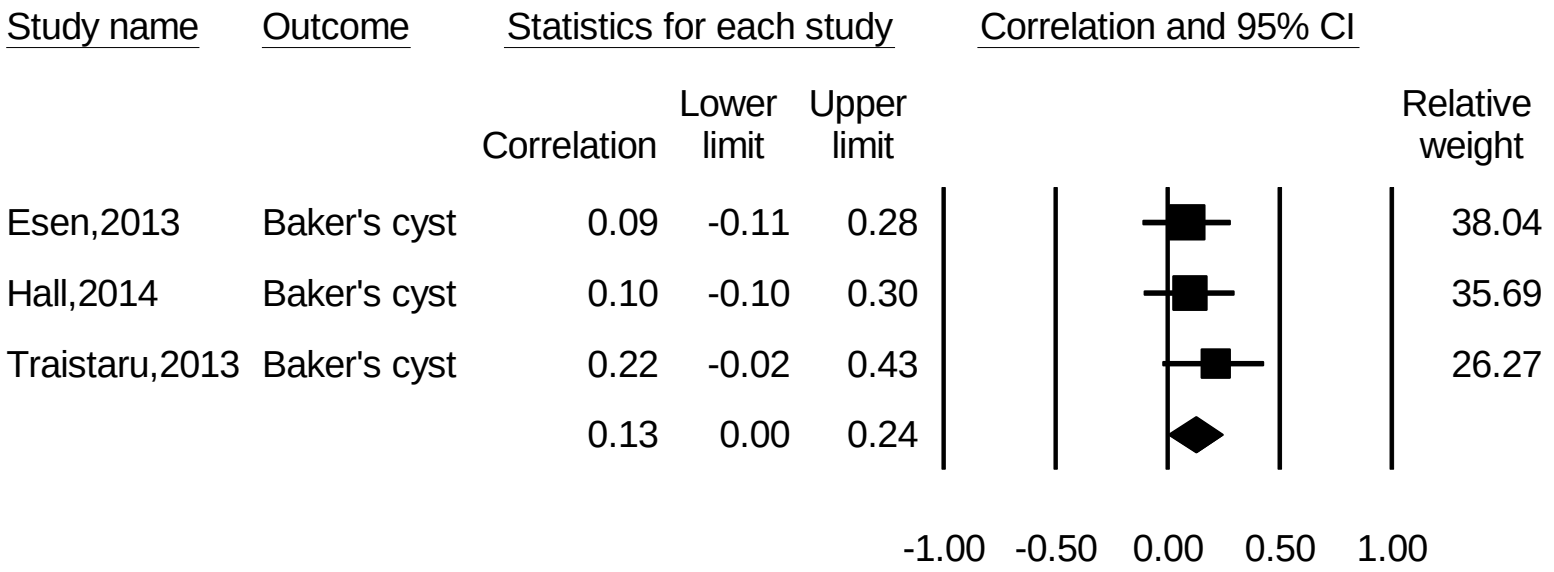
5. Forest plot for meta-analysis of meniscal protrusion in knee OA



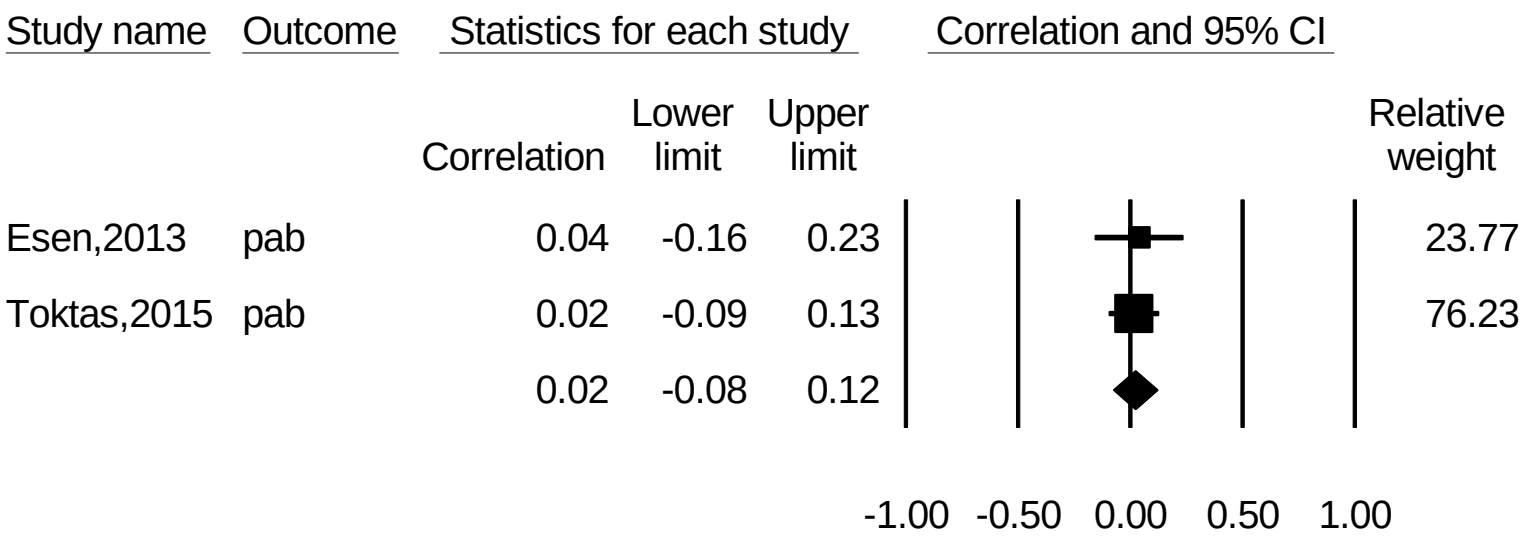
6. Forest plot for meta-analysis of cartilage thickness in knee OA



7. Forest plot for meta-analysis of Baker's cyst in knee OA



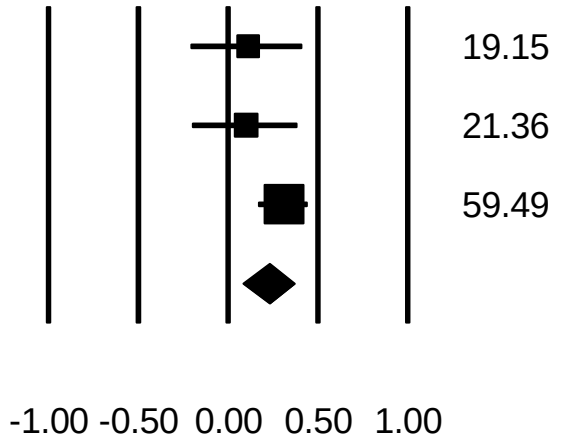
8. Forest plot for meta-analysis of pes anserine bursitis (pab) in knee OA



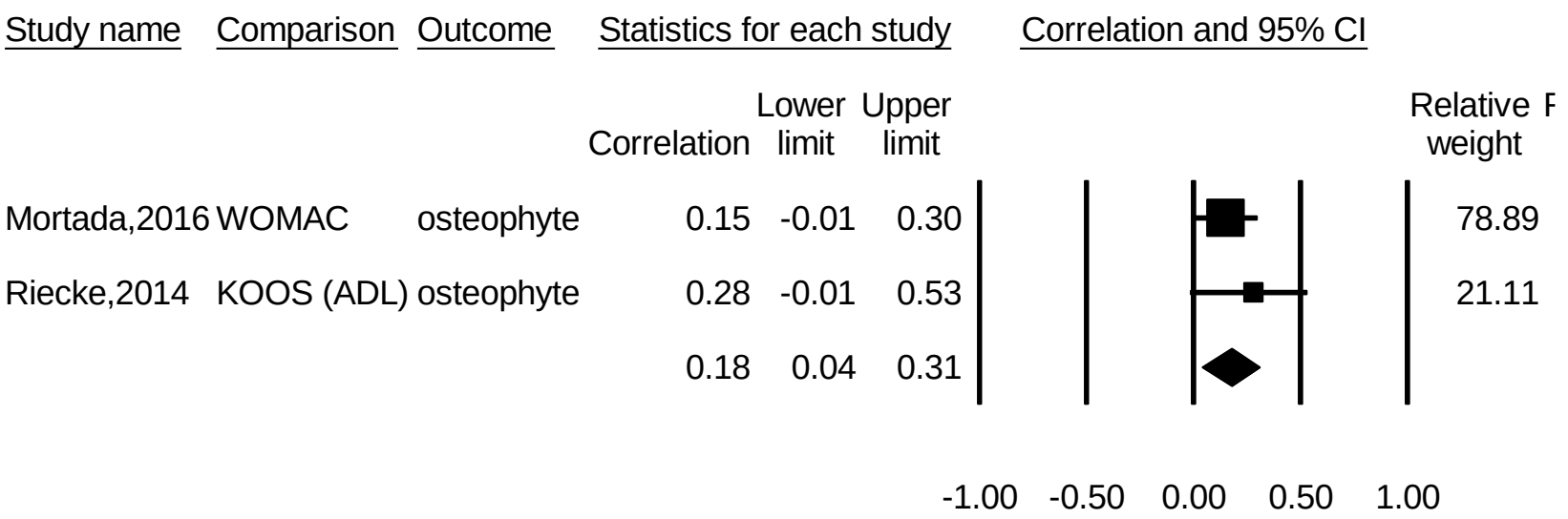
III. Construct validity of ultrasound features with function

1. Forest plot for meta-analysis of effusion in knee OA

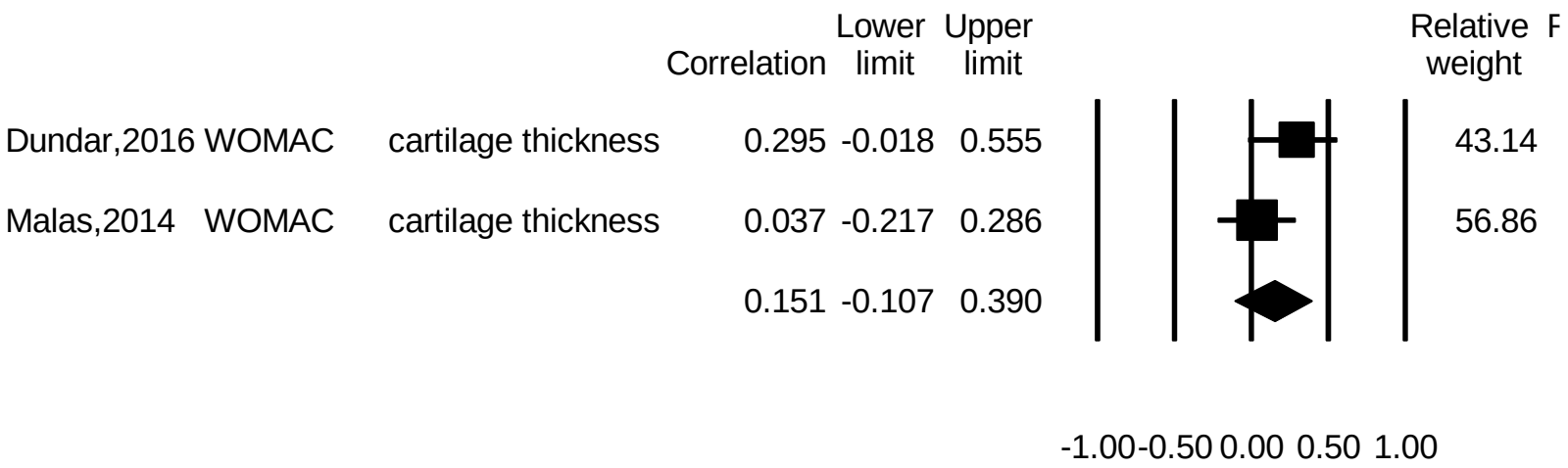
Study name	Comparison	Outcome	Correlation	Lower limit	Upper limit	Relative weight
Dundar,2016	WOMAC	effusion	0.11	-0.21	0.41	19.15
Riecke,2014	KOOS (ADL)	effusion	0.10	-0.20	0.38	21.36
Ulasli,2014	WOMAC	effusion	0.31	0.17	0.44	59.49
			0.23	0.08	0.37	



2. Forest plot for meta-analysis of osteophyte in knee OA

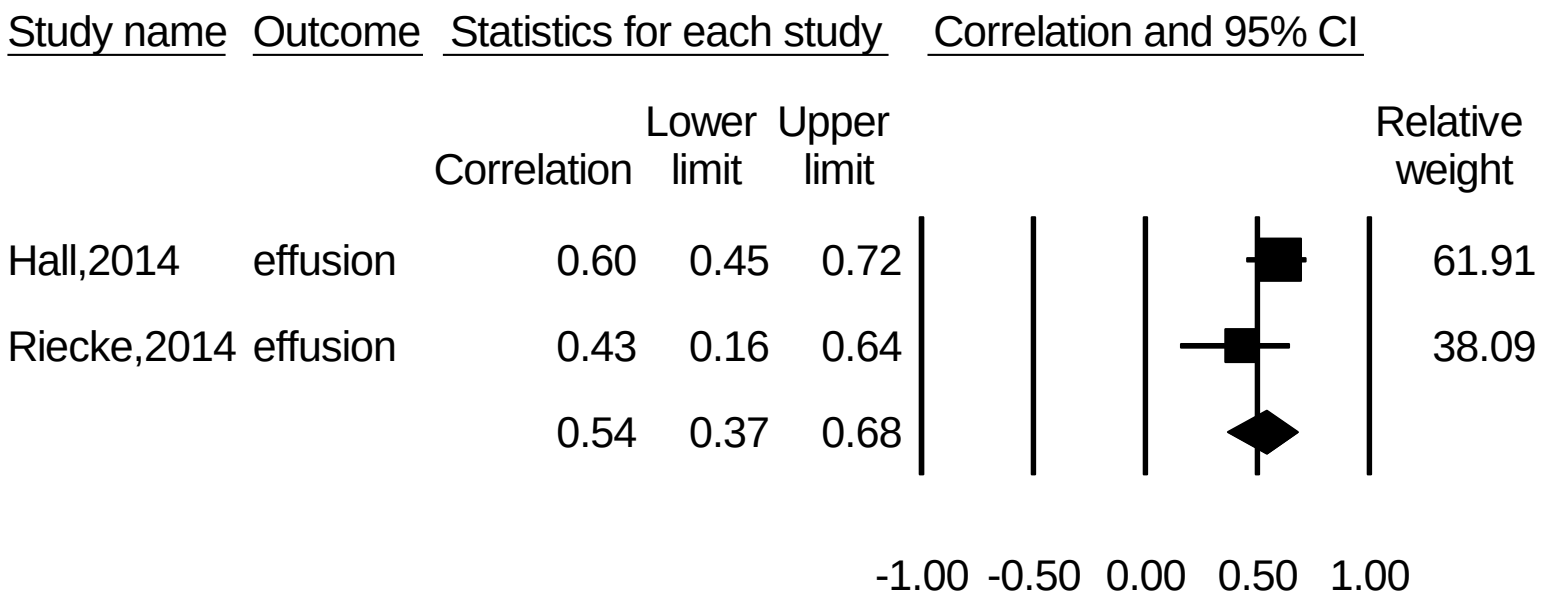


3. Forest plot for meta-analysis of cartilage thickness in knee OA

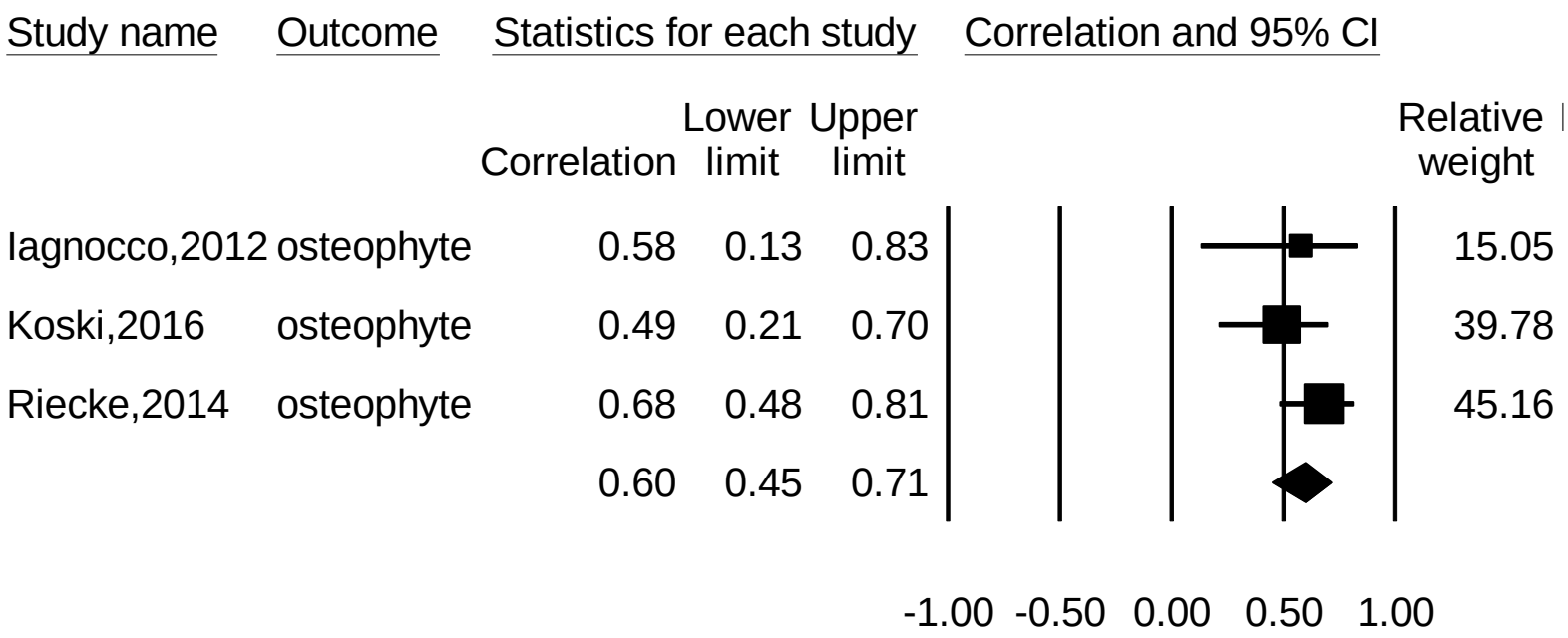


IV. Construct validity of ultrasound features with X rays

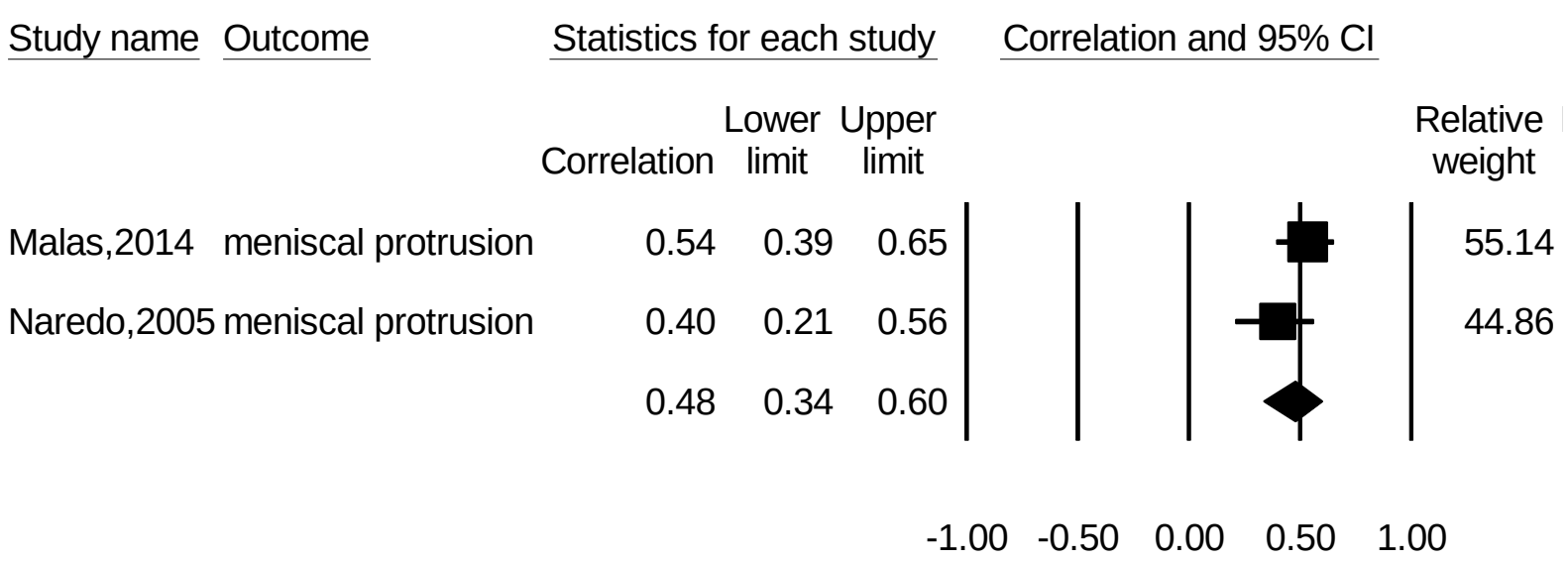
1. Forest plot for meta-analysis of effusion in knee OA



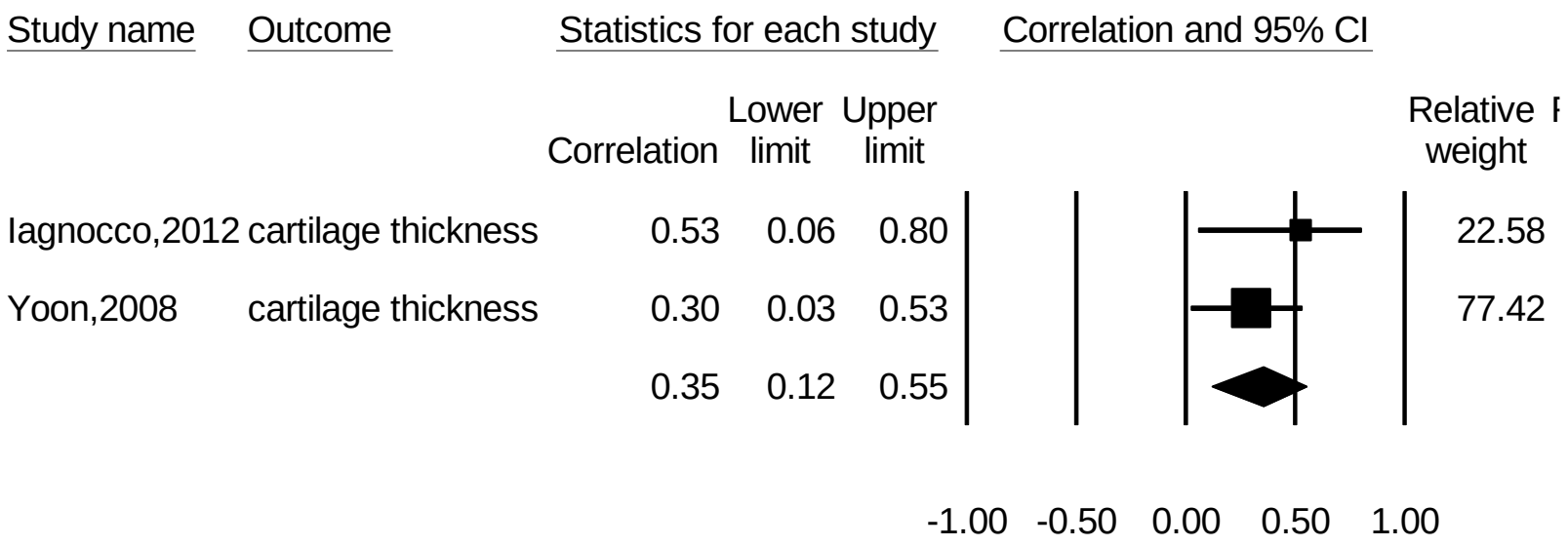
2. Forest plot for meta-analysis of osteophyte in knee OA



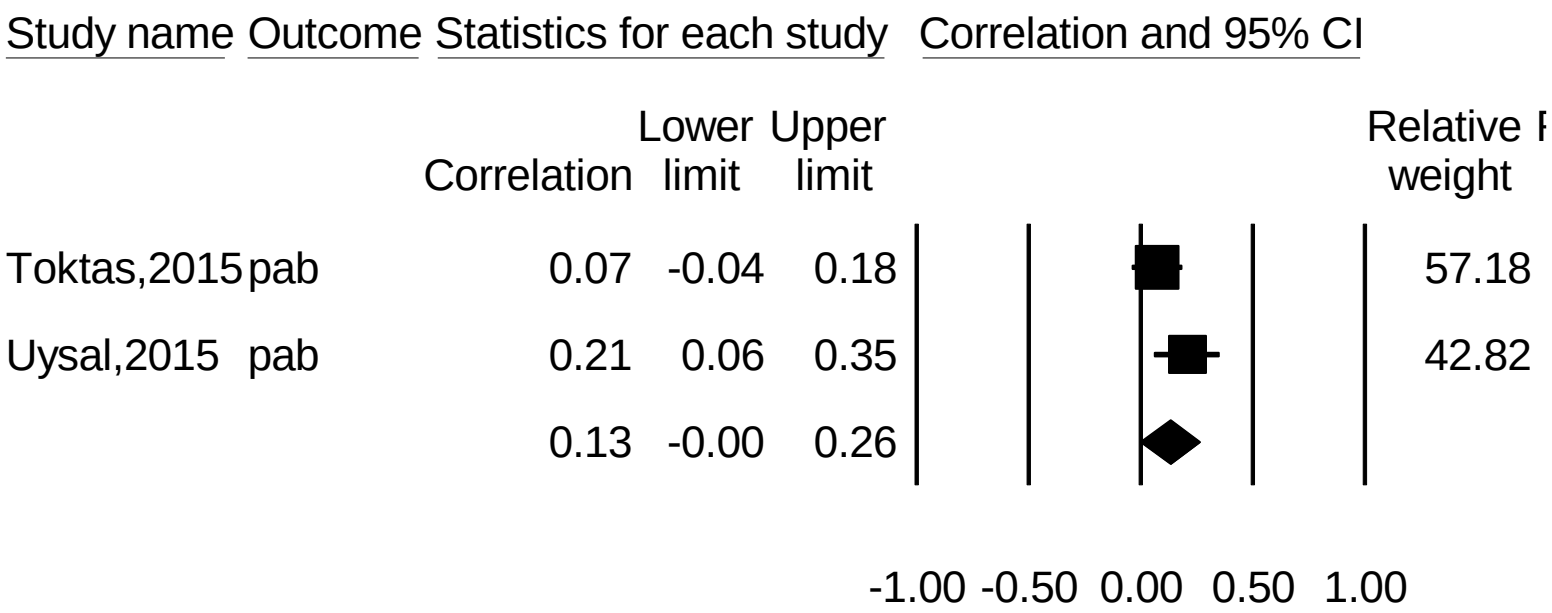
3. Forest plot for meta-analysis of meniscal protrusion in knee OA



4. Forest plot for meta-analysis of cartilage thickness in knee OA

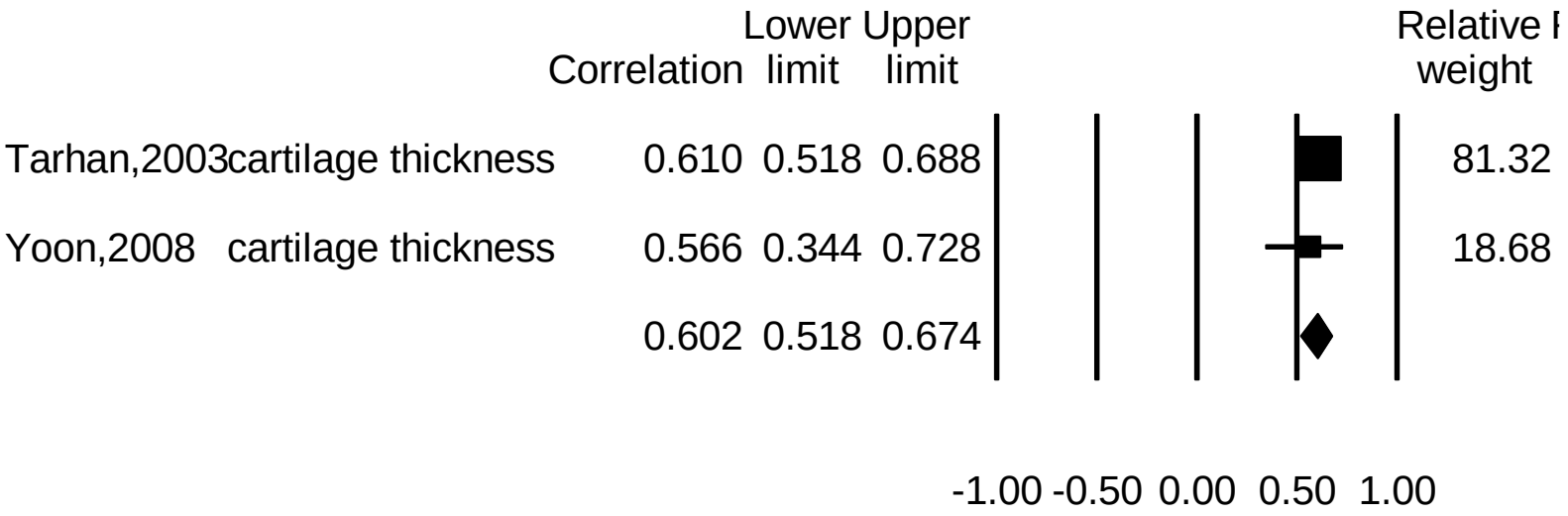


5. Forest plot for meta-analysis of pes anserine bursitis (pab) in knee OA



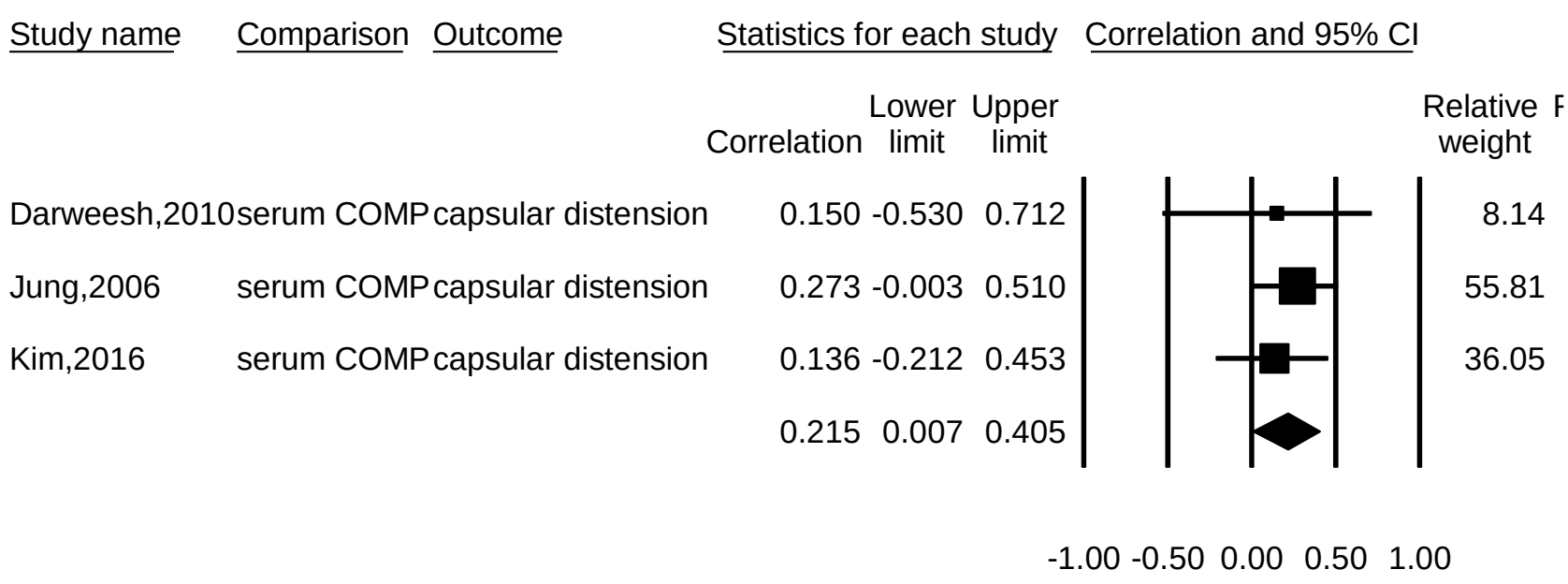
V. Construct validity of ultrasound features with MRI

1. Forest plot for meta-analysis of cartilage thickness in knee OA

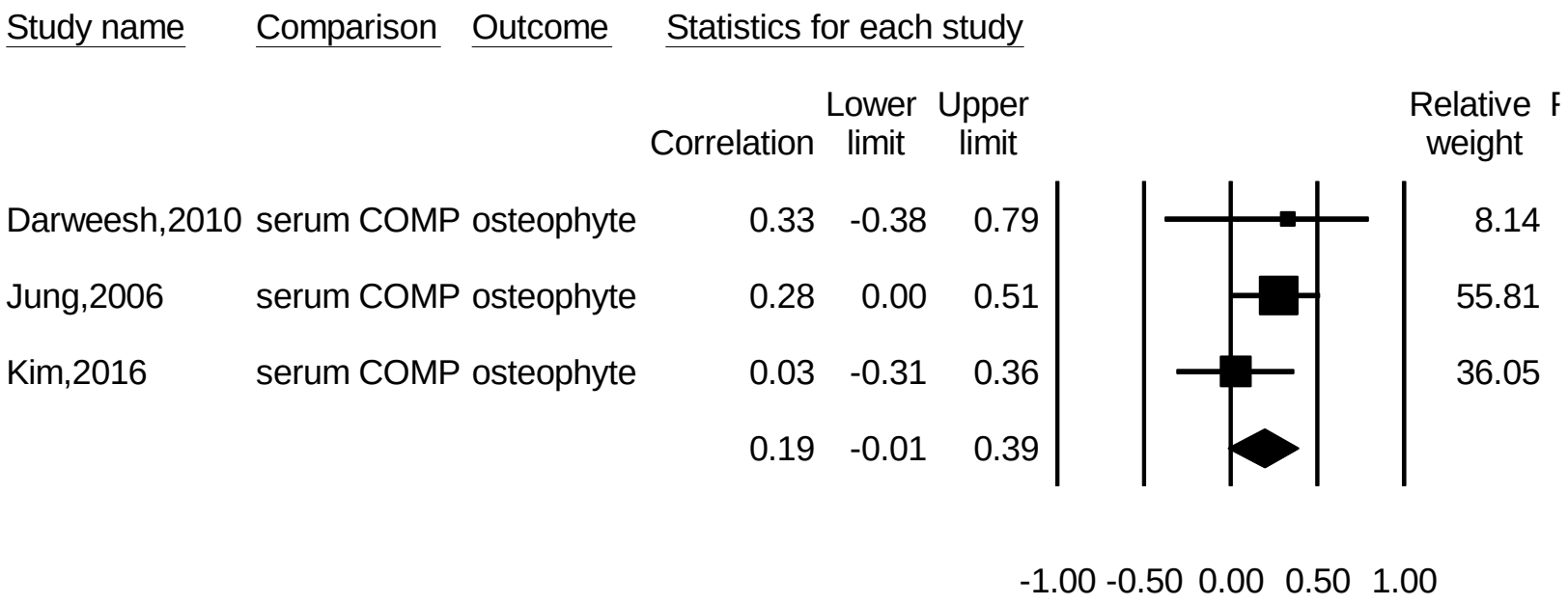


VI. Construct validity of ultrasound features with blood biomarkers

1. Forest plot for meta-analysis of capsular distension in knee OA



2. Forest plot for meta-analysis of osteophyte in knee OA

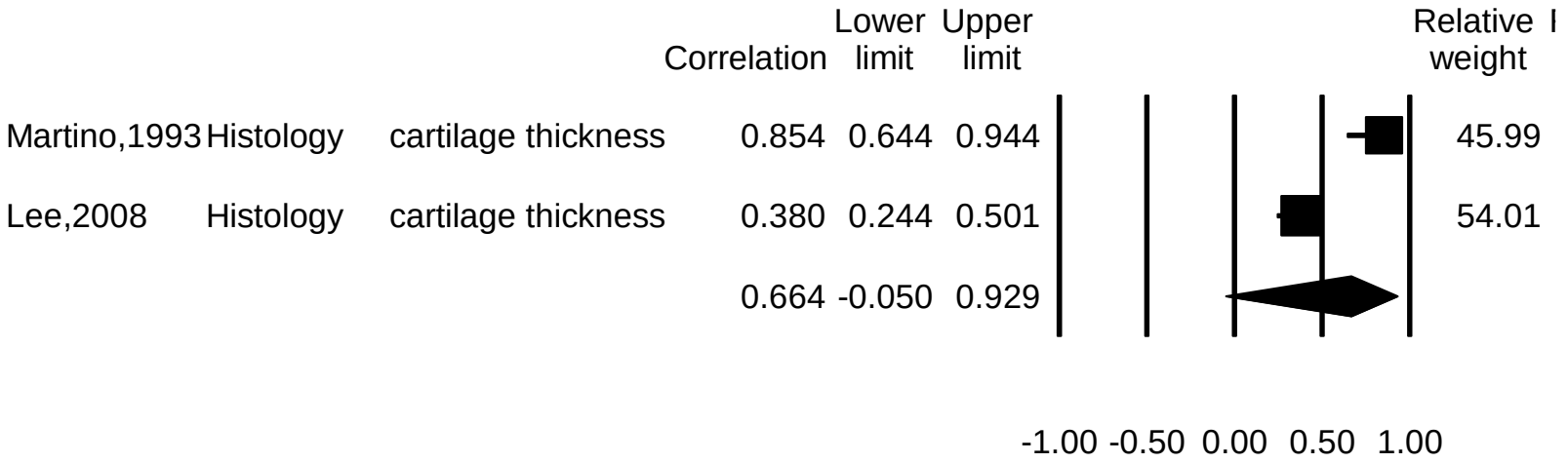


3. Forest plot for meta-analysis of cartilage thickness in knee OA

C. Criteria validity

I. Criteria validity of ultrasound features with histology

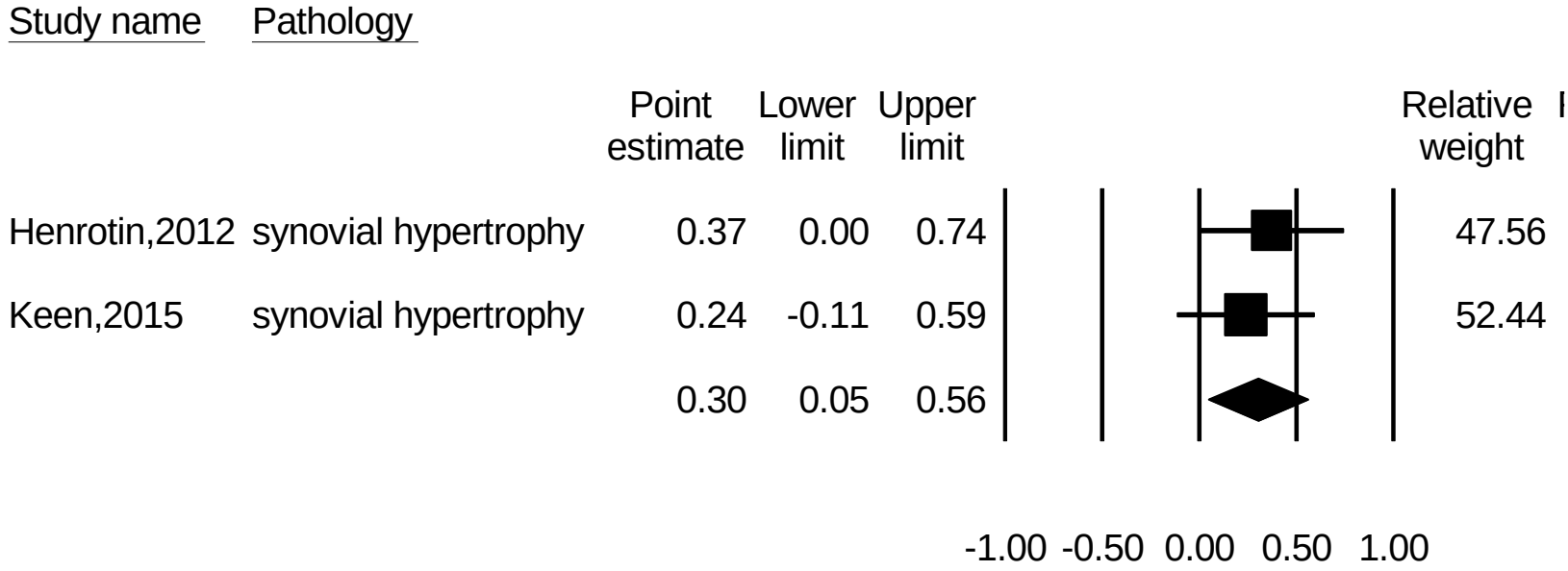
1. Forest plot for meta-analysis of cartilage thickness in knee OA



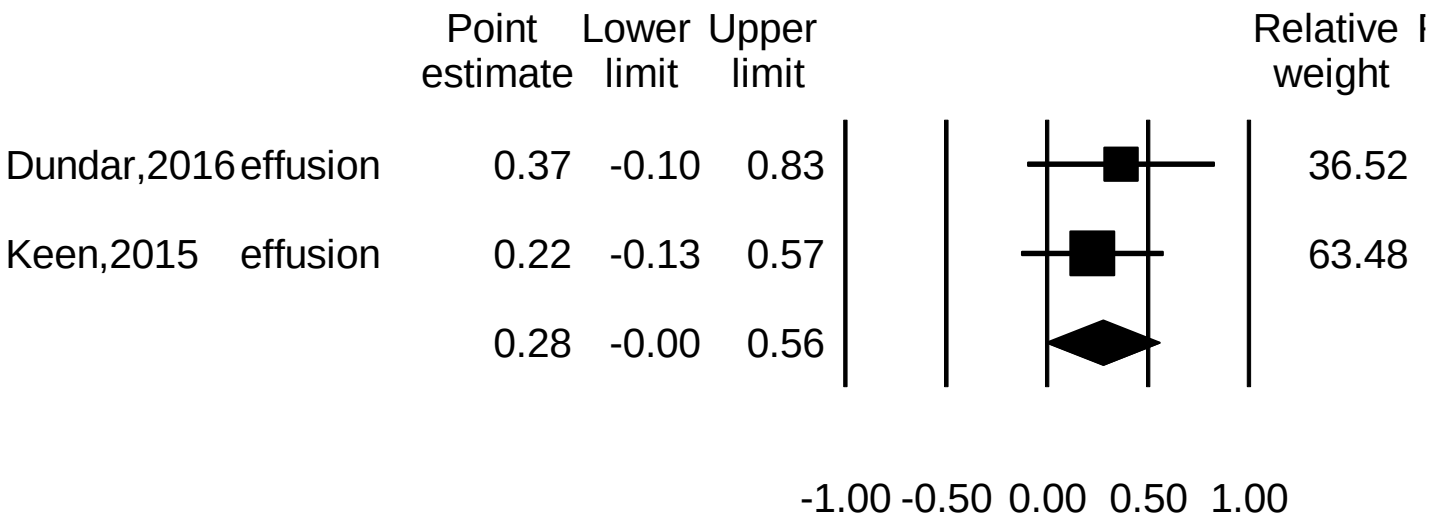
D. Responsiveness

I. Internal responsiveness of ultrasound features (paired sample)

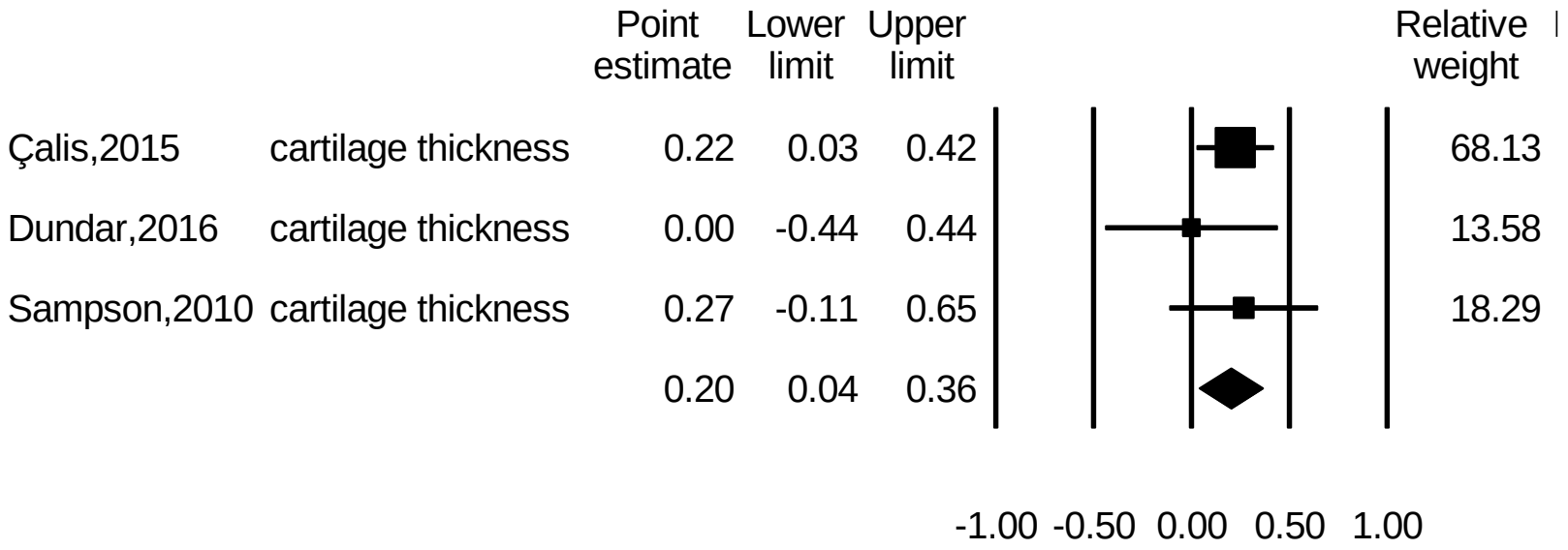
1. Forest plot for meta-analysis of synovial hypertrophy in knee OA



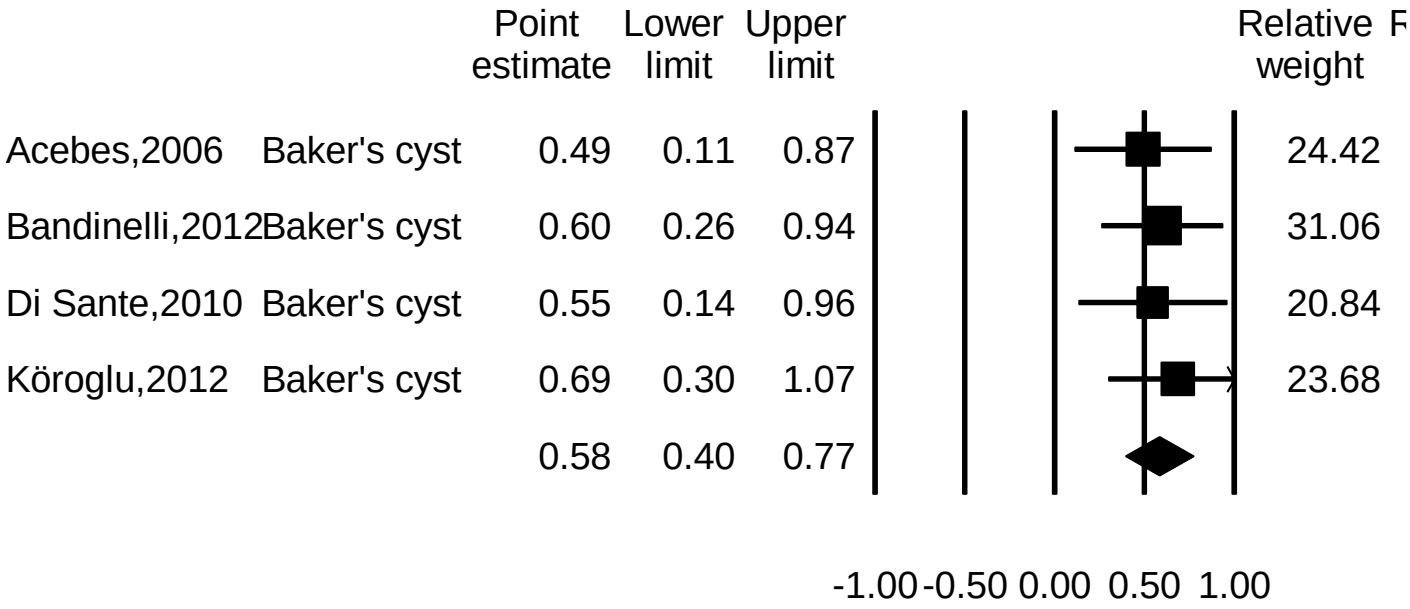
2. Forest plot for meta-analysis of effusion in knee OA



3. Forest plot for meta-analysis of cartilage thickness in knee OA

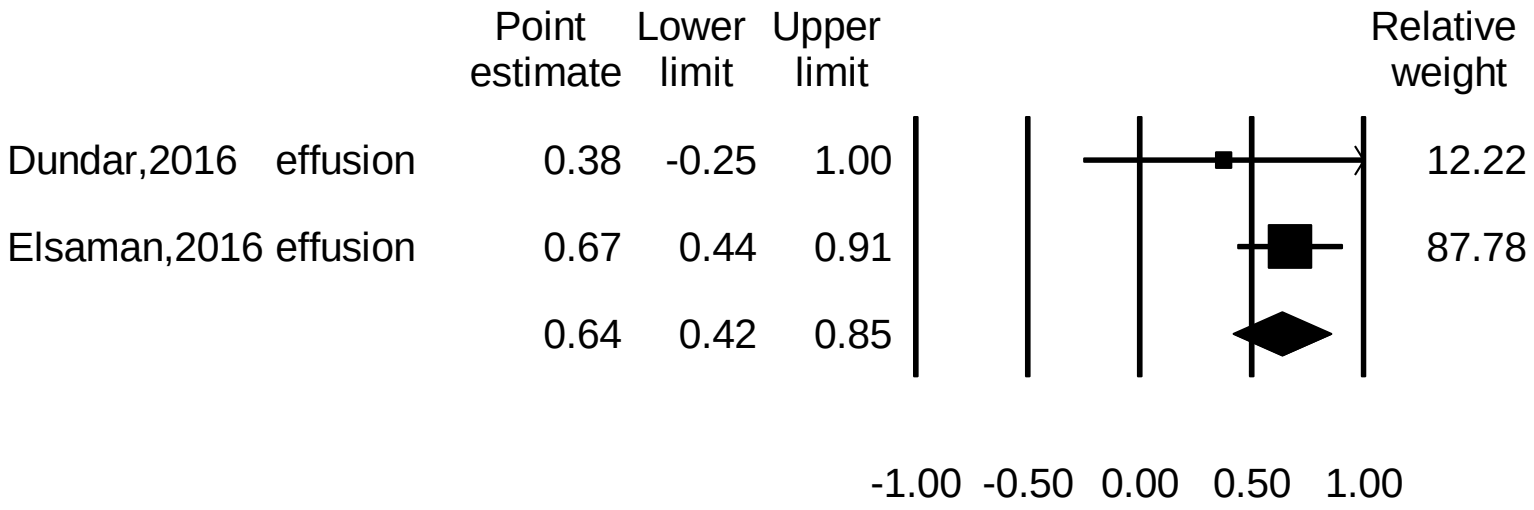


4. Forest plot for meta-analysis of Baker's cyst in knee OA

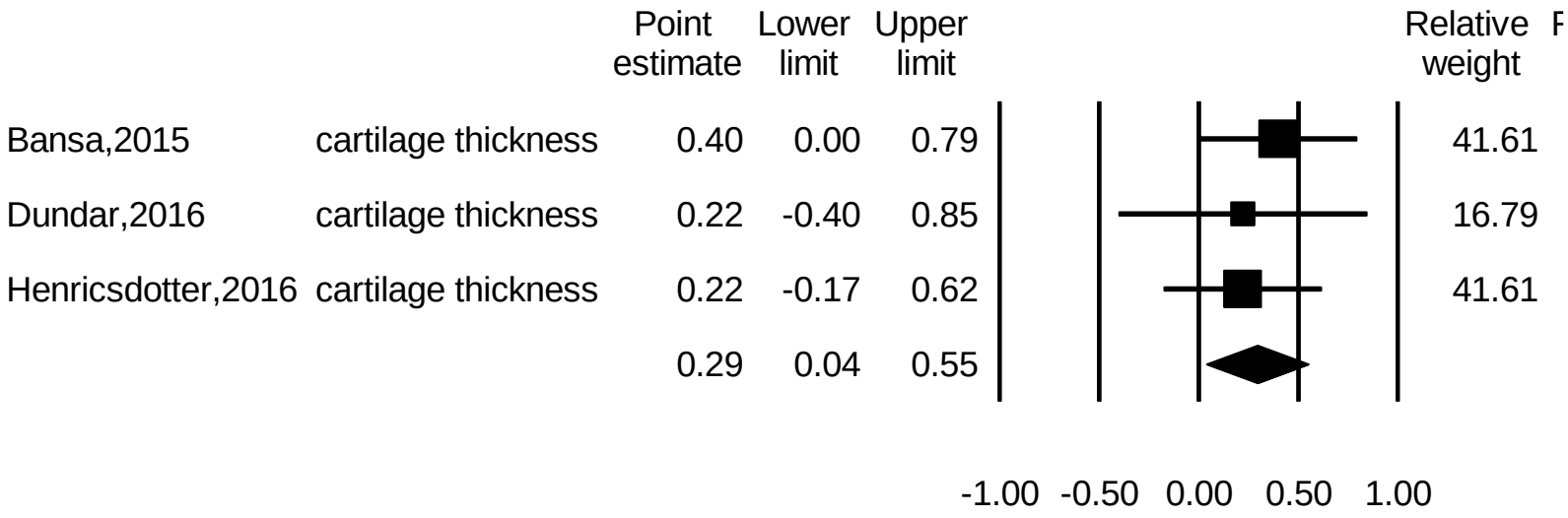


II. Internal responsiveness (independent sample)

1. Forest plot for meta-analysis of effusion in knee OA

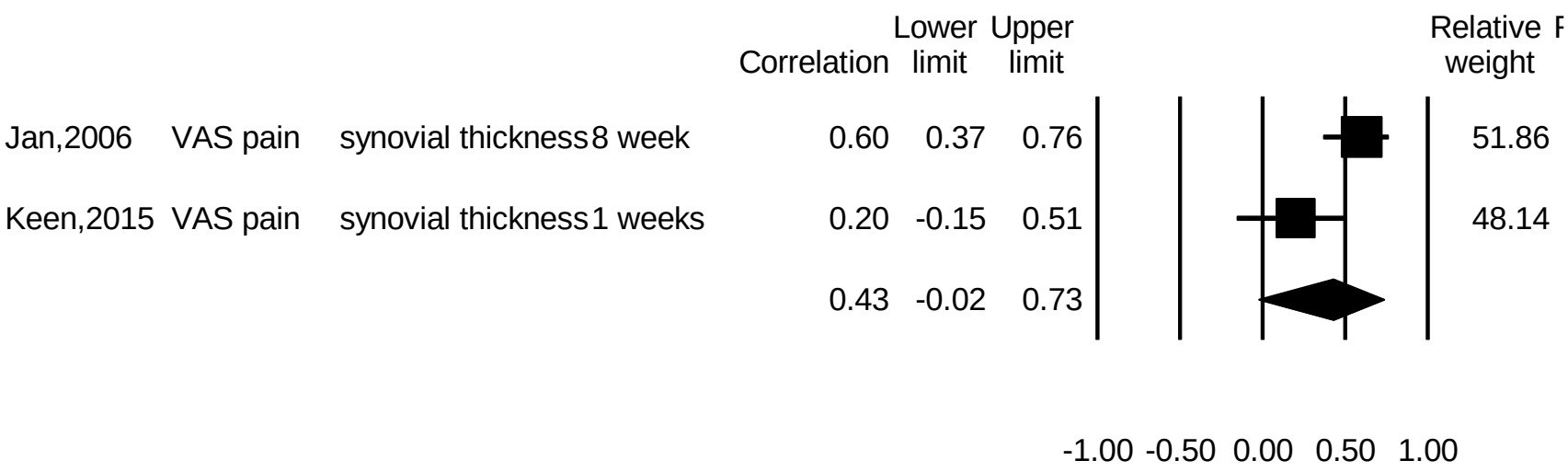


2. Forest plot for meta-analysis of cartilage thickness in knee OA

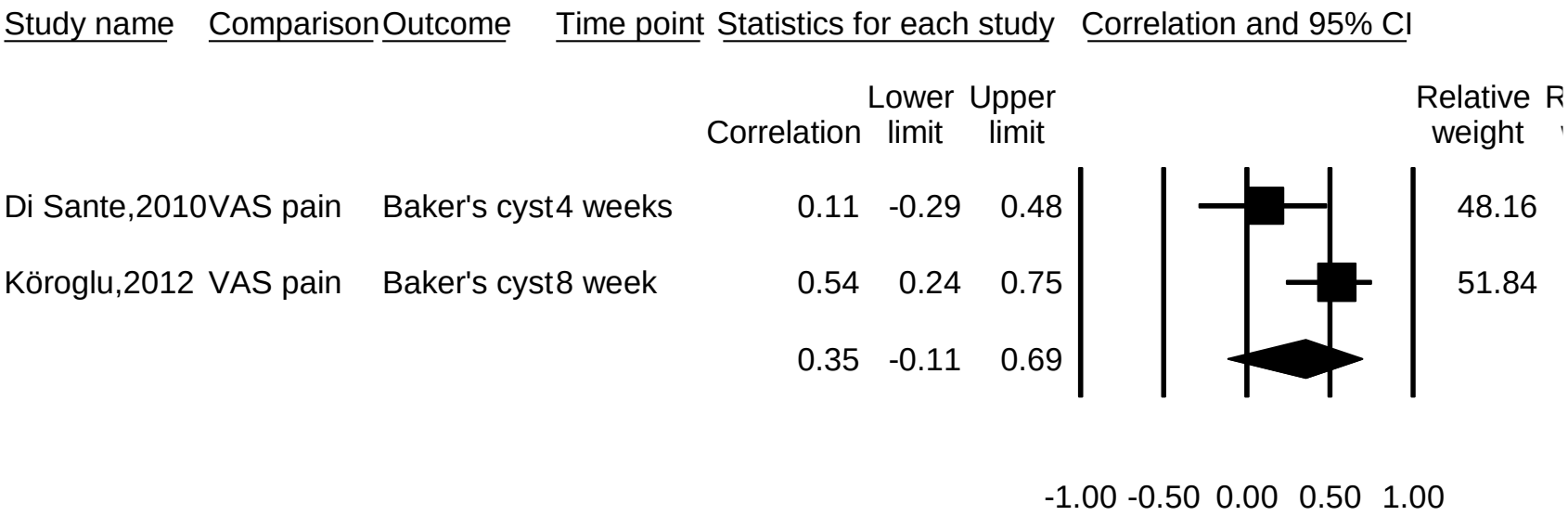


III. External responsiveness

1. Forest plot for meta-analysis of synovial thickness in knee OA



2. Forest plot for meta-analysis of Baker's cyst in knee OA



Appendix 4: Supplementary files for chapter five

Supplementary file 1

Table 1. The OMERACT Ultrasound Scanning Methods

Scoring for	Range	Location	Patient Position	Scanning Plane
Synovitis	0-3	Suprapatellar recess	Supine with the knee flexed 30º	Longitudinal (lateral to medial)
		Medial and lateral parapatellar recess	Supine with the knee in a neutral position	Transverse (proximal to distal)
Synovial hypertrophy	Each for 0-1	Suprapatellar recess	Supine with the knee flexed 30º	Longitudinal (lateral to medial)
Effusion		Medial and lateral parapatellar recess	Supine with the knee in a neutral position	Transverse (proximal to distal)
Synovial PD signal				
Cartilage damage	0-3	Trochlear cartilage	Supine with full flexion of the knee.	Transverse (lateral to medial)
Meniscal damage	0-2	medial horn of the medial meniscus	supine with the knee flexed 10º	longitudinal
Osteophytes	0-3	Medial and lateral femorotibial space	supine with the knee flexed 10º	longitudinal

PD=Power Doppler **Modified from the original table with permission from BMJ publisher[42]**

Table 2. Definitions of OMERACT Grading of Ultrasound Pathologies in Knee Osteoarthritis

Pathology	**Grade 0**	**Grade 1**	**Grade0 2**	**Grade 3**
Synovitis	no synovitis	minimal distension of the recess by abnormal internal hypoechoic or anechoic (relative to subdermal fat tissue) material	moderate distension or enlargement of the recess by abnormal internal hypoechoic or anechoic (relative to subdermal fat tissue) material with flat or concave superficial limit	severe distension or enlargement of the recess by abnormal internal hypoechoic or anechoic (relative to subdermal fat tissue) material with bulging superficial limit
Synovial hypertrophy	No synovial hypertrophy	Abnormal hypoechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intraarticular tissue that is non displaceable and poorly compressible and which may exhibit Doppler signal > 4mm		
Effusion	No effusion	Abnormal hypoechoic or anechoic (relative to subdermal fat, but sometimes may be isoechoic or hyperechoic) intraarticular material that is displaceable and compressible, but does not exhibit Doppler signal >4mm		

Power Doppler	no colour was observed in the synovium	single colour signals were observed (up to 3) in the synovium		
Cartilage	normal	irregularities or loss of sharpness of superficial and/or deep cartilage margins without thinning	partial or complete loss of thickness of the cartilage in one trochlear facet	partial or complete loss of thickness of the cartilage in both trochlear facets
Meniscal extrusion	hyperechoic triangle with the outer edge at the level of the femorotibial joint space	hyperechoic triangle protruded, ie, partially out of the femorotibial joint spac	hyperechoic triangle extruded, ie, completely out of the femorotibial joint space	
Osteophyte	no osteophytes, i.e. a smooth cortical surface.	small and distinct cortical protrusion(s) of the bony surface.	larger protrusion(s) of the bony surface.	very large protrusion(s) of the bony surface

Modified from the original table with permission from BMJ publisher[42]

Supplementary file 2

MRI sequences for RESTORE knee study using knee coil.

MRI Sequence	Slices	Slice thickness (mm)	Slice Gap (mm)	Phase Encoding	Scan time	Ipat	Resolution	Turbo Factor (TSE)	Voxel size	TR	TE	Averages (NSA)	Bandwidth	Fat Sat
PD FS Sag	40	2.2	0.2	H>F	2.36	2	307x384	7	0.4x0.4 x2.2	3500	38	2	200	Yes
Ax PD FS	40	2.5	0.3	R>L	3.12	2	384x278	7	0.4x0.4 x2.5	4170	30	2	221	Yes
PD Cor	40	2.5	0.3	R>L	1.59	2	358x448	7	0.3x0.3 x2.5	3300	38	1	222	No
PD FS Cor	40	2.5	0.3	R>L	1.59	2	307x384	7	0.4x0.4 x2.5	3600	36	1	224	Yes
T1 3D Gradient DESS Sag	192	0.6		A>P	6.32	2	265 95%phase 90%slice	-	Acq & Rec 0.66x0. 63x0.66	14.1 0	5	2	250	Yes

Ax=Axial; Cor=Coronal; MRI=Magnetic resonance imaging; PD=proton density; FS=fat saturation; DESS=Dual echo steady state; Sag=Sagittal; TE= Echo time; TR=Repitition time; TSE= Turbo spin echo

Supplementary file 3

Table 1. The intra-reader and inter-reader reliability of MOAKS score in knee OA

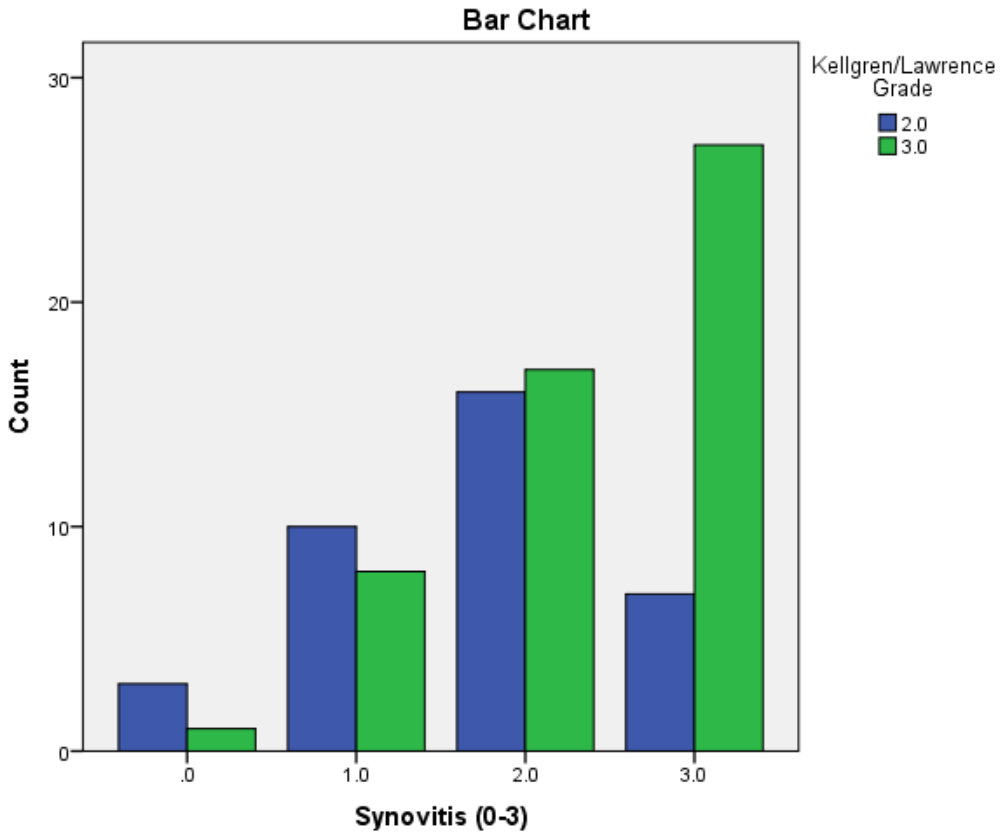
MOAKS	Intra-rater reliability (Kappa)	Percent agreement	Inter-rater reliability (Kappa)	Percent agreement
Cartilage Area F	0.82(0.46 to 1.00)	90	0.77(0.30 to 1.00)	90
Cartilage Area T	0.64(0.30 to 0.98)	80	0.42(-0.01 to 0.85)	70
Cartilage Area P	0.89(0.68 to 1.00)	90	0.90(0.75 to 1.00)	90
Cartilage Depth F	0.90(0.71 to 1.00)	90	0.69(0.39 to 1.00)	70
Cartilage Depth T	0.66(0.37 to 0.94)	60	0.53(0.21 to 0.85)	50
Cartilage Depth P	0.67(0.36 to 0.97)	60	0.60(0.24 to 0.97)	60
MME	0.92(0.75 to 1.00)	90	0.83(0.62 to 1.00)	80
LME	0.68(0.24 to 1.00)	80	0.26(-0.06 to 0.58)	80
Osteophyte F	0.69(0.33 to 1.00)	80	0.77 (0.30 to 1.00)	80
Osteophyte T	0.66(0.31 to 1.00)	70	0.45(0.09 to 0.82)	60
Osteophyte P	0.79(0.54 to 1.00)	80	0.63(0.22 to 1.00)	80
efffusion synovitis	0.91(0.74 to 1.00)	90	0.80(0.56 to 1.00)	80
Hoffa synovitis	0.83(0.55 to 1.00)	90	0.50(0.044 to 0.96)	70

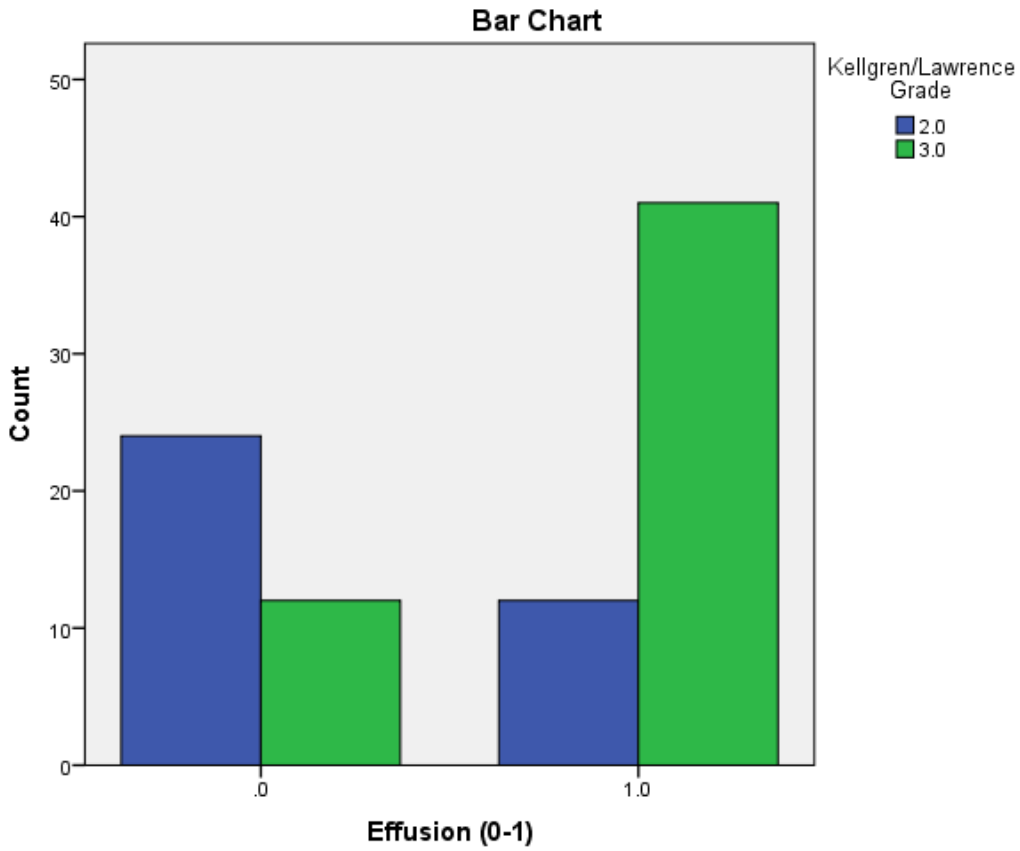
F=Femur; IPB=Infra-patella Bursitis; LME=Lateral meniscal extrusion; MME= Medial meniscal extrusion; P=Patella; T=Tibia;

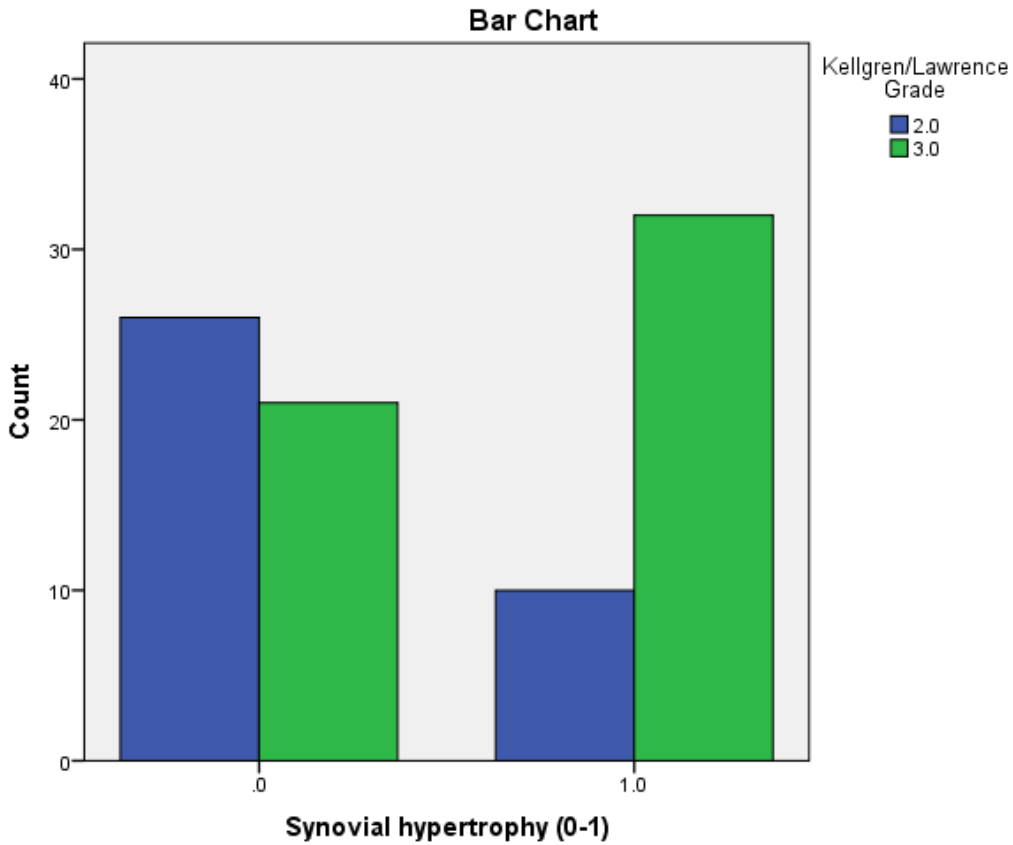
Appendices

Supplementary file 4

Plots of gradings of ultrasound pathologies vs radiographic KL grades




Bar Chart
Kellgren/Lawrence Grade
2.0
3.0
Count
50
40
30
20
10
0
.0
1.0
Effusion (0-1)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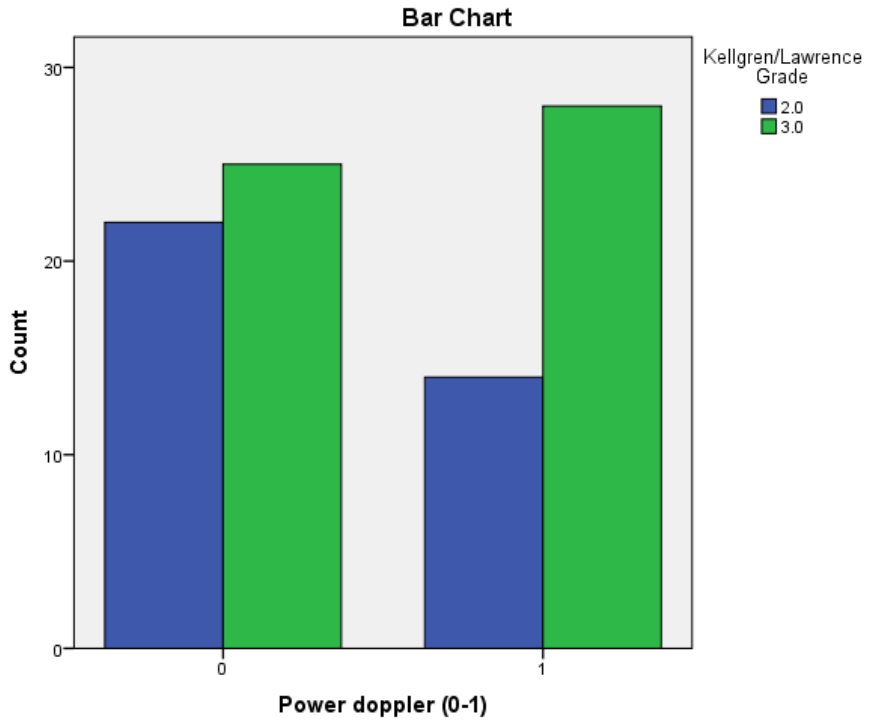
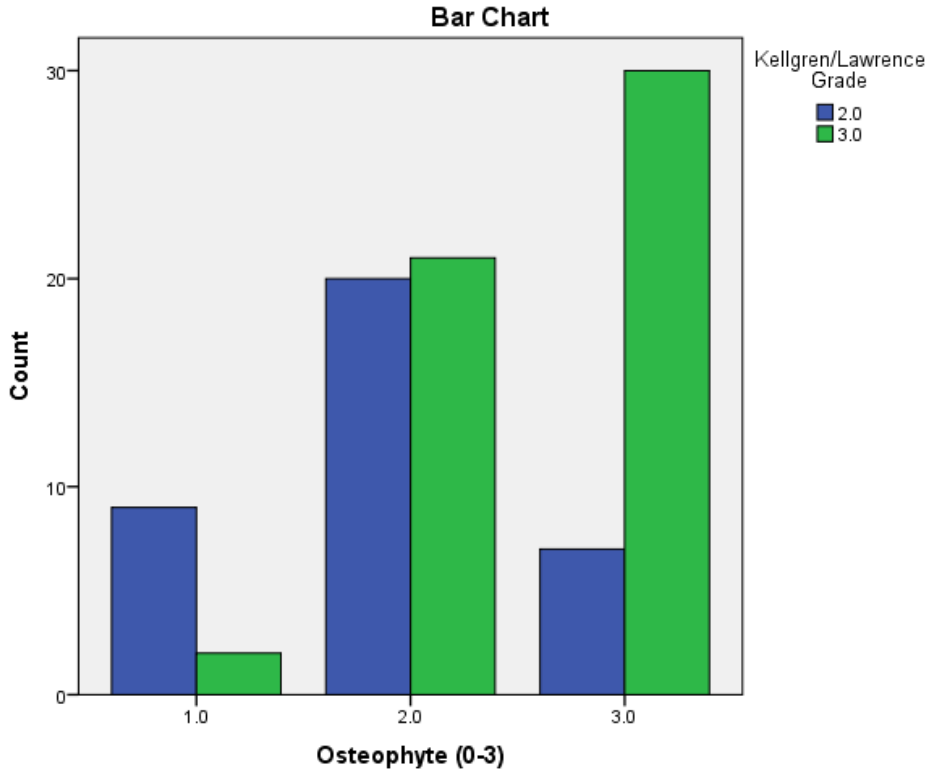
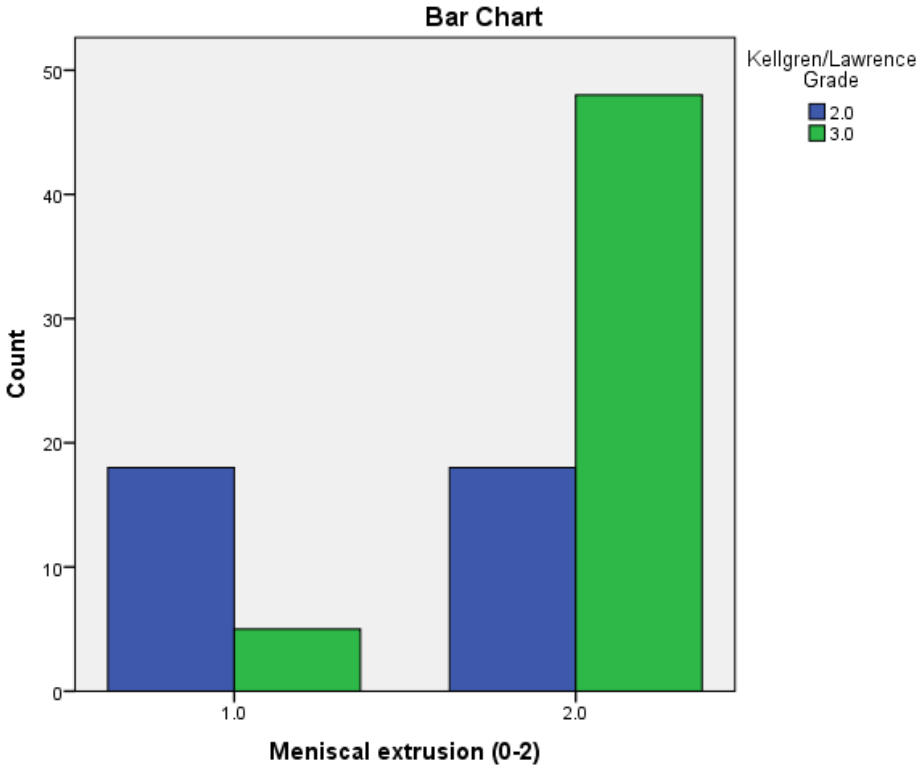
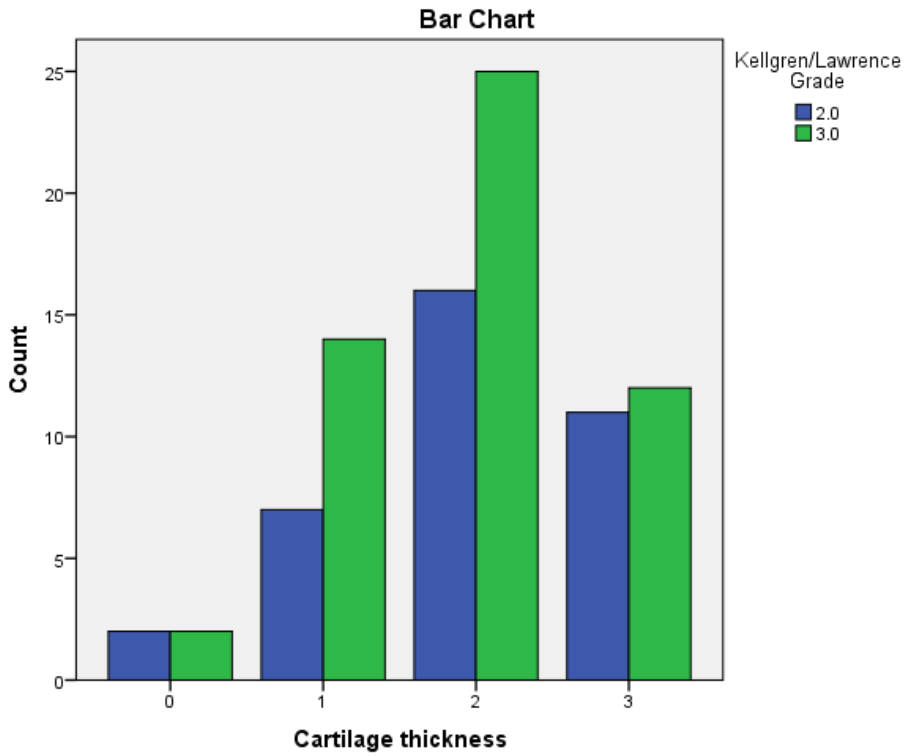
Kellgren/Lawrence Grade
2.0
3.0
Count
40
30
20
10
0
.0
1.0
Synovial hypertrophy (0-1)


Bar Chart
Kellgren/Lawrence Grade
2.0
3.0
Count
30
20
10
0
0
1
Power doppler (0-1)


Bar Chart
Kellgren/Lawrence Grade
2.0
3.0
Count
30
20
10
0
1.0
2.0
3.0
Osteophyte (0-3)

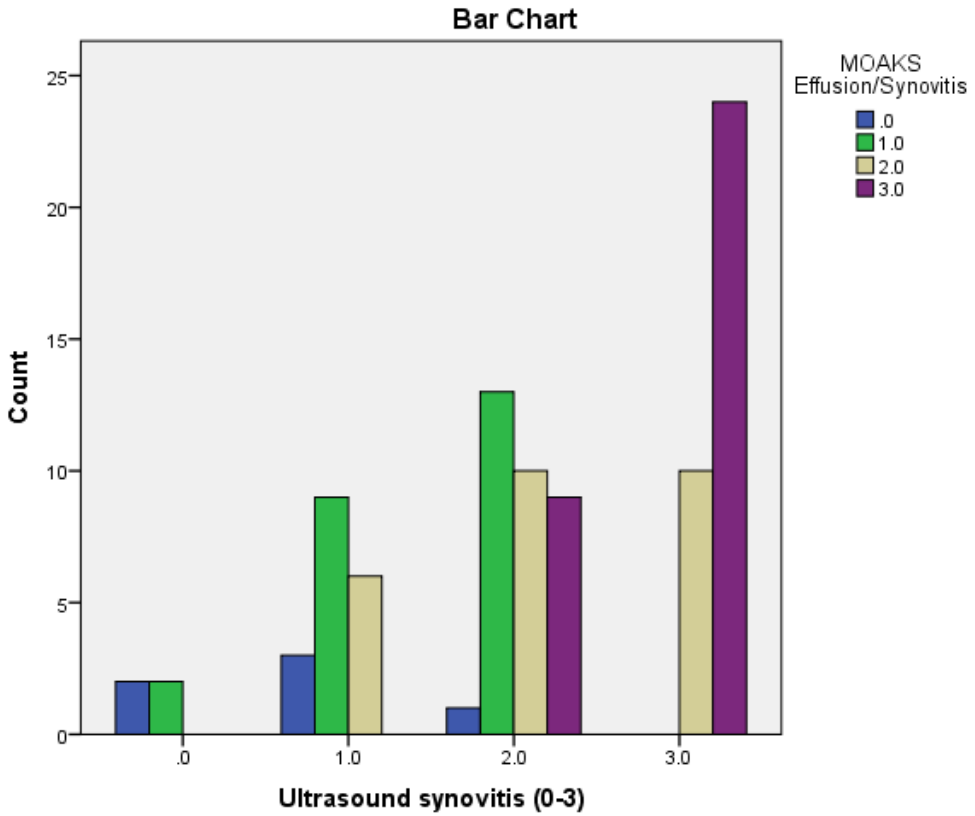

Bar Chart
Kellgren/Lawrence Grade
2.0
3.0
Count
50
40
30
20
10
0
1.0
2.0
Meniscal extrusion (0-2)

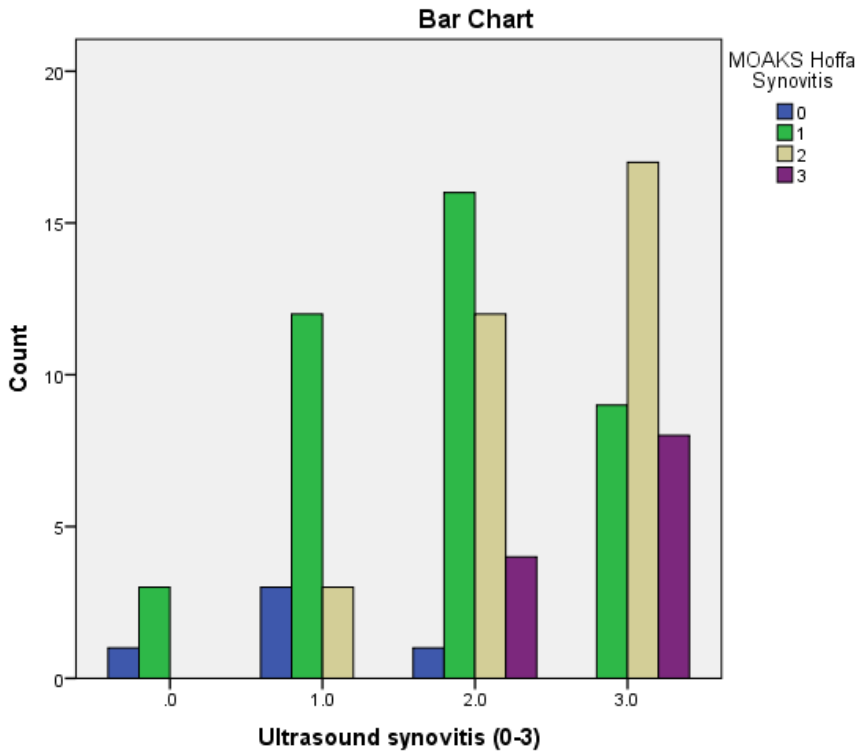

Bar Chart
Kellgren/Lawrence Grade
2.0
3.0
Count
25
20
15
10
5
0
0
1
2
3
Cartilage thickness

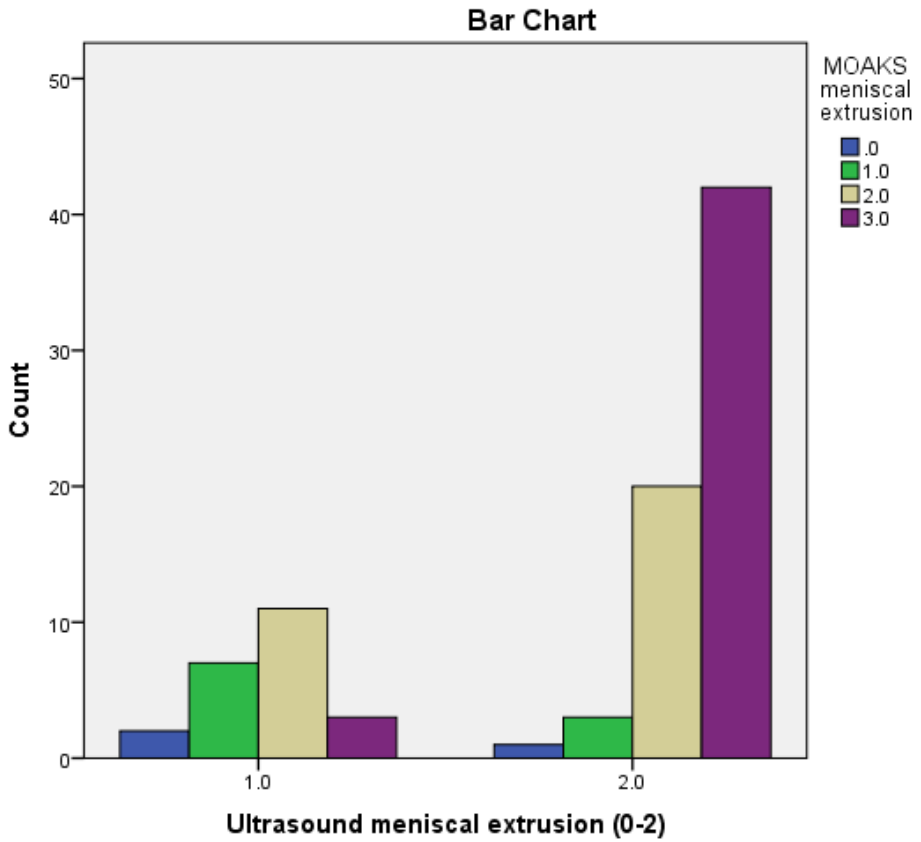
Appendices

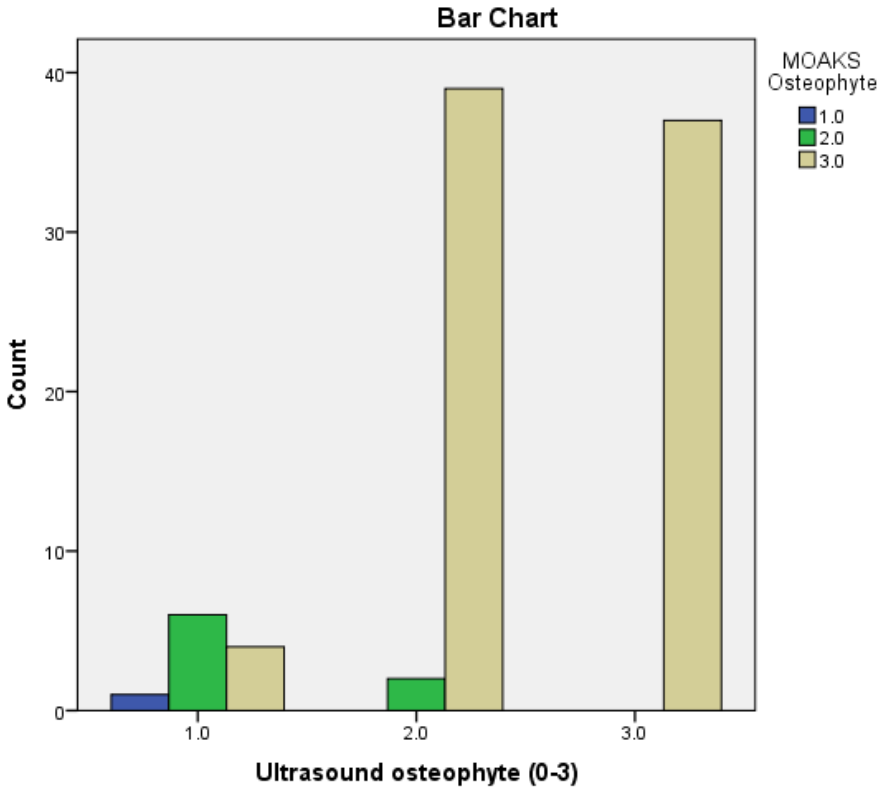
Supplementary file 5

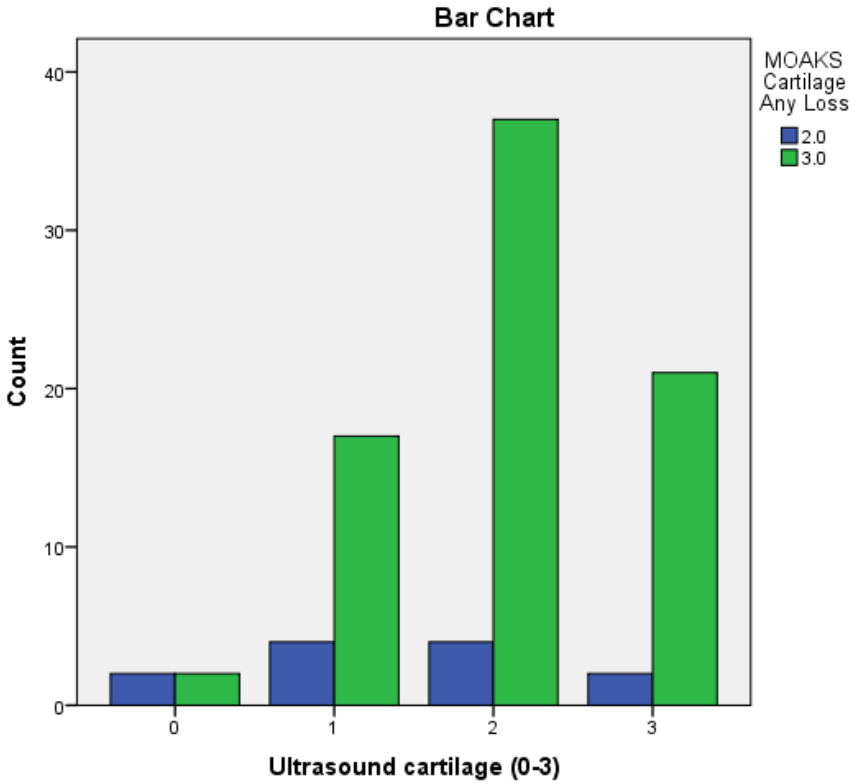
Plot of grading of ultrasound pathologies vs MOAKS counterparts

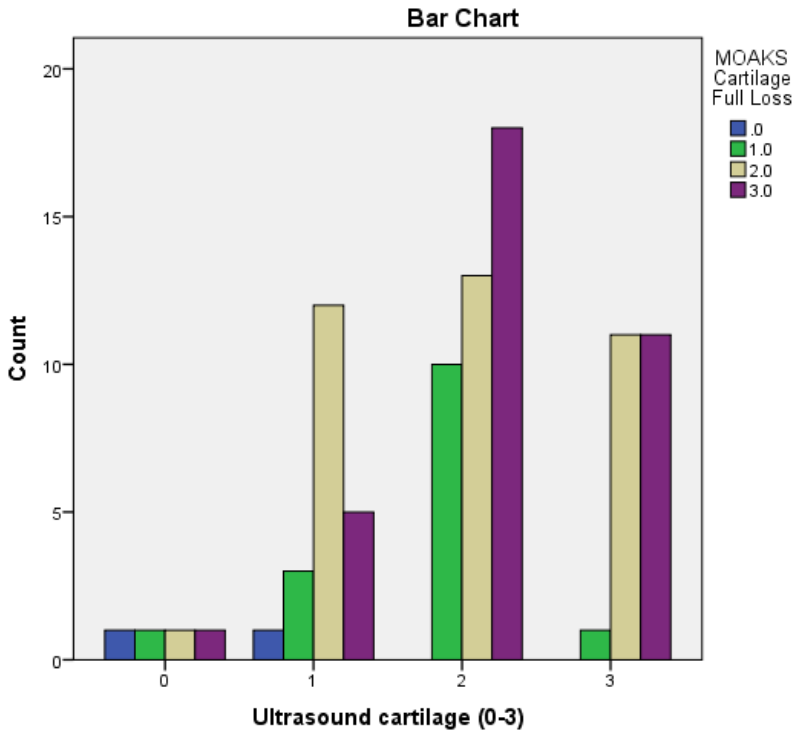



Bar Chart
MOAKS Hoffa Synovitis
0
1
2
3
Count
20
15
10
5
0
.0
1.0
2.0
3.0
Ultrasound synovitis (0-3)


Bar Chart
MOAKS meniscal extrusion
.0
1.0
2.0
3.0
Count
50
40
30
20
10
0
1.0
2.0
Ultrasound meniscal extrusion (0-2)


Bar Chart
MOAKS Osteophyte
1.0
2.0
3.0
Count
40
30
20
10
0
1.0
2.0
3.0
Ultrasound osteophyte (0-3)


Bar Chart
MOAKS Cartilage Any Loss
2.0
3.0
Count
40
30
20
10
0
0
1
2
3
Ultrasound cartilage (0-3)


Bar Chart
MOAKS Cartilage Full Loss
.0
1.0
2.0
3.0
Count
20
15
10
5
0
0
1
2
3
Ultrasound cartilage (0-3)

Appendix 5. Supplementary files for chapter six

Supplementary file 1

The Ultrasound Scanning Methods

Scoring for	Range	Location	Patient Position	Scanning Plane
SMI/cPD	0-3	Suprapatellar recess	Supine with the knee flexed 30º	Longitudinal (lateral to medial)
		Medial and lateral parapatellar recess	Supine with the knee in a neutral position	Transverse (proximal to distal)

cPD= Conventional Power Doppler; SMI=Superb Microvascular Imaging

Modified from the original table with permission from BMJ publisher[42]

(Bruyn, G.A.W., et al., An OMERACT reliability exercise of inflammatory and structural abnormalities in patients with knee osteoarthritis using ultrasound assessment. Annals of the Rheumatic Diseases, 2016. 75(5): p. 842-846.)

Supplementary file 2

Proposed sequences for RESTORE knee study using knee coil.

MRI Sequence	Slices	Slice thickness (mm)	Slice Gap (mm)	Phase Encoding	Scan time	Ipat	Resolution	Turbo Factor (TSE)	Voxel size	TR	TE	Averages (NSA)	Bandwidth	Fat Sat
PD FS Sag	40	2.2	0.2	H>F	2.36	2	307x384	7	0.4x0.4 x2.2	3500	38	2	200	Yes
Ax PD FS	40	2.5	0.3	R>L	3.12	2	384x278	7	0.4x0.4 x2.5	4170	30	2	221	Yes

MRI=Magnetic resonance imaging; PD=proton density; FS=fat saturation; DESS=Dual echo steady state

Supplementary file 3

Intra-rater and inter-rater reliability of OMERACT ultrasound scores in knee OA

Kappa/ Weighted Kappa	Intra-rater reliability	Percent agreement
SMI	0.78 (0.52 to 1.00)	80
PD	0.67(0.33,1.00)	80

cPD= Conventional Power Doppler; SMI=Superb Microvascular Imaging

Supplementary file 4

The intra-reader and inter-reader reliability of MOAKS score in knee OA

MOAKS	Intra-rater reliability (Kappa)	Percent agreement	Inter-rater reliability (Kappa)	Percent agreement
efffusion synovitis	0.91(0.74 to 1.00)	90	0.80(0.56 to 1.00)	80
Hoffa synovitis	0.83(0.55 to 1.00)	90	0.50(0.044 to 0.96)	70

BML=Bone marrow lesions(s); F=Femur; IPB=Infra-patella Bursitis; LME=Lateral meniscal extrusion; MME= Medial meniscal extrusion; P=Patella; T=Tibia

Appendix 6: Published Papers

Appendix 6.1: Imaging in Knee Osteoarthritis (Review)

Imaging in knee osteoarthritis

Win M. Oo[a], *James M. Linklater*[b], *and David J. Hunter*[a]

Purpose of review
Osteoarthritis is the most prevalent and disabling disease still necessitating research in pathogenic mechanisms, predictors of disease progression and responsive techniques to detect the slow structural changes within a short time frame. In this scenario, imaging modalities are essential. With recent advancements in technology and availability of large longitudinal datasets, tremendous advances are occurring. The present review discusses and summarizes recent original publications in this area.

Recent findings
MRI has been the most popular modality used to evaluate the different roles of structural disorders in incident knee osteoarthritis, to compare predictability of individual features of semiquantitative scores for knee replacement and to formulate different disease progression models. More ultrasound studies have been published, including the proposed semiquantitative scoring system by the Outcome Measures in Rheumatoid Arthritis Clinical Trial group.

Summary
As more advanced emerging technologies are developed in imaging, there are great opportunities to formulate new incident and prediction osteoarthritis models and to discover tissue-targeted disease-modifying drugs.

Keywords
MRI, osteoarthritis, plain radiography, ultrasound, x-rays

INTRODUCTION

Knee osteoarthritis is a complex, multifactorial and prevalent joint disease with multitissue alterations [1]. Therefore, comprehensive assessment of the whole joint structure is required for advances in our knowledge of person-level and local risk factors, demonstration of pathologic changes and clarification of their relationship to symptoms and structural progression.

Although plain radiography still is the principal imaging tool for osteoarthritis diagnosis, MRI has become the most widely utilized modality in the research community to evaluate osteoarthritis risk factors, identify predictors of disease progression and assess treatment change due to its reliable clinimetrics. Recently, ultrasound is becoming popular in osteoarthritis evaluation, taking advantage of its relatively low cost and easy accessibility.

The current narrative review, covering the period from 1 January 2015 until 30 April 2016, was based on PubMed database with search strategy focusing on but not limited to terms 'Knee osteoarthritis', 'MRI', 'Magnetic Resonance Imaging', 'Ultrasonography', 'Ultrasound' and 'Radiography'. Only original articles were included while excluding animal studies, review articles, publications focusing on surgery and publications 25 observations or less (usually patients or joints). This is a time of rapid change in knowledge as it relates to imaging use, application and interpretation in the context of knee osteoarthritis (KOA), and we have tried to focus on articles deemed to provide a purposeful increase in our knowledge base.

PLAIN RADIOGRAPHY

Recognizing technical challenges and increased radiation exposure to measure conventional mechanical axis [hip–knee–ankle (HKA) angle], anatomical axis [femorotibial angle (FTA)] on short knee posterior–anterior 20–30° fixed flexion weight-bearing radiographs were studied in 934 knees from Osteoarthritis Initiative (OAI) knees, and FTA was

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KEY POINTS

- Hidden osteophyte formation at intracondylar notch of femur, detected by MRI, identifies persons at risk for incident radiographic osteoarthritis.
- The greater amount of structural lesion load than the presence of any specific feature alone posed a higher risk of incident osteoarthritis.
- Individual subscores of WORMS, BLOKS and MOAKS have respective advantages in predicting knee replacement.
- The OMERACT Ultrasound scoring system has substantial reliability in KOA and should be studied for validity and sensitivity to treatment change.

comparable with the HKA in predicting medial and lateral cartilage loss after adjusting the sex-specific varus shift [2▪]. Therefore, FTA measurements from fixed flexion radiographs, commonly used for staging radiographic joint space narrowing during recruitment, might be used in future clinical trials.

Osteophyte formation is a typical radiographic sign of osteoarthritis. Using incident cohort data ($n = 132$) of the OAI with Kellgren–Lawrence [3] severity grade (0/1), hidden osteophyte formation at intracondylar notch of femur detected by MRI was associated with an increased risk for incident radiographic osteoarthritis by 48 months [4]. This study provoked some interest in using new radiographic views to increase the sensitivity of plain radiography in demonstrating intracondylar notch osteophytes.

In 219 middle-aged osteoarthritis patients, baseline joint space narrowing and osteophytes did not independently predict cartilage volume loss over 10 years after adjusting for MRI-assessed copathologies [5]. This calls into question the role of these radiographic parameters as a prognostic measure in early osteoarthritis. MRI Whole-Organ Magnetic Resonance Imaging Score (WORMS) composite score [6] was used as a reference standard to assess the validity and sensitivity of the Kellgren–Lawrence scale [3], OARSI joint space narrowing scale [7] and compartmental grading scale [8]. Although all three scoring methods were highly correlated to WORM composite score, score changes over 30 months show just a moderate sensitivity to change in WORMS cartilage morphology [9], suggesting caution in using these tools for monitoring structural changes.

MAGNETIC RESONANCE IMAGING

Disorder

Symptomatic KOA patients often have multiple coexistent structural disorders. Recent studies showed that synovitis on noncontrast MRI (Fig. 1) could precede development of radiographic osteoarthritis, albeit that contrast-enhanced MRI (Fig. 2) provided superior demonstration of synovitis in osteoarthritis [10,11]. In a nested case–control study over 4 years using OAI data, effusion synovitis and Hoffa synovitis on MRI Osteoarthritis Knee Score (MOAKS) system [12] strongly predicted development of incident radiographic osteoarthritis with an odds ratio (OR) for synovitis being 1.56 at baseline, 3.23 at 1 year prior to incident osteoarthritis and 4.7 at the time of incident osteoarthritis, respectively [10]. In a separate longitudinal case–control 84-month Multicenter Osteoarthritis Study (MOST) study, synovitis on WORMS system was an independent risk factor for incident KOA after adjusting for other structural disorders, and the greater the synovitis score, the higher the risk [11]. These findings highlight the potential for developing targeted therapies towards inflammation to prevent incident KOA.

Quantification of chondral T2 relaxation times indirectly demonstrates reversible collagen matrix abnormalities in articular cartilage prior to onset of changes on morphologic MRI. This technique shows promise in early osteoarthritis assessment. The first reference database of normative T2 values for morphologically normal knee cartilage (Kellgren–Lawrence 0/1 and WORMS 0/1) showed a weak trend towards higher T2 values with age and sex but a stronger trend with BMI. However, these normal values can vary depending on the type of MRI scanner, field strength, radiofrequency coil, pulse sequence, artefacts such as magic angle and T2 fitting method used [13]. Another study demonstrated racial differences in T2 values in normal participants [14]. Baseline T2 values in all compartments except the medial tibia predicted later onset of radiographic tibiofemoral osteoarthritis over 4 years in normal participants with a baseline Kellgren–Lawrence grade = 0 and BMI less than 35 [15]. In another study, a decrease in BMI of at least 10% was related to a slower T2 progression over 4 years, highlighting a beneficial effect of weight loss on cartilage matrix integrity [16]. There was a 1.2-μl reduction in the loss of medial tibial cartilage volume for every 1% of weight loss achieved over 2.3 years [17]. A significant association was observed between medial meniscal extrusion area and cartilage loss over 1 year [18]. A separate study reported the association of plasma phylloquinone (vitamin K1) with progression of articular cartilage and meniscus damage [19].

Meniscal lesions may be one of the earliest changes in the KOA pathogenesis pathway [20]. In an 8-year longitudinal study of mostly middle-aged

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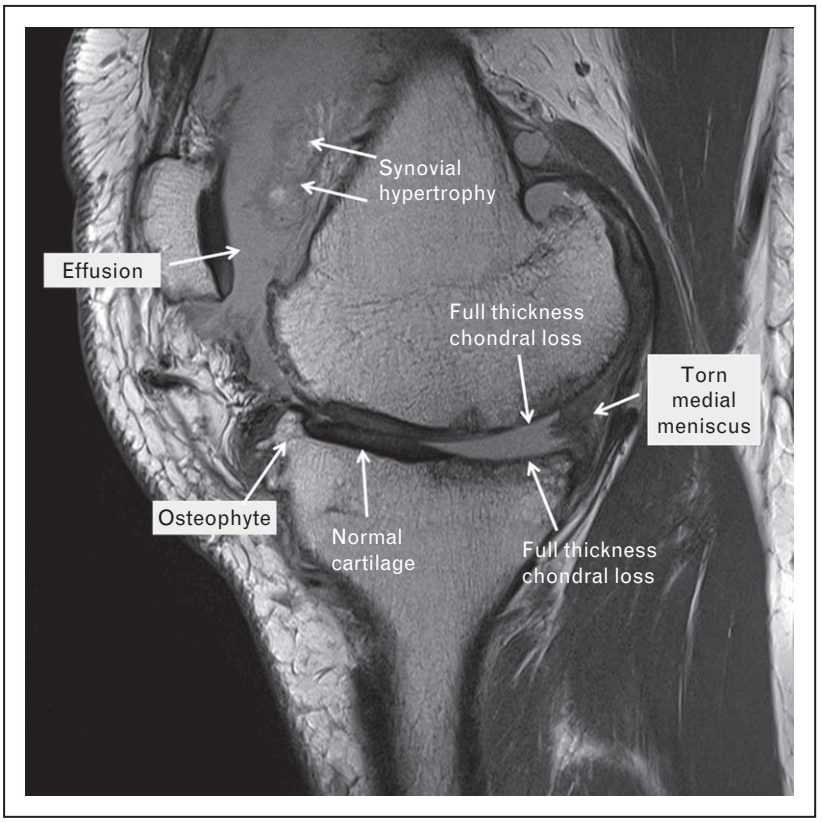

FIGURE 1. Sagittal proton density MRI showing advanced medial femorotibial compartment osteoarthritis, with full thickness cartilage loss, large effusion and prominent synovial thickening. Note also the chronically torn medial meniscus and osteophyte formation.

adults ($n = 198$), 16% of the participants had an increase in mean meniscal score that measured the meniscal tears and meniscal extrusion of each anterior, body and posterior meniscal horns separately from 0 to 2 [21]. Change in meniscal tears had an independent association with cartilage volume loss, change in bone marrow lesions (BMLs) and change in meniscal extrusion [21]. In a study ($n = 137$) with preradiographic KOA, posterior root/horn radial tears in medial meniscus were independent factors that increased T1ρ values of medial femorotibial cartilage, suggesting its potential usefulness in screening very early-stage osteoarthritis [22].

In a 6-year longitudinal study in an OAI subcohort ($n = 340$) without KOA (Kellgren–Lawrence grade = 0), female sex, baseline extrusion ratio [(meniscus body extrusion)/(tibia width) × 100] and incident meniscal tear during follow-up were associated with increased meniscal body extrusion [23]. In a separate longitudinal 4-year study, greater medial meniscus extrusion predicted incident radiographic KOA. The earlier the onset of incident KOA, the greater meniscus extrusion was found at baseline [24]. In an 84-month study, different patterns of coexisting MRI lesions were identified for incident osteoarthritis for tibiofemoral and patellofemoral joints by using a latent class analysis. Therefore, meniscal damage seemed to play a different role in the development of incident osteoarthritis in tibiofemoral versus patellofemoral joints [25▪].

Most past epidemiological and clinical osteoarthritis studies have focused only on role of BMLs in tibiofemoral compartment rather than the patellofemoral joint. In a recent study ($n = 904$), patellar BMLs were associated with increased patellar cartilage defects and decreased patellar cartilage volume both cross-sectionally and longitudinally, independent of tibiofemoral BMLs [26]. This might suggest site-specific association between BMLs and cartilage changes and support concept of possible crosstalk between subchondral bone and cartilage, with resultant progression of chondral lesions [27]. BML quantification on intermediate-weighted fat suppressed turbo spin echo offered better validity and sensitivity to change than BML quantification on three-dimensional dual echo steady state (3D DESS) sequences against knee pain both cross-sectionally and longitudinally [28], highlighting that DESS is far from an optimal sequence for depicting BMLs to their maximal extent [29].

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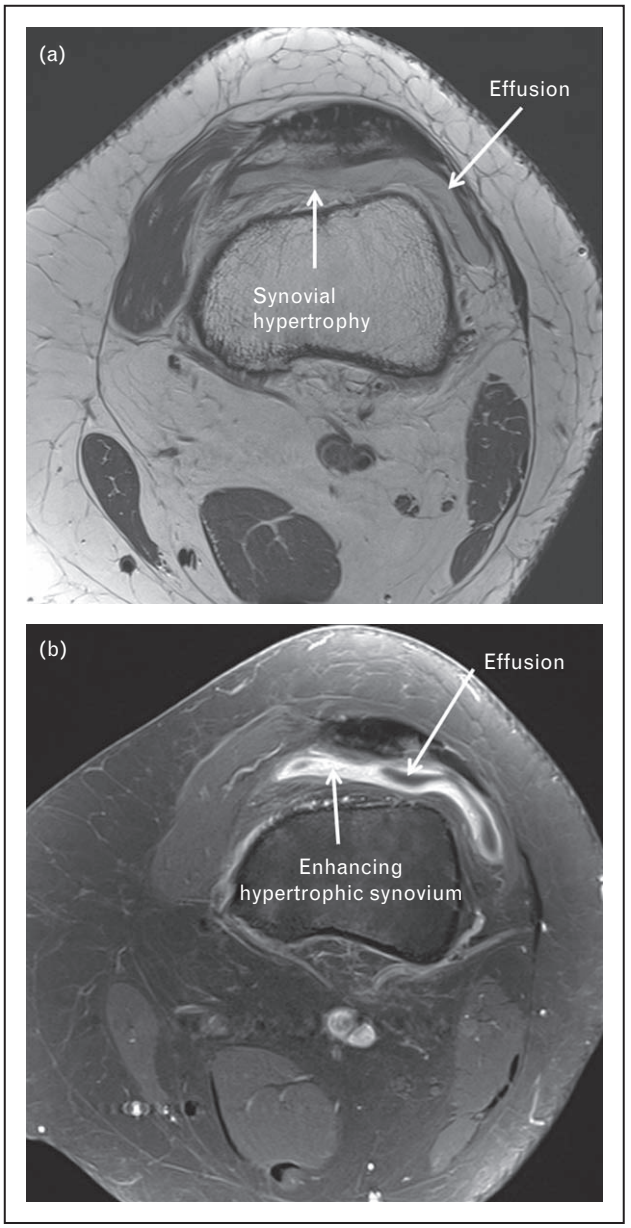

FIGURE 2. Axial proton density (a) and axial postintravenous contrast fat-suppressed T1 (b) MRIs demonstrating synovial thickening and small effusion on the noncontrast PD image (a) and moderately intense enhancement of the thickened synovium, with small nonenhancing simple fluid component on the contrast-enhanced image (b).

Greater joint space width (JSW) loss and cartilage volume loss were demonstrated when meniscal extrusion and BML were colocalized than when each existed separately [30▪]. This combined, cumulative negative impact on cartilage loss was 0.31 mm for radiographic JSW loss and 2.22% for MRI cartilage volume loss per additional colocalized factor [30▪]. Both radiographic changes and MRI abnormalities such as cartilage damage and BMLs in both knees exhibited a more bilateral symmetric pattern than expected, supporting presence of person-based risk factors for osteoarthritis–related tissue changes [31].

Maximal cross-sectional area of the infrapatella fat pad (IPFP) was predominantly located in lateral (54.2%), rather than medial tibiofemoral compartment (1.7%) [32]. A large IPFP prevented knee cartilage loss mainly in the lateral compartment and development of knee pain in generalized KOA, suggesting its role in a local shock-absorbing mechanism [32] and favouring IPFP preservation at total knee arthroplasty for reduced recurrent knee pain [33,34]. Similar protective role of IPFP size was reported in other studies as well [35,36]. A measure of 1 cm^3 more IPFP volume was associated with 30–80 cm^3 greater knee cartilage volume [35]. In a 2.6-year longitudinal study, change in IPFP maximal area in women had a positive significant association with change in tibial cartilage volume per annum (β: +1.56% per cm^2 at medial site and +0.86% per cm^2 at lateral site) [36].

In contrast, a recent cross-sectional study in patellofemoral osteoarthritis patients ($n = 41$) found that a larger IPFP volume explained 20.1% of variance in KOOS-pain and was associated with worse pain [37]. These findings suggest that different impacts of IPFP on osteoarthritis principally affect patellofemoral joint (PFJ) versus tibiofemoral joint. Healthy men in OAI normal control cohort showed a significantly greater ratio of IPFP volume/body weight than women, similar amounts of intermuscular fat and less subcutaneous fat in thigh [38].

Studies on other periarticular structures reported that concurrent presence of low vastus medialis area, high vastus medialis %fat and high BMI could identify a subgroup of patients with medial femur cartilage volume loss [39]. In a nested case–control study, loss of anterior cruciate ligament integrity on MRI did not confer a significantly increased risk of incident radiographic osteoarthritis in an older adult cohort with the average age of 60.1 ± 8.5 years [40], in contrast to findings in young adults mostly less than 30 years [41]. In another study, anterior cruciate ligament reconstruction using single-bundle hamstring tendon autograft was a risk factor for early patellofemoral osteoarthritis [42]. Other studies awaiting future confirmation are the age-adjusted significant association of popliteal artery wall thickness with medial tibial cartilage volume loss [43] and relationship of increased Dual-energy X-ray absorptiometry-assessed ipsilateral bone strength with KOA severity after age adjustment [44].

Roemer *et al.* [45▪▪] highlighted importance of concomitant structural MRI lesion load (i.e. cartilage morphology, BMLs, meniscal status, meniscal extrusion, Hoffa synovitis and effusion synovitis)

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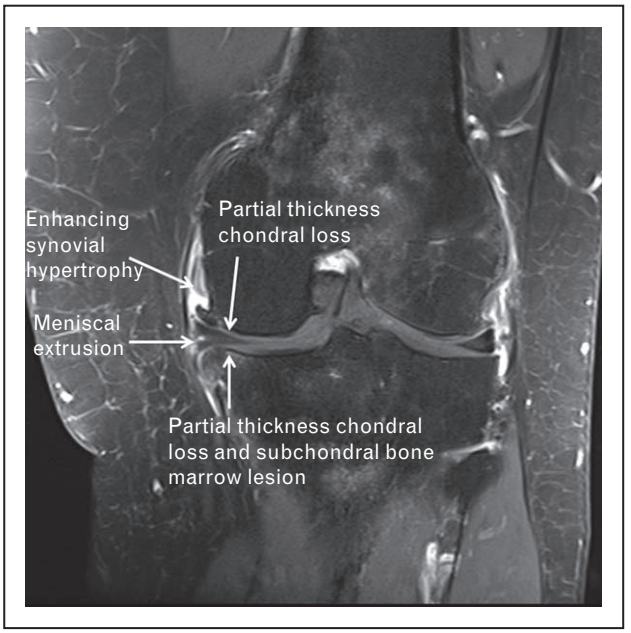

FIGURE 3. Coronal contrast-enhanced fat-suppressed T1 MRI of an osteoarthritic knee demonstrating partial thickness chondral loss towards the medial joint line involving the medial femoral condyle and medial tibial plateau, with small subchondral bone marrow lesions, moderate medial joint line osteophyte formation, meniscal extrusion and adjacent enhancing synovitis in the meniscofemoral recess.

than the presence of any specific feature alone (Fig. 3), reporting a 12-fold increased risk for presence of five or six concomitant features 1 year prior to diagnosis, compared with knees with only one feature or with no features. In addition, incidence of new features over time might be more important than presence of any given feature alone [45▪▪].

MRI scoring system

Although radiography is still used in grading KOA severity, MRI is now increasingly used in evaluating KOA due to several advantages [46]. In a 6.2-year longitudinal study to evaluate whether Boston–Leeds Osteoarthritis Knee Score (BLOKS) [47] and WORMS [6] could predict knee replacement in OAI database, a one score increase in the average BLOKS full thickness cartilage score posed the greatest risk [hazard ratio: 13.55 (3.61–50.89)]. Both BLOKS and WORMS cartilage scores were independent predictors of subsequent knee replacement (KR), whereas the BLOKS cartilage and meniscus scores and WORMS BML score were superior to their counterparts (Table 1). However, there was no significant additional predictive value of follow-up MRI assessment at 24 months for KR [48▪▪].

Uses in clinical trial

In a prospective pharmacological trial, presence of meniscal extrusion had a significant association with more JSW loss and cartilage volume loss independent of NSAID treatment [49]. In a meniscal extrusion-positive subgroup without analgesics/NSAIDs, those taking glucosamine/chondroitin had significantly less cartilage volume loss than those not taking glucosamine/chondroitin, whereas no significant difference was seen in JSW [49]. Quantitative MRI seems to be a more sensitive and reliable method to evaluate disease-modifying agents than radiograph.

In a large 2-year trial, vitamin D supplementation did not provide any MRI structural benefits [50]. In a phase III trial, strontium ranelate (2 g/day) had protective effects on medial cartilage volume at 36 months in osteoarthritis patients with meniscal extrusion as well as when both meniscal extrusion and BML were colocalized [30▪]. Another clinical trial demonstrated poor effectiveness of percutaneous calcium phosphate injection in symptomatic BMLs of the knee [51].

Among three nonpharmacological studies, one study ($n = 112$) showed a significant negative association of every 1% weight change with 1.2 μl change in medial tibial cartilage volume over 2.3 years [17]. Another study reported no significant difference in structural progression between intensive weight loss

Table 1. Significant risk of subsequent knee replacement with regard to one-score increase in the average baseline Boston–Leeds Osteoarthritis Knee Score and Whole-Organ Magnetic Resonance Imaging Score scores of cartilage, bone marrow lesion and meniscus (as indicators of structural tissue damage)

	BLOKS	Adjusted HR	WORMS	Adjusted HR
1	Average cartilage score (full thickness)	13.55 (3.61–50.89)	Average cartilage score	2.60 (1.19–5.68)
2	Average cartilage score (lesion extent)	3.02 (1.07–8.52)	Average BML score	3.99 (1.25–12.77)
3	Average meniscal extrusion score	4.19 (1.08–16.19)		

P value is 0.05 or less. Adjustment includes age, sex and BMI, maximum baseline radiographic Kellgren–Lawrence score, Physical Activity Scale for the Elderly and WOMAC. Modified from [48▪▪]. BLOKS, Boston–Leeds Osteoarthritis Knee Score; BML, bone marrow lesion; HR, hazard ratio; WORMS, Whole-Organ Magnetic Resonance Imaging Score.

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(10% of baseline) through diet, with and without exercise and exercise alone over 18 months [52] probably due to cancelling benefit of dietary arm by benefit of exercise arm. The beneficial compartment-specific effects of a patella brace were found in decreasing BML volume in patellofemoral osteoarthritis over 6 weeks [53].

Predictors for disease progression

In the past year, more studies have focused on prediction of structural progression than symptomatic progression. In a 4-year nested case–control OAI study ($n = 600$), loss of medial femorotibial cartilage thickness over 24 months was associated with combination of radiographic and pain progression in knee osteoarthritis over 48 months, confirming MRI cartilage thickness change as a robust imaging biomarker for KOA progression. In this study, the medial tibiofemoral radiographic joint space loss ($\geq$0.7 mm) was used for radiographic progression and a persistent increase in the WOMAC score ($\geq$9 on a 0–100 scale) for pain progression [54].

In middle-aged KOA patients, baseline tibiofemoral cartilage volume predicted greater absolute cartilage volume loss over 10 years independent of other copathologies [5]. One cross-sectional study in patellofemoral osteoarthritis from MOST ($n = 1137$) and Framingham osteoarthritis ($n = 934$) database found that knee pain risk and severity was associated with cartilage loss in lateral patellofemoral joint and large BMLs in either the medial or lateral PFJ [55].

The 3-year Strontium Ranelate Efficacy in Knee Osteoarthritis Trial study reported that the presence of BML, but not other MRI abnormalities at baseline, could predict change in JSW per year of follow-up. Average annualized JSW was reduced by 0.18 mm in men and by 0.13 mm in women. However, limitations were lacking of assessing meniscal extrusion and synovitis as other potential confounders [56]. Cartilage damage, bone marrow lesions, medial meniscal damage, and synovitis and effusion measured with MOAKS [12] could predict knee replacement in the following year, with severe cartilage damage having the highest association (OR, 16.5; 3.96–68.76) [57].

Additional studies reported a positive association of thigh adipose tissue with structural progression of KOA over 2 years [58], predictability of vastus medialis fat content for cartilage volume loss and BMLs progression [39], and an independent association of meniscal tear score with pain and structural progression over 8 years [21]. A latent class cluster analysis determined existence of distinct subtypes of KOA with different structural progression and symptoms using baseline radiographic scores, quantitative MRI measures of cartilage quantity and denuded bone, and self-reported clinical scores. The first cluster represented no areas of denuded bone and limited progression. Cluster 2 included small areas of denuded bone. The third and fourth clusters showed larger areas of denuded bone with increasing osteoarthritis severity [59] but the study was limited by not including other important MRI lesions.

Novel MRI methods

A cross-sectional study showed that dynamic contrast-enhanced MRI analytic approaches (heuristic and pharmacokinetic) were highly reproducible and might provide novel insights into the role of synovial inflammation and vascularity in KOA [60].

Longitudinal active appearance models (AAM)-determined three-dimensional bone area changes [total area of subchondral bone (tAB)] were more responsive than radiographic medial joint space width and MRI cartilage thickness for assessing structural progression [61]. The femur, medial femur/medial trochlear femur (MF/MedPF) and lateral femur/lateral trochlear femur (LF/LatPF) boundary was defined as a line on bone corresponding to the anterior edge of medial or lateral meniscus, and extended smoothly to the edge of the tAB. The MedPF/LatPF boundary was defined as the centre of the trochlear groove. In their methodology, autosegmentation of these regions with AAMs was used for measurement of tAB, and spatial distribution of change greater than measurement error was shown with a colour scale.

A 0.25-T rotating open-configuration MRI scanner was used to scan while lying supine (clinostatic position) or while standing in a true weight-bearing position (orthostatic position) in 26 KOA patients. Medial meniscal extrusion (MME) (clinostatic MME, orthostatic MME and ΔMME) was correlated with WORMS and Kellgren–Lawrence score. In univariate analyses, ΔMME was significantly correlated with tibiofemoral cartilage loss, meniscal damage, osteophytes, global WORMS and radiographic Kellgren–Lawrence score, whereas significant correlation existed only between orthostatic MME and osteophyte WORMS subscore. In multivariate analysis, ΔMME was independently correlated with cartilage loss [62].

ULTRASONOGRAPHY

Disorder

Ultrasound is traditionally labelled somewhat disparagingly as being highly operator-dependent.

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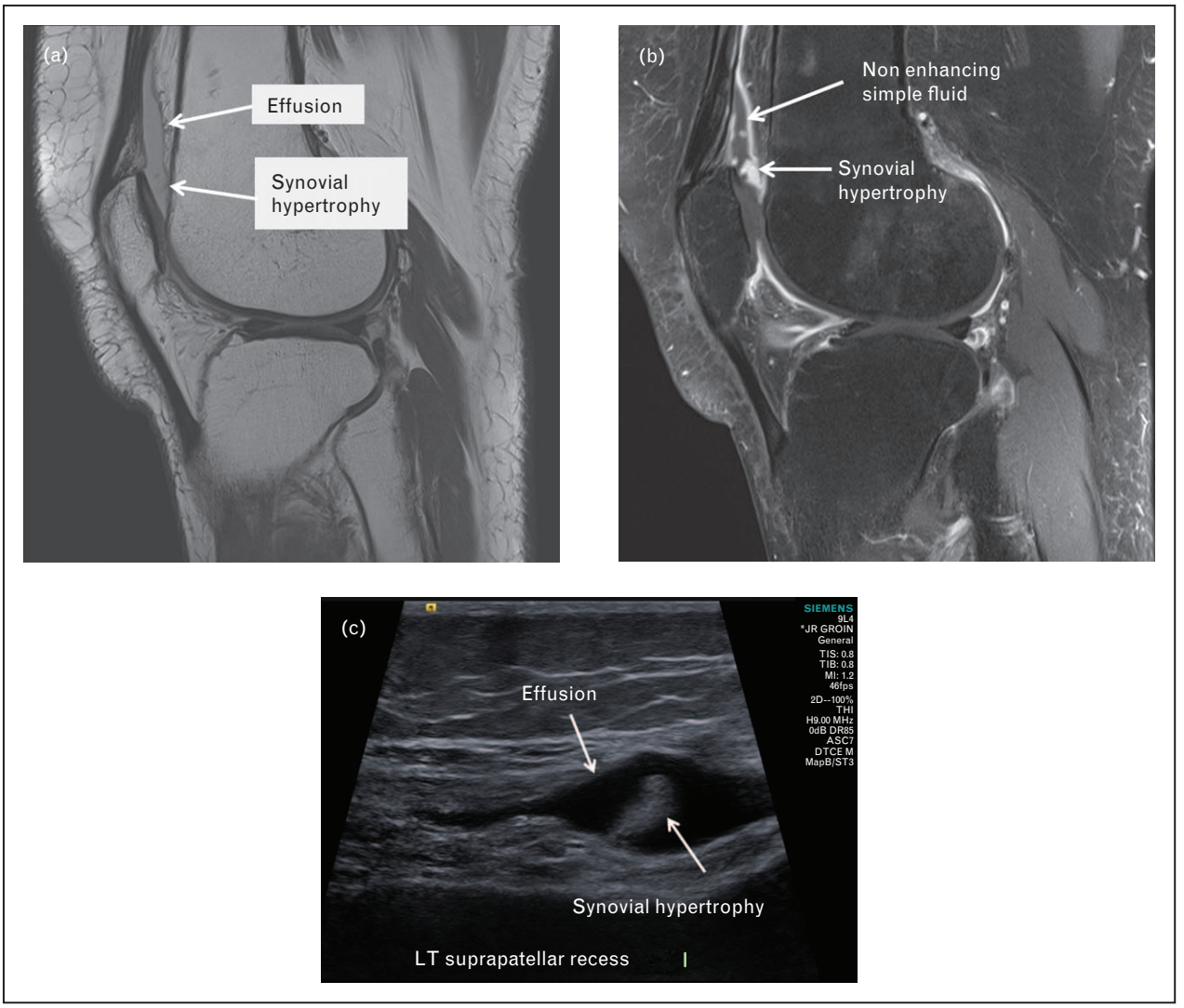

FIGURE 4. Sagittal fat-suppressed proton density (a), postintravenous contrast sagittal fat-suppressed T1(b) MRIs and transverse ultrasound image (c) demonstrating synovial hypertrophy and effusion in the suprapatellar bursa of a knee in which there was moderate osteoarthritis in the medial femorotibial compartment.

However, for dichotomous scales, a recent study ($n = 80$) demonstrated excellent interobserver agreement for femoral cartilage thinning ($k = 0.99$), osteophytes ($k = 0.94$), synovial effusion ($k = 0.98$), synovial thickening ($k = 0.96$), popliteal cyst ($k = 1.00$) and meniscal protrusion ($k = 0.86$) (Figs. 4 and 5) [63]. The authors demonstrated better assessment of ultrasound for tibiofemoral osteophytes, medial meniscal extrusion (Fig. 6) and medial femoral cartilage changes, in comparison with radiography, using MRI as a reference standard. Ultrasound can serve as a complementary modality to radiography, providing a cost-effective tool in depicting relevant soft tissue disorder [64].

Variations in quality and quantity (muscle thickness and echogenicity) of lower limb muscles with varying severity of KOA were reported recently

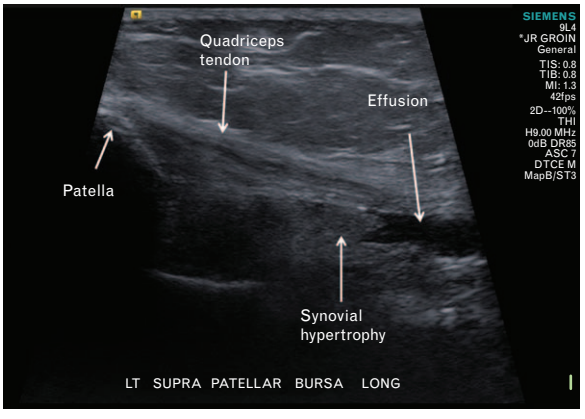

FIGURE 5. Longitudinal ultrasound image of the suprapatellar bursa in an osteoarthritic knee demonstrating a moderate effusion and synovial hypertrophy.

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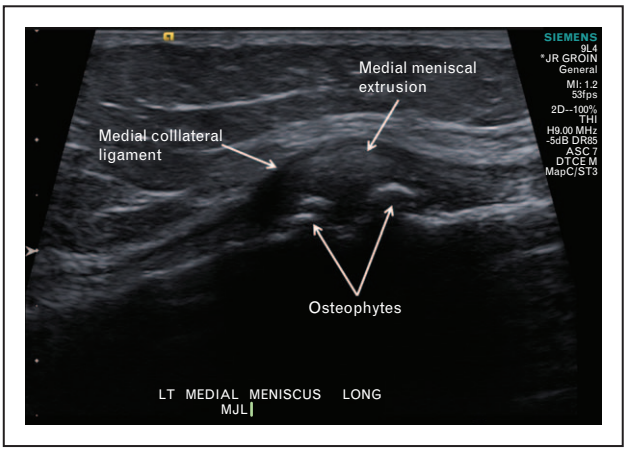

FIGURE 6. Longitudinal ultrasound image at the medial joint line of the knee demonstrating osteophytes and medial meniscal extrusion in a patient with osteoarthritis.

[65]. Another study ($n = 85$) demonstrated a relatively high prevalence of pes anserine bursitis (20%) with a positive correlation of osteoarthritis grade with bursitis size and area [66].

Ultrasonography grading system

The Outcome Measures in Rheumatoid Arthritis Clinical Trial Ultrasound group developed scoring systems for inflammatory and structural changes in KOA by a consensus process [67▪▪]. The scoring scale is shown in Table 2. Intraobserver and interobserver reliability scores were moderate to good for synovitis and global synovitis, fair to good for cartilage damage, medial meniscal damage and osteophytes. Limitations included small sample size ($n = 13$) and lack of validation of this score with other constructs such as clinical scores or MRI [67▪▪].

Ultrasonography as an outcome measure in clinical trials

In recent years, pharmacological trials for KOA have incorporated ultrasound in their outcome measures. Ultrasound demonstrated reduction in synovial thickness, effusion and power Doppler flow 1 week after intra-articular steroid injection (80 mg), reflecting the anti-inflammatory effects of steroid on synovium. In one study, power Doppler flow in synovium was more sensitive and more strongly associated with pain than synovial thickening and effusion [68]. In contrast, a different KOA study reported no significant effects of intra-articular steroid injection (40 mg) on synovial hypertrophy, synovial Doppler flow or Baker's cyst presence at 3 months. The difference may be due to different endpoints (1 week versus 3 months), highlighting transient benefits of intra-articular steroid for KOA, or reduced steroid dosage (80 versus 40 mg) or using dichotomous scales for power Doppler and Baker's cyst [69].

In a longitudinal study to evaluate intra-articular platelet-rich plasma in severe KOA patients (Kellgren–Lawrence grade = 3–4), quantitative ultrasonographic cartilage thickness, measured as a distance perpendicular to the articular surface of medial condyle at the level of which the cartilage was well differentiated, was sensitive to treatment change [70].

Ultrasonography as predictors of disease progression

In a 2-year longitudinal study in KOA ($n = 125$), a strong consistent association with clinical and radiographic progression was found for the presence of Baker's cyst (found in 26% of participants in their study), and to a lesser extent for synovial hypertrophy, suggesting the potential role of ultrasound

Table 2. The Outcome Measures in Rheumatoid Arthritis Clinical Trial Ultrasound scoring system

Scoring for	Range	Location	Patient position	Scanning plane
Synovitis	0–3	Suprapatellar recess	Supine with the knee flexed 30°	Longitudinal
		Medial and lateral parapatellar recess	Supine with the knee in neutral position	Transverse
Synovial hypertrophy	Each for 0–1	Suprapatellar recess	Supine with the knee flexed 30°	Longitudinal
Effusion		Medial and lateral parapatellar recess	Supine with the knee in neutral position	Transverse
Synovial PD signal				
Cartilage damage	0–3	Trochlear cartilage	Supine with full flexion of the knee	Transverse
Meniscal damage	0–2	Anterior horn of the medial meniscus	Supine with the knee flexed 10°	Longitudinal
Osteophytes	0–3	Medial and lateral femorotibial space	Supine with the knee flexed 10°	Longitudinal

Modified from [67▪▪].

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in defining patients at risk of more rapid progression in clinical practice [71]. Cartilage changes, osteophytes and synovial thickening in dichotomous scale were associated with higher WOMAC index and worse clinical symptoms in their cross-sectional study [63]. Another study reported the significant association of a semiquantitative ultrasonographic grading system of femoral cartilage with the VAS, WOMAC and Lequesne index [72].

CONCLUSION

MRI remains the dominant imaging modality in osteoarthritis research community. Many research efforts are focusing on tissue-targeted disorders and on prediction models for disease progression. New imaging techniques continue to be developed to identify more specific and responsive measures for assessing treatment change. The ready availability of large datasets such as OAI has facilitated activity within the research community formulating different models for risk factors and fast progressors. In addition, the use of ultrasound is also increasingly being deployed for imaging of KOA. The future potential of KOA imaging will offer exciting opportunities to examine targeted structure-modifying therapies.

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Conflicts of interest

Prof D.J.H. – consultant to Nestle, Merck Serono and Flexion Therapeutics and Drs J.M.L. and W.M.O. do not have any conflict of interest.

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Appendix 6.2: Role of Ultrasonography in Knee Osteoarthritis (review)

Role of Ultrasonography in Knee Osteoarthritis

Win Min Oo, MBBS, MMedSc† and Myat Thae Bo, MBBS†*

Abstract: Ultrasound has become popular among rheumatologists as the first-choice imaging investigation for the evaluation and monitoring of osteoarthritis (OA). Because of recent improvement in technology, ultrasound has the ability to demonstrate and assess the minimal structural abnormalities, which involve the pathophysiology and progression of OA, such as articular cartilage, synovial tissue, bony cortex, and other soft tissue. Nowadays, ultrasonography is a promising technique for assessing soft tissue abnormalities such as joint effusion, synovial hypertrophy, Baker cyst, and other structural changes including the decrease in cartilage thickness, meniscus bulging, and formation of osteophyte. Ultrasonography not only possesses diagnostic potential in knee OA but also reveals long-term predictability for disease progress as imaging biomarker. Ultrasonography has also been proven as a useful tool in guiding therapeutic interventions and monitoring treatment effectiveness. This review addresses the utility, reliability, and potential utilization of ultrasonography as an imaging technique in knee OA.

Key Words: cartilage, knee osteoarthritis, musculoskeletal ultrasound, osteophytes, synovitis, ultrasonography

(*J Clin Rheumatol* 2016;22: 324–329)

Osteoarthritis (OA) is the most common cause of rheumatic disorder and a frequent health problem in the community where symptomatic knee OA has been prevalent in 6% to 10% of the adult population. Traditionally, OA has been defined as degenerative changes in bone, cartilage, and the soft tissues of the joints. Recently, OA is regarded as a failure of the joint as an organ, much like renal or cardiac failure.[1,2] Nondestructive synovial proliferation, joint effusions, popliteal cysts, tendonitis, and bursitis are frequent findings in OA.[3] Therefore, an imaging modality is requisite in order to assess the various structures within and around the joint, to measure a variety of the pathological aspects of OA.[4]

As a criterion standard, radiological imaging has been used to diagnose and classify the severity of knee OA such as the Kellgren and Lawrence system.[5] However, radiographs have several limitations, such as the inability to evaluate soft tissue structures and the related inflammation.[6] In addition, radiographic features of OA do not agree with the symptoms of OA.[7]

In recent years, the imaging techniques such as ultrasonography (US) have been used for better understanding and assessing the pathology of different musculoskeletal diseases.[4] Ultrasonography affords the abilities of scanning multiple planes at the same joint, providing a "one-stop" answer to many rheumatic problems, which is not answerable only by clinical examination. Ultrasonography has no hazard of ionizing radiation and can provide the multiplanar nature of the modality. It can also visualize soft tissue structures such as the meniscal extrusion and cartilage, which involve the pathophysiology and progression of OA.[8,9] This relatively inexpensive technology with the added advantages of portability and real-time dynamic examination can lead to a diagnostics service in the community.[10] Modern US systems can use beam steering and compound imaging technologies to allow wider fields of view. High-resolution probes with frequencies of up to 20 MHz are being applied in routine joint assessment.[11] To address the utility, reliability, and potential uses of US as an imaging technique in knee OA, we searched the articles in MEDLINE (34), EMBASE (65), EBM Reviews (29), AMED (3), Scopus (63), Web of Science (76), and the Cochrane Central Registers for Controlled Trials from their conception up to September 2015. These databases were looked up individually for all possible terms and combination of terms to accommodate differences in their search engines. Hand searches were also performed in addition to additional searches through Google Scholar and Reference Manager Search engines. The keywords used in combination (OR) are knee *osteoarthritis*, *knee osteoarthrosis*, *osteoarthritis*, ultrasonography, and *ultrasound*. The combination (AND) is used between *knee osteoarthritis*/*knee osteoarthritis* and *ultrasonography*/*ultrasound*. All key terms are limited to title/abstract. Then the duplicate terms are removed, and among the maximum 105 full texts, articles concerning therapeutic ultrasound or animal studies are excluded for narrative review.

Cartilaginous Changes

Cartilage thickness ranges from 0.1 mm on the articular surface of the head of the proximal phalanx to 2.6 mm on the lateral femoral condyle of the knee joint.[12] In 1984, ultrasound was used to determine the thickness of the articular cartilage, as well as to detect changes in its surface and internal characteristics such as the ratings of clarity and sharpness.[13] Loss of clarity of the cartilaginous layer and loss of the normal sharpness of the synovial space–cartilage interface are the earlier features of cartilage damage.[9]

The weight-bearing surfaces of the femoral cartilage can be assessed by transverse suprapatellar scan with the knee in maximal flexion (Fig. 1) or with an infrapatellar transverse scan with the leg fully extended. Cartilage is characterized in early OA by loss of the sharp contour and the various echogenicities of the cartilage matrix on the ultrasound images. An asymmetric narrowing of the cartilaginous band follows in the later disease process. It was reported that multiple sonographers demonstrated good reproducibility and high levels of agreement between US and histology in assessing the normal to moderately damaged cartilage.[14] In addition, measurement of cartilage thickness is rapid (several seconds), painless, and noninvasive.

It has been demonstrated that the ultrasonographic grading (in vitro) of femoral cartilage correlated well with the histologic grading (OARSI Osteoarthritis Cartilage Histopathology Assessment System)[15] of anterior and middle areas of femoral articular cartilage ($\rho = 0.78, 0.89$, both $P < 0.001$).[16] According to this ultrasonographic grading, grade 1 showed a homogenously anechoic cartilage band with sharp anterior and posterior margins; grade 2 showed blurring or obliteration of the margin of the cartilage band; grade 3 included blurring, obliteration of the margin, and narrowing of the cartilage band; grade 4 was coded if the cartilage band could not be visualized.

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The authors declare no conflict of interest.
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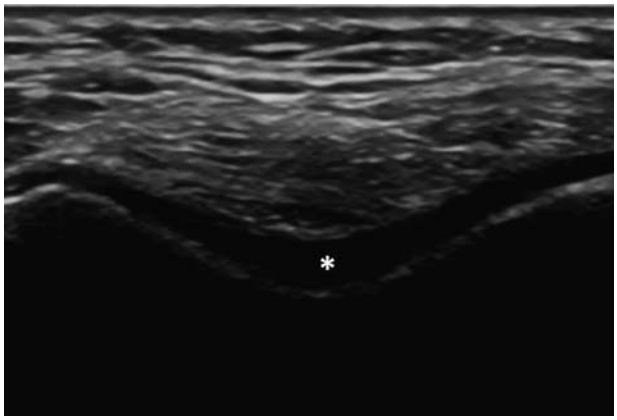

FIGURE 1. Suprapatellar transverse scan showing the normal hyaline cartilage.

Recently, it was reported that the semiquantitative ultrasonographic grading system may well reflect the clinical symptoms and functions in knee OA on evaluation against the visual analog scale, Western Ontario and McMaster Universities Arthritis Index, and Lequesne index.[17,18] The US grading system for femoral cartilage has been proposed after validating against the arthroscopic Noyes grading[19] for cartilage degeneration, and this outcome score includes assessment of local reduction of thickness, loss of the normal sharpness of cartilage interfaces, and increased echogenicity. The cartilage was evaluated as grade 0 if they showed a monotonous anechoic band with sharp hyperechoic anterior and posterior interfaces. Grade 1 changes include loss of the normal sharpness of cartilage interfaces and/or increased echogenicity of the cartilage. Grade 2A changes were as follows: in addition to the previously mentioned changes, clear local thinning (<50%) of the cartilage. Grade 2B changes showed local thinning of the cartilage of more than 50% but less than 100%. Grade 3 changes included 100% local loss of the cartilage tissue (Fig. 2). The sum of cartilage grades in all 3 sites of the femoral cartilage at the medial and lateral femoral condyles, as well as at the intercondylar notch area (sulcus) had the highest correlation between US and arthroscopy ($r_s = 0.655$, $P < 0.001$). However, it still needs further validation studies, which might include, for example, quantitative magnetic resonance imaging or histology as references. Noninvasive knee US is a promising technique for screening and evaluating degenerative changes of articular cartilage.[20]

Bony Changes

The early bone changes in the OA joint are characterized by hyperechoic signal at the site of the attachment of the joint capsule to the bony cartilaginous margin, which will eventually form as

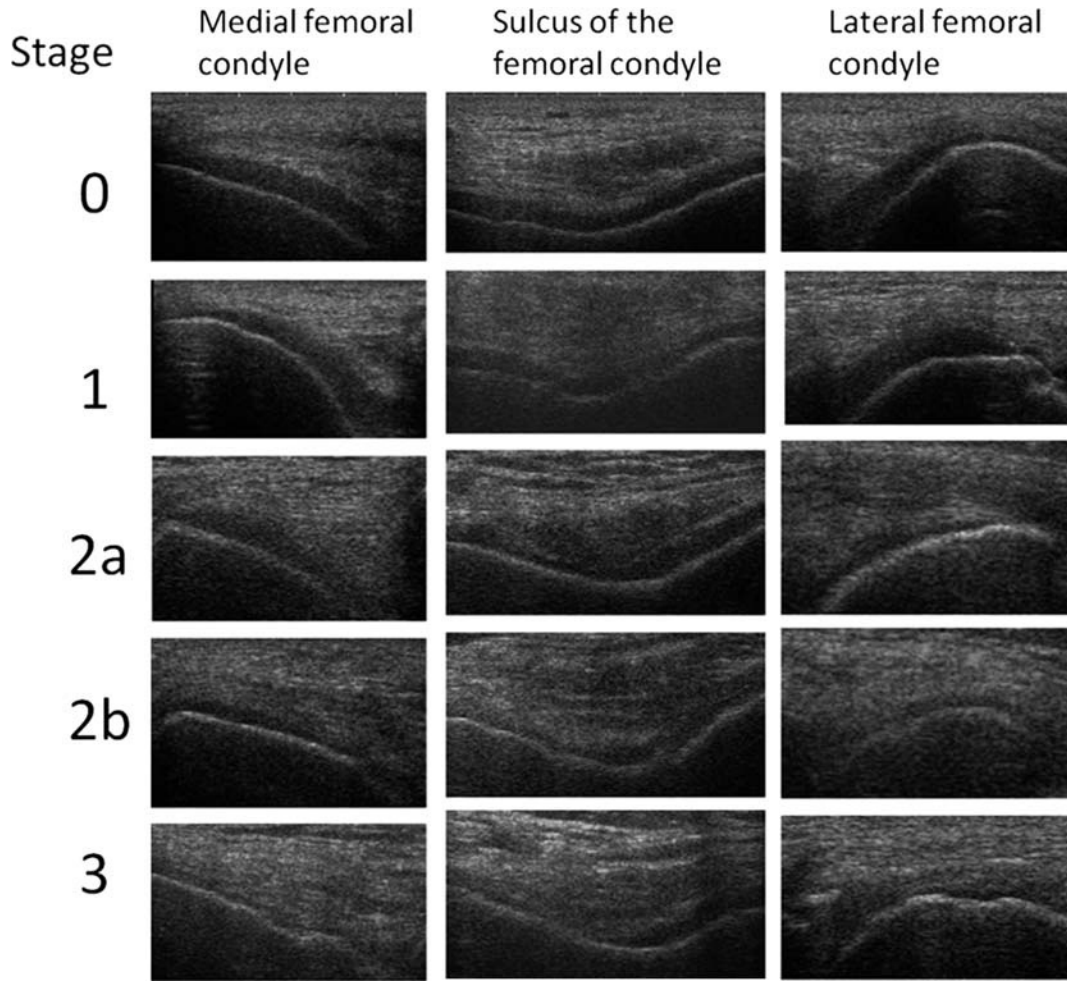

FIGURE 2. Typical examples of different cartilage degenerative US grades (0, 1, 2A, 2B, 3) in the knee joint.[20] Reprinted with permission from Elsevier.

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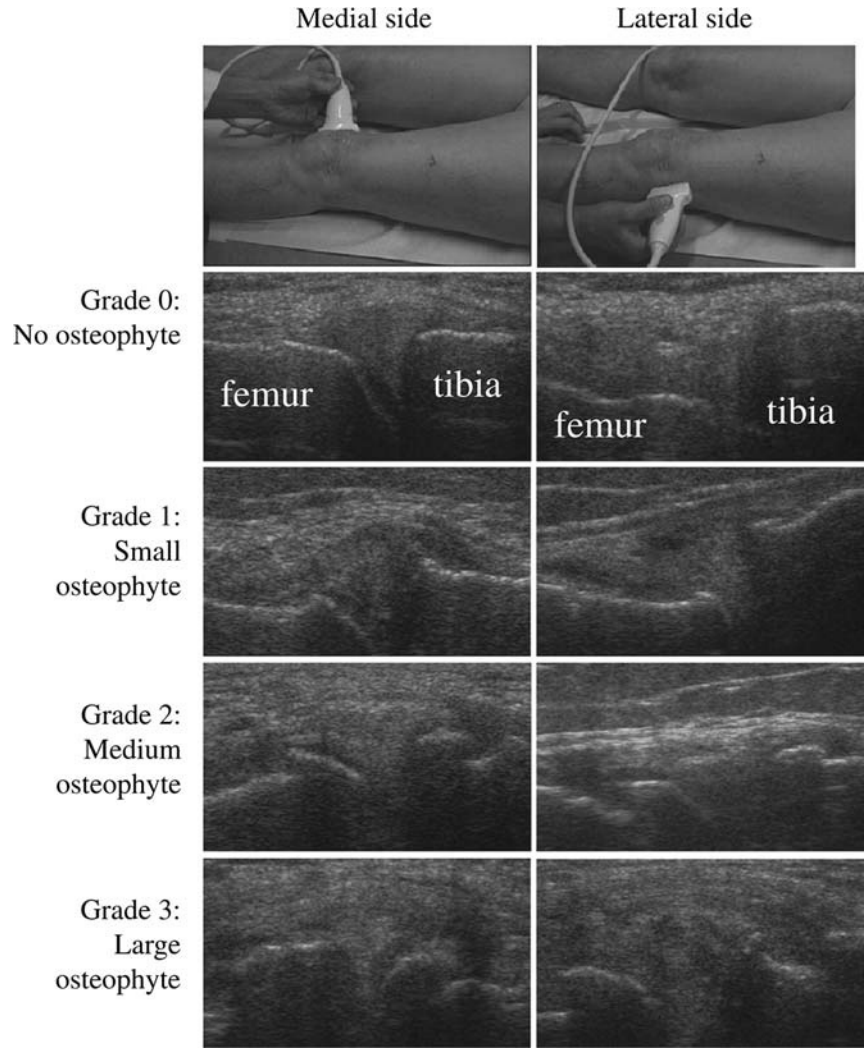

FIGURE 3. The US atlas for knee osteophyte detection.[23] Reprinted with permission from Taylor & Francis.

osteophytes on the conventional radiography. In advanced disease, the bony profile of the osteophytes is evident.[21] Moderate to substantial validity was reported in comparing ultrasonographic osteophytes to those seen on radiographs.[22]

A novel atlas for scoring osteophytes in the tibiofemoral joint was used to prove that the US was more sensitive in detecting osteophytes than plain radiographs at the medial compartment of the tibiofemoral joint (Fig. 3). Furthermore, osteophyte size detected with US, compared with only their presence, is a better predictor of the articular cartilage degeneration as there is a significant correlation between osteophyte size (summed US grade) and the arthroscopic grade of degenerative changes of the articular cartilage at the medial compartment.[23] The grading of osteophyte size was as follows: grade 0 included no osteophytes, that is, a smooth cortical surface; grade 1 demonstrated small and distinct cortical protrusion(s) of the bony surface; grade 2 showed larger protrusion(s) of the bony surface; grade 3 included very large protrusion(s) of the bony surface. However, it should be noted that this result is based on a small trial of 26 patients.

Recently, US score is developed in knee OA and includes relevant domains measuring (1) morphological changes in the medial compartment and lateral compartment such as osteophyte and meniscus extrusion, (2) inflammatory markers in medial compartment and lateral compartment such as synovial hypertrophy and Doppler activity, and (3) effusion. Bony changes demonstrated a strong correlation between the morphological changes in

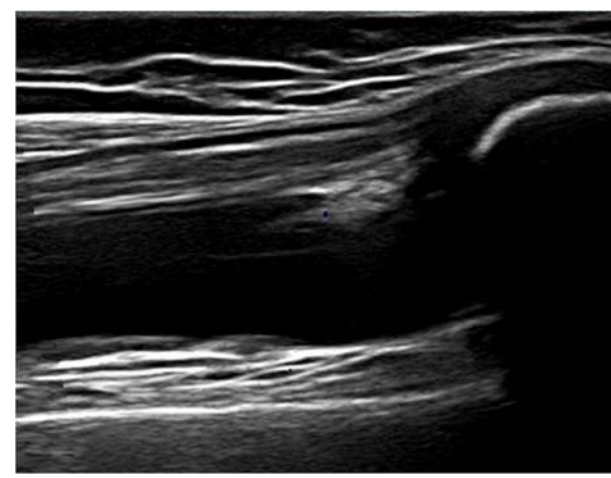

FIGURE 4. Large effusion in the suprapatellar recess. Sagittal plane.

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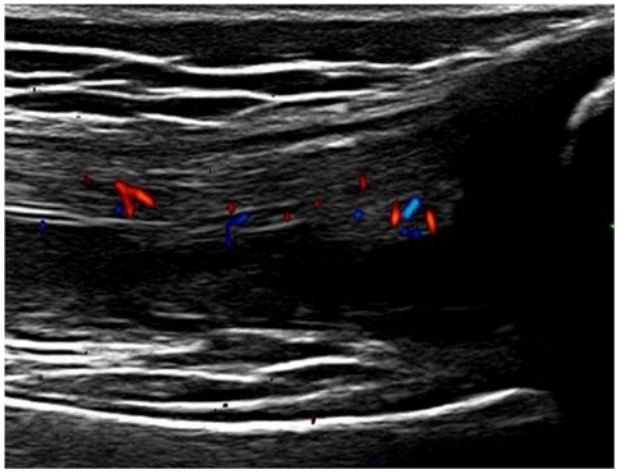

FIGURE 5. Increased bidirectional Power Doppler signals in the suprapatellar fat pad and quadriceps tendon around the suprapatellar recess. Sagittal plane (in black and white).

the medial and lateral compartments and the corresponding Kellgren-Lawrence score. Total ultrasound score displayed substantial reliability and reproducibility, with interclass correlations coefficients ranging from 0.75 to 0.97. Construct validity was confirmed with statistically significant correlation coefficients (0.47–0.81, $P < 0.01$). However, relevance for longitudinal studies remains to be demonstrated, for example, during treatment.[24]

Soft Tissue Changes

It has been increasingly recognized that synovitis plays a more important role in the pathogenesis of OA than previously thought. A small to moderate amount of synovitis and effusion is commonly detected in patients with knee OA (Fig. 4). Depending on the study, between 47% and 100% of patients were noted to have synovitis and/or effusion of the symptomatic knee.[25,26] A large European League Against Rheumatism study of 600 people with knee OA demonstrated synovial hypertrophy or effusion in 46%. Synovial hypertrophy was defined as synovial thickening of ≥4 mm and effusion recorded as present or absent based on the depth of fluid of more than 4 mm or less than 4 mm in the suprapatellar recess.[26] Ultrasonography is more sensitive than clinical examination in detecting synovitis[27] and correlates well with magnetic resonance imaging and arthroscopic findings. Synovitis or joint effusion detected by US also shows a relationship with pain in knee OA.[28–30]

The serial arthroscopies performed on knees with symptomatic but preradiographic OA revealed a clear association between the presence of synovitis and the future development of medial cartilage loss (an odds ratio for progression of the arthroscopic chondropathy score of 3.11 [1.07–5.69]), suggesting that, at its earliest stages, before visible cartilage degeneration has occurred, ultrasonographic synovitis has a potential role in predicting the structural progression of knee OA.[31]

Power Doppler can be utilized to assess synovial flow, which denotes increased synovial vascularization (Fig. 5).[32] Increased Doppler signal correlates with increased vascularity seen on histologic examination of synovial tissue of knee OA.[33] In a study that used a novel technique of digital synovial vascularization quantification with contrast enhancement for detecting synovitis in patients with knee OA, US of the superior recess revealed an effusion or synovial thickening in 58% in B-mode, 63% in power Doppler sonography, and 95% with contrast medium enhancement.[34]

On the other hand, there were reports that no association between US features and the degree of knee pain was detected after 1-year follow-up,[35] and further studies are still warranted to answer which part of pain in knee OA is explained by soft tissue

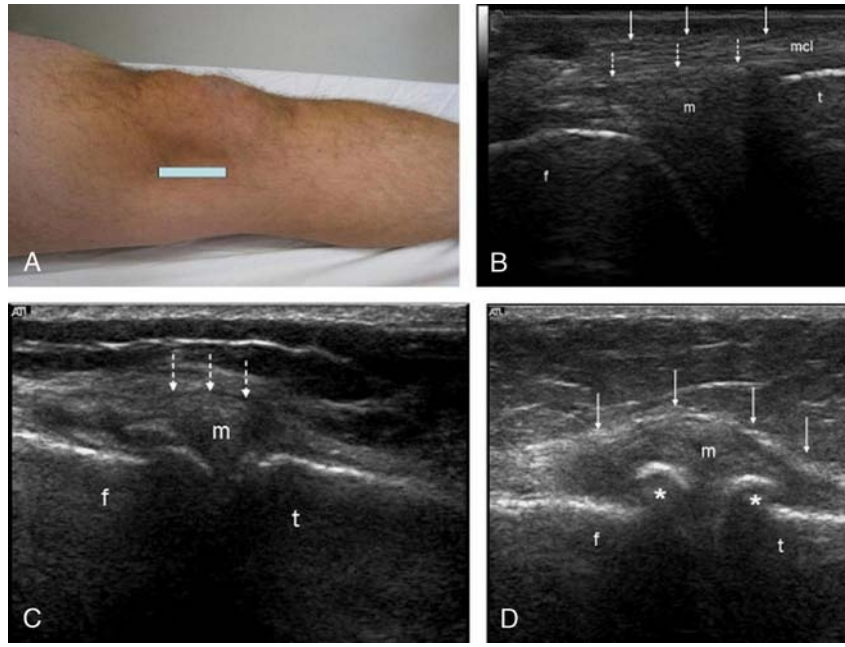

FIGURE 6. Longitudinal ultrasonographic images of the medial joint line (in black and white). A, Position of probe footprint. B, Ultrasonographic image of a normal knee shows distal femur (f), proximal tibia (t), triangular outline of the medial meniscus (m, dashed arrows), and the linear echoes produced by the medial collateral ligament (mcl, solid arrows). C, Ultrasonographic image shows medial meniscal extrusion (m, dashed arrows). D, Ultrasonographic image in knee OA demonstrates medial meniscal extrusion (m) with resulting displacement of the medial collateral ligament (arrows) and obvious osteophytes (*) proximal and distal to the joint line.[11] Reprinted with permission from Elsevier.

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pathology and whether US is the imaging method of choice to measure this pathology.

In a systemic review in 2009, a paucity of reliability data was highlighted with regard to interreader and intrareader reliability in image acquisition and the scoring of stored images.[4]

Monitoring and Intervention

In clinical trials in knee OA, outcome measures usually include structural assessment, functional status, and the level of pain. Serological markers are unavailable for monitoring disease progression in OA, and imaging markers using US abnormalities will be valuable in this scenario. Studies are still lacking to identify and precisely determine a population in which OA progresses more rapidly.[36]

Recently, US prediction in the long-term progress of knee OA is reported. After 1-year follow-up, meniscal protrusion (Fig. 6) and Baker cyst (Fig. 7) might be useful for long-term prediction of clinical or radiological outcome, although effusion, synovial hypertrophy, and infrapatellar bursitis seem to be more temporary phenomena.[35] A longitudinal association between Baker cyst at baseline and radiological and clinical progression was found after 2-year follow-up.[37]

In another study, increased meniscal bulging and presence of Baker cyst/joint effusion were correlated with worse pain or poorer function.[38]

A 3-year multicenter European League Against Rheumatism prospective study determined the predictors for joint replacement in more than 500 subjects with knee OA. The multivariate analysis demonstrated that the presence of a joint effusion (≥4 vs. <4 mm) at baseline was a significant independent predictor of joint replacement at 3 years (hazard ratio, 2.63 [95% confidence interval, 1.70–4.06]).[39]

Ultrasonography has proved to be an effective and safe imaging method for guiding intra-articular injections because of the advantage of visualizing the proper needle positioning inside the joint cavity. In a study of 62 patients with symptomatic knee OA to investigate the predictive value of US characteristics by defining responders as patients with numeric rating pain scale of 4 or less at 4 weeks after glucocorticoid injection, no US characteristic of inflammation has the ability to reliably predict those who respond to intra-articular glucocorticoids, requiring further study in a large-scale trial.[40] Given the disagreement between radiographic morphological changes and symptoms in OA, further studies should establish the usefulness and value of US-detected changes in terms of effectiveness of therapeutic interventions.[10]

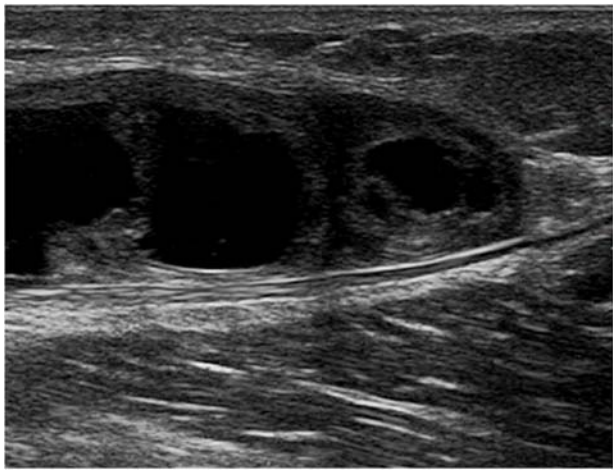

FIGURE 7. Baker cyst. Synovial hypertrophy and fluid in the Baker cyst. Sagittal plane.

LIMITATIONS

Application of ultrasound to assess large joints seems still challenging because of the inherent inability of ultrasound to pass through bony structures and scan deeper portions of the joint.[41,42] Thus, US visualization of the articular cartilage is limited by the width of the acoustic windows that depends on the anatomy of the joint. Even with advances in the resolution of the transducers, deeper structures are difficult to visualize as the higher-frequency transducers have lower tissue penetration.

In patients with arthritis, however, assessment of the cartilage of the weight-bearing areas can be difficult in patients with advanced OA and/or painful knee resulting from limited maximal active flexion. In addition, the cartilages of the patella and the tibia are always inaccessible to US. Although US can be used to detect bone erosions, it is not applicable for estimation of bone erosion depth, because it visualizes only the bone surface and not the subchondral bone.[42]

Moreover, US has been regarded as a highly operator-dependent imaging method with poor reproducibility, partly due to the intrinsic real-time nature of US image acquisition.[11] However, its usage is reassured by recent studies that have established moderate to good interobserver reliability.[43–45]

Acquisition of US skills takes time depending on the trainee's hand-eye coordination skills. A long learning curve may be an important limiting factor in widespread use of US. In addition, examination of multiple scanning planes in the clinical setting can be time consuming. Focused examination is proposed with concentration on a small number of scanning planes to reduce examination time.[46]

CONCLUSIONS

Ultrasound provides a safe, cost-effective, and reliable technique to assess knee OA. Ultrasonography is more sensitive than clinical examination and plain radiography in recognition of important abnormalities prevalent in knee OA. It is an excellent tool not only to recognize the bony profile but also to visualize the soft tissues, helping the rheumatologist to determine the type and extent of these structural damages. The semiquantitative ultrasonographic grading system has been validated and will be valuable in monitoring disease progression. Ultrasonography also has the potential to further clarify the role of soft tissues and provide new insights in the disease genesis, pathology, progression, and prediction of OA. However, the long learning curve is still an important limitation to be overcome for widespread application of US in routine clinical practice.

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Appendix 6.3: Clinimetrics of Ultrasound Pathologies in Osteoarthritis: Systematic Literature Review and Meta-analysis

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Osteoarthritis and Cartilage

Review

Clinimetrics of ultrasound pathologies in osteoarthritis: systematic literature review and meta-analysis

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SUMMARY

Objective: The aims of this study were to systematically review clinimetrics of commonly assessed ultrasound pathologies in knee, hip and hand osteoarthritis (OA), and to conduct a meta-analysis for each clinimetric.

Methods: Medline, Embase, and Cochrane Library databases were searched from their inceptions to September 2016. According to the Outcome Measures in Rheumatology (OMERACT) Instrument Selection Algorithm, data extraction focused on ultrasound technical features and performance metrics. Methodological quality was assessed with modified 19-item Downs and Black score and 11-item Quality Appraisal of Diagnostic Reliability (QAREL) score. Separate meta-analyses were performed for clinimetrics: (1) inter-rater/intra-rater reliability; (2) construct validity; (3) criteria validity; and (4) internal/external responsiveness. Statistical Package for the Social Sciences (SPSS), Excel and Comprehensive Meta-analysis were used.

Result: Our search identified 1126 records; of these, 100 were eligible, including a total of 8542 patients and 32,373 joints. The average Downs and Black score was 13.01, and average QAREL was 5.93. The stratified meta-analysis was performed only for knee OA, which demonstrated moderate to substantial reliability [minimum kappa > 0.44(0.15,0.74), minimum intraclass correlation coefficient (ICC) > 0.82(0.73–0.89)], weak construct validity against pain (r = 0.12 to 0.27), function (r = 0.15 to 0.23), and blood biomarkers (r = 0.01 to 0.21), but weak to strong correlation with plain radiography (r = 0.13 to 0.60), strong association with Magnetic Resonance Imaging (MRI) [minimum r = 0.60(0.52,0.67)] and strong discrimination against symptomatic patients (OR = 3.08 to 7.46). There was strong criterion validity against cartilage histology [r = 0.66(−0.05,0.93)], and small to moderate internal [standardized mean difference(SMD) = 0.20 to 0.58] and external (r = 0.35 to 0.43) responsiveness to interventions.

Conclusion: Ultrasound demonstrated strong criterion validity with cartilage histology, poor to strong correlation with patient findings and MRI, moderate reliability, and low responsiveness to interventions.

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Introduction

Osteoarthritis (OA) is the ubiquitous joint disease, predisposing to severe disability and economic burden on the community[1], with its prevalence surging world-wide due to an increase in ageing population[2]. Pathophysiology of OA is complex and involves multiple tissue pathologies; there is currently no consensus on which

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manifestations should be measured in OA clinical studies. In attempting to objectively evaluate OA structural components, X-ray and MRI have been commonly employed as they visualize constructs related to cartilage. Ultrasound has been less well studied, but does provide certain advantages such as real-time assessment of multiple joints, sensitive visualisation of synovitis without the need for contrast agents[3–5], its detection of pathologies such as meniscus extrusion[6–9], osteophytes[10–12], degeneration of femoral trochlear cartilage[13–16], and effusions (which might be missed on clinical examination or plain radiography)[5,17–19]. As a result of these attributes, and likely because of widespread uptake in the rheumatology community, ultrasound has increasingly been applied as an outcome tool in OA clinical studies over the last decade.

Since Keen *et al.* reported its clinimetrics, mainly with a focus on validity, in a systematic review in 2009, based on PubMed and Medline database searches[20], many ultrasound OA studies have been published according to recent narrative reviews[21,22], with most papers having sound methodology, utilizing more advanced technology such as high-frequency probes, and use of definitions and techniques from OMERACT[23] and European League Against Rheumatism (EULAR) Ultrasound Working Groups[24]. The increase in knowledge base in this area, therefore, warrants an update of the previous review in terms of clinimetrics (clinical measurement) such as reliability, validity, responsiveness[25]. Moreover, there is no published meta-analysis on these clinimetric of commonly assessed ultrasound pathologies in OA.

Therefore, the purposes of this study were: (1) to systematically review the performance metrics of ultrasound as applied to the detection of commonly assessed pathologies in people with OA with a focus on knee, hand and hip joints and (2) to conduct a meta-analysis of each clinimetric property for the ultrasound findings if feasible.

Methodology

Selection criteria

Manuscripts were included if (1) they reported clinimetrics of commonly assessed ultrasound pathologies in knee or hand or hip OA in adults, and (2) separate clinimetrics for OA were recorded if the sample included different rheumatic diseases. Articles were excluded if (1) they were not related to the use of B-mode or color/power Doppler ultrasound, (2) they utilized ultrasound only for injection guidance, (3) they did not provide any ultrasound clinimetrics, or (4) they were review or editorial articles, non-human or non-English publications. The study protocol was registered in PROSPERO database with CRD42016039954.

Information source and selection process

One reviewer (WMO) searched MEDLINE via Ovid, EMBASE, and Cochrane Library databases from their respective inception to September 2016. The search strategy for each database was developed in consultation with an experienced librarian (Supplementary data 1). The same reviewer implemented the secondary searching in reference lists of included articles, ultrasound chapters in reference books, and conference abstracts of Osteoarthritis Research Society International (OARSI), EULAR and American College of Rheumatology (ACR) from 2014 to 2016.

The retrieved articles were imported into Covidence systematic review software[26], and two reviewers (WMO and MD) screened the titles and abstracts independently. Subsequently, the full texts of the selected articles were retrieved and judged against the inclusion and exclusion criteria. Any disagreement was resolved with a third reviewer (DJH). When the included studies referred to a previous paper for methodology or reliability, it was obtained, and appraised if it met the selection criteria.

Data extraction and quality assessment

According to the OMERACT Instrument Selection Algorithm[27], the same two reviewers conducted data extraction with a standardized excel template including: (1) characteristics of studies such as study design, setting, sample size, participants selection and diagnostic criteria; (2) technical features such as ultrasound mode (i.e., B-mode, Power Doppler), machine settings, scanning methods, the particular joints and structures scanned; (3) pathological findings such as ultrasound definitions of pathologies and scoring methods; (4) types of clinimetrics.

For reliability, imaging and operator characteristics were recorded. Construct validity was defined if the study correlated ultrasound findings with clinical assessment, plain radiography or MRI. Criterion/predictive validity was defined when ultrasound findings were concurrently or predictively compared with the gold standard, i.e., histopathology, arthroscopy. Discriminative validity was also assessed in two aspects: internal responsiveness (the ability of ultrasound measure to change over a pre-specified time frame) or external responsiveness (the extent to which changes in ultrasound measure relate to corresponding changes in a reference measure of health status) for interventional studies. Feasibility was calculated in scanning time required for the whole ultrasound examination. One reviewer (WMO) appraised the methodological quality, using the modified 19-item version (Supplementary data 2) derived from Downs and Black score system[28,29] for all included papers, and 11-item QAREL score for reliability papers[30].

Pooling criteria for meta-analysis

For meta-analysis, data were pooled if the paper reported sufficient data to calculate (1) kappa or ICC for reliability, (2) Pearson and Spearman correlation coefficients for validity, (3) SMD for internal responsiveness, (4) correlation coefficient for external responsiveness. For validity, all types of regression coefficients (β) were omitted from pooling due to controversy in combining them[31].

Statistical analysis

Qualitative analysis

Frequencies and percentages were computed for categorical variables of included papers.

Meta-analysis and meta-regression

Unit of analysis: Each sample of subjects from studies was assumed as one unit of analysis. When two or more articles documented reliability/correlation coefficients, using the same sample, the coefficient was included only once as the unit of analysis. When one article reported more than one reliability/correlation coefficients of the same clinimetric measurement from the same sample, the mean coefficient was calculated, and then analysed in the meta-analysis. If the study comprised independent subgroups, the subgroups were pooled as a separate unit of analysis[32].

Pooling data: Separate meta-analyses were performed for each type of clinimetrics: (1) kappa or ICC for inter-rater or intra-rater reliability (2) construct validity against healthy control, pain, functional assessment, conventional X-rays, MRI, or biomarkers, (3) internal or external responsiveness. These data were pooled, based on each ultrasound pathology (synovitis/effusion/osteophyte/etc.) to be clinically meaningful. For reliability statistics, pooling was

stratified for each grading method (binary/semi-quantitative/quantitative) of the same ultrasound pathology.

For weighted meta-analysis of kappa estimates, when the standard error (SE) was unavailable, it was calculated from 95% confidence interval (CI) bounds[33]. If both SEs and CIs were not reported, the largest observed SE from the included studies was used. For ICC statistics of reliability and Pearson or Spearman correlation coefficients of validity, effect sizes were first obtained through the z-transformations, and then the resulting pooled effect sizes were back-transformed (z to r transformation) to the level of original coefficients for easier interpretation[34]. For merging odd ratios in validity studies, the log odds ratio and the SE of the log odds ratio were determined[35]. The SMD, using Hedges' g due to inclusion of small studies (<30 patients/joints), was calculated for internal responsiveness[36], and correlation coefficients were pooled for external responsiveness through the z-transformations[37].

For assessment of heterogeneity, Cochran Q test was computed[34]. The I^2 was used to quantify how much of the total variability can be attributed to heterogeneity[38]. To scrutinize possible publication bias, it was intended to evaluate with funnel plot techniques[39], Begg's rank test[40] and Egger's regression test[41], as appropriate, given the known limitations of these methods, if the minimum number of studies could be pooled. All analyses for calculating the estimates from primary studies, and for pooling data were carried out by using the SPSS, Excel and Comprehensive Meta-analysis software.

Results

Identification of included studies

Our search identified 1246 records (468 Medline, 774 Embase and four Cochrane library) with 120 duplicates. After screening the titles and abstracts, 195 articles remained. Furthermore, 10 articles were retrieved from the reference lists, totalling 205 articles eligible for full-text review. Of these, 100 articles were selected as shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Fig. 1).

Study characteristics

One hundred articles (listed in Supplementary data 3), having a total of 8542 patients and 32,373 OA joints, and published between 1982 and 2016, were included in the systematic review. The studies' characteristics were summarized in Supplementary data 4. Majority of studies (79%) were documented after 2008. Knee OA was the most widely investigated ($n = 64$), followed by hand OA ($n = 28$), and hip OA ($n = 8$).

According to Oxford Centre for Evidence-Based Medicine guidelines (www.cebm.net/), 42 papers utilized a cross-sectional design (42%) and 28 papers applied a cohort design (28%). The participants were recruited from out-patient rheumatology clinics in 46 papers; the setting was not mentioned in 23 papers. The selection method was not described in half of the studies, followed by a consecutive method ($n = 40$), convenience ($n = 5$) and random methods ($n = 5$). ACR criteria was employed for diagnosis in most of studies ($n = 81$); 14 papers did not disclose diagnostic criteria. The mean age of included studies ranged from 50.1 ± 9.2 to 71.9 ± 5.9 years; female participants varied from 37% to 100%; the mean BMI from 22.2 ± 2.6 to 33.5 ± 4.6 kg/m^2. Eight studies recruited mixed samples with different diseases, but delineated separate clinimetrics of OA sub-group.

Ultrasound scanning techniques and definition

For simplicity, the EULAR scanning method[42] and OMERACT definitions[23] were assumed as the standard criteria to identify respective OA pathologies. Out of 100 papers, power Doppler was

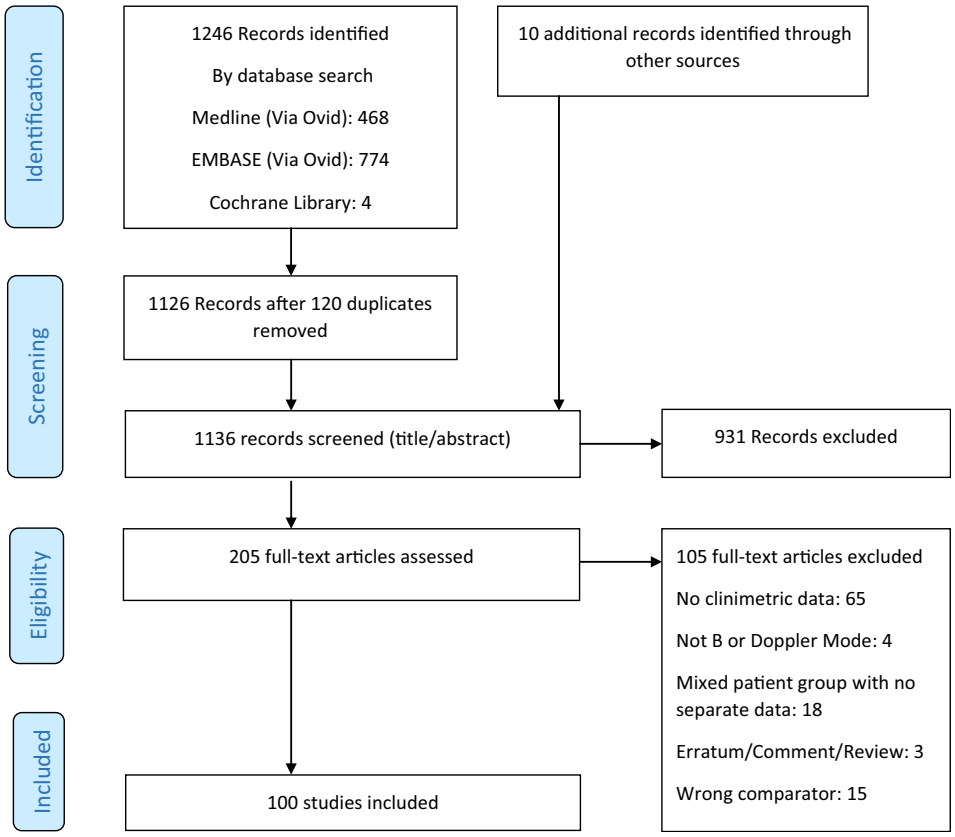

Fig. 1. PRISMA flow diagram of included studies.

investigated in 31 (Supplementary data 5). Doppler specifications were detailed in 19 papers: Doppler frequency was reported in 9 (from 12 MHz to 6.3 MHz); pulse repetition frequency (PRF) in 10 (from 13.2 KHz to 3 Hz); wall filter and gain in 17. One paper examined contrast ultrasound.

Eighty-eight papers defined ultrasound pathology; 26 papers referred the EULAR scanning protocol; 59 papers administered their own methods or modification from previous papers; 13 papers did not delineate the specific scanning method. Thirty-nine studies applied the OMERACT definitions, which were found to be increasingly used across the years from one paper in 2008, and then five papers in 2012 to 10 papers in 2016 (Supplementary data 6).

Ultrasound lesions and scoring system

Overall, synovial pathologies were more extensively examined, i.e., effusion (52%), synovial hypertrophy (37%), Doppler activity (31%), Baker's cyst (25%), compared to structural lesions, i.e., osteophyte (29%), cartilage thinning (28%). A variety of grading systems was evaluated [binary (n = 49,49%), semi-quantitative (n = 42, 42%), and quantitative (n = 40,40%)].

Qualification of ultrasound operator

Only twenty papers declared the number of operator's training years in musculoskeletal ultrasound, ranging from 3 months to 24 years. The operator/readers were also of diverse academic backgrounds: rheumatologist (27% of all papers), ultrasonographer (16%), radiologist (11%), others such as physiatrist, surgeon, fellow-in-training (26%), and no report (20%).

Methodological quality

The average quality score across the studies assessed with the modified Downs and Black instrument was 13.01 out of 19 items (taking into account the questions that were not applicable for certain studies). The chart in Supplementary data 7 outlined the proportion of the 100 studies that met each of the quality assessment items. The papers, in general, had a good rating (>60%) on the 13 items. However, most papers fell short severely on some items such as reporting of sample size calculation and sufficient power (10%).

The average QAREL score was 5.93 out of 11 items across all reliability studies (n = 43). Blindness to other raters, own prior findings, clinical information and non-clinical clues were described in 40% (n = 17), 28% (n = 12), 56% (n = 24) and 5% (n = 2), respectively (Supplementary data 8). Randomization of patients/raters was found only in 53% (n = 23). As there was no definite consensus related to time interval for stability of ultrasound findings between repeated measurements, only evaluation of stored images was given as yes (n = 17), and rating of the acquired image as unclear (n = 26). Overall, the regression plot displayed the significant improvement of QAREL quality score across the years (β = 0.40, P = 0.01) (Supplementary data 9).

Clinimetric properties

Among the 100 studies, 32 papers were identified for the intra-rater reliability, 25 for inter-rater reliability, 57 for construct validity, five for criterion validity in knee, 10 for clinical predictive validity, six for structural predictive validity, 21 for intrinsic responsiveness, eight for extrinsic responsiveness and seven for feasibility.

Meta-analysis

The meta-analysis was conducted only for knee OA. Pooling could not be performed for hand and hip OA due to a paucity of reported clinimetric data for ultrasound, and so descriptive analysis was presented. Publication bias was not examined due to inadequate numbers of included papers for a specific OA pathology, which did not allow proper assessment of funnel plots or more advanced regression-based assessments.

Knee OA

Reliability

Inter-rater reliability: According to the pooling criteria, stratified kappa meta-analysis was conducted across 11 knee studies, including 38 kappa estimates and 556 joints of 506 patients. ICC estimates was pooled across seven knee studies with a total of 19 ICC estimates in 340 joints of 308 participants. Kappa coefficients were interpreted according to Landis and Koch (0: poor; 0.01–0.20: slight; 0.21–0.40: fair; 0.41–0.60: moderate; 0.61–0.80: substantial; 0.81–1.00: almost perfect)[43].

The pooled kappa of binary score (Table I) was almost perfect for Baker's cyst [0.92(0.83–1)], and substantial for effusion

Table I
Stratified meta-analysis of ultrasound features for inter-rater reliability in knee OA

Stratified meta-analysis		No. of studies	No. of patients	No. of joints	Kappa (95% CI)		Heterogeneity		
Knee					Fixed	Random	P value	I^2	Tau
Kappa (Binary)	Effusion	6	242	281	0.46(0.44–48)	0.75(0.41,1)	0.00	99	0.41
	Synovial hypertrophy	5	224	245	0.37(0.34–0.40)	0.52(0.18,0.86)	0.00	98	0.38
	Osteophyte	3	107	133	0.89(0.83–0.95)	0.76(0.53,1)	0.00	83	0.19
	Cartilage thickness	2	89	97	0.98(0.95–1)	0.76(0.28,1)	0.00	95	0.34
	Meniscal extrusion	4	211	219	0.71(0.62–0.79)	0.66(0.49,0.83)	0.02	70	0.15
	Baker's cyst	4	211	219	0.92(0.83–1)	0.92(0.83,1)	0.58	0.00	0.00
Kappa (Semi-quantitative)	Synovitis	2	24	48	0.52(0.48–0.56)	0.63(0.36,0.90)	0.01	86	0.18
	Effusion	1	11	22	0.74(0.54–0.94)				
	Osteophyte	4	150	174	0.58(0.55–0.61)	0.66(0.50,0.82)	0.00	78	0.14
	Cartilage thickness	2	47	60	0.33(0.28–0.39)	0.44(0.15,0.74)	0.00	87	0.20
	Meniscal extrusion	3	117	141	0.84(0.81–0.87)	0.75(0.41,1)	0.00	98	0.30
ICC	Effusion	2	63	81	0.84(0.76–0.89)	0.84(0.74,0.90)	0.24	27	0.1
	Osteophyte	1	45	45	0.97(0.95–0.98)				
	Cartilage thickness	5	236	254	0.86(0.82–0.89)	0.86(0.53,0.97)	0.00	97	0.81
	Meniscal extrusion	3	137	151	0.94(0.92–0.96)	0.95(0.79,0.99)	0.00	95	0.65
	Baker cyst	2	85	85	0.95(0.92–0.97)	0.95(076,0.99)	0.00	93	0.60

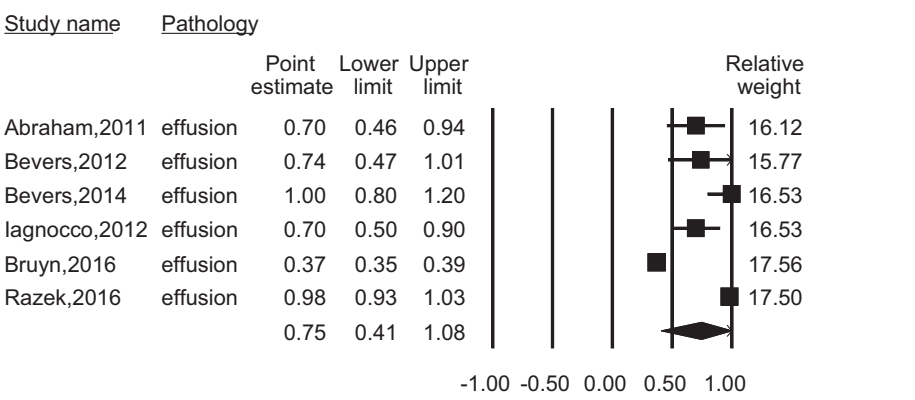

Fig. 2. Meta-analysis for inter-rater reliability (kappa) in binary score of effusion in knee OA.

[0.75(0.41,1)] (Fig. 2), with nearly all pathologies revealing considerable heterogeneity (I^2 = 70 to 99). For semi-quantitative score, pooled kappa values were moderate for cartilage thinness [0.44(0.15–0.74)], and substantial for all pathologies, with high heterogeneity (I^2 = 78–98). For quantitative scores, all pathologies provided almost perfect reliability for pooled ICC estimate.

Intra-rater reliability: Stratified kappa meta-analysis was performed from eight knee studies, including a total of 23 kappa estimates for 502 joints of 465 patients. For ICC values, data were pooled from nine knee studies with a total of 21 ICC estimates for 566 joints of 490 participants.

The pooled kappa of semi-quantitative score (Table II) was varied from moderate for cartilage thinness [0.55(0.45–0.66)], substantial for synovitis [0.69(0.60–0.78)] and osteophyte [0.74(0.67–0.81)] to almost perfect for meniscal extrusion [0.81(0.66–0.96)], exhibiting low heterogeneity (I^2 = 7 to 51). For quantitative scores, reliability was almost perfect in all pathologies.

Validity

Meta-analysis was stratified for each comparator such as asymptomatic controls, pain, function, X-rays, MRI or blood biomarkers or histology or arthroscopy. Correlation coefficients were interpreted according to the Evans' classification[44], <0.20: very weak; 0.20–0.39: weak; 0.40–0.59:moderate; 0.60–0.79; strong and >0.80: very strong.

Construct validity against asymptomatic controls: Six studies, including 643 joints from 582 participants, provided 23 odd ratios. In symptomatic patients (Table III), the pooled odd ratio demonstrated a very strong association with effusion [7.46(2.56,21.70)], and a strong association with Baker's cyst [3.23(1.57,6.67)] and meniscal extrusion [3.08(1.06,8.92)]. Heterogeneity was generally moderate (I^2 = 41 to 61).

Construct validity against pain: Pooling 37 estimates out of 16 studies, including 2577 joints from 2085 patients, revealed weak correlation with trivial heterogeneity [I^2 = 0] (Table IV).

Table II
Stratified meta-analysis of ultrasound features for intra-rater reliability in knee OA

Stratified meta-analysis		No. of studies	No. of patients	No. of joints	Kappa (95% CI)		Heterogeneity		
Knee					Fixed	Random	*P* value	I^2	Tau
Kappa (Binary)	Effusion	1	13	26	0.56(0.47–0.65)				
	Synovial Hypertrophy	1	13	26	0.49(0.34–0.64)				
Kappa (Semi-quantitative)	Synovitis	2	24	48	0.69(0.60–0.77)	0.69(0.60–0.78)	0.30	7	0.02
	Effusion	1	11	22	0.78(0.55–1)				
	Doppler activity	2	28	28	0.88(0.72–1)	0.88(0.65–1)	0.15	51	0.12
	Osteophyte	5	309	333	0.74(0.68–0.79)	0.74(0.67–0.81)	0.30	18	0.03
	Cartilage thickness	2	172	185	0.55(0.45–0.66)	0.55(0.45–0.66)	0.91	0.00	0.00
	Meniscal extrusion	3	117	141	0.80(0.69–0.90)	0.81(0.66–0.96)	0.18	42	0.09
ICC	Effusion	3	108	121	0.89(0.85–0.92)	0.90(0.74–0.96)	0.00	86	0.41
	Synovial hypertrophy	3	108	121	0.82(0.75–0.87)	0.82(0.73–0.89)	0.20	37	0.13
	Doppler activity	1	45	45	0.75(0.59–0.86)				
	Osteophyte	2	126	176	0.93(0.91–0.95)	0.89(0.49–0.98)	0.00	96	0.64
	Cartilage thickness	3	114	114	0.88(0.83–0.92)	0.80(0.05–0.97)	0.00	96	0.90
	Meniscal extrusion	4	318	381	0.91(0.89–0.93)	0.91(0.78–0.96)	0.00	95	0.48
	JSN	1	81	131	0.93(0.90–0.95)				
	Baker cyst	3	113	113	0.90(0.86–0.93)	0.90(0.53–0.98)	0.00	95	0.75

Table III
Stratified meta-analysis of ultrasound features for construct validity in knee OA (asymptomatic control)

Stratified meta-analysis	No. of studies	No. of patients	No. of joints	Odd ratio (95% CI)		Heterogeneity		
Knee				Fixed	Random	*P* value	I^2	Tau
Synovitis	1	56	122	10.53(3.42,32.44)				
Effusion	5	421	598	5.20(2.89,9.35)	7.46(2.56,21.70)	0.04	61	0.9
Osteophyte	1	56	122	3.23(0.20,53.47)				
Meniscal extrusion	4	360	476	2.38(1.21,4.69)	3.08(1.06,8.92)	0.14	45	0.70
Infra-patella bursitis	1	101	101	4.13(0.23,75.33)				
Baker cyst	5	421	598	2.87(1.73,4.75)	3.23(1.57,6.67)	0.15	41	0.52
Pes anserine bursitis	1	101	101	2.95(0.16,55.53)				

Table IV
Stratified meta-analysis of ultrasound features for construct validity in knee OA (pain)

Stratified meta-analysis	No. of studies	No. of patients	No. of joints	Correlation coefficient (95% CI)		Heterogeneity		
Knee				Fixed	Random	*P* value	I^2	Tau
Synovitis	2	287	287	0.27(0.16,0.38)	0.27(0.16,0.38)	0.72	0	0
Effusion	7	1006	1092	0.12(0.06,0.18)	0.12(0.06,0.18)	0.46	0	0
Synovial hypertrophy	2	71	85	0.20(0.07,0.32)	0.20(0.07,0.32)	0.43	0	0
Power Doppler	1	41	41	0.37(0.07,0.61)				
Osteophyte	2	353	353	0.15(0.05,0.25)	0.15(0.05,0.25)	0.83	0	0
Meniscal extrusion	2	238	238	0.17(0.04,0.29)	0.17(0.04,0.29)	0.99	0	0
Cartilage thickness	4	287	295	0.22(0.11,0.33)	0.22(0.11,0.33)	0.45	0	0
Baker cyst	3	264	264	0.13(0.00,0.24)	0.13(0.00,0.24)	0.68	0	0
Pes anserine bursitis	2	257	414	0.02(−0.08,0.12)	0.02(−0.08,0.12)	0.83	0	0

Table V
Stratified meta-analysis of ultrasound features for construct validity in knee OA (X rays)

Stratified meta-analysis	No. of studies	No. of patients	No. of joints	Correlation coefficient (95% CI)		Heterogeneity		
Knee				Fixed	Random	*P* value	I^2	Tau
Synovitis	1	45	45	0.39(0.11,0.62)				
Effusion	2	139	139	0.55(0.42,0.66)	0.54(0.37,0.68)	0.21	35	0.10
Synovial hypertrophy	1	94	94	0.70(0.58,0.79)				
Osteophyte	3	94	102	0.60(0.45,0.71)	0.60(0.45,0.71)	0.43	0	0
Meniscal protrusion	2	111	212	0.48(0.37,0.58)	0.48(0.34,0.60)	0.22	34	0.07
Cartilage thickness	2	60	68	0.35(0.12,0.55)	0.35(0.12,0.55)	0.37	0	0
Baker cyst	1	94	94	0.30(0.10,0.47)				
Pes anserine bursitis	2	242	484	0.12(0.03,0.21)	0.13(0.00,0.26)	0.15	52	0.07

Construct validity against function: Meta-analysis of 15 estimates out of nine studies, including 1333 joints and 802 patients, resulted in weak correlation, and mild heterogeneity [$I^2 = 20–38$] (Supplementary data 10). Six studies used Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[45].

Construct validity against X-rays: Pooling across a total of 49 estimates from 11 studies (1956 joints, and 1530 patients) indicated strong correlation with osteophyte [0.60(0.45,0.71)], moderate correlation with effusion [0.54(0.37,0.68)] and meniscal extrusion [0.48(0.34,0.60)], and weak association with cartilage thickness [0.35(0.12,0.55)]. Heterogeneity was moderate [$I^2 = 34–52$] (Table V). Kellgren Lawrence score[46] was applied in 10 studies.

Construct validity against MRI: Strong correlation ($r > 0.60$) was detected on pooling 29 estimates across four studies examining 306 knee joints in 230 patients, using 0.2 T to 1.5 T MRI with dedicated knee coils (Supplementary data 10).

Construct validity against biomarkers: Twenty-three estimates of serum cartilage oligomeric matrix protein (COMP) were pooled across four studies involving 95 knee joints from 95 patients, generating weak correlation [$r = 0.003–0.21$] with trivial heterogeneity [$I^2 = 0$] (Supplementary data 10).

Criteria validity against histology: Pooling of four estimates from two studies, evaluating histological cartilage thickness in 190 knee joints from 113 patients, produced a moderate correlation [$r = 0.66(-0.05–0.93)$], and considerable heterogeneity [$I^2 = 90$] (Supplementary data 10).

Criteria validity against arthroscopy: Ultrasound pathologies focused by three arthroscopic studies, using Noyes' grading scale[47], were not the same among the papers, and so pooling could not be executed. Generally, arthroscopic gradings correlated strongly with osteophyte[11], moderately with cartilage grading[14]and weakly with subchondral bone[48].

Responsiveness

According to Cohen[49], values of 0.0, 0.20, 0.50, and 0.80 or greater represented trivial, small, moderate, and large responsiveness, respectively.

Internal responsiveness: Pooling 31 estimates across 10 studies, comprising 480 joints from 393 patients, produced a moderate effect size for Baker's cyst [0.58(0.40,0.77)], and small effect size for synovial hypertrophy [0.30(0.05,0.56)], effusion [0.28(0.00,0.56)] and cartilage thickness [0.20(0.04,0.36)] (Table VI). The interventions included injections of different steroids ($n = 6$), platelet rich plasma ($n = 2$), glucosamine ($n = 1$), and exercises ($n = 1$). The study duration ranged from 2 weeks to 6 months.

Table VI
Stratified meta-analysis of ultrasound features for internal responsiveness in knee OA (paired sample)

Stratified meta-analysis	No. of studies	No. of patients	No. of joints	Correlation coefficient (95% CI)		Heterogeneity		
Knee				Fixed	Random	*P* value	I^2	Tau
Effusion	2	73	73	0.28(0.00,0.56)	0.28(0.00,0.56)	0.63	0	0
Synovial hypertrophy	2	63	63	0.30(0.05,0.56)	0.30(0.05,0.56)	0.61	0	0
Cartilage thickness	3	136	157	0.20(0.04,0.36)	0.20(0.04,0.36)	0.61	0	0
Baker cyst	4	128	128	0.58(0.40,0.77)	0.58(0.40,0.77)	0.78	0	0
Quadraceps thickness	1	66	132	0.32(0.17,0.47)				

External responsiveness: Pooling seven estimates across four studies with a total of 121 joints and 121 patients, provided moderate correlation for synovial hypertrophy [0.43(−0.02,0.73)], and weak correlation for Baker's cyst [0.35(−0.11,0.69)]. Substantial heterogeneity was detected [$I^2 = 68–74$] (Supplementary data 10). The interventions were intra-articular steroid injections ($n = 3$), and shortwave diathermy ($n = 1$). (Tables for stratified meta-analysis, and figures for forest plots were also described as Supplementary data 10 and 11).

Feasibility

Five studies reported the scanning time for complete examination, which varied from 5 min to 15 min depending on how many pathologies were scanned (Supplementary data 10).

Hand OA

Reliability

There were four inter-rater reliability studies for binary scores[50–53], three for semi-quantitative scores[5,12,51] and one for quantitative scores[54].The binary scoring system provided the kappa ranging from slight in cartilage thickness[51] to excellent in synovitis, effusion and osteophyte[52]. For semi-quantitative score, the kappa values varied from slight in cartilage thickness[51] to substantial in osteophyte and synovitis[5,12]. For quantitative score, ICC was excellent in synovial hypertrophy[54].

Among intra-reliability studies, seven studies applied binary scores[5,10,12,50,51,55,56]; five studies used semi-quantitative scores[5,12,51,57,58]; one study examined quantitative scores[59]. Similar findings of kappa values were reported for different pathologies but with a higher actual kappa values.

Validity

Only two studies reported construct validity of ultrasound with pain, disclosing very weak correlation[57,60]. Four studies documented ultrasound data for functional correlation which varied from very weak to weak in most pathologies[55,57,60,61]. Validity of ultrasound with X-rays was investigated in two studies, providing very weak correlation[56,60]. However, ultrasound provided moderate correlation with MRI for osteophyte ($r = 0.49$) and synovitis ($r = 0.43$) on semi-quantitative scale[62].

Responsiveness

Two studies supplied sufficient information to calculate the internal responsiveness. One study revealed trivial effect size for synovitis and power Doppler outcomes at 12 weeks after intramuscular methylprednisolone injection[63], and small effect size was detected at 4 weeks for the same pathologies in another study, using intra-articular injections of hyaluronic acid as an intervention[64].

For external responsiveness, one study reported strong correlation of synovial thickening and power Doppler with Visual Analog Scale (VAS) pain at 4 weeks[64].

Hip OA

Reliability

Inter-rater reliability of binary score ranged from fair in effusion to moderate for osteophyte in one study[65] while another study recorded excellent reliability for the same pathologies[66].

Intra-rater reliability of binary score was moderate in joint effusion and substantial in osteophyte[65] while the other revealed the excellent kappa[66]. For semi-quantitative scores by radiologists, excellent kappa was reported for the synovial thickness[67].

Validity

Ultrasound synovitis and osteophyte scores demonstrated a strong association with pain on activity[65]. Weak correlation was documented between effusion and Lequesne index[68], and between osteophyte and Kellgren–Lawrence (KL) grading ($r = 0.26$)[65].

Responsiveness

One study applied ultrasound synovial hypertrophy and effusion as outcome measure to evaluate internal responsiveness, providing moderate effect size (SMD = 0.44) at 3 months after intra-articular injection of 8 mg betamethasone[69].

Discussion

Overall, the main findings of our meta-analysis suggest various (weak to very strong) construct validity with patients findings and other imaging modalities, depending on pathologies and comparators, moderate to substantial reliability, strong criterion validity with cartilage histology, and small to moderate responsiveness to interventions. On qualitative analysis, this systematic review revealed substantial clinical, technical and methodological heterogeneity of ultrasound within OA literature, requiring caution in interpreting these meta-analytic results. However, on quantitative analysis, I^2, which denotes statistical heterogeneity, was only low or moderate for most of clinimetrics.

Although ultrasound possesses promising potential in OA clinical trials, fewer studies in hand and hip joints were detected in the literature, compared to the knee. Although utilization/reporting of OMERACT definitions has gained a significantly positive trend over last decade, a marked variability of ultrasound scanning characteristics was noted, highlighting the necessity of following/reporting international consensus protocols in future studies.

In the context of methodological quality, a modified Downs and Black quality assessment score[28] was administered to identify the potential bias and display the summary of these bias. All studies, which documented the clinimetric data for each pathology, were pooled without applying exclusion on the basis of study quality scale because the threshold for exclusion reduced the precision[70], and was necessarily subjective[71]. According to Detsky *et al.*, it seemed highly unlikely that these quality scores would generate a linear or monotonically increasing association with true quality, and no objective reference standard simply existed for determining the "true" scientific rigour of a trial[72]. Moreover, due to a limited number of papers which documented clinimetric data for each ultrasound pathology, the sensitivity analysis, based on study quality score, could not be examined (i.e., there were some pathologies for each of which only one paper existed as a unit of analysis).

In addition, definitions in OA are difficult in terms of what is normal, and what is defined for OA (radiographic OA or ACR criteria, which means totally different things), making validity research not easy.

Our meta-analysis results indicated moderate to substantial reliability [minimum kappa $\geq$ 0.44(0.15,0.74) and minimum ICC $\geq$ 0.82(0.73−0.89)] for ultrasound pathologies of knee OA. Generally, the binary and quantitative scores produced higher reliability statistics than semi-quantitative score. Some papers calibrated the semi-quantitative scores by utilizing the atlas-based grading methods[11,73] while some defined the grading by quantitative cut-offs[6]. The reliability of Baker's cyst, meniscal extrusion, osteophyte, synovitis and effusion were at least substantial for the semi-quantitative scores.

The musculoskeletal experience of ultrasound operators ranged from those with short-course training to very experienced specialist, and so the meta-analysis results represented the generalizability of reliability statistics across different levels of ultrasound experience. However, it should be noted that operator-dependent nature of ultrasound measurement and quality of ultrasound machines could largely influence on the performance of the reliability statistics, especially when smaller joints are addressed.

The limited data for criterion validity of OA ultrasound features focused predominantly on cartilage histology, with overall strong correlation. Conflicting reports were found for correlations of synovitis/Doppler signals with synovial vascularity in a mixed sample of inflammatory arthritis and OA[74–77]. Semi-quantitative grading scores currently applied for OA synovitis were adopted from those validated for inflammatory rheumatoid arthritis, assuming that synovitis was only quantitatively but not qualitatively different between the inflammatory arthritis and OA[78]. However, replication of these semi-quantitative scoring systems in OA might require consideration due to the low degree of inflammation, sustained in OA compared to rheumatoid arthritis[18], which is likely to contribute to floor effects, and thereby impairs the capability to detect improvement changes in interventional studies.

Pooling construct validity of ultrasound findings in case−control studies (OA versus healthy population) exhibited strong discrimination in some pathologies, suggesting that ultrasound might be a potential tool for developing ultrasonographic OA propositions, similar to preliminary OA propositions with MRI[79]. Furthermore, ultrasound demonstrated a strong correlation with MRI in principal OA features, indicating the promising usefulness of ultrasound in clinical care where MRI is not readily accessible.

Generally, ultrasound, as expected, had a very weak association with pain, function and blood biomarker (COMP). Almost all individual studies incorporated in the meta-analysis consistently denoted weak correlation between ultrasound features and pain ($r \leq 0.40$). This finding may be attributed to a number of reasons such as complex causes of symptoms in OA, multi-factorial subjective experience of pain (biopsychosocial factors), and that the ultrasound outcomes used in individual studies might not captured the multi-dimensional nature of pain (measurement issues)[80]. In contrast, relationship of ultrasound with X rays produced various values ranging from weak to strong correlation, depending on ultrasound pathologies.

At least small effect size (SMD $\geq$ 0.2) was documented in most of interventional studies, and the low I^2 in pooled meta-analysis was detected. Generally, the inflammatory features such as Baker's cyst, synovial hypertrophy provides greater internal responsiveness, compared to cartilage changes, perhaps due to short follow-up duration (maximum 24 weeks). However, this result should be interpreted with caution as the included studies for sensitivity to change were all small studies with some limitations. Combining external responsiveness of inflammatory pathologies revealed a moderate correlation with pain while no studies examined external responsiveness for structural pathologies.

Ultrasound scanning duration largely depended on the number of joints and pathologies assessed and the scoring systems employed, which were varied across studies. Development of international consensus guidelines for feasible composite scoring methods is essential, and still undergoing.

It should be noted that several papers included in the validity assessment of previous systematic review[20] had to be excluded as our inclusion criteria was focused only on knee, hand and hip, not other joints such as foot, shoulder, cervical spine, etc and some papers did not publish the comparator for validity assessment, clinimetric data, etc. However, more than additional 60 papers were included in this updated review.

Our review had several potential limitations. The first was the considerable clinical and methodological heterogeneity of included studies, requiring caution in interpreting the pooled results. However, I^2 was low for validity and responsiveness measures. The second limitation was that we could not rule out some publication bias although a thorough literature search was attempted. The third limitation is the application of SMD for internal responsiveness instead of calculating standardized response mean (SRM), as most interventional studies did not describe standard deviation of mean change[81]. However, in the literature, the best statistics for treatment responsiveness and interpretation is still controversial, and according to mathematical formulae proposed by Norman *et al.*[36], SRMs tend to be higher than SMDs. The fourth limitation is that we could not appropriately analyse the confounding effects over technology changes over the years because there were numerous confounders such as machine model, probe frequency, operator's clinical background, qualification, training period, the severity of the sample, the sensitivity of comparator machine models in examining construct validity against X rays and MRI, while a limited number of papers with clinimetric data for each pathology existed, causing a lack of power to examine the impact of these confounders on the clinimetrics by regression analysis.

To our knowledge, this is the first meta-analytic systematic review comprehensively examining clinimetrics of ultrasound utilized to evaluate common features of OA, covering the original OMERACT filter components. Stratified meta-analysis demonstrated moderate to substantial reliability, various construct validity with several clinical and imaging comparators, strong criterion validity with cartilage histology and small to moderate responsiveness. Future studies should improve the conduct and reporting of clinimetric studies especially for the areas of several poor quality-items. As most of individual studies were of small

sample size and just focused on some individual pathologies, larger studies with comprehensive ultrasound outcomes in future would provide more clear insight into the clinimetrics of commonly assessed ultrasound pathologies in OA.

Contributions

WMO and DJH conceived and designed the study. JML, PGC, HK, SS, JS and LAD were also involved in the design of the study. WMO, MD and DJH contributed to acquisition of the main clinimetric data of included papers. WMO had full access to all the data and analysis, drafted the manuscript and takes responsibility for the integrity of the work from inception to finished article. All authors critically revised the manuscript and gave final approval of the article for submission.

Conflict of interest

None.

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Supplementary data

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Appendix 6.4: Superb Microvascular Imaging in Low-Grade Inflammation of Knee Osteoarthritis Compared With Power Doppler: Clinical, Radiographic and MRI Relationship.

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● *Original Contribution*

SUPERB MICROVASCULAR IMAGING IN LOW-GRADE INFLAMMATION OF KNEE OSTEOARTHRITIS COMPARED WITH POWER DOPPLER: CLINICAL, RADIOGRAPHIC AND MRI RELATIONSHIP

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Abstract—We compared the assessment of active synovitis in knee osteoarthritis (OA) by utilising superb microvascular imaging (SMI) and conventional power Doppler (cPD) techniques, and then correlated each technique with paients' symptoms, radiographic features and magnetic resonance imaging (MRI)-detected synovitis. A subgroup of participants with symptomatic knee OA underwent dynamic ultrasound assessment for semi-quantitative scores for SMI and cPD in the suprapatellar, medial and lateral parapatellar knee recesses. Knee pain and other symptoms were evaluated with the knee injury and osteoarthritis outcome score (KOOS). OA severity was assessed using the Kellgren and Lawrence grade (KLG) on radiograph and effusion-synovitis and Hoffa's synovitis score of MRI osteoarthritis knee score on non-contrast–enhanced MRI sequences. The χ^2 test and κ statistics were conducted to compare detectability of SMI and cPD for low-grade inflammation, and the Spearman's correlation and Fisher's r to z transformation were conducted to compare correlations of both techniques with symptoms and imaging severity. A total of 89 participants were included in the analyses. SMI increased the detection rate by 25.5% for grade 0 cPD, by 35.4% for grade 1 cPD and by 9% for grade 2 cPD. SMI showed significant correlations with KOOS symptoms, KLG, MRI effusion-synovitis and Hoffa's synovitis scores (r = −0.24 [−0.45, −0.01]; r = 0.31 [0.10, 0.50]; r = 0.49 [0.33, 0.63]; and r = 0.54 [0.37, 0.68]). The cPD was significantly correlated with KOOS pain, other symptoms, MRI effusion-synovitis and Hoffa's synovitis (r = −0.23 [−0.44, −0.01]; r = −0.29 [−0.49, −0.06]; r = 0.46 [0.28, 61], r = 0.46 [0.25, 0.63]). However, no significant differences were detected in their extent of correlations. SMI can detect low-grade inflammation implicated in OA disease better than cPD and reveal a significant correlation with symptoms, radiographic features and MRI synovitis. The added clinical value of SMI over cPD is still not clear. (E-mail: wioo3335@uni.sydney.edu.au) **© 2019 World Federation for Ultrasound in Medicine & Biology. All rights reserved.**

Key Words: **Ultrasound, Osteoarthritis, Power Doppler, SMI, Inflammation.**

INTRODUCTION

Osteoarthritis (OA) is one of most prevalent joint diseases, leading to severe disability and economic burden globally. In spite of being assumed to be a degenerative disease of the cartilage, OA has been shown to be a complex, multi-factorial disease with multiple tissue alterations within the entire joint (Hunter et al. 2014). An emerging and important research interest has been the implication of synovial inflammation (*i.e.,* synovitis) in the pathogenesis and progression of the OA disease process throughout the past decade (Oo et al. 2017).

Musculoskeletal ultrasound is a safe, non-invasive imaging modality that can assess the elements of synovitis of the joints, using sound waves (Wang et al. 2018). On a basic ultrasound machine, the B mode and power Doppler mode are used to detect gray-scale pathologies and slow blood flow of the inflammatory process. The conventional power Doppler (cPD) can detect slow blood flow rates and small vessels in the region of interest (Boote 2003; Oo and Bo 2016), so it is often used to visualise the site of active synovitis, which is represented

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by the angiogenesis and increased blood flow in the synovium tissue (Paleolog 2009). The cPD was demonstrated to be reliable in the detection of the vascularity of histologic synovial inflammation of knee arthritis in a mixed sample of patients with rheumatoid arthritis (RA) and OA (Walther et al. 2001).

However, cPD technology has many limitations. The ability of Doppler, especially power or color Doppler imaging, depends on the settings and optimization. In addition, Doppler's slow flow detection may be impaired by the noise sources of PD images, such as thermal noises and clutter (Li et al. 2016). Slow moving signals could appear as flash artifacts. Flow in small vessels may be problematic because the flow is slow, and noise is present.

Koski et al. (2006) determined that a negative cPD finding in the synovium could not exclude the presence of synovitis seen on histopathologic specimens in patients with inflammatory arthritis ($r = 0.239$, non-significant). Osteoarthritis is believed to involve chronic low-grade patchy inflammation unlike the high-grade diffuse synovitis of rheumatoid arthritis, the prototypical inflammatory arthritis (Walther et al. 2001; Oo et al. 2018b). However, several studies reported that the cPD signal is not very common in OA populations (Hall et al. 2014; Oo et al. 2018a), which might be attributable to low-grade inflammation, which cPD is unable to pick up (Koski et al. 2006). Several studies have highlighted the crucial role of such low-grade inflammation in the disease pathogenesis, being a risk-factor for developing radiographic OA (Atukorala et al. 2016) as well as imaging markers for structural progression of OA (Oo et al. 2017).

Superb microvascular imaging (SMI) is an innovative Doppler technology specifically designed for detecting low-velocity blood flow states (Ma et al. 2015) as it can utilise a specialised algorithm with a novel wall filter to distinguish true very slow blood flow from clutter artefacts traditionally experienced in cPD signal (Yokota et al. 2018; Yu et al. 2018). The advantages include the effective separation of flow signals from overlying tissue motion artifacts, preserving subtle low-flow components, high resolution of the image, minimal motion artefact and high frame rates (Hata 2014). SMI is superior to cPD in detecting synovial vessel signals in inflammatory arthritis conditions such as RA (Orlandi et al. 2017; Lim et al. 2018), and well associated with clinical outcomes such as disease activity score 28-C-reactive protein (Yokota et al. 2018).

Based on these preliminary data of SMI and the importance of the detection of low-grade inflammation in OA described earlier in this report, we aimed to examine whether SMI can be used to detect low-grade inflammation of OA compared with cPD. The primary objectives of this study were (i) assessing the potential of SMI to detect inflammatory flow and compare it with cPD and (ii) comparing these modalities with other symptom scoring schemes and modalities such as the knee injury and osteoarthritis outcome score (KOOS) pain and other symptoms subscores (Roos et al. 1998), the Kellgren and Lawrence grade ([KLG] Kellgren and Lawrence 1957) on plain radiograph and magnetic resonance imaging osteoarthritis knee score (MOAKS) effusion-synovitis and Hoffa's synovitis (Hunter et al. 2011).

MATERIALS AND METHODS

Study design and selection criteria

We used a cross-sectional analysis using baseline data of a sub-sample from the Sydney, Australia, site of the ongoing platelet-Rich plasma as a symptom- and disEaSe-modifying Treatment fOR knee ostEoarthritis (RESTORE) clinical trial. Selection criteria were the same as for the RESTORE study (trial registration no: ACTRN12617000853347) (Paterson et al. 2018). Briefly, eligible patients met the following inclusion criteria:

- Age >50 y;
- Knee pain on most day during the past month;
- Osteophytes on X-ray; and
- A minimum pain score of 4 on an 11-point numeric rating scale during the past week.

The exclusion criteria included (i) KLG 1 or 4; (ii) predominant lateral tibiofemoral disease; (iii) inflammatory or systemic joint disease; (iv) history of neuropathic or crystalline arthropathy; and (v) unwillingness to stop non-steroidal anti-inflammatory drug and other analgesic usage for knee pain, except for paracetamol for rescue pain relief, from 2 wk before baseline assessment.

For those participants with bilaterally eligible knees, the most symptomatic knee was the study knee. Data from those who attended for a baseline ultrasound examination between September 2017 and February 2019 were analysed.

Demographic data, including age, sex, weight, height and duration of knee symptoms, were recorded as described in Paterson et al. (2018). Body mass index (BMI) was calculated using height and weight (kg/m^2).

This study was approved by the Northern Sydney Local Health Districts Human Research Ethics Committee (HREC/16/HAWKE/430). We received informed consent from each participant in the study.

Knee symptoms

KOOS pain and other symptoms scores were collected. KOOS is a knee-specific self-reported outcome measure with high test-retest reliability, internal consistency and face and content validity (Collins et al. 2016). Likert responses range from none to extreme, and scores are measured from 0−100, with lower scores denoting worse symptoms, function or quality of life. The KOOS

pain is scored from 9 questions regarding knee pain frequency that occurred during the past week, and the amount of knee pain encountered during specific activities, such as twisting, bending and walking. Other KOOS symptoms are measured from 7 questions for other symptoms experienced during the past week, such as swelling, restricted range of motion and mechanical symptoms.

Radiologic assessment

Participants underwent bilateral weight-bearing postero-anterior radiography ([Model R-20 J] Shimadzu Corporation, Nakagyō-ku, Kyoto, Japan) before ultrasound and magnetic resonance imaging (MRI) examinations. Radiographs were independently assessed for KLG by a rheumatologist (S.L.Y.) who was unaware of clinical, ultrasound and MRI scores.

Ultrasound evaluation

At the baseline assessment, following the MRI scan, a physician operator (W.M.O.), who was blinded to the clinical, radiograph and MRI findings, performed the dynamic ultrasound scan of the study knee with a multi-frequency linear transducer (using 10 MHz with 14 L5 MHz probe) of the Aplio Platinum 500 machine (Toshiba Medical Systems, Ōtawara, Tochigi, Japan). The physician operator (W.M.O.) had 6 y of musculoskeletal ultrasound experience and Musculoskeletal Ultrasound in Rheumatology certification from the American College of Rheumatology. To be able to detect synovial blood flow to the level just below random noise, SMI and cPD settings were optimized by an application specialist from Toshiba Medical Systems by adjusting color gain, pulse repetition frequency, wall filter and Doppler frequency (SMI parameters: color map = 5, color frequency = SMI6, color gain = 40%, pulse repetition frequency = 11.6 k, filter = 2; cPD parameters: color map = 6, color frequency = 6,color gain = 40%, pulse repetition frequency = 14.8 k, filter = 5). The settings remained consistent for the duration of the study. The only settings changed were the depth and focus of the images.

During power Doppler imaging and SMI evaluation, the transducer was placed lightly on the skin surface with minimum pressure to prevent the collapse of blood vessels. Scanning gel should be visible in the image as a sign of light transducer pressure because excessive transducer pressure can be observed as abnormal compression of tissue planes and obliteration of blood vessels. Once maximum colour flow signals were found, the transducer was held in the same scan position to observe colour flow signals by the SMI technique in the background of synovial hypertrophy (abnormal hypoechoic intra-articular tissue that is non-displaceable and poorly compressible). The colour grading 0−3 was used in power Doppler ultrasound images and SMI, respectively, as follows (Szkudlarek et al. 2003):

- For grade 0, no colour was observed in the synovium.
- For grade 1, single colour signals were observed (up to 3) in the synovium.
- For grade 2, confluent colour signals were observed in less than half of the area of the synovium.
- For grade 3, more than 50% of the synovium were observed as being covered by colour signals.

The ultrasound scores were obtained for cPD and SMI from the suprapatellar recess, medial and lateral para-patella recesses, respectively, according to standardized scanning protocol (Bruyn et al. 2016) (Fig. 1; Supplementary File 1). The maximum score of three synovial recesses was then used as the score of the entire knee for the comparison with clinical and radiographic and MRI data of the study knee.

Intra-rater reliability

To evaluate intra-rater reliability, the same operator re-scanned 10 patients 1 wk later and calculated the intra-rater reliability, being unaware of the earlier scores. The κ statistics ranged from 0.63−1.00, indicating good to excellent results (Supplementary File 2).

MRI evaluation

All participants underwent MRI scan on their index knee with a 3 T whole-body magnetic resonance unit (Siemens Healthcare, Erlangen, Germany) and a 15-channel transmit/ receive knee coil. A total of 2 MRI sequences were used, including a sagittal proton-density−weighted fat-suppressed non-contrast turbo spin-echo and an axial proton-density−weighted fat-suppressed turbo spin-echo. Technical details of the sequences are reported in Supplementary File 3.

Knee effusion-synovitis and Hoffa's synovitis were assessed using validated semi-quantitative criteria, MOAKS (Hunter et al. 2011). Hoffa's synovitis is defined as the degree of hyperintense signal in Hoffa's fat pad on midsagittal fluid-sensitive sequences (0: normal, 1: mild, 2: moderate, 3: severe). Effusion synovitis is the combination of effusion and synovitis, defined as the hyperintense signal in the suprapatellar recess on fluid-sensitive sequences (0: physiological amount; 1: small − fluid continuous with the retropatellar space; 2: medium − with slight convexity of the suprapatellar recess; 3: large evidence of capsular distension). The maximum score was then calculated to determine the entire knee score.

Inter-rater and intra-rater reliability of the MRI

Scoring of the MOAKS was performed by W.M.O., who obtained imaging training from an experienced musculoskeletal radiologist (J.M.L., 25 y of experience in musculoskeletal MRI). Both readers independently

scored the MRI images of 10 consecutive participants. The κ statistics ranged from 0.42−0.90, indicating moderate to excellent agreement for individual MRI lesions (Supplementary File 4). The readers were blinded to clinical features, symptoms, radiographic and ultrasound scores.

WMO also performed the second reading of all MRI images 1 mo later, intra-rater reliability was good to excellent as shown by κ statistics, ranging from 0.52−0.91 (Supplementary File 4).

Statistics

Descriptive analysis of categorical data were described as frequencies and percentages, and continuous variables were expressed as mean and standard deviation. To investigate whether SMI can detect more vascular signals than cPD, the cross-tabulation and χ^2 test were conducted for the presence of SMI or cPD, and κ statistics for semi-quantitative scores of both techniques. Spearman's correlations were conducted to determine the association of SMI and cPD with symptoms, KLG and MOAKS synovitis scores. The correlation coefficients of both techniques for symptoms and imaging findings were compared to investigate any significant difference. All statistics were analysed using SPSS v. 23 (IBM Corp., Armonk, NY, USA) and a p value <0.05 denotes a significant association or correlation. The difference in correlations was calculated by Fisher's r to z transformation, using MedCalc v. 18 (MedCalc Software, Ostend, Belgium).

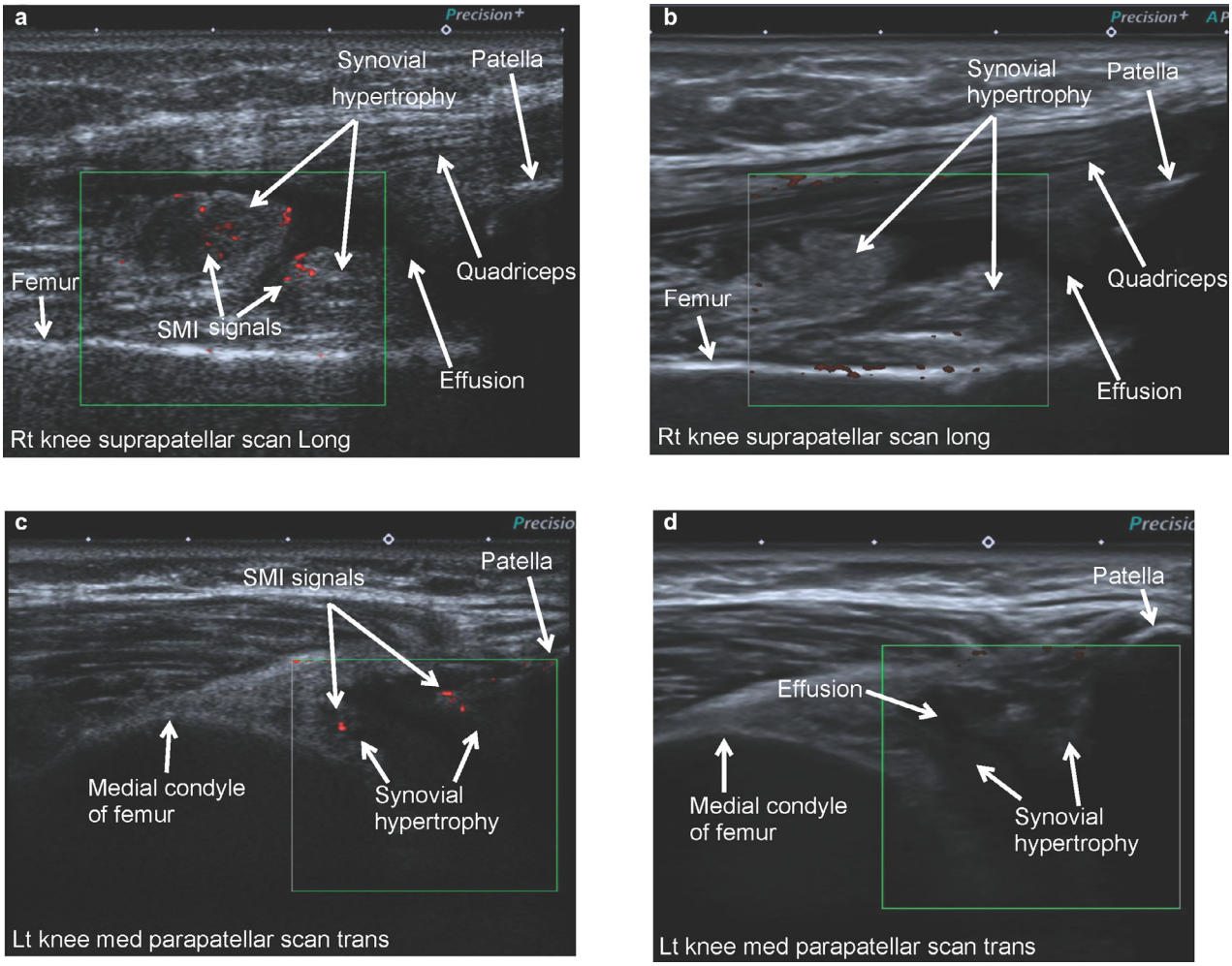

Fig. 1. The demonstration of SMI and cPD from three synovial recesses of the knee. (a) and (b) represent the same patient. (c) and (d) represent the same patient. (a) Grade 2 SMI signals at the suprapatellar recess on a longitudinal scan. (b) Grade 0 cPD signals at the same site of suprapatellar recess. (c) Grade 1 SMI signals at the medial parapatellar recess on a transverse scan. (d) Grade 0 cPD signals at the same site of the medial parapatellar recess synovial hypertrophy (abnormal hypoechoic intra-articular tissue that is nondisplaceable and poorly compressible).

Table 1. Baseline clinical, radiographic, ultrasound and MRI data of study participants

Population, N	89
Age, y, mean (SD)	61.5 ± 6.9
Female, N (%)	48 (53.9)
BMI, kg/m^2, mean (SD)	27.5 ± 6.4
Disease duration, y, mean (SD)	8.9 ± 9.4
KOOS symptom, mean (SD)	49.5 ± 16.4
KOOS pain, mean (SD)	51.3 ± 14.5
Radiologic scores	
Kellgren and Lawrence grade, N (%)	
II	36 (40.4)
III	53 (59.6)
Ultrasound OMERACT scores (maximum score of the whole knee)	
PD grade, N (%)	
0	47 (52.8)
I	31 (34.8)
II	11 (12.4)
III	0
SMI grade, N (%)	
0	36 (40.4)
I	31 (34.8)
II	21 (23.6)
III	1 (1.1)
MRI MOAKS scores (maximum score of the whole knee)	
Effusion-synovitis grade, N (%)	
0	6 (6.7)
I	24 (27)
II	26 (29.2)
III	33 (37.1)
Hoffa synovitis grade, N (%)	
0	5 (5.6)
I	40 (44.9)
II	32 (36)
III	12 (13.5)

BMI = body mass index; KOOS = knee injury and osteoarthritis outcome score; MRI = magnetic resonance imaging; MOAKS = MRI osteoarthritis knee score; OMERACT = outcome measure in rheumatology; cPD = conventional power Doppler; SMI = superb microvascular imaging.

RESULTS

Demographic, clinical characteristics, ultrasound and MRI findings

The present study included 89 participants with 48 (53.9%) females, mean BMI of 27.5 ± 6.4. A total of 59.6% of participants had a KLG of 3. Other detailed characteristics are presented in Table 1.

Comparison of the grades by SMI and cPD

A total of 41 knee joints revealed blood flow signals with both cPD and SMI, but either technique detected no flow signal in 35 cases. Flow signals were detected only with SMI in 12 joints but not with cPD, but vascularity was found only with cPD in 1 joint but not with SMI. These data are summarised in Table 2. SMI could visualize the presence of synovial flow signals in a significantly greater number of joints compared with cPD (60% vs. 47%, $p < 0.001$).

Table 2. Comparison of presence of SMI and cPD

	SMI grade −	SMI grade +	Total
PD grade −	35	12	47
PD grade +	1	41	42
Total	36	53	89

cPD = conventional power Doppler; SMI = superb micro-vascular imaging.
NOTE: The χ^2 value is 47.85 and the p value < 0.001.

Table 3 presents the comparison of the semi-quantitative grades (0−3) of flow signals detected by both techniques. Using SMI, 25.5 % of the cPD flow signals raised grade 0 to 1, but 35.4% increased from grade 1 to 2 and 9% from grade 2 to 3. In addition, 1 joint determined as grade 1, using cPD, was determined as 0, using SMI. SMI visualized more signals than cPD when using semi-quantitative score (κ statistic: 0.56, 95% confidence interval [CI] 0.41−0.71). There were significant linear associations between cPD and SMI (Spearman's r = 0.82, 95% CI 0.74−0.89), demonstrating that one consistently scores higher than the other.

Spearman's correlation of SMI and cPD with symptoms and imaging scores

Except for KOOS pain, SMI showed significant (weak to moderate) correlation with KOOS symptoms, KLG, MRI effusion-synovitis and MRI Hoffa's synovitis scores. The strongest correlation was between SMI and MRI Hoffa's synovitis (r = 0.54, 95% CI 0.37−0.68), but cPD is significantly correlated with other scores except for KLG (Figs. 2−6). When comparing these correlation coefficients of SMI and cPD, a weaker correlation was found between SMI and symptoms, and a stronger correlation was found between SMI and imaging measures. However, no significant differences in the extent of correlation were detected (Table 4).

Table 3. Comparison of semi-quantitative grades of SMI and cPD

	SMI grade 0	SMI grade 1	SMI grade 2	SMI grade 3	Total
PD grade 0	35	12	0	0	47
PD grade 1	1	19	11	0	31
PD grade 2	0	0	10	1	11
PD grade 3	0	0	0	0	0
Total	36	31	21	1	89

cPD = conventional power Doppler; SMI = superb microvascular imaging.
NOTE: The κ statistic is 0.56 (95% CI: 0.41−0.71, agreement: 71.91%, expected agreement: 36.41%).

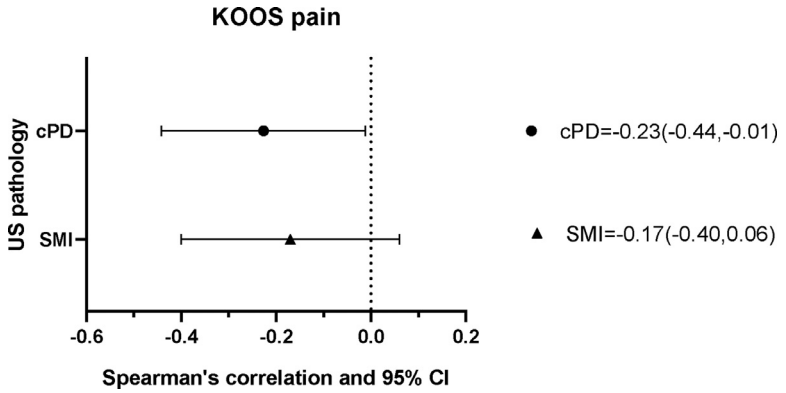

Fig. 2. The association of SMI and cPD scores with KOOS pain. CI = confidence interval; cPD = conventional power Doppler; KOOS = knee injury and osteoarthritis outcome score; SMI = superb microvascular imaging.

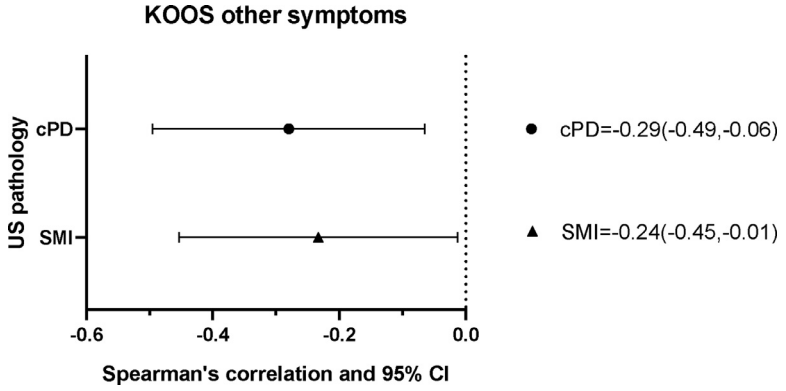

Fig. 3. The association of SMI and cPD scores with KOOS other symptoms. CI = confidence interval; cPD = conventional power Doppler; KOOS = knee injury and osteoarthritis outcome score; SMI = superb microvascular imaging.

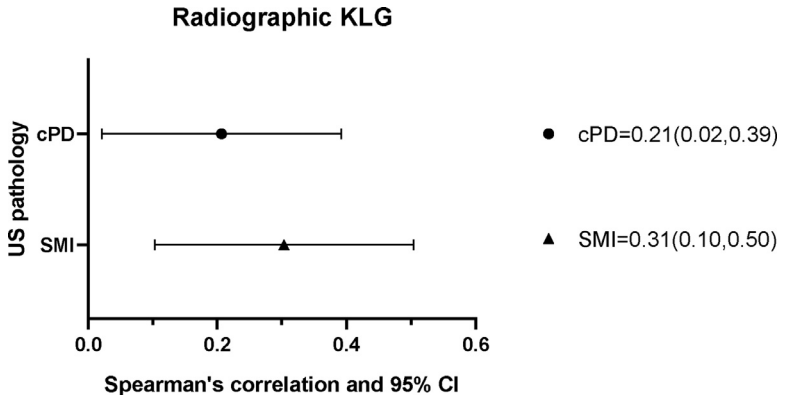

Fig. 4. The association of SMI and cPD scores with KLG on radiograph. CI = confidence interval; cPD = conventional power Doppler; KLG = Kellgren and Lawrence grade; SMI = superb microvascular imaging.

DISCUSSION

This study is the first to compare the detectability of SMI with cPD in detecting low-grade inflammation and examine their relationships with symptoms, features on radiograph and MRI in a knee OA population. We demonstrated several interesting findings. First, SMI can detect increased blood flow signals compared with cPD. Second, both techniques showed significant and mild to moderate associations with validated self-reported clinical outcomes, radiographic and MRI assessment criteria for synovitis in knee OA. Third, even though SMI was able to detect a higher proportion of low-grade blood flow, the clinical preference/relevance of

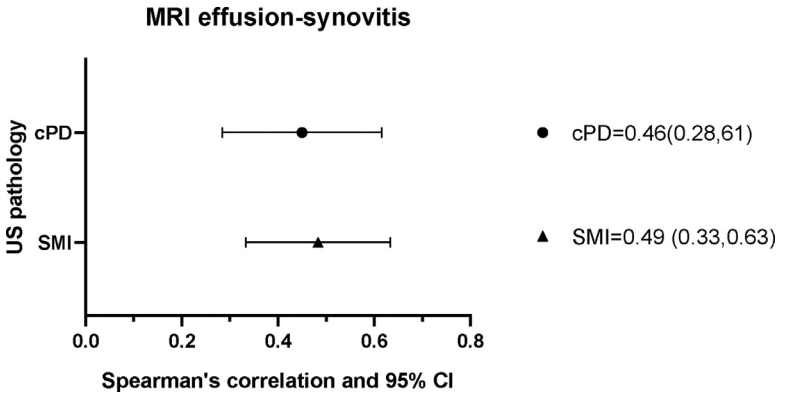

Fig. 5. The association of SMI and cPD scores with MRI effusion-synovitis. CI = confidence interval; cPD = conventional power Doppler; KOOS = knee injury and osteoarthritis outcome score; SMI = superb microvascular imaging.

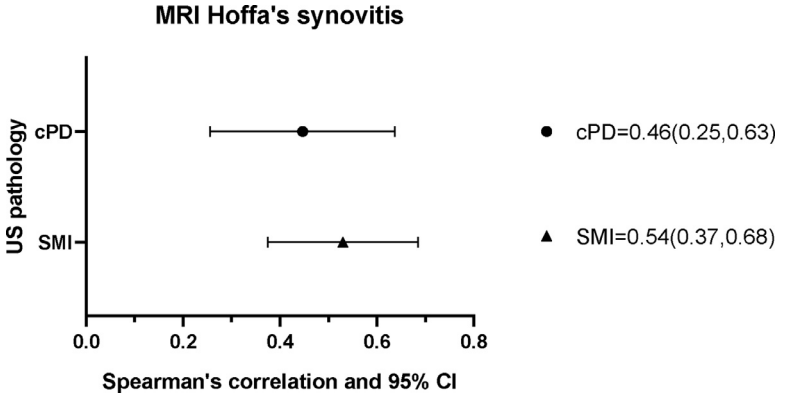

Fig. 6. The association of SMI and cPD scores with Hoffa's synovitis on MRI. CI = confidence interval; cPD = conventional power Doppler; KOOS = knee injury and osteoarthritis outcome score; SMI = superb microvascular imaging.

Table 4. Spearman's correlation of SMI and cPD*

Spearman's correlation	SMI (r and 95% CI)	cPD (r and 95% CI)	Comparison of correlation
KOOS symptoms	−0.24 (−0.45, −0.01) $p = 0.02$	−0.29 (−0.49, −0.06) $p = 0.01$	Z statistics = 0.35 $p = 0.72$
KOOS pain	−0.17 (−0.40, 0.06) $p = 0.11$	−0.23 (−0.44, −0.01) $p = 0.03$	Z statistics = 0.41 $p = 0.68$
KLG	0.31 (0.10, 0.50) $p = 0.004$	0.21 (0.02, 0.39) $p = 0.05$	Z statistics = 0.70 $p = 0.48$
MRI effusion-synovitis	0.49 (0.33, 0.63) $p < 0.001$	0.46 (0.28, 61) $p < 0.001$	Z statistics = 0.25 $p = 0.80$
MRI Hoffa's synovitis	0.54 (0.37, 0.68) $p < 0.001$	0.46 (0.25, 0.63) $p < 0.001$	Z statistics = 0.70 $p = 0.48$

CI = confidence interval; KLG = Kellgren and Lawrence grade; KOOS = knee injury and osteoarthritis outcome score; MRI = magnetic resonance imaging; cPD = conventional power Doppler; r=Spearman's correlation; SMI = superb microvascular imaging.

* With KOOS pain and symptoms subscores, radiographic KL grading and MRI effusion-synovitis and Hoffa's synovitis scores (whole knee).

SMI over cPD is still questionable at least in the OA population.

Both blood flow and tissue motion can generate Doppler activity. There is overlapping of strong clutter signals with the components of slow blood flow. The cPD utilized a wall filter to discard clutter and motion artefacts, leading to a loss of slow flow signals. However, SMI utilized a novel algorithm for removing tissue motion artefacts, showing true flow signals. It allows detection of fine vessels (Boote 2003). Therefore, it was assumed that SMI would be useful to detect low-grade inflammation of OA synovium.

Our study showed that SMI displayed a 25% increase in the detection rate of vascularisation compared

with cPD, suggesting that SMI visualizes low-grade, inflammatory activity that cannot be detected by cPD. Our results agree with the rheumatoid arthritis study that reported a 60% increase in the detection rate of vascularization (Wenxue Li 2016). There are also several studies that have shown that SMI can increase the detection rate of minute blood flows compared with cPD in patients who have rheumatoid arthritis (Orlandi et al. 2017; Lim et al. 2018; Yokota et al. 2018; Yu et al. 2018).

Although SMI could compensate for the deficiency of cPD in visualizing minute blood vessels in low-grade inflammation, there was a weaker correlation of SMI with symptom measures. This may suggest that higher sensitivity of SMI to very low flows appears to have no association with symptoms severity. In addition, there are conflicting reports related to the clinical relevance of SMI's better sensitivity compared with cPD when both techniques were correlated with clinical measures, such as disease activity score, and the health assessment questionnaire disability index in the population with rheumatoid arthritis (Orlandi et al. 2017; Yokota et al. 2018).

On the other hand, SMI did reveal a higher correlation with KLG as well as MRI effusion-synovitis and Hoffa's synovitis than cPD. However, the extent of correlation is not significant. This might suggest that the increased blood flow signals detected by SMI seems to be a true flow. However, there is no such earlier study in either the rheumatoid arthritis or OA population.

These findings put forward some interesting points for consideration. First, the added clinical usefulness of SMI over PDI is still controversial in OA patients, given poorer performance in its relationship to symptoms. It might be assumed that SMI could misinterpret the normal vascularization as positive signals because of its higher sensitivity, leading to a weaker correlation with symptoms. However, its higher correlation with MRI synovitis and Hoffa's synovitis seems to dispute it. Therefore, the clinical relevance of positive findings in SMI vascularization warrants further research.

Low-grade inflammation detected by MRI up to 4 y before OA incidence is implicated in the development of radiographic knee OA (Atukorala et al. 2016; Robinson et al. 2016). Therefore, it would be interesting to see whether patients with SMI positivity—but who were negative on cPD—progress more quickly or have higher odds of developing OA as a distinct OA phenotype in a future study.

One of the limitations of this study is that it did not include an age-matched control group with normal knees. Another limitation is that the MRI sequence used in our study was not contrast-enhanced and not optimal for detecting synovial hypertrophy. Last, we did not obtain a synovial biopsy to confirm the vascularization. However, synovial biopsy is very unusual for people with mild-moderate knee OA.

CONCLUSION

SMI can detect low-grade inflammation implicated in the OA disease process compared with cPD and revealed a significant correlation with symptoms and features on radiograph and MRI synovitis. However, there is no difference in the extent of such correlations. Therefore, the clinical utility of SMI in knee OA is still unclear and further research is required to establish its validity.

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Conflict of interest disclosure—David J. Hunter provides consulting services to Pfizer, Lilly, Merck Serono and TLC bio.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ultrasmedbio.2019.11.017.

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Appendix 6.5: Musculoskeletal Ultrasound in Symptomatic Thumb-base Osteoarthritis: Clinical, Functional, Radiological and Muscle Strength Associations

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RESEARCH ARTICLE Open Access

Musculoskeletal ultrasound in symptomatic thumb-base osteoarthritis: clinical, functional, radiological and muscle strength associations

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Abstract

Background: Thumb-base osteoarthritis (OA) is a common cause of pain and disability This study aimed to investigate the associations of musculoskeletal ultrasound OA pathologies with the extent of pain, function, radiographic scores, and muscle strength in symptomatic thumb-base osteoarthritis.

Methods: This is a cross-sectional study of an ongoing clinical trial with eligibility criteria including thumb-base pain on Visual Analogue Scale (VAS) ≥40 (0 to 100 mm), Functional Index for Hand OA (FIHOA) ≥ 6 (0 to 30) and Kellgren Lawrence (KL) grade ≥ 2. The most symptomatic side was scanned to measure synovitis and osteophyte severity using a 0–3 semi-quantitative score, power Doppler and erosion in binary score. A linear regression model was used for associations of ultrasound findings with VAS pain, FIHOA and hand grip and pinch strength tests after adjusting for age, gender, body mass index, disease duration and KL grade as appropriate. For correlation of ultrasound features with KL grade, OARSI ((Osteoarthritis Research Society International) osteophyte and JSN scores, Eaton grades, Spearman coefficients were calculated, and a significant test defined as a *p*-value less than 0.05.

Results: The study included 93 participants (mean age of 67.04 years, 78.5% females). Presence of power Doppler has a significant association with VAS pain [adjusted β coefficient = 11.29, $P = 0.02$] while other ultrasound pathologies revealed no significant associations with all clinical outcomes.
In comparison to radiograph, ultrasonographic osteophyte score was significantly associated with KL grade [$r_s = 0.44$ ($P < 0.001$)], OARSI osteophyte grade [$r_s = 0.35$ ($P = 0.001$)], OARSI JSN grade [$r_s = 0.43$ ($P < 0.001$)] and Eaton grade [$r_s = 0.30$ ($P < 0.01$)]. Ultrasonographic erosion was significantly related with radiographic erosion [$r_s = -0.49$ ($P = 0.001$)].

Conclusion: From a clinical perspective the significant relationship of power Doppler with pain severity in thumb base OA suggests this might be a useful tool in understanding pain aetiology. It is important to recognise that power Doppler activity was only detected in 14% of the study so this might be an important subgroup of persons to monitor more closely.

Trial registration: Registered at Australian New Zealand Clinical Trials Registry (ANZCTR), http://www.anzctr.org.au/, ACTRN12616000353493.

Keywords: Ultrasonography, Hand osteoarthritis, Arthritis, Inflammation

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Background

Thumb-base osteoarthritis (OA) denotes structural alteration of the thumb carpometacarpal joint with a female predominance up to 6:1 [1]. It is a common cause of pain and disability, restricting the ability to perform simple tasks of daily living, and is characterized by hand weakness and radiographic abnormalities [2]. The lifetime prevalence is nearly 10%, with the epidemiological radiographic prevalence varying from 4 to 33% for middle-aged and elderly populations [3].

OA is traditionally imaged with plain radiograph which has several limitations, such as inability to visualize soft tissue pathologies which can contribute to pain and symptoms [4]. Ultrasound may afford some advantages including higher sensitivity for detecting osteophytes than plain radiographs [5, 6]. In addition, the use of ultrasound would permit the study of OA phenotypes with respect to inflammatory and structural changes that cannot be visualized with a plain radiograph [7].

A number of studies have examined the association of ultrasound findings with symptoms, function and radiographic findings in multifocal hand OA [7, 8] and other large joints such as knee and hip [9–12]; however, only three studies utilized ultrasound specifically for thumb-base OA, pinpointing on comparative prevalence of ultrasound-detected effusion (31 OA vs 37 controls) [13], the relationship of ultrasound features with disability ($n = 57$) [14] and the association of inflammatory ultrasound features with presence of pain on palpation ($n = 87$) [15]. As a diagnostic tool to be used in clinical research and practice, the validity of the tool should be determined using comparators such as disease symptoms, functional status in daily living activities, strength and other routine imaging. As yet, there is a lack of ultrasound studies focusing on its construct validity using all relevant symptomatic and structural outcomes as comparators in thumb-base OA.

This study aimed to determine the associations of ultrasound features of OA with extent of pain at the thumb-base joint, grip and pinch strength, functional score and radiographic findings.

Method

Study design and participant selection

This is a cross-sectional analysis from baseline assessment of the ongoing COMBO (Effect of Combined Conservative Therapies on Clinical Outcomes in Patients with Thumb-base Osteoarthritis) clinical trial starting from May 2016 (Trial registration No: ACTRN12616000353493) [16]. Approval for this study was obtained from the local research ethics committee (HREC/15/HAWKE/479).

Participants were recruited from the community and our research volunteer database by using the recruitment strategies such as affixation of posters/flyers on notice boards of waiting rooms of medical practices and community areas; advertisement in newsletters, radio, and local and major newspapers and advertisements on social media networks. Firstly, a preliminary screening was conducted by phone/internet, and then if the participant passed this initial screening, a face-to-face visit was arranged to confirm their eligibility. The inclusion criteria were: 1) age ≥ 40 years; 2) thumb-base pain at least half of the days in the past month; 3) average pain ≥40 on a 100 mm Visual Analogue Scale (VAS) [17] over the 48 h prior to the study enrollment; 4) Functional Index for Hand Osteoarthritis scores ≥6 (FIHOA, range 0–30) [18]; 5) Kellgren Lawrence grade (KLG) [19] ≥2 in the index thumb-base joint.

Exclusion criteria were: 1) known diagnosis of crystal-related arthritis (e.g., gout); 2) autoimmune arthritis (e.g., rheumatoid arthritis); 3) hemochromatosis 4) fibromyalgia; 5) significant injury to the index joint in the past 6 months; 6) any other self-reported hand condition that is likely to cause pain at the thumb base (e.g., scaphoid fracture). All participants provided informed consent.

The most symptomatic hand, as defined by pain on VAS score or worst function over the prior 48 h if the same VAS score in both hands, was included in cases of bilateral symptomatic thumb-base OA.

The cohort included here is a convenience sample recruited from the baseline visit of the COMBO clinical trial, and all participants available for an ultrasound visit between May 2016 and August 2017 were included. One hundred and seventy-two potential participants were screened to get the current sample size.

Clinical, functional and radiological assessment

Demographic data such as age, gender, height, weight and symptom duration were collected. Pain at the thumb base was scored on a 100 mm VAS. Bilateral grip and tip-pinch strength measured in kilogram-force (Kg-F), using the hand dynamometer (Jamar Hand Dynamometer, Model: A7291, Patterson Medical) and pinch gauge (Model: PG-30, B&L Engineering), respectively. Participants were seated with both feet flat on the ground and the elbow flexed at 90 degrees and were instructed to use their maximum force; the average score of the three trials was used in the analysis.

Hand function was assessed by FIHOA questionnaire which includes ten self-reported items scored on a 4-point Likert scale of 0 (possible without difficulty) to 3 (impossible). The outcomes measures were validated instruments recommended to be measured in hand OA clinical trials [20].

Bilateral hand radiograph (posteroanterior view) was used to score KLG [19], osteophyte and joint space narrowing (JSN) scores of the Osteoarthritis Research

Society International (OARSI) atlas [21], and Eaton classification [22]. Radiographic KLG, OARSI osteophyte and JSN were graded by a rheumatologist (LD), and Eaton grades by a physician (ER), respectively. The intra-rater reliability was assessed using 20 radiographs with a 6-month interval between two sessions, providing the weighted kappa of (0.76, 0.72, 0.78, and 0.82) for KLG, OARSI osteophyte, OARSI JSN and Eaton grade, respectively.

Ultrasound examination

The physician sonographer (WMO, four years of musculoskeletal ultrasound experience, designated with a RhMSUS certification by American College of Rheumatology and having attended EULAR ultrasound courses) performed the ultrasound on the index hand in the air-conditioned radiological setting, being unaware of the other clinical and radiographic outcomes. The thumb-base joint was scanned on the longitudinal and transverse plane of the palmar and dorsal aspect according to the OMERACT ultrasound definitions and scanning methods of published papers [23, 24]. A 12 MHz linear probe (L12–4, Philips Sparq Model) was used with fixed ultrasound parameters throughout the study. Power Doppler was assessed with a frequency of 4.4 MHz and medium wall filter, using minimal pressure during the scanning. The gain was adjusted until the background signal was removed.

Effusion was defined as hypoechoic or anechoic fully compressible material, synovial hypertrophy as echogenic or hypoechoic slightly compressible or non-compressible intra-articular tissue [25]. Synovial hypertrophy and effusion were considered together as a single domain "synovitis" which was graded on a 0–3 scale (absent, mild, moderate and severe) as suggested by Keen et al [24]. Doppler signal as a pulsating colour spot found within the synovial structure [23], and graded in binary score (present/absent) (Fig. 1). Osteophytes were defined as cortical protrusions at the joint margin seen in two planes [23], and severity of osteophytes was scored semi-quantitatively (0–3) using the atlas by Mathiessen et al. [26], based on the largest osteophyte independently of the number, size and location of other osteophytes (Fig. 2). Erosion was defined as an intra-articular discontinuity of the bone surface that is visible in two perpendicular planes [23] and scored on a binary scale. An evaluation sheet form was used for documenting the ultrasonographic findings.

Intra-rater reliability

Utilizing still images of 40 randomly selected cases, the intra-rater reliability was examined 6 months after the first session, with a K_W value of 0.77 (0.60 to 0.94) for synovitis, 0.79 (0.63 to 0.96) for osteophyte, and unweighted kappa of 0.89 (0.69 to 1.00) for power Doppler.

Inter-machine reliability

To evaluate the inter-machine reliability, the same scanning procedures and scoring system were performed in 40 patients, using a latest high-end ultrasound machine

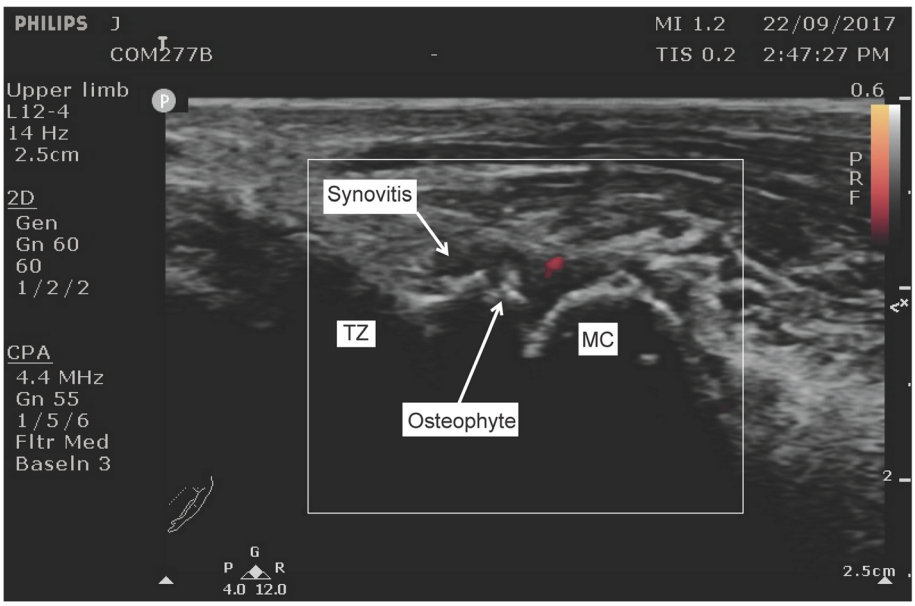

Fig. 1 Power Doppler activity in thumb-base osteoarthritis. TZ = Trapezium; MC = Metacarpal

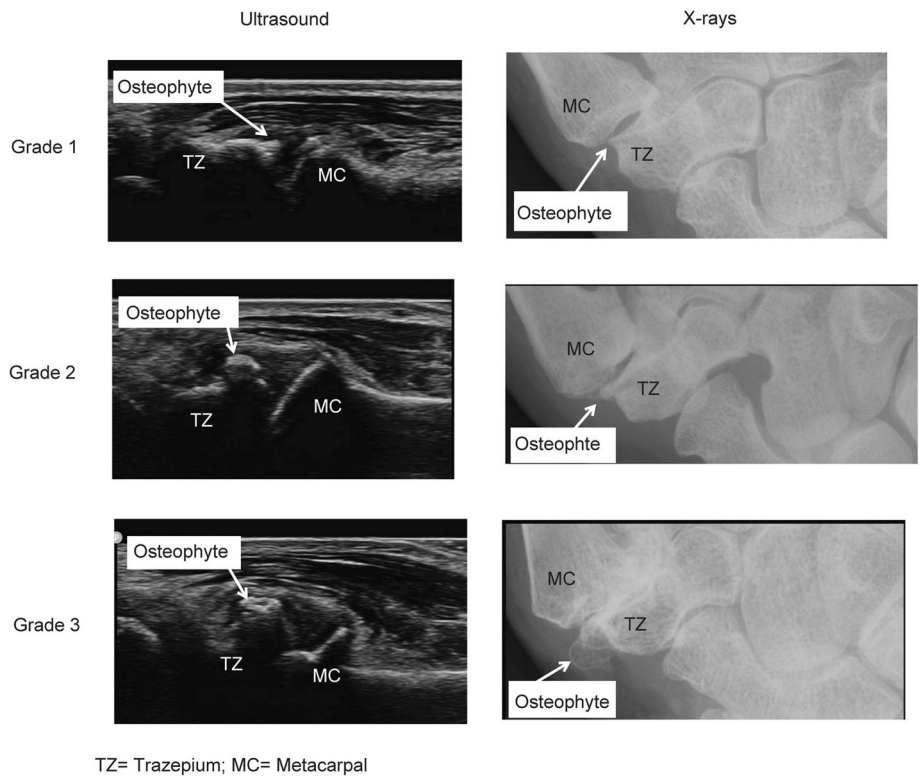

Fig. 2 Atlas for Osteophyte grading of ultrasound and plain radiograph in our sample. Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe. TZ = Trapezium; MC = metacarpal

(Aplio Platinum 500, Toshiba, Japan) equipped with multi-frequency linear transducers (6-18 MHz). The B-mode and power Doppler settings of the machine were optimized by the application specialist from Toshiba. Due to low prevalence of some ultrasound pathologies, prevalence-adjusted bias-adjusted kappa (PABAK) was calculated, giving rise to a PABAK value of 0.81(0.65, 0.97) and percentage agreement of 87.5% for synovitis, 0.78(0.60, 0.95) and percentage agreement of 85% for osteophyte, 0.60(0.34,0.86) and percentage agreement 80% for power Doppler.

Statistics

To investigate whether US features were independently associated with pain, function and strength tests, linear regression analyses were conducted for synovitis and power Doppler, adjusting for age, sex, body mass index (BMI), duration of disease and KLG. Adjustments for age, sex, body mass index (BMI), duration of disease were performed for regressing structural ultrasound features such as osteophyte, erosion. Spearman correlations were calculated to calculate the relationship of ultrasound features with radiographic gradings. Correlation coefficients were interpreted according to the Evans' classification [27], <0.20:very weak; 0.20–0.39:weak; 0.40–0.59:moderate; 0.60–0.79;strong and >0.80:very strong. All statistics were conducted with SPSS version 23 and a significant association/correlation was defined as a p-value less than 0.05.

Results

Demographic and clinical characteristics

A total of 93 participants were included in this study with 73 females. The demographics of the participants are shown in Table 1.

Radiographic findings

According to KLG, grade 3 was found in more than half of the participants (n = 48,51.6%), grade 2 in 27 (29.0%) and grade 4 in 18 (19.4%). Osteophytes were not detected in 6 (6.5%) of participants, respectively, using the OARSI atlas. Radiographic erosion was present in 2 participants. The distribution of all radiographic findings is outlined in Table 1.

Distribution of ultrasound-detected pathologies

On ultrasound, synovitis and power Doppler was detected in 52 (55.9%) and 13 (14.0%), respectively. No participants showed severe synovitis (grade 3) on ultrasound. The majority of participants (n = 65, 69.9%) demonstrated large osteophytes on ultrasound. Ultrasound-detected erosion

Table 1 Baseline, clinical and radiographic data of study participants

Population, n	93
Age, mean (S.D.); years	67.04 ± 6.95
Female, n (%)	73 (78.5%)
BMI, mean (S.D.); kg/m2	29.35 ± 6.73
Disease duration, mean (S.D.), years	3.06 ± 1.10
VAS pain, mean (S.D.)	61.61 ± 14.37
Pinch Strength, mean (S.D.), Kg-F	3.21 ± 1.16
Grip Strength, mean (S.D.), Kg-F	20.06 ± 8.16
FIHOA, mean (S.D.)	11.33 ± 3.91
Kellgren and Lawrence grade, n (%)	
0	0
I	0
II	27 (29.0)
III	48 (51.6)
IV	18 (19.4)
OARSI osteophyte, n (%)	
0	6 (6.5)
I	37 (39.8)
II	21 (22.6)
III	29 (31.2)
OARSI JSN, n (%)	
0	13 (14.0)
I	28 (30.1)
II	33 (35.5)
III	19 (20.4)
Eaton grade, n (%)	
0	2 (2.2)
I	22 (23.7)
II	18 (19.4)
III	47 (50.5)
Radiographic erosion on X-rays, n (%)	2 (2.2)

BMI Body mass index, *FIHOA* Functional index for hand osteoarthritis, *JSN* Joint space narrowing, *OARSI* Osteoarthritis research society international, *VAS* Visual analogue scale

was found in 2 patients. The frequency of different ultrasound findings is shown in Table 2.

There were significant associations synovitis vs erosion ($r_s = 0.23$ ($P = 0.026$).

Association of ultrasound findings with pain, strength and function

The presence of power Doppler was significantly associated with degree of VAS pain [βcoefficient = 11.29, P = 0.02] after adjusting the confounders. The synovitis and osteophyte were not significantly associated with pain, pinch and grip strength, and FIHOA score (Table 3).

Table 2 Ultrasonographic findings in study participants

Population, n	93
Synovitis, n (%)	
0	41 (44.1)
I	36 (38.7)
II	16 (17.2)
III	0
Power Doppler, n (%)	13 (14.0)
Osteophyte, n (%)	
0	0
I	3 (3.2)
II	25 (26.9)
III	65 (69.9)
Erosion on ultrasound, n (%)	2 (2.2)

Association of ultrasound findings with radiographic findings

The ultrasonographic osteophyte scores were significantly correlated with KLG [$r_s = 0.44$ ($P < 0.001$)], OARSI osteophyte grade [$r_s = 0.35$ ($P = 0.001$)], OARSI JSN grade [$r_s = 0.43$ ($P < 0.001$)] and Eaton grade [$r_s = 0.30$ ($P < 0.01$)] as shown in Table 4. Erosion detected on ultrasound had a correlation of 0.49 with radiographic erosion as ultrasound could not visualize the radiographic erosion in one patient with florid osteophytes. In addition, in 6 patients, ultrasound could detect osteophytes which the plain radiograph could not.

Discussion

The current study revealed the frequent finding of some ultrasound pathologies, the significant association of the presence of power Doppler with the severity of pain, and significant correlations of ultrasound-detected osteophyte with radiographic scores in thumb-base OA. However, the study could not detect any significant correlation of ultrasound pathologies with strength and functional measures.

This study showed that synovitis, when present, were mostly scored toward the lower end of the semi-quantitative scale as these grading scores were adopted from the scoring system created originally for rheumatoid arthritis [23], which is quantitatively different in inflammatory severity from OA [28]. Recent papers questioned the use or relevance of semi-quantitative scores in OA as it can lead to unequal distribution of the scores [29] and floor effects causing less sensitivity to detect an improvement in interventional trials [30].

Our participants had worse grades of osteophyte compared to the counterparts of thumb-base joint recorded in multifocal hand OA study by Naguib et al. [8]. This discordant result might be accounted for by the older age in our study population and different study selection

Table 3 Association between ultrasound-detected pathologies and clinical and functional measures

	Synovitis[a]	Power Doppler[a]	Osteophyte[b]	Erosion[b]
VAS pain				
Adjusted β	0.60	11.29	0.24	−12.91
(95% CI)	(−3.91–5.12)	(2.47–20.12)	(− 6.12–6.61)	(− 33.88–8.07)
P (2-tailed)	0.79	**0.02**	0.94	0.22
Pinch strength				
Adjusted β	0.120	−0.01	−0.16	0.85
(95% CI)	(−0.22–0.46)	(− 0.63–0.66)	(−0.64–0.33)	(− 0.76–2.46)
P (2-tailed)	0.48	0.97	0.53	0.30
Grip Strength				
Adjusted β	0.82	−0.71	1.27	1.84
(95% CI)	(−1.17–2.81)	(−4.56–3.13)	(− 1.50–4.04)	(−7.28–10.97)
P (2-tailed)	0.42	0.71	0.36	0.69
FIHOA				
Adjusted β	−.35	0.40	0.21	−2.84
(95% CI)	(−1.47–0.78)	(−1.93–2.72)	(−1.52–1.94)	(−8.53–2.86)
P (2-tailed)	0.54	0.74	0.81	0.32

B β coefficient, *FIHOA* Functional index for hand osteoarthritis, *VAS* Visual analogue scale;
95% CI = 95% confidence interval
[a]Adjusted for age, sex, and body mass index, disease duration and KL grade
[b]Adjusted for age, sex, body mass index, and disease duration

criteria (American College of Rheumatology criteria vs radiological criteria), number of joint involvement (multifocal vs mono-articular OA) and severity of the disease. Structural changes of the hand joints tend to be more commonly found with increasing age. About 6% of adults aged > 30 years [31] and 13% of persons aged 60 and over [32] had radiographic OA features. Such demographic and selection criteria differences might lead to our study population having more participants with fully established OA features.

Table 4 Relationship between ultrasound-detected pathologies and radiological findings

	Synovitis	Power Doppler	Osteophyte	Erosion
KL score				
r_s	−0.09	− 0.03	0.44	− 0.09
P (2-tailed)	0.41	0.76	0.001	0.41
OARSI OST				
r_s	−0.13	−0.14	0.35	−0.13
P (2-tailed)	0.21	0.19	0.001	0.22
OARSI JSN				
r_s	−0.03	−0.06	0.43	−0.08
P (2-tailed)	0.75	0.57	0.001	0.43
Eaton SUB				
r_s	−0.11	−0.01	0.30	−0.03
P (2-tailed)	0.29	0.98	0.01	0.75
Erosion				
r_s	0.15	0.15	0.10	0.49
P (2-tailed)	0.14	0.14	0.36	0.001

KL Kellgren Lawrence, *OARSI* Osteoarthritis research society international; *OST* Osteophyte, *rs* Spearman's correlation, *SUB* Subluxation

Poor correlation between clinical symptoms and radiographic findings has previously been demonstrated in knee OA [33], and a similar discordance was suggested by our findings which revealed significant association of only power Doppler with VAS pain, and no significant association with other ultrasound features. The finding of a significant correlation of power Doppler signal is in agreement with increasing evidence of MRI literature, which implied that active synovial inflammation plays a critical role as pain generator of OA [34, 35]. This result is also consistent with meta-analytic reports in knee OA ultrasound [30].

However, the lack of significant correlation of grey-scale synovitis with pain raised several questions about its role in pain generation in OA. Hall et al. [36] postulated that perhaps synovial hypertrophy as seen on grey-scale ultrasound might not be inflammatory as grey-scale ultrasound cannot differentiate between active and indolent synovitis, tissue debris and fibrosis. Synovial hypertrophy and effusion could be the results of altered joint biomechanics [37] and reduction in lymphatic vessels [38]. In addition, pain in OA can be partly due to bone marrow oedema (BMOs) [39], which ultrasound cannot detect as sound waves cannot penetrate the bone, reducing the strength of correlation

between grey-scale synovitis and VAS pain. The other reason might be a measurement issue. Pain is a subjective phenomenon, and inter-individual differences may modify the pain experience and intensity [40]. Subjects sustaining the same degree of structural damage experienced widely different degrees of pain, a phenomenon that is poorly elucidated [41]. Kroon et al reported no significant association between inflammatory OA features of ultrasound and presence of pain on palpation although MRI synovitis and BMOs showed a significant relationship with pain in a different cohort [15]. In multifocal hand OA as well, conflicting results were reported in this aspect as Keen et al. [7] reported no significant association of synovitis, power Doppler, osteophyte and joint space width (JSW) with pain whilst Naguib et al. [8] documented a significant relationship of osteophyte, JSW and cartilage thinning with pain.

The relationship of grip and pinch strength with OA imaging features are broadly discordant in the radiological literature [42]. We found no correlation between ultrasound features and grip or pinch strength, which was contradictory with those of Naguib et al. [8], which found that significant associations existed between the grip strength and osteophyte in multifocal hand OA (n = 30). However, Naguib et al. [8] did not find a significant correlation between strength and JSW, which was comparable with our findings. This disparity might be perhaps due to demographic differences such as greater strength (19.3 Kg-F vs 15.0 Kg-F) and older age (67.3 vs 60.0 years) in our study. Baron et al. [43] did not find a correlation between hand function, grip strength, and radiographic features of hand OA, and postulated that hand function and strength were related more to neuromuscular condition than to the articular damage.

Regarding the correlation between ultrasound features and functional measures, the current study was consistent with most of the multifocal hand OA reports in the literature [7, 14, 44]. In multifocal hand OA, Keen et al. [7] demonstrated that synovitis, power Doppler and osteophyte had no significant correlation with functional impairments, utilizing the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) while Koutroumpas et al. [44] reported no correlation of synovitis and power Doppler with FIHOA score. In thumb-base OA, most ultrasound features had no correlation with Disabilities of the Arm Shoulder and Hand (DASH) score [14]; the only difference being that they found a correlation of osteophyte with function while we did not. However, contrary to these findings, Naguib et al. [8] determined a significant correlation of the structural features of ultrasound such as osteophyte with AUSCAN questionnaire in multifocal hand OA. It should be noted that the measures of hand function depend on multiple joints acting in concert, whereas our study looked at only one of those joints and so we could not exclude the impact of other finger joints OA on the associations. A recent meta-analysis in clinimetrics of ultrasound in knee OA reported that functional impairments are significantly but weakly correlated with effusion [r = 0.23 (0.08, 0.37)] and osteophyte [r = 0.18 (0.04, 0.31)] [30]. The reason for this discrepancy was unclear.

Our study found that ultrasound had the ability to detect osteophytes which plain radiographs failed to visualize. These findings are in agreement with those of Mathiessen et al. [26], Keen et al. [5] and Vlychou et al. [6], which demonstrated more osteophytes on ultrasound than on plain radiograph in multifocal hand OA. This can be explained by the capability of ultrasound to perform dynamic multiplanar imaging both longitudinally and transversely, and two-dimensional nature of plain radiograph which is likely to miss the small osteophyte localized to either palmar or dorsal aspect of the joint on standard PA view. However, the current radiographs are single-view only and this may position radiography at a disadvantage.

Although Vlychou et al. [6] reported that ultrasound could reveal more erosions than plain radiograph in erosive multifocal hand OA, our study could not detect more erosions on ultrasound than plain radiograph perhaps due to higher prevalence of osteophyte (100% vs 41%) and reduced number of erosive OA (2% vs 100%) in our study. In one patient, erosion was near the central joint area with the overhanging osteophyte, which could not be visualized on ultrasound due to limited acoustic window. Our finding was consistent with Keen et al. [5] who reported 6 erosions on plain radiograph (3 DIP, 2 PIP and 1 MCP); 2 joints were normal on ultrasound while the other 4 had marked osteophytosis. The similar conclusion was documented in another study [45] which implied that ultrasound could not detect 27.3% of erosions seen on plain radiograph. In small joints having severe osteophytes, deformities and subluxation, ultrasound was distinctly cumbersome due to acoustic artefacts and small acoustic window. Ultrasound appears to be more useful for detection of non-radiographic phase of erosive OA before the appearance of frank erosion which plain radiograph can visualize at this stage.

Naguib et al. [8] demonstrated the significant correlation of osteophyte with KLG, which is concordant with the current study. However, the correlation is just moderate probably due to different measurement methods of plain radiograph and ultrasound in scoring the grades of severity (each grades of ultrasound osteophyte atlas was not standardized exactly with the same grade of OARSI radiographic atlas; this might lead to over- or under-estimation of ultrasound severity score), more scanning planes for ultrasound and the fact that the comparison was not site-specific.

Limitation

As this was a cross-sectional study, we cannot establish a cause-effect relationship and determine clinical importance of variability of the power Doppler with longitudinal changes in pain. Another limitation was the lack of a reference method such as MRI in detecting synovial and bony pathologies, and so we are not able to comment on the percentage of false positive and false negative ultrasound features. Ideally, the inter-rater reliability data should be conducted but only one ultrasound operator was available for this study. In addition, the ultrasound machine used in our study is not the optimal high-end machine equipped with the latest high-frequency probe. In an ideal world, we would also have included a cohort of healthy individuals for comparison of ultrasound pathologies. Another important study limitation was that the ultrasound operator was not blinded to diagnosis; however, in practice, blinding a sonographer to joint deformities and joint tenderness is not feasible.

Conclusion

From a clinical perspective, the significant association of power Doppler with pain severity in thumb base OA suggests that ultrasound might be a useful tool in understanding pain aetiology. It is important to recognise that power Doppler activity was only detected in 14% of the study so this might be an important subgroup of persons to monitor more closely. In addition, the lack of association of other ultrasound structural features with hand function and strength reinforces the complex biopsychosocial origins of pain and function and the ongoing challenge of pain and structure dissociation in osteoarthritis. Further study with longitudinal follow-up may contribute to more clarification.

Abbreviations

BMOs: Bone Marrow Oedema; FIHOA: Functional Index for Hand OA; JSW: Joint space width; KLG: Kellgren Lawrence Grading; OA: Osteoarthritis; OARSI: Osteoarthritis Research Society International; VAS: Visual Analogue Scale

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Author's contributions

WMO, DJH and JML conceived and designed the study. LAD, VD and SRR were also involved in the design of the study. WMO, LAD, VD, KF, JML, EAR, SRR, DJH contributed to acquisition of clinical data of the study. WMO had full access to all the data and analysis and drafted the first manuscript. All authors critically revised the manuscript and gave final approval of the article for submission.

Ethics approval and consent to participate

The informed consent obtained from study participants was written. Approval for this study was obtained from the Human Research Ethics Committee (HREC) of the University of Sydney and by Northern Sydney Local Health District HREC - reference number HREC/15/HAWKE/479.

Consent for publication

Non-applicable.

Competing interests

The authors declare that they have no competing interests.

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