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PSYCHOLOGICAL DISTRESS AMONG LYMPHOMA SURVIVORS

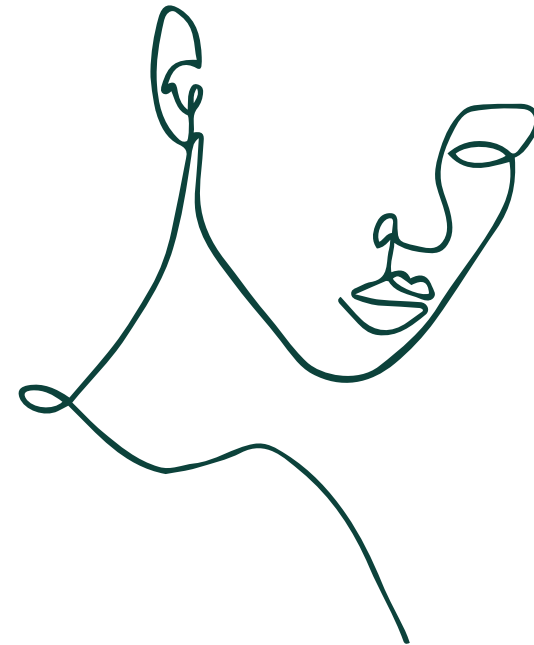
FROM INVENTORY TO INTERVENTION



LINDY ARTS

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SURVIVORS**
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CHAPTER 1

GENERAL INTRODUCTION



RATIONALE FOR THIS THESIS

Healthcare systems increasingly strive to put patients at the center of care [1]. Information about patients' perceptions of their health and their experiences are important to provide excellent patient-centered care [2]. Patient-reported outcomes (PROs) are a powerful tool to assess and understand patients' experiences and provide insight in their health, quality of life, functional status, or symptoms associated with their disease, its treatment and the care they received [3]. Since 2004, the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) registry has been used to collect PROs among more than 20,000 short- and long-term cancer survivors in the Netherlands. PROFILES is linked directly to clinical data from the population-based Netherlands Cancer Registry [4]. Previous PROFILES studies among 1,444 lymphoma survivors have shown that patients who have or ever had lymphoma may experience substantial physical and psychosocial problems due to the cancer and its treatment [5,6]. These problems include – but are not limited to – fatigue, neuropathy, cognitive limitations, and psychological distress [6-9]. In addition, it has been demonstrated that up to one third of lymphoma survivors were not satisfied with the information they received and would have liked more information about, for example, adverse problems [10].

Starting point of this thesis were the adverse problems experienced by a substantial part lymphoma survivors, with a special focus on psychological distress. It is expected that the presence of adverse problems may result in an increasing burden on healthcare services in hematology. Self-management interventions intend to enhance patients' knowledge and skills and empower them to self-manage their cancer-related problems. The overarching research questions to be answered in this thesis are which factors are associated with psychological distress, and whether self-management interventions may have a beneficial effect on PROs.

LYMPHOMA: SUBTYPES, SURVIVAL AND PREVALENCE

Lymphomas are cancers that originate from lymph nodes and the lymphatic system and have classically been divided into two distinct groups: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) [11]. Indolent or low-grade NHLs grow slowly and are more chronic and long-lasting because they flare up

and need treatment from time-to-time [7,12,13], whereas aggressive or high-grade lymphomas grow at a faster rate and usually require immediate treatment [14].

Improvements in the treatment of lymphoma have led to improved survival, also in the Netherlands [15-18]. Approximately 85% of patients with HL and indolent lymphomas are expected to be alive at five years after diagnosis, whereas this is 62% of patients with aggressive lymphomas [19]. Survival statistics vary, depending on stage of disease, treatment and age of the patient. The improved survival results in an increasing number of individuals who have ever been diagnosed with lymphoma. In 2020, there will be more than 40,000 individuals in the Netherlands who have or ever had lymphoma [19,20], an increase of approximately 65% compared with 2010. Moreover, in the United States, there will be over one million lymphoma survivors in 2020 [21].

The term 'lymphoma survivor' refers to all individuals who have ever been diagnosed with lymphoma and thus includes individuals diagnosed with lymphoma in the past as well those who were recently diagnosed [22]. Nevertheless, not all individuals who have been diagnosed with lymphoma identify themselves with the term 'survivor', especially not individuals with indolent and thus more chronic types of lymphoma. As the studies included in this thesis include patients from various phases of the cancer care continuum [23], the term 'patients' and 'survivors' are being used interchangeable in this thesis.

PSYCHOLOGICAL DISTRESS AND ADJUSTMENT AFTER CANCER

Improved survival is associated with increasing awareness that PROs are an important aspect of cancer survivorship [24], especially because approximately 30% of lymphoma survivors continue to experience adverse long-term physical and psychological problems. Previous research has revealed that up to a quarter of lymphoma survivors experienced a state of emotional suffering characterized by symptoms of depression and anxiety [5]. Psychological distress involves a range of feelings from commonly experienced vulnerability, fears, and sadness to problems that can become disabling, such as anxiety, depression, social isolation and panic [25]. For the majority of survivors, feelings of psychological distress diminish after diagnosis and treatment and they do not experience persistent psychological problems. For some survivors, however, the cancer experience triggers a

psychological response that has a persistent impact on their functioning and quality of life [5,26,27].

Receiving a cancer diagnosis is a stressful experience that requires adequate coping strategies to maintain balance. Whether or not patients experience adverse problems highly depends on their coping resources. Lazarus and Folkman's theory of stress and coping was used as the theoretical framework [28]. Psychological well-being is determined by the relative balance between the stress posed by the stressful situation – the cancer experience – and the resources available to cope with this stressful situation (Figure 1), which is dynamic and may fluctuate over time [29,30]. When coping resources are inadequate, patients may be at risk for adverse problems, even when the stress posed by the cancer experience appears to be low. Alternatively, the risk for adverse problems may be low when the stress posed by the cancer experience appears to be considerable and/or the resources are considerable as well [28-30]. Serious psychological distress occurs when the experience is perceived as threatening and is either exceeding or taxing the patient's resources to cope with the experience [28].

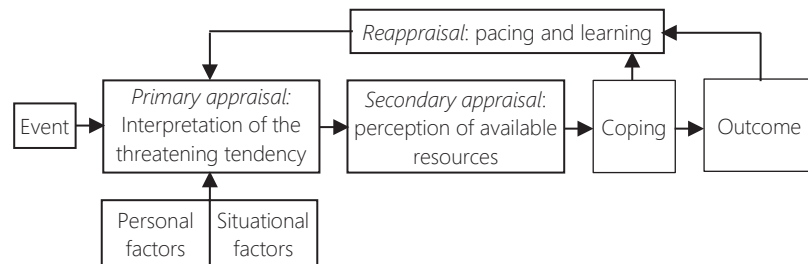


Figure 1. The transactional stress-coping model of Lazarus and Folkman

SELF-MANAGEMENT AND SELF-MONITORING

Effective self-management provides patients with the ability to 'monitor their condition and to effect the cognitive, behavioral, and emotional responses that are needed to keep up a good quality of life' [31]. It provides knowledge and skills to manage the physical and psychosocial aspects of (chronic) illness [32]. Effective self-management contributes to empowering patients to take responsibility for their own health, improving patients' health and well-being, and reducing patients' need to have constant visits to health professionals [33,34]. Self-management does

not mean the exclusion of healthcare providers, but it represents a new model of active collaboration between patients and healthcare providers [35]. Self-management is considered crucial to bridge the gap between the needs of cancer survivors and the ability of healthcare services to meet those needs [23,32]. An important element of self-management is monitoring one's physical and psychosocial functioning and making appropriate management decisions based on the results of self-monitoring [36]. PROs are not only useful at population level for aggregating population-based or trial data, but have also the potential to improve care at the individual patient level for patients with cancer [37]. Regular screening of physical and psychosocial symptoms can help identify symptoms or problems and enable patients to become more involved in managing their own health [38,43]. Self-monitoring motivates and maintains behavior change by promoting self-efficacy, increasing awareness, and monitoring progress [35]. In addition, it has been demonstrated that feedback on PROs can result in improved symptom detection and improved communication between patients and health care providers [38-42,44-48]. Feedback on PROs however was mostly provided to healthcare providers, who may not always see the urgency of specific problems or may forget to discuss these topics with the patients. Alternatively, providing feedback on PROs directly to patients can enable them to self-monitor their symptoms and reassure them that their symptoms are not abnormal, or motivate them to discuss their symptoms with healthcare providers.

SELF-MANAGEMENT INTERVENTIONS

The theoretical framework of Greenhalgh et al demonstrated that providing feedback on PROs is particularly effective in the identification of problems and unmet needs, but intervening steps may be necessary to actually improve health outcomes [49]. Self-management interventions typically include educational components or intervention techniques that can help patients identify and manage persistent adverse problems [32] and motivate them to influence their health [35,50]. Information provision, or education, is an essential component of self-management interventions as patients need information about their disease.

Information provision

Knowledge of the disease and its management can make the cancer experience seem less mysterious and frightening. Adequate information provision about the disease, treatment, and aftercare may lead to improved abilities to cope with the

stressful situation [51,52], and subsequent reductions in anxiety and mood disturbances [53]. It has previously been demonstrated that one third of patients with lymphoma are not satisfied with the information they received and would have liked to receive more information [10]. In addition, previous literature has shown that the majority of patients wants as much information as possible and tend to actively search for information [54]. This group of information seeking patients has been classified as ‘information monitors’ [55]. Alternatively, other patients seem to actively avoid information and are uncomfortable with large amounts of information. This group of information avoiding patients has been classified as ‘information blunters’ [55]. Thus, providing all available information may enhance coping abilities and reduce the risk for adverse problems in some patients, whereas it may increase fears and worries for others [30]. Therefore, it is important to pay more attention to patient-centered information provision and to tailor information provision to the needs of patients.

Supporting skills

In addition to education, effective self-management of adverse cancer-related physical and psychological problems requires patients to develop a new set of skills that may not be in their usual repertoire of health behaviors [56]. This requires patients to be able to monitor their psychological adjustment and to potentially alter the cognitive, behavioral, and emotional responses in order to maintain a good quality of life [31,57]. Interventions to support self-management should therefore contain more than solely psychoeducation – in the form of the provision of systematic, relevant, broad, and up-to-date information – and also include components that can produce behavior change. Cognitive behavioral therapy (CBT) aims to alter dysfunctional perceptions and coping strategies. CBT techniques include – but are not limited to – psychoeducation, self-monitoring, goal setting, cognitive restructuring, coping and process evaluation [58,59]. CBT techniques can be incorporated into self-management interventions to increase the repertoire of self-management skills that cancer survivors can apply to manage adjustment to cancer. The process in which patients change their underlying appraisals that contribute to poor adjustment to cancer fits in the reappraisal phase of the transactional stress-coping model of Lazarus and Folkman (Figure 1) [28]. Cognitive reappraisal is a stress-coping technique based on CBT that helps patients to identify negative thoughts and behavior patterns and then change the related thoughts and underlying beliefs to reflect more positivity when dealing with psychological distress [60]. Ideally, patients may recognize the negative pattern

their thoughts have fallen into and they change the pattern to one that is more effective.

Summarized, self-management interventions will increase patient involvement in, and responsibly for, their own health and care [35]. This may subsequently result in decreased burden on the health care system and will support more optimized use of limited resources.

THE LYMPHOMA INTERVENTION [LIVE] TRIAL

In this thesis, two interventions that enable patients to participate in managing their care along the cancer care continuum are discussed within the Lymphoma InterVEntion (LIVE) trial. The LIVE trial consists of 1) feedback on PROs, and 2) a web-based self-management intervention named *Living with lymphoma*. The PRO feedback has the potential to enable patients to monitor their symptoms and compare them with peers, which may reassure them that what they experience is ‘normal’ or may empower them to take action. The web-based self-management intervention *Living with lymphoma* is an adaptation from the evidence-based BREast cancer e-health (BREATH) intervention, that was developed to facilitate adjustment after curative breast cancer [61]. Access to BREATH was found to be associated with reduced psychological distress, and higher self-efficacy among breast cancer survivors [62]. The web-based self-management intervention *Living with lymphoma* intends to enhance knowledge and skills and empower patients to better manage their cancer-related problems.

AIMS AND ORGANIZATION OF THIS THESIS

The chapters in this thesis describe the process from making an inventory of factors associated with psychological distress among lymphoma survivors to the development and evaluation of an intervention that aims to increase resources to cope with the stress and burden posed by the cancer experience and reduce psychological distress.

Part I Inventory: factors associated with psychological distress

This thesis starts with an inventory of factors that are associated with psychological distress among lymphoma survivors. Considering that coping strategies greatly influence how patients adjust to cancer and whether they will experience

psychological distress [63], the aim of **Chapter 2** is to investigate which coping strategies – but also sociodemographic and clinical factors – are associated with an increased risk of psychological distress among patients with lymphoma. Further, the aim of **Chapter 3** is to evaluate the use of healthcare services among distressed compared to non-distressed lymphoma survivors. In addition, sociodemographic and clinical characteristics associated with increased healthcare use in lymphoma survivors are identified.

Part II Intervention: Lymphoma InterVention [LIVE] trial

In **Chapter 4**, we investigate whether patients with lymphoma wished to receive PRO feedback, including the option to compare their scores with those of their peers, and how this feedback was evaluated. The rationale and study design of the Lymphoma InterVention [LIVE] trial are presented in **Chapter 5**. Further, the main effects of the interventions on self-management skills, satisfaction with information provision, and psychological distress are described in **Chapter 6**. In addition, the aim of **Chapter 7** is to identify the reach of a web-based self-management intervention within the context of an RCT. Thereafter, in **Chapter 8**, the main findings and methodological considerations of this thesis are discussed, and implications for clinical practice and future research are outlined.

METHODS: RCT EMBEDDED WITHIN A POPULATION-BASED REGISTRY

For the LIVE-trial, patients with lymphoma were selected from the population-based Netherlands Cancer Registry (NCR) that routinely collects data on sociodemographic and clinical characteristics. Data collection regarding PROs was conducted within the PROFILES registry, a tool that enables data collection management; from inviting patients to participation in studies, to collecting PRO data via web-based or mailed questionnaires and linking these data with clinical data from the NCR [4]. Patients who completed the web-based questionnaire were enrolled in the trial and automatically randomized to one of the RCT arms. Alternatively, patients who completed a paper questionnaire were observationally followed within the PROFILES lymphoma registry.

Results from the studies within this thesis are based on data from the LIVE-trial, except for the results of Chapter 3 and Chapter 4, which are based on data from a previous, retrospective lymphoma cohort.

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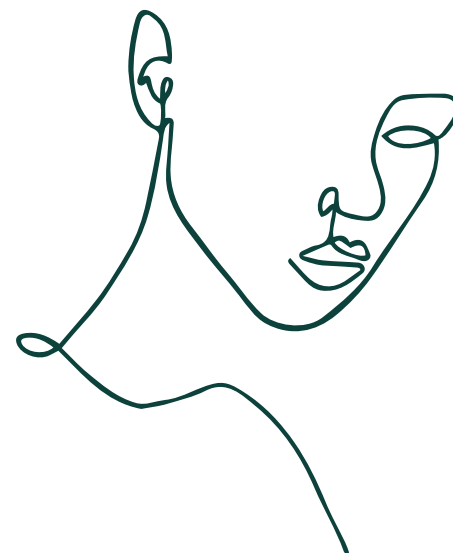
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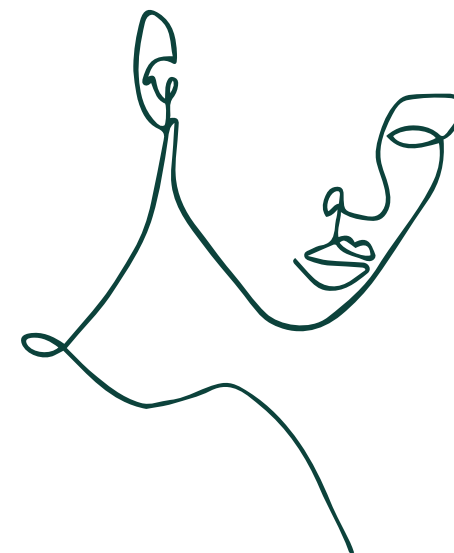
PART I

INVENTORY: FACTORS ASSOCIATED WITH PSYCHOLOGICAL DISTRESS



CHAPTER 2

PSYCHOLOGICAL DISTRESS AMONG PATIENTS WITH LYMPHOMA: THE ASSOCIATION WITH PERSONALITY AND COPING STRATEGIES



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ABSTRACT

Background

Up to a quarter of patients with lymphoma experience persisting levels of psychological distress. This study aims to examine the extent to which personality traits and coping strategies, separately and together, are associated with psychological distress among patients with lymphoma, controlling for sociodemographic and clinical characteristics.

Methods

A population-based sample of patients with lymphoma, selected from the Netherlands Cancer Registry (NCR) was invited to complete a questionnaire about psychological distress (HADS), personality (BFI) and coping strategies (MAC). Sociodemographic and clinical data were retrieved from the NCR. Multivariable linear regression models were constructed to assess the unique variance in psychological distress explained by personality traits and coping strategies separately and together.

Results

A total of 456 patients completed the questionnaire (51%). The mean age was 65 years, 64% were male and 17% reported psychological distress. Of sociodemographic and clinical characteristics, comorbidity ($\beta=.14$, $P<.001$) and age ($\beta=-.10$, $P=.03$) were independently associated with psychological distress. In addition, of personality traits, only neuroticism was related to psychological distress ($\beta=.43$, $P<.001$). Furthermore, coping styles helplessness/hopelessness ($\beta=.30$, $P<.001$) and anxious preoccupation ($\beta=.12$, $P=.01$) were associated with more psychological distress, whereas avoidance was associated to less psychological distress ($\beta=-.09$, $P=.01$).

Conclusions

In conclusion, besides comorbidity and age, both personality traits – in particular neuroticism – and coping strategies including helplessness/hopelessness, anxious preoccupation, and avoidance were significantly independently associated with psychological distress. Unlike personality, coping strategies are considered to be changeable and could be targeted by interventions such as cognitive-behavioral therapy (CBT).

INTRODUCTION

Each year, over 4,500 patients in the Netherlands and 100,000 patients in the US are diagnosed with lymphoma including chronic lymphocytic leukemia (CLL) [1,2]. Approximately 40% of lymphoma diagnoses are indolent diseases and are not curable, but can be controlled and managed for long periods of time [3].

Receiving a cancer diagnosis is considered to be a very stressful experience. According to the stress-coping theory of Lazarus and Folkman, psychological well-being is determined by the balance between the stress posed by the cancer experience and the resources available to cope with this experience [4,5]. Whereas the majority of patients adjust well to cancer and do not report adverse psychological problems, up to a quarter of patients with lymphoma experience persistent levels of anxiety and depressive feelings, also known as psychological distress [6,7]. Psychological distress may lead to lower health-related quality of life [6] and increased healthcare use [8]. Knowledge of the predisposing factors and their managements may help healthcare providers to prevent or manage psychological distress. Previous literature has demonstrated that psychological distress has been associated with patient and disease-related factors, including – but not limited to – age, treatment and time since diagnosis [6,9-11]. It has, however, also been suggested that a patient's subjective appraisal of how cancer and its treatment impacts their life may be a more substantial predisposing factor than patient or disease-related factors [12].

The identification of personality traits that may predispose patients with cancer to experience psychological distress has been a major emphasis in psychology. Neuroticism is known to be the most consistent personality trait that is associated with psychological distress [13,14], although inconsistent results were reported regarding the roles of extraversion, agreeableness, conscientiousness, and openness [15]. Personality traits determine the way of reacting and adapting – also considered coping – to given situations [13,16]. Those with high scores on neuroticism have the tendency to experience more negative affect and are prone to experience more negative appraisals of cancer on their lives [13-15,17]. In addition, they may be less flexible in adapting their own standards and values [14]. Those scoring high on neuroticism tend to use more passive or nonadaptive coping strategies when they are confronted with a stressful situation, such as a cancer diagnosis, which makes it more difficult for them to adapt to cancer [14].

Although a large body of research exists on the relationship between personality and psychological distress, or the relationship between coping strategies and psychological distress [16,18-23], little is known about the unique variance in psychological distress explained by personality traits and coping strategies separately and together. This study aims to examine the extent to which personality traits and coping strategies, separately and together, are associated with psychological distress among patients with lymphoma, while controlling for sociodemographic and clinical characteristics.

METHODS

Study design, participants and recruitment procedure

Patients who were diagnosed with Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), including CLL, as defined by the International Classification of Diseases for Oncology-3 codes (ICD-O-3) [24], in thirteen hospitals in the Netherlands were selected for participation in the Lymphoma InterVEntion (LIVE) trial [25] via the Netherlands Cancer Registry (NCR). Details of the LIVE-trial have been previously described in the protocol paper [25]. Patients who completed the first questionnaire online were enrolled in the trial, whereas those who completed the questionnaire on paper were observationally followed. This study included both online and paper respondents. Patients were selected approximately 9 to 18 months after diagnosis and had to be 18 years or older. Patients who had deceased, were too ill, or who had serious cognitive impairment (e.g., dementia) were excluded. Data collection took place between October 2016 and February 2019.

Measures

Psychological distress was assessed with the 14-item Hospital Anxiety and Depression Scale (HADS) [26]. Each item is rated on a 4-point scale from 0 to 3. The sum can be scored through addition of the item scores with a range from 0 to 42. Higher sum scores indicate higher levels of psychological distress. Patients with a HADS sum score ≥ 13 were categorized as "psychologically distressed" [27].

Personality traits were assessed with the Big Five Inventory (BFI) [28]. The BFI is a 44-item inventory designed to measure the Big Five personality traits: neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness. Each item is scored on a 5-point scale. Scale scores were obtained by averaging all items

for each trait and range from 0 to 5. Each trait is assumed to represent a continuum from high to low on the specific attribute and is partnered with an trait on the opposite pole of the spectrum [29].

The 40-item Mental Adjustment to Cancer (MAC) scale was used to assess adjustment to cancer in terms of coping strategies [30,31]. Items can be grouped on five categories representing different coping strategies: helplessness/hopelessness, anxious preoccupation, fighting spirit, fatalism and avoidance. Each item is rated on a four-point scale from 1 to 4. The subscales can be scored separately through simple addition of the items. Higher scores represent higher endorsement of the coping strategy.

Sociodemographic and clinical characteristics were available from the NCR that routinely collects data on patients' age and sex, date of cancer diagnosis, cancer type, and primary treatment. Information on educational level and marital status was assessed in the questionnaire. Comorbidity at the time of questionnaire completion was assessed with an adapted version of the Self-Administered Comorbidity Questionnaire [32]. Patients were asked to identify comorbid conditions present within the past 12 months: heart disease, hypertension, arthritis, stroke, lung disease, diabetes, stomach disease, kidney disease, liver disease, anemia, thyroid disease, and rheumatoid arthritis. Positive responses were summed to obtain a total score that ranges from 0 to 12.

Statistical analyses

All statistical analyses were performed with SAS version 9.4 (Cary, NC, USA). Two-sided *P*-values of $< .05$ was considered statistically significant. Differences on sociodemographic and clinical characteristics between respondents and nonrespondents, as well as differences between patients with and without psychological distress were compared using t-tests for continuous variables and chi-square tests for categorical variables. Furthermore, differences on personality traits and coping strategies between patients with and without psychological distress were compared using t-tests.

Multivariable linear regression models were constructed to assess the unique variance in psychological distress explained by personality traits and coping strategies separately and together. First, a crude model was run entering only the covariates sociodemographic and clinical characteristics (model 1). Thereafter,

either personality traits (model 2) or coping strategies were added (model 3). Finally, personality traits and coping strategies were entered simultaneously while controlling for sociodemographic and clinical characteristics (model 4).

RESULTS

Patients' characteristics

In total, 456 respondents completed the questionnaire (51%). The sociodemographic and clinical characteristics of respondents are summarized in Table 1. Respondents were more often male than nonrespondents (64% vs 56%; $P=.02$) and more often received active treatment (75% vs 66%, $P=.01$). No differences regarding age, cancer type and time since diagnosis were observed between respondents and nonrespondents ($P>.05$). Respondents were on average 64.5 years old, with a mean time since diagnosis of 14.2 months. More than half of the respondents followed medium education (57%) and the majority had a partner (79%). In addition, two thirds of the respondents reported one or more comorbid conditions, the most common being arthritis (24%) and hypertension (23%). In total, 17% of the respondents scored above the cutoff for psychological distress ($N=79$).

Differences between patients with and without psychological distress

Patients who scored above the cutoff for psychological distress (≥ 13) were less often highly educated (20 vs 38%; $P=.01$; Table 1) and reported more comorbid conditions (1.9 vs 1.1, $P<.01$). No statistically significant differences according to psychological distress were found between cancer types ($P=0.11$). In addition, no differences regarding sex, having a partner, time since diagnosis, and primary treatment were observed between those with and without psychological distress ($P>.05$).

Association between personality, coping and psychological distress

The crude model showed that sociodemographic and clinical covariates accounted for approximately 9.7% of the variance in psychological distress. Comorbidity was the greatest factor associated with psychological distress in this model ($\beta=.28$, $P<.001$). In addition, higher age was associated with less psychological distress ($\beta=-.12$, $P=.03$), even as high education ($\beta=-.14$, $P=.003$).

Table 1. Sociodemographic and clinical characteristics of patients with psychological distress ($N=79$) and patients without psychological distress ($N=377$)

	Patients with psychological distress N=79 n(%)	Patients without psychological distress N=377 n(%)	P	Total respondents N=456
Sociodemographic characteristics				
Sex			.89	
Male	51 (65)	241 (64)		291 (64)
Female	28 (35)	137 (36)		165 (36)
Age: mean (SD)	63.5 (13.8)	64.7 (13.4)	.48	64.5 (13.5)
Education [#]			.01	
Low	7 (9)	26 (7)		33 (7)
Medium	56 (71)	205 (55)		260 (57)
High	16 (20)	143 (38)		159 (35)
Unknown	0 (0)	4 (1)		4 (1)
Partner (yes)	59 (78)	296 (80)	.70	354 (79)
Clinical characteristics				
Months since diagnosis: mean (SD)	14.5 (3.4)	14.2 (3.2)	.45	14.2 (3.3)
Cancer type			.11	
HL	8 (10)	38 (10)		46 (10)
NHL-HG	39 (49)	220 (58)		259 (57)
NHL-LG	28 (35)	87 (23)		114 (25)
CLL	4 (5)	33 (9)		37 (8)
Treatment			.75	
Active surveillance	20 (25)	93 (25)		112 (25)
Active treatment	58 (73)	283 (75)		341 (75)
Unknown	1 (1)	2 (1)		3 (1)
Comorbid conditions: mean (SD)	1.9 (1.3)	1.1 (1.2)	<.01	1.3 (1.2)
Most frequent comorbid conditions				
Arthritis	28 (35)	80 (22)	<.01	108 (24)
Hypertension	23 (29)	82 (22)	.19	105 (23)
Heart disease	24 (31)	67 (18)	.01	91 (20)

Note: Bold type indicates statistical significance ($P<.05$).

Abbreviations: CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; NHL-HG, high-grade non-Hodgkin lymphoma; NHL-LG, low-grade non-Hodgkin lymphoma; SD, standard deviation.

[#] For education, low indicates none/primary school; medium, lower general secondary education/vocational training; and high, pre-university education/high-level vocational training/university.

When personality traits were added to the crude model (model 2), the model accounted for 42.8% of the variance in psychological distress. Of personality traits only neuroticism was statistically significantly associated with more psychological distress ($\beta=.57, P<.001$). In addition, comorbidity and higher age remained associated with psychological distress, whereas the association of high education was no longer statistically significant in this model.

When coping strategies were added to the crude model (model 3), the model accounted for 38.8% of the variance in psychological distress. Helplessness/hopelessness ($\beta=.36, P<.001$) and anxious preoccupation ($\beta=.23, P=.01$) were statistically significantly associated with more psychological distress, whereas higher fighting spirit ($\beta=-.12, P=.01$) and avoidance ($\beta=-.10, P=.02$) were associated with less psychological distress. Also in this model, comorbidity and higher age remained statistically significantly associated with psychological distress.

Entering both personality traits and coping strategies simultaneously into the crude model, while controlling for sociodemographic and clinical characteristics (model 4), the model accounted for 50.6% of the variance in psychological distress. Also in this model, comorbidity remained associated with more psychological distress ($\beta=.14, P<.001$) and higher age with less psychological distress ($\beta=-.10, P=.02$). As in model 2, with personality traits added, only neuroticism was significantly associated with psychological distress ($\beta=.43, P<.001$). In addition, as in model 3, helplessness/hopelessness ($\beta=.30, P<.001$) and anxious preoccupation ($\beta=.12, P=.01$) were still associated with more psychological distress, while avoidance was associated with less psychological distress ($\beta=-.09, P=.01$). However, fighting spirit was no longer statistically significantly associated with psychological distress, when personality traits and coping strategies were added to the model simultaneously, which seems to indicate that the association between fighting spirit and psychological distress might be fully explained by personality traits. In addition, the association between neuroticism and psychological distress became weaker when coping strategies were added to the model, as well as the association between anxious preoccupation and psychological distress became weaker when personality traits were added. This might suggest that the association between personality traits and psychological distress may be partially explained by anxious preoccupation.

Table 2. Multivariable linear regression models of characteristics associated with psychological distress among patients with lymphoma

	Model 1		Model 2		Model 3		Model 4	
	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>	β	<i>P</i>
Sociodemographic characteristics								
Age	-.12	.03	-.10	.02	-.12	.01	-.10	.03
Male sex	.001	.97	.03	.38	-.01	.80	.02	.65
Education [#]								
Low	-.002	.96	-.02	.69	.005	.91	-.01	.80
Middle (ref)								
High	-.14	.003	-.02	.58	-.07	.08	-.02	.61
Clinical characteristics								
Cancer type								
HL	.02	.99	.005	.90	.06	.14	.04	.29
NHL-HG (ref)								
NHL-LG	.06	.66	.02	.59	.02	.66	.02	.64
CLL	-.07	.11	-.04	.26	-.07	.07	-.04	.23
Comorbidity	.28	<.001	.19	<.001	.16	<.001	.14	<.001
Personality								
Neuroticism			.57	<.001			.43	<.001
Extraversion			-.04	.37			.03	.47
Openness			.04	.32			.04	.32
Agreeableness			-.02	.67			-.02	.71
Conscientiousness			-.05	.27			-.02	.63
Coping strategies								
Fighting Spirit					-.12	.01	-.004	.92
Anxious Preoccupation					.23	<.001	.12	.01
Helplessness/Hopelessness					.36	<.001	.30	<.001
Fatalism					.05	.30	.02	.69
Avoidance					-.10	.02	-.09	.01

Note. Bold type indicates statistical significance ($P<.05$).

Abbreviations: CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; NHL-HG, high-grade non-Hodgkin lymphoma; NHL-LG, low-grade non-Hodgkin lymphoma

[#] For education, low indicates none/primary school; medium, lower general secondary education/vocational training; and high, pre-university education/high-level vocational training/university.

DISCUSSION

The results of the present study indicated that besides comorbidity and age, both personality traits – in particular neuroticism – and coping strategies including helplessness/hopelessness, anxious preoccupation, and avoidance were significantly associated with psychological distress. The association between personality traits and psychological distress might be partially explained by anxious preoccupation.

The crude model – with sociodemographic and clinical characteristics – accounted for approximately 10% of the variance in psychological distress. Changes in the variance of the multivariate analysis suggested that the associations of sociodemographic and clinical characteristics were relatively small, whereas the associations of psychological factors, such as personality traits and coping strategies, were much greater. The model in which only personality traits were added to the crude model (model 2) accounted for approximately 43% of the variance, whereas the model in which only coping strategies were added to the crude model (model 3) accounted for approximately 39% of the variance. Finally, the fourth model, in which both personality traits and coping strategies were added together to the crude model, accounted for approximately 51% of the variance in psychological distress among patients with lymphoma.

When looking at sociodemographic and clinical characteristics, our results revealed that older patients experienced less psychological distress. Younger patients may experience more problems with adjustment to cancer, for example because of the stress of loss of fertility, child care, healthcare expenses, missed work because of their cancer treatment or side effects, and lack of financial or employment stability [33]. They might therefore be more vulnerable to experience psychological distress compared to older patients. In addition, patients who have more comorbidities experienced more psychological distress. The presence of comorbidities may interact with cancer to result in greater overall symptom and emotional burden.

Of the five personality traits, only neuroticism was statistically significantly associated with psychological distress, both in the model with only personality (model 2), as well as while controlling for coping strategies (model 4). Patients scoring high on neuroticism respond worse to stressful situations, experience more negative emotions, and are more likely to interpret situations as threatening and

minor frustration as hopelessly difficult [34]. The results of this study might suggest that the association between neuroticism and psychological distress may be partially explained by coping strategies. How patients cope with and adjust to cancer is reportedly associated with psychological distress. Indeed, our results showed that patients with passive coping strategies including helplessness/hopelessness or anxious preoccupation experienced more psychological distress, which is in line with studies among patients with different cancer types [18,20,21]. Passive coping refers to a sense of helplessness in dealing with the stressor and relying on others to resolve the problems [35]. On the other hand, fighting spirit has been consistently shown to be associated with less psychological distress [30,36,37], which seemed to be supported by the results in our third model, in which coping strategies were added separately. However, in the fourth model – with coping strategies and personality traits added together – fighting spirit was no longer statistically significantly associated with psychological distress. This seems to indicate that the association between fighting spirit and psychological distress may be fully explained by personality traits. Furthermore, avoidance was associated with less psychological distress. This is most likely due to the measurement of this coping style, as our measurement included a single item, whereas it has been suggested that this coping style should be measured in other ways [30,38].

The significance of coping strategies in relation to psychological distress was supported in our multivariable analysis, as it accounted for a large part of the variance in psychological distress. Unlike personality, coping strategies are considered to be changeable and could be targeted by interventions such as cognitive-behavioral therapy (CBT) [39]. Targeting the modification of dysfunctional thoughts and beliefs by cognitive restructuring is a common strategy in CBT [40]. In addition, CBT is frequently used to modify behavioral tendencies (e.g., rumination) of individuals scoring high on neuroticism [41].

This study had several limitations. Although information was available regarding the sociodemographic and clinical variables of nonrespondents, it remains unknown why they declined to participate. Comparing respondents and nonrespondents indicated differences in sex and primary treatment. This perhaps resulted in a small selection bias, although these characteristics were not significantly associated to psychological distress. In addition, the cross-sectional design of this study limits the ability to draw conclusions about the direction of the relationships between the study variables. Nevertheless, an important strength of

the study is its population-based sampling frame that facilitates the extrapolation of the results to a broad range of patients.

In conclusion, besides comorbidity and age, both personality traits – in particular neuroticism – and coping strategies helplessness/hopelessness, anxious preoccupation, and avoidance were significantly independently associated with psychological distress. Unlike personality, coping strategies are considered to be changeable and could be targeted by interventions such as cognitive-behavioral therapy (CBT).

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CHAPTER 3

MORE FREQUENT USE OF HEALTH CARE SERVICES AMONG DISTRESSED COMPARED WITH NON- DISTRESSED SURVIVORS OF LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA: RESULTS FROM THE POPULATION-BASED PROFILES-REGISTRY



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ABSTRACT

Background

Follow-up care for a growing population of survivors of lymphoma and chronic lymphocytic leukemia (CLL) together with the adverse effects these survivors may experience as a result of their cancer and treatment have led to more pressure being placed on health care services. The objectives of the current study were to: 1) compare the use of medical care services by survivors with that of a normative population; 2) evaluate the use of medical and psychosocial care services among distressed and non-distressed survivors; and 3) identify associated sociodemographic and clinical factors.

Methods

Survivors of lymphoma and CLL diagnosed between 1999 and 2012 were selected via the population-based Netherlands Cancer Registry and completed the Hospital Anxiety and Depression Questionnaire and questions on health care. Outcomes were compared to an age-matched and sex-matched normative population.

Results

A total of 1444 survivors responded (69%). Survivors of lymphoma and CLL contacted their general practitioner (3.8 vs 2.3, $P < .001$) and medical specialist (5.7 vs 1.6, $P < .001$) more often within the last year compared with a normative population. In addition, psychologically distressed survivors had even more medical contacts and received psychosocial care more often compared with non-distressed survivors. In addition to psychological distress, comorbidity, female sex, and older age were found to be associated with greater use of medical services, whereas younger age was associated with receiving psychosocial care.

Conclusions

Survivors of lymphoma and CLL, especially those who are psychologically distressed, report an increased use of health care services compared with a normative population. Further studies are needed to explore whether the use of widely applicable psychosocial interventions could reduce the frequency of medical contacts.

INTRODUCTION

Due to advances in the treatment of lymphoma and chronic lymphocytic leukemia (CLL), a rising incidence, and aging of the population, the number of patients who are living with a history of lymphoma or CLL continues to grow [1-6]. It is expected that in 2020 there will be approximately 40,000 patients in the Netherlands who either are cured of their lymphoma or are living with it as a chronic disease [7], an increase of approximately 65% compared with 2010.

As a result of the disease and its treatment, survivors of lymphoma and CLL are at risk of experiencing adverse physical and psychosocial effects such as second malignancies, neuropathy, persistent fatigue, cognitive impairment and psychological distress [8-14]. Therefore, regular follow-up care with monitoring of long-term and late adverse effects is extremely important [15]. Follow-up care for a growing population of survivors of lymphoma and CLL together with various adverse effects that these survivors may experience has resulted in more pressure being placed on health care services [16].

Psychological distress is a significant psychosocial issue for at least 25% of patients with lymphoma and CLL [12,17]. Psychological distress includes persistent levels of anxiety, depressive feelings and fears [18], and has a great impact on a patient's daily life. Some patients experience psychological distress as somatic symptoms such as headaches, sleeping problems and gastrointestinal complaints and seek medical help for these issues [18-22]. Research has suggested that patients with a background of psychological problems contact their general practitioner (GP) nearly twice as often for both psychological and somatic symptoms compared with patients without a background of psychological problems [23]. Evidence has demonstrated that integrated psychosocial care, which combines psychological screening and psychological interventions, is an effective means of treating psychological distress [18,24]. However, psychosocial care appears to be suboptimal [18,25]. Although patients with high levels of distress are more likely to receive psychosocial care [25,26], nearly one-half of distressed cancer survivors did not [26].

To our knowledge to date, the association between psychological distress and the use of medical and psychosocial care services rarely has been studied among survivors of lymphoma and CLL. Insights regarding this association will provide

information concerning the potential value of screening for psychological distress and the use of psychosocial interventions in the care of patients with lymphoma. Therefore, the objectives of the current study were to: 1) compare the use of medical care services by survivors with that of a normative population without cancer; 2) evaluate the use of medical and psychosocial care services among distressed and non-distressed survivors of lymphoma and CLL; and (3) identify factors that are associated with use of medical and psychosocial care services among survivors of lymphoma and CLL. We hypothesized that survivors of lymphoma and CLL overall have more medical contacts compared with a normative population without cancer, and that distressed survivors have more medical contacts and receive more psychosocial care than non-distressed survivors. Furthermore, based on the model of health services use of Andersen and Newman [27], we hypothesized that not only psychological distress, but also individual sociodemographic and clinical factors such as age, sex, education level, cancer type, treatment, and comorbidity, are associated with the use of health care.

METHODS AND DESIGN

Setting and population

Data from the Eindhoven area of the population-based Netherlands Cancer Registry were used to select patients with a diagnosis of Hodgkin lymphoma, non-Hodgkin lymphoma, and CLL between January 1999 and May 2012 [28]. Only patients aged ≥ 18 years at the time of diagnosis were included. Patients who had died, were in transition to terminal care, or who had serious cognitive impairment (i.e., dementia) were excluded. We used the term ‘survivors’ to include all living individuals who ever received a diagnosis of lymphoma or CLL [29].

Study measures

Two open questions were asked to assess the use of medical care services: 1) “How often did you contact a GP in the past 12 months?” and 2) “How often did you visit a medical specialist in the past 12 months?”. Patients also were asked whether they received care after their cancer treatment (no/yes). If they answered yes, patients could choose multiple additional care services from a list. Psychosocial care was defined as receiving care from a psychologist, social worker, oncological rehabilitation, or oncology nurse.

The 14-item Hospital Anxiety and Depression Scale (HADS) was used to assess psychological distress [30]. The scale consists of two 7-item joined subscales:

HADS-anxiety and HADS-depression. Items were scored on a 4-point scale. A sum score was obtained by adding all items, with a higher score indicating more distress [31]. Survivors with a HADS score ≥ 13 were categorized as “distressed” [32].

Comorbidity at the time of the survey was categorized according to the adapted Self-administered Comorbidity Questionnaire (SCQ) [33]. Patients were asked to identify comorbid conditions present within the past 12 months. Positive responses were summed to obtain a total score (range, 0-13).

Sociodemographic characteristics and clinical information were available from the Netherlands Cancer Registry, which routinely collects data on patient age and sex, date of cancer diagnosis, cancer type, and treatment. Information concerning marital status, educational level, and employment status was assessed in the questionnaire.

Data collection

Data were collected within Patient-Reported Outcomes Following Initial Treatment and Long-term Evaluation of Survivorship (PROFILES). Details regarding the data collection method have been described previously [34]. In May 2009, patients diagnosed between January 1999 and January 2009 were included in the study and received the first questionnaire. In November 2009, May 2011, May 2012, and May 2013 patients newly diagnosed up to June 1, 2012, subsequently were invited to participate and all completed a baseline questionnaire.

Normative population

Data regarding a normative population were obtained from CentERpanel, an online household panel that is representative for the Dutch population. The process of the annual collection of data, which was initiated in 2009 by our study group, has been described elsewhere [35]. Data collected in 2011 included the assessment of health care use. From this normative population, an age-matched and sex-matched selection was made to compare health care use with that of survivors of lymphoma and CLL. For matching, 14 strata were formed using sex and age (7 categories). Within each stratum, a maximum number of individuals from the reference cohort were randomly matched according to the strata frequency distribution of the patients. This resulted in 563 matched cancer-free individuals for the 1444 survivors of lymphoma and CLL who completed the baseline questionnaire.

Statistical Analyses

All comparisons of the number of medical contacts were adjusted for age, sex, and comorbidity. Continuous variables were compared using analysis of variance and categorical data were compared using chi-square tests. Multivariable logistic regression analyses were performed to investigate the independent association between sociodemographic, clinical and psychological variables and health care use. Statistical significance was set at $P < .05$ and analyses were performed using SAS statistical software (version 9.4; SAS Institute Inc, Cary, North Carolina).

RESULTS

Study sample

Of the 2101 survivors of lymphoma and CLL who were invited to participate, 1,444 completed the questionnaire (69%). Respondents on average were older compared with non-responding survivors with unverifiable addresses ($P < .01$). Furthermore, respondents were further from diagnosis compared with non-respondents ($P < .01$) (Table 1). The mean age at the time of completion of the questionnaire was 62.0 years, with a mean time since diagnosis of 3.3 years. Approximately 60% of respondents were male. Systemic therapy was the most frequent primary treatment (45%) (Table 1). Approximately 50% of survivors of lymphoma and CLL reported ≥ 1 comorbid conditions, with the most common being arthritis and hypertension. Approximately 26% of the survivors reported being psychologically distressed. The mean age of the age-matched and sex-matched normative population at the time of completion of the questionnaire was 62.0 years. Approximately 61% were male. Nearly 6 of every 10 respondents (59%) reported ≥ 1 comorbid conditions, with the most common being hypertension and arthritis (Table 1). Compared with the survivors, the normative population more often had a higher educational level (20% vs 41%; $P \leq .001$) and less often had a partner (77% vs 70%; $P = .001$).

Use of medical and psychosocial care services

Approximately 89% of all survivors of lymphoma and CLL reported having contacted a GP at least once within the last 12 months, with 4 contacts on average.

Table 1. Patient characteristics of respondents (N=1,444), nonrespondents, and patients with unverifiable addresses, and of an age- and sex-matched normative population (n=563).

	Respondents N=1,444 n(%)	Non-respondents N=381 n(%)	Patients with unverifiable addresses N=276 n(%)	Normative population N=563
Characteristics				
Sex				
Male	870 (60)	223 (59)	159 (58)	341 (61)
Female	574 (40)	158 (41)	117 (42)	222 (39)
Age: mean (SD)	62.0 (14.5)	61.9 (16.6)	55.9 (16.8)	62.0 (14.6)
Years since diagnosis: mean (SD)	3.3 (2.5)	2.6 (2.8)	3.4 (2.9)	
Cancer type				
HL	210 (15)	61 (16)	64 (23)	
NHL-HG	554 (38)	116 (30)	92 (33)	
NHL-LG	454 (31)	126 (33)	78 (28)	
CLL	226 (16)	78 (21)	42 (15)	
Primary treatment				
Active surveillance	340 (24)	125 (33)	78 (28)	
Systemic therapy	644 (45)	148 (39)	124 (45)	
Radiotherapy	97 (7)	25 (6)	16 (6)	
Chemoradiotherapy	248 (17)	64 (17)	52 (19)	
Unknown	115 (8)	19 (5)	6 (2)	
Self-reported comorbidity				
No comorbidity	652 (45)			228 (41)
1 comorbidity	371 (26)			177 (31)
≥ 2 comorbidity	346 (24)			158 (28)
Missing data	75 (5)			0 (0)
Most frequent comorbidities				
Hypertension	223 (16)			173 (31)
Arthritis	252 (18)			118 (21)
Education [#]				
Low	286 (21)			22 (4)
Medium	804 (59)			313 (56)
High	273 (20)			228 (41)
Partner (yes)	1096 (77)			395 (70)

Note. Bold type indicates statistically significantly different from respondents ($P < .05$).

Abbreviations: CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; NHL-HG, high-grade non-Hodgkin lymphoma; NHL-LG, low-grade non-Hodgkin lymphoma; SD, standard deviation.

[#] For education, low indicates none/primary school; medium, lower general secondary education/vocational training; and high pre-university education/high level vocational training/university.

Compared with an age-matched and sex-matched normative population, survivors of lymphoma and CLL contacted their GP more often (3.8 vs 2.3 times within the last 12 months, respectively; $P < .001$). No differences in the number of GP contacts between male and female survivors were observed. The average number of GP contacts was highest within the first year after diagnosis compared with the other time periods ($P = .002$) (Figure 1A). Distressed survivors contacted their GP more often than non-distressed survivors (5.2 vs 3.3 contacts, respectively; $P < .001$). Approximately 98% of all survivors of lymphoma and CLL reported having contacted a medical specialist at least once within the last 12 months. Survivors contacted their medical specialist more often compared with an age-matched and sex-matched normative population (5.7 vs 1.6 contacts; $P < .001$). Male survivors contacted their medical specialist more often compared to female survivors (6.0 vs 5.1 contacts, $P = .004$). Survivors of lymphoma and CLL were found to have contacted their medical specialist most often within the first year after diagnosis, with on average 7 contacts. Between 2 to 4 years, 5 to 7 years and 8 to 10 years after diagnosis, the average number of contacts with the medical specialist decreased to 5.7 contacts, 4.2 contacts, and 4.1 contacts, respectively. At all timepoints, distressed survivors contacted their medical specialist more often than survivors who were not distressed (Figure 1B).

Approximately 22% of all survivors of lymphoma and CLL reported that they received psychosocial care after treatment. The percentage of distressed survivors who received psychosocial care was significantly higher compared with survivors without psychological distress (32% vs 19%; $P < .001$). Survivors aged ≤ 35 years (adolescents and young adults) received psychosocial care more often compared with survivors > 35 years (42% vs 20%, $P < .001$), although they reported being distressed somewhat less often compared with older survivors (Figure 2).

Factors associated with the use of psychosocial and medical care services

Multivariable logistic regression analyses showed that survivors who received psychosocial care after treatment were more likely to be psychologically distressed. Receiving psychosocial care was also found to be associated with being female and of a younger age at the time of questionnaire completion. Furthermore, receiving psychosocial care was associated with having multiple comorbidities and treatment with systemic therapy (Table 2).

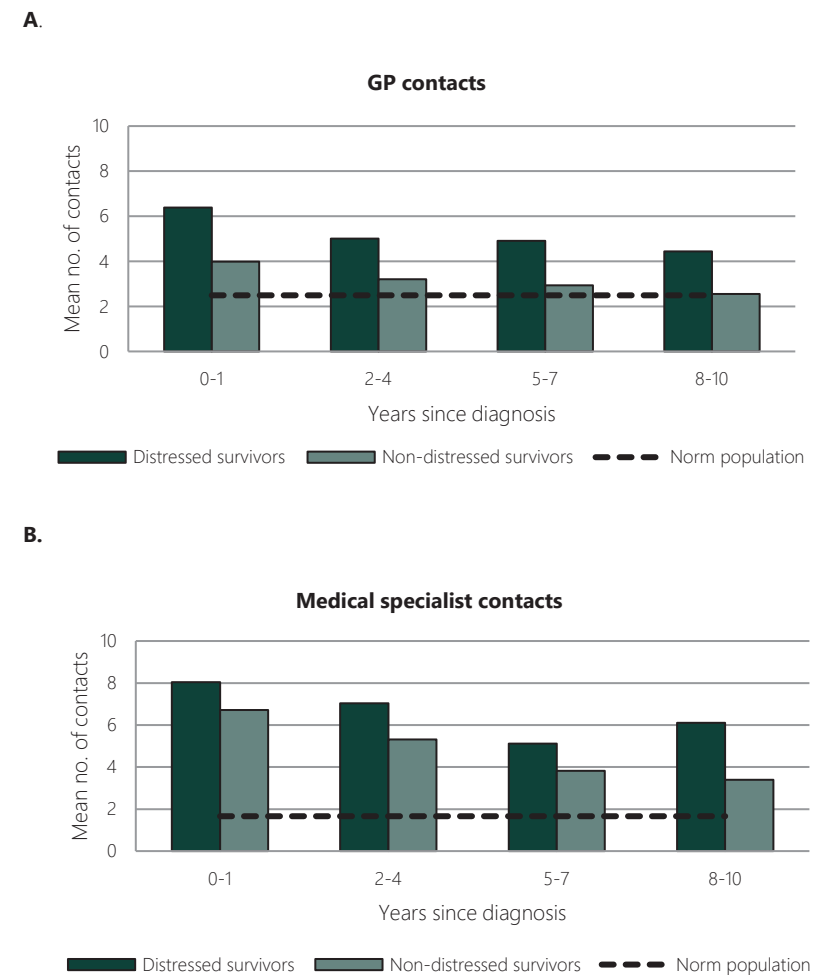


Figure 1. Differences between number of GP (A) and medical specialist (B) contacts in the last 12 months of distressed (N=345) and non-distressed (N=971) lymphoma and CLL survivors according to years since diagnosis, compared to an age- and sex-matched normative population (N=563).

Survivors of lymphoma and CLL who visited a GP ≥ 3 times within the last 12 months (median split) were more likely to have psychological distress. In addition, visiting a GP ≥ 3 times was found to be associated with being female, of older age, and reporting ≥ 1 comorbid conditions. Furthermore, visiting a GP ≥ 3 times was associated with a more recent diagnosis.

Survivors who visited their medical specialist ≥ 4 times within the last 12 months (median split) were found to be more likely to have psychological distress. Visiting a medical specialist ≥ 4 times also was associated with a more recent diagnosis and reporting more comorbid conditions. In addition, survivors who visited their medical specialist ≥ 4 times were less likely to be diagnosed with Hodgkin lymphoma.

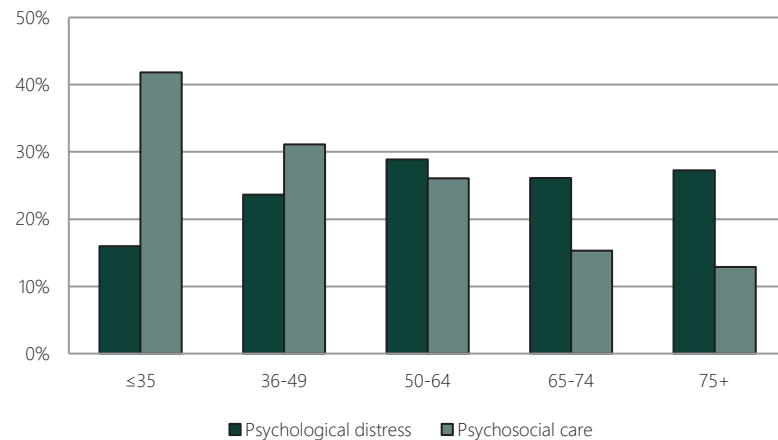


Figure 2. Percentages of lymphoma and CLL survivors who reported to be psychologically distressed and percentages survivors who reported they received psychosocial care after treatment according to age categories.

DISCUSSION

Survivors of lymphoma and CLL contacted both a GP and medical specialist more frequently compared with an age-matched and sex-matched normative population without cancer, which is in keeping with our hypothesis. Survivors who reported being psychologically distressed contacted a GP and medical specialist even more

Table 2. ORs with 95% CIs of the multivariable logistic regression model evaluating psychosocial, sociodemographic, and clinical variables for receipt of psychosocial care after treatment and contact with GP and medical specialist within the last 12 months (median split).

	Receiving psychosocial care (N=282) OR (95% CI)	Contacting the GP ≥ 3 times (N=691) OR (95% CI)	Contacting the medical specialist ≥ 4 times (N=783) OR (95% CI)
Psychological variables			
Psychological distress (yes)	2.19 (1.62-2.98)	2.06 (1.57-2.69)	1.80 (1.36-2.38)
Sociodemographic variables			
Age	0.97 (0.96-0.98)	1.02 (1.01-1.02)	1.00 (0.99-1.01)
Sex (female)	2.00 (1.51-2.65)	1.41 (1.12-1.78)	1.00 (0.78-1.26)
Partner (yes)	1.19 (0.85-1.67)	0.83 (0.63-1.08)	1.16 (0.88-1.53)
Education level			
Low	1.32 (0.93-1.88)	0.83 (0.63-1.11)	1.05 (0.78-1.42)
Middle (ref.)	-	-	-
High	1.02 (0.70-1.47)	1.07 (0.80-1.44)	1.06 (0.78-1.43)
Clinical variables			
Time since diagnosis	0.96 (0.91-1.02)	0.93 (0.89-0.98)	0.79 (0.75-0.83)
Tumor type			
HL	0.93 (0.60-1.44)	1.16 (0.79-1.72)	0.67 (0.45-0.99)
NHL-HG (ref.)	-	-	-
NHL-LG	0.73 (0.50-1.07)	1.09 (0.80-1.50)	1.21 (0.88-1.68)
CLL	0.43 (0.23-0.79)	0.83 (0.54-1.28)	0.97 (0.62-1.51)
Treatment			
Active surveillance (yes)	0.99 (0.50-1.97)	1.31 (0.80-2.14)	1.36 (0.76-2.09)
Systemic therapy (yes)	1.81 (1.00-3.27)	1.25 (0.80-1.50)	1.61 (1.03-2.54)
Radiotherapy (yes)	0.84 (0.59-1.21)	0.91 (0.67-1.24)	0.97 (0.71-1.33)
Comorbidities			
No comorbidities	-	-	-
1 comorbidity	0.89 (0.62-1.27)	1.14 (0.87-1.51)	1.27 (0.95-1.70)
≥ 2 comorbidities	1.49 (1.03-2.15)	2.36 (1.73-3.21)	1.92 (1.40-2.65)

Note. Bold type indicates statistical significance ($P < .05$).

Abbreviations: 95% CI, 95% confidence interval; CLL, chronic lymphocytic leukemia; GP, general practitioner; HL, Hodgkin lymphoma; NHL-HG, high-grade non-Hodgkin lymphoma; NHL-LG, low-grade non-Hodgkin lymphoma; OR, odds ratio.

often. In addition to psychological distress, comorbidity, female sex and older age, were found to be associated with more frequent medical contacts, whereas younger age was associated with receiving psychosocial care.

Previous findings of our group demonstrated that the frequency of contacts with both a GP and medical specialist was higher among long-term cancer survivors compared to a normative population [36]. These results also correspond with findings from studies among specific cancer groups that reported the more frequent use of health services for cancer survivors [37-40]. The difference between cancer survivors and the normative population in the number of contacts with a medical specialist persisted, even 10 years after diagnosis. However, the number of GP contacts normalized over time, which is in keeping with previous studies [36,39]. The higher number of contacts with a medical specialist observed among survivors of lymphoma and CLL can be explained by follow-up appointments as advised in the Dutch guidelines for the treatment of patients with lymphoma (available at: <http://www.hovon.nl/>).

The current study findings that survivors who were psychologically distressed had more frequent medical contacts compared to non-distressed survivors correspond with previous results demonstrating that patients with cancer and psychological problems contacted a health care professional more frequently than patients without psychological problems [21,23,41]. Psychological problems that arise from or are aggravated by cancer might cause additional suffering resulting in more frequent medical contacts. Adequate recognition and treatment of psychological distress might help in reducing medical contacts among distressed survivors [18]. Psychosocial care should be considered to be an integral and standardized part of cancer care [42]. However, some healthcare professionals believe that psychosocial care is too costly to be part of standard cancer care [43], although to the best of our knowledge one study found that minimal psychosocial interventions may increase patient's quality of life and reduce overall health care expenditures [43].

Many survivors are faced with psychosocial issues, and they may not receive the support they need. It is important to learn what support might benefit survivors of lymphoma and CLL [45]. The results of the current study demonstrated that patients who are psychologically distressed more often reported having received psychosocial care after treatment compared with non-distressed survivors, which is positive. Conversely, fewer than 1 in every 3 distressed survivors of lymphoma

and CLL received psychosocial care. Therefore, although information is lacking regarding the percentage of patients who refused psychosocial care when offered, potentially many more survivors could have benefitted from it. It is possible that survivors are unwilling to ask their GP or medical specialist for help with psychosocial concerns because they believe it is not the physician's role to help with such problems [46]. Moreover, survivors may normalize or somatize their psychological distress, and consequently psychological distress may be underrecognized and undertreated [47]. Screening tools for psychological distress can be useful for its better recognition. In addition, providing feedback to survivors on their patient-reported outcomes can help them to monitor their functioning and symptoms and may help to empower them to discuss their symptoms with a GP or medical specialist [48].

Because survivors with psychological distress may be unwilling to visit a mental health care professional, it is important to offer help in a way that is acceptable to them, without increasing the overall use of resources. In addition, the treatment of psychological distress has to be widely applicable, since the number of distressed survivors continues to grow [7]. In the current study, approximately 22% of survivors of lymphoma and CLL reported that they received psychosocial care after treatment. This does not correspond with results of an American study by Hewitt and Rowland that reported that survivors of various cancer types contacted a mental health provider in only 7% of cases [49]. However, this could be due to different definitions. Hewitt and Rowland defined mental health care as talking to a psychiatrist, psychologist, psychiatric nurse, or social worker [49]. In the current study, we also included oncology nurses as providers of psychosocial care because they appeared to be the ones who detect psychosocial concerns in patients [50]. Furthermore, previous studies have indicated that the use of psychosocial care services among cancer survivors was somewhat higher compared with in a population without cancer [49,51]. We could not relate these findings to the current study data because data regarding psychosocial care in the normative population were missing.

According to the Andersen and Newman model of health services use [27], not only psychological distress is associated with the use of health care services, but also individual sociodemographic and clinical factors. In the current study, comorbidity and a more recent diagnosis were found to be associated with more medical contacts. This corresponds to the findings of a previous Dutch study that

also demonstrated a strong association between comorbidity and the volume and variety of health care services that are used [52]. It also was reported previously that the frequency of medical visits is highest within the first year after diagnosis [38,39].

The use of psychosocial care services is greater among younger survivors, females, those with ≥ 2 comorbid conditions, and those who received systemic therapy. Raphael et al found that younger age was an indicator of increased distress [45], which might explain the greater use of psychosocial care services noted among younger survivors herein. Furthermore, the results of the current study correspond to those of a study that observed a greater use of psychosocial care services among younger survivors, those with more comorbid conditions, and those with psychological problems [49]. Another study also reported that older age was associated with lower likelihood of being referred for psychosocial care regardless of the level of psychological distress and provided some possible explanations [53]. It could be that physicians tend to perceive older survivors as less likely to need or to derive benefit from psychosocial care, or that physicians may underestimate the needs of older cancer survivors. More attention should be paid to older survivors with psychological problems because psychosocial care use in this group appears to be suboptimal.

The current study has a few limitations. Although information was available regarding the sociodemographic and clinical variables of the non-respondents and patients with unverifiable addresses, it remains unknown why non-respondents declined to participate in the study. In addition, the cross-sectional design of the current study limited the determination of causal associations between the study variables. The strengths of the study are its population-based sampling frame, the high response rate, and the large range in time since diagnosis. This facilitates extrapolation of the results to a broad range of survivors of lymphoma.

Survivors of lymphoma and CLL, especially those who report psychological distress, demonstrate an increased use of health care services compared with a normative population without cancer. Further studies are needed to explore whether the use of widely applicable psychosocial interventions could reduce the frequency of medical contacts among distressed survivors and improve their quality of life.

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PART II

INTERVENTION: LYMPHOMA INTERVENTION [LIVE] TRIAL



CHAPTER 4

“AM I NORMAL?” THE WISHES OF PATIENTS WITH LYMPHOMA TO COMPARE THEIR PATIENT-REPORTED OUTCOMES WITH THOSE OF THEIR PEERS



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ABSTRACT

Background

Providing feedback to patients on their patient-reported outcomes (PROs) can help patients in monitoring their functioning and symptoms and may help empower them. The objective of this study was to investigate whether patients with lymphoma wished to receive PRO feedback, including the option to compare their scores with those of their peers, and how this feedback was evaluated.

Methods

We invited 64 patients participating in a lymphoma cohort who were eligible for a follow-up questionnaire and gave them the option to receive PRO feedback. Patients completed questions about health-related quality of life (HRQoL) and symptoms. PRO feedback was provided via bar charts.

Results

Of the 64 invited patients, 45 participated (response rate 70%) and 36 of those (80%) wished to receive PRO feedback. The vast majority (34/36, 94%) compared their scores with those of a lymphoma reference cohort, and 64% (23/36) compared their score with those of a normative population without cancer. All patients wished to receive feedback on their HRQoL, and 29 (81%) to 33 (92%) wanted feedback on their functioning, fatigue, neuropathy, anxiety, and depressive symptoms. Of the 36 participants wishing to receive PRO feedback, 35 (97%) viewed it as being useful, with reassurance and knowledge about their own functioning in relation to what is "normal" being the most frequently mentioned reasons.

Conclusions

A high number of patients with lymphoma wished to receive PRO feedback. Patients reported the comparison of their scores versus a lymphoma reference cohort as most valuable. Further research should investigate whether PRO feedback could increase empowerment and possibly improve HRQoL.

INTRODUCTION

Patients with lymphoma are at risk of experiencing adverse physical and psychosocial effects of their cancer and its treatment such as fatigue, cognitive problems, anxiety and depression [1-4]. Management of these symptoms is often complex, and patients do not always know if their symptoms are common and are caused by their disease or treatment [5].

Patient-reported outcomes (PROs) provide information about the subjective well-being of patients [6]. PROs are standardized questionnaires that are completed by patients and measure a broad range of health related constructs including symptom assessment, and evaluation of function and health-related quality of life (HRQoL) [6,7]. Regular screening of physical and psychosocial symptoms by use of PROs could increase awareness and recognition of symptoms and can contribute to managing them [7-11]. PROs are furthermore useful in identifying issues that are most bothersome to patients [12] and can enable patients and their health professionals to jointly identify goals and priorities for future health and healthcare [13].

The use of PROs in clinical practice has increased in the past years [14]. Studies have shown that feedback from PROs can lead to improved symptom detection and more dialogue about problems between patients and physicians [7-11,15-19]. However, some studies reported no benefit from PRO feedback in the number of patients referred to psychosocial care or in clinical actions taken [16,18,20,21]. In most of these studies, PRO feedback was provided to a health-care provider (e.g., a physician or nurse). A limitation of providing feedback to health-care providers might be that they may not always see the urgency of a specific problem and forget to discuss it. Some health-care providers were found to downgrade or miss symptoms such as fatigue and pain [22-24]. Physicians are furthermore most interested in PRO scores that indicate worsening symptoms, whereas patients prefer to see both worsened and improved scores [25]. The provision of PRO feedback to patients themselves might therefore be another and maybe better solution. Patients can then monitor all symptoms and initiate discussion on symptoms that bother them the most. Patients are moreover best placed to interpret their own subjective PROs within the complex context of their experience [26]. Patients also report that the inclusion of PROs in their clinical follow-up made them feel more in control of their care [27].

Comparison of a patients' outcomes with those of patients with the same age and sex may help to reassure that what he or she is experiencing is "normal" or may empower the patient to take action. The aim of this study was therefore to investigate if patients with lymphoma wished to receive PRO feedback including the option to compare their scores with those of their peers. We furthermore investigated how patients evaluated the PRO feedback. We hypothesized that around two-third of patients would like to receive feedback, as research shows that about 62% of patients with lymphoma wants to be fully informed about their illness [28].

METHODS

Participants and Setting

This study was part of the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) lymphoma registry [29]. This is a longitudinal population-based observational study whereby patients with Hodgkin lymphoma and non-Hodgkin lymphoma as diagnosed by the Netherlands Cancer Registry in 9 hospitals in the Netherlands complete questionnaires either on paper or online for research purposes. The first patients were included in 2009, and each year patient with a new diagnosis between 9 months and 1.5 year after diagnosis are invited for questionnaire completion. Patients diagnosed less than 3 years ago are invited to complete a questionnaire every 6 months and patients diagnosed more than 3 years ago are invited to complete a questionnaire once a year. In January 2016, we invited patients with a diagnosis made less than 3 years previously and who were eligible for a follow-up questionnaire to participate in this study. Patients who participated online were given an option to receive PRO feedback.

Questionnaire

The questionnaire completed by patients consisted of the following: We used the Dutch validated version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) to assess HRQoL [30]. We added the symptom tingling in hands or feet, as it appeared from the literature and focus groups that this might be a prevalent symptom among patients with lymphoma. Answer categories range from 0 (not at all) to 3 (very much). After linear transformation, all scales and single item measures range from 0-100 [30].

We used the Hospital Anxiety and Depression Scale (HADS) [31] to measure anxiety and depressive symptoms in separate subscales of 7 items each. Answers range from 0 to 3 and we calculated scores by addition of the items, with a higher score meaning more anxiety or depressive symptoms [31].

We also assessed patients' marital status, educational level, and comorbidity in the questionnaire and categorized comorbidity at the time of survey according to the adapted Self-administered Comorbidity Questionnaire (SCQ) [32]. We obtained clinical characteristics (i.e., sex, age, type of lymphoma, date of diagnosis, stage at diagnosis, and primary treatment) from the Netherlands Cancer Registry.

Procedure

Eligible patients received a letter or email with an invitation to complete the questionnaire. Patients were informed that when they completed the questionnaire online they would have the possibility to receive PRO feedback. After completing the online questionnaire patients received the following question: "Would you like to receive feedback on your answers to the questionnaire?" If patients answered yes, we asked them on what topics they would like to receive feedback. They could choose from general quality of life, physical functioning, emotional functioning, cognitive functioning, social functioning, fatigue (based on their scores on the EORTC QLQ-C30), tingling hands or feet (based on their score on the question with respect to tingling hands or feet), anxiety or worries, and depressive symptoms (based on their scores on the HADS), or all topics. Subsequently, patients were asked whether they only wanted to see their own scores, and whether they would like to compare their scores with those of other patients with lymphoma or with those of people without cancer, or both. After that, the feedback was generated automatically by computer and was directly shown on the patients' screens. If patients indicated that they did not wish to receive feedback, the feedback was not generated. Patients who viewed their PRO feedback received evaluation questions afterward.

Patient-reported outcome feedback

We based the content and layout of the PRO feedback on examples in the literature [33,34] and on lymphoma patients' preferences reported in an earlier survey on how to provide PRO feedback. In this survey, we presented respondents with 2 examples of PRO feedback: in a bar chart and in a line chart. Respondents had a slight preference for the bar chart. Several examples of PRO feedback

presented as bar charts were subsequently evaluated by 12 persons (mean age 55 years; 8/12, 67% female; 5/12, 42% low level of educational attainment). We asked them which colorway they preferred: traffic light colors, pastel colors, or PROFILES house-style colors. Here respondents preferred traffic light colors. Patients furthermore preferred a dotted line over a solid line to indicate “your score” in the bar chart. In this study, we therefore provided the PRO feedback via bar charts in traffic light colors with a dotted line to indicate a patient’s score.

If patients wanted to view their own scores, a single bar chart was shown for each PRO feedback topic. If patients had indicated that they wanted to compare their scores with those of a lymphoma reference cohort or a normative population without cancer, both of the same sex and age, either 1 or 2 traffic light-colored bar charts were shown (see Figure 1 for an example).

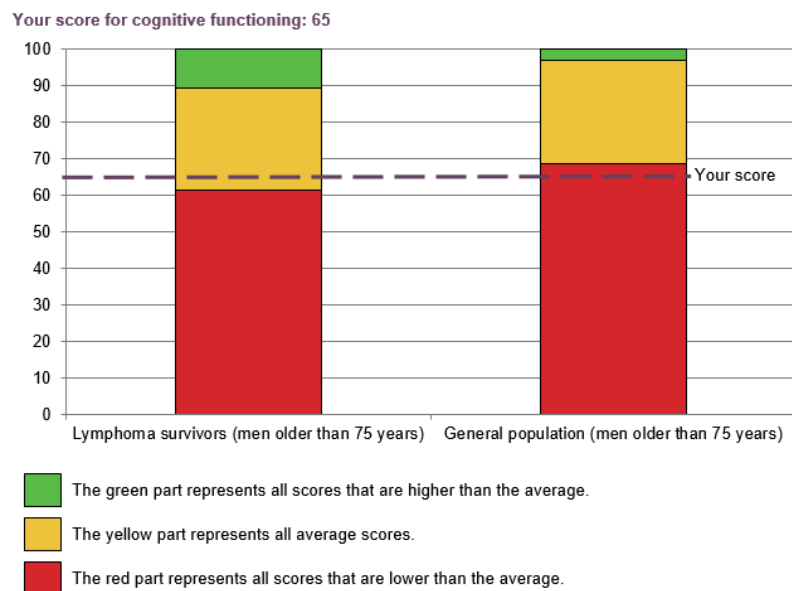


Figure 1. The example of cognitive functioning as part of patient-reported outcome feedback provided to participants

Age was grouped into categories of 10-15 years, ranging from 18-30 years to older than 75 years. The colors of the bar charts were related to clinically relevant mean differences of the evidence-based guidelines of the EORTC QLQ-C30 [35]. A score that differed by less than the minimal medium clinically relevant difference from the mean score was considered average (amber). A score that differed as much or more than the minimal medium clinically relevant difference from the mean score was considered above average (green) or below average (red). We interpreted anxiety and depressive symptoms according to the published scoring algorithm with 0-7 indicating no or mild symptoms (green), 8-10 indicating moderate symptoms (amber), and ≥ 11 indicating severe symptoms (red) [31]. We added a detailed description of the meaning of the colors (traffic light model) and how to interpret the scores to assist patients in understanding the graphs (Textbox 1 shows cognitive functioning as an example). Patients with a symptom score in the red part of the bar chart were advised to contact their general practitioner.

Textbox 1. Description of cognitive functioning (concentration and memory) as an example for interpreting the bar charts.

Cognitive functioning is a component of quality of life. Cognitive functioning, for example, refers to the extent to which one can concentrate or can remember things.

On the cognitive function component, you can score between 0 and 100. The higher the score, and the closer the score is to 100, the higher you will experience your quality of life in this part. Your score is shown in the graph by the purple line.

Your score in comparison with *other lymphoma survivors*:

- Your score falls in the yellow part. This indicates that your score is similar to that of other people with lymphoma with your age and sex.

Your score in comparison with *the general population*:

- Your score falls in the red part. This indicates that your score is lower than the average score of people from the general population with your age and sex.

People with lymphoma score generally lower on cognitive functioning than the general population. Memory and concentration problems are common among people with cancer. Some also experience difficulty working under time pressure or doing different things at the same time. Others must make a greater mental effort to reach the same results compared with the period they were living without cancer [36].

Lymphoma reference cohort and normative population

We based the mean scores of the lymphoma reference cohort on data from our previous population-based study on HRQoL among 856 patients with lymphoma³⁷. We extracted the mean scores of an age- and sex-matched normative population of 1859 individuals without cancer from a reference cohort from the general Dutch population (CentERpanel) [38].

Evaluation questions

The evaluation questions consisted of 5 open questions with respect to the usefulness, accessibility, clarity, and missing features of the feedback. Patients were furthermore asked whether they would have liked to see different features in the PRO feedback. Based on the average scores on HRQoL and anxiety and depressive symptoms, we evaluated whether both patients with or patients without symptoms wanted to receive PRO feedback.

Statistical analysis

Analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina). $P < .05$ were considered statistically significant. We determined clinically relevant differences using the evidence-based guidelines of the EORTC QLQ-C30 [35]. We used Fischer exact tests or t-tests to compare differences in sociodemographic and clinical characteristics between respondents and nonrespondents and between patients who wished and those who did not wish to receive PRO feedback.

To evaluate whether scores were on average comparable with those of a lymphoma reference cohort, we compared patients' mean EORTC QLQ-C30 and HADS scores with mean scores of a lymphoma reference group using analysis of covariance with age and sex as covariates. We also compared patients' mean scores, in the same way, to those of a normative population. The numbers of patients scoring in the red, amber or green part were computed to evaluate whether both patients with and without symptoms wished to receive PRO feedback.

RESULTS

Participants

Of the 64 patients who were invited, 45 participated (response rate 70%). Their mean age was 60.7 years and 58% (N=26) were male. Mean time since diagnosis was 2.8 years, and 82% (N=37) had a diagnosis of non-Hodgkin lymphoma. Most patients underwent systemic therapy or radiotherapy, or both. Sociodemographic and clinical characteristics did not statistically differ between respondents and non-respondents (Table 1).

Evaluation of patient-reported outcome feedback

A total of 36 (80%) participants wished to receive PRO feedback, with similar percentages for males and females (21/26, 81% vs 15/19, 79%; $P = .29$) and for patients under and above 65 years of age (20/26, 77% vs 16/19, 84%; $P = .25$). Patients who wished to receive PRO feedback had scores on overall HRQoL ($P = .14$) and anxiety ($P = .47$) and depressive symptoms ($P = .25$) similar to those of patients who did not wish to receive feedback.

The vast majority (34/36, 94%) compared their scores with those of the lymphoma reference cohort and 64% (23/36) compared their scores with those of the normative population without cancer, whereas 6% (2/36) viewed only their own scores. All patients viewed the PRO feedback on their overall HRQoL, and 81% to 92% viewed feedback on their physical, emotional, social, and cognitive functioning, fatigue, tingling in hands or feet, anxiety, and depressive symptoms (Table 2).

Almost all patients (except 1) viewed the PRO feedback as being useful, with reassurance and knowledge about their own functioning in relation to what is "normal" being the most frequently mentioned reasons. The option to compare their scores with those of a lymphoma reference cohort of the same age and sex was reported as most valuable:

"This score shows what I actually did expect of my quality of life. The comparison with other patients with lymphoma feels right. I mean, I do not score that different and that again reassures me." - Female patient with non-Hodgkin lymphoma, 69 years old

Table 1. Sociodemographic and clinical characteristics of respondents and nonrespondents.

	Respondents (N=45)	Nonrespondents (N=19)	<i>P</i>
	n(%)	n(%)	
Sociodemographic characteristics			
Sex			.27
Male	26 (58)	14 (74)	
Female	19 (42)	5 (26)	
Age: mean (SD)	60.7 (13.6)	63.8 (14.7)	.28
<65	26 (58)	8 (42)	
≥65	19 (42)	11 (58)	
Marital status			
Partner	34 (76)	N/A	
No partner	11 (24)	N/A	
Education			
Secondary	8 (18)	N/A	
Intermediate vocational	17 (38)	N/A	
High vocational or university	20 (44)	N/A	
Clinical characteristics			
Type of lymphoma			.26
Hodgkin	8 (18)	1 (5)	
Non-Hodgkin	37 (82)	18 (95)	
Years since diagnosis (mean SD)	2.8 (0.8)	2.6 (0.7)	.84
Cancer stage at diagnosis			.50
I	8 (22)	4 (29)	
II	10 (28)	2 (14)	
III	5 (14)	4 (29)	
IV	13 (36)	4 (29)	
Primary treatment			.11
Radiotherapy only	2 (4)	1 (5)	
Systemic therapy (e.g., chemotherapy, immunotherapy)	19 (42)	8 (42)	
Systemic therapy plus radiotherapy	13 (29)	1 (5)	
Active surveillance	11 (25)	9 (47)	
Self-reported comorbidities: mean (SD)	1.3 (1.3)	N/A	
Most frequent comorbidities			
Arthritis	10 (22)	N/A	
Heart problems	8 (18)	N/A	
High blood pressure	8 (18)	N/A	

Note: N/A: not available.

Abbreviations: SD: standard deviation

Table 2. Overview of PRO feedback topics with number and percentage of interested patients.

Topic	n	%
EORTC QLQ-C30		
General health-related quality of life	36	100
Physical functioning	33	92
Emotional functioning	32	89
Social functioning	33	92
Cognitive functioning	31	86
Fatigue	31	86
Neuropathy	29	81
HADS		
Anxiety	30	83
Depressive symptoms	30	83

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HADS, Hospital Anxiety and Depression Scale.

"It is interesting to see how I stand compared to other patients with lymphoma and the general population." - Male patient with Hodgkin lymphoma, 22 years old

"The PRO feedback clarifies if symptoms are shared by others or not." - Female patient with Hodgkin lymphoma, 37 years old

Some patients reported that the PRO feedback was useful, since it provided new insights for discussion with their physician. No reason was provided by the patient who indicated that the PRO feedback was not useful.

A total of 2 patients reported that the PRO feedback had missing features; 1 patient advised us to provide more information on how to limit symptom burden or improve symptoms; and 1 patient suggested that it would be good to advise patients to go to their general practitioner when experiencing problems:

"Not everyone has good and regular contact with their doctors, so it would be helpful to advise a patient to contact a doctor when he or she reports problems." - Female patient with non-Hodgkin lymphoma, 54 years old

The comment regarding contacting a general practitioner was already covered for the symptoms in the current PRO feedback for patients scoring in the red part of the bar chart, but not for the functioning scales.

With respect to the clarity of the PRO feedback, 1 patient missed the possibility to go back to his answers in the questionnaire to verify that the PRO feedback was correct, because his score on neuropathy was very low according to the PRO feedback, but not in his experience. Furthermore, 1 patient had trouble understanding the colors of the PRO feedback at first, but after looking for a second time it became clear. With respect to things that should be different, some patients indicated that they wished to save their scores for future comparison purposes and to keep track of their scores:

"Is it possible to download my PRO feedback, so I can compare my scores over time and determine potential deterioration?" - Male patient with non-Hodgkin lymphoma, 84 years old

Health-related quality of life, anxiety, and depression scores

Mean scores on HRQoL, anxiety, and depressive symptoms of participating patients in this study were not different from the mean scores of the lymphoma reference cohort (Table 3). Compared with the normative population, patients had on average statistically and clinically relevant lower scores on physical, cognitive, and social functioning and higher scores on fatigue (all $P < .05$).

With respect to patients' individual scores on HRQoL, 33% (N=15) of patients reported scores that were lower than the average of the lymphoma reference cohort (red part of bar chart) and 31% (N=14) reported scores higher than the average range of scores (green part of bar chart; Table 4). Compared with the normative population, 33% (N=15) of patients reported scores that were lower than the average and 20% (N=9) reported scores higher than the average of the normative population. The percentages were similar for the other scales (data not shown).

DISCUSSION

Principal findings

Of the participating patients with lymphoma, 80% wished to receive PRO feedback, which was higher than the two-thirds of patients that we hypothesized. A similar

Table 3. EORTC QLQ-C30 plus tingling hands or feet and HADS scores of patients, a lymphoma reference cohort, and a normative population, and clinically important differences between these groups.

	Patients (N=45)	Lymphoma reference cohort (N=876)	Normative population (N=1852)	Patients vs lymphoma cohort		Patients vs normative population	
				P	Clinical relevance	P	Clinical relevance
EORTC QLQ-C30: mean (SD)							
Physical functioning	83.1 (20)	79.4 (21)	90.5 (15)	.21	No	<.001	Small
Emotional functioning	82.2 (21)	82.8 (21)	87.9 (17)	.86	No	.02	Trivial
Cognitive functioning	80.4 (22)	82.4 (23)	92.5 (14)	.57	No	<.001	Medium
Social functioning	85.9 (25)	84.4 (24)	93.6 (16)	.68	No	.002	Small
Global health status/QoL	73.3 (20)	74.0 (20)	77.6 (17)	.82	No	.10	Small
Fatigue	24.7 (23)	28.9 (27)	17.0 (20)	.30	No	.01	Small
Tingling hands or feet	18.5 (28)	17.0 (29)	N/A ^e	.73	No	N/A	N/A
HADS: mean (SD)							
Anxiety	4.0 (3.8)	4.4 (3.8)	3.6 (3.2)	.51	No	.34	No
Depressive symptoms	3.9 (3.8)	4.7 (3.8)	3.6 (3.2)	.17	No	.54	No

Note: N/A: not available
 Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HADS: Hospital Anxiety and Depression Scale; QoL, quality of life.

Table 4. Number and percentages of patients scoring lower than average, average, or higher than average compared with the lymphoma reference cohort and normative population on EORTC QLQ-C30 global health status/quality of life.

	Compared with lymphoma reference cohort	Compared with normative population
Lower than average (red)	15 (33)	15 (33)
Average (amber)	16 (36)	21 (47)
Higher than average (green)	14 (31)	9 (20)

Abbreviations: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

percentage of men and women and patients younger and older than 65 years wished to receive PRO feedback. They reported the comparison of their scores with those of a lymphoma reference cohort as being very valuable, since it provided information about their functioning in relation to what is “normal”.

An advantage of providing PRO feedback to patients themselves is that patients can monitor their symptoms at any specific point in time. Patients are furthermore provided with information that they can use to actively engage with their physician when discussing symptoms [26,27]. However, not all patients will be self-assertive enough to bring up their problems and, in that case, providing feedback to both patients and physicians, as is done in some studies [16-18], might be more effective for discussing problems and taking action with respect to referral to other health care professionals. Almost all patients indicated that the PRO feedback was useful and reassuring. Even when patients had scores that were below average, they still viewed PRO feedback as useful. The latter pleads for providing PRO feedback as a standard option in care. However, before PRO feedback is provided, patients need to be asked for their preference, as still 20% indicated that they did not want to receive PRO feedback. This is the case for information provision in general, as patients fare psychologically, behaviorally, and physiologically better when the information they receive about their medical condition is tailored to their coping styles, whereby those with a monitoring style tend to do better when given more information, and those with a blunting style do better with less information [39].

Since the feedback was generated automatically after patients completed the questionnaire, implementation in our PROFILES registry is relatively simple. In

addition, providing PRO feedback is valuable for other research that is performed with online questionnaires, as well as for patients with other medical conditions in terms of empowering patients and monitoring their functioning and symptoms.

In this study, we evaluated PRO feedback in a research setting at a fixed time point, but this kind of PRO feedback could also be of merit for patients at any given point in time outside of a research setting. It can, for example, be used as a tool for keeping track of their scores, which may help patients to feel more in control of their cancer and care [27].

Limitations

The sample size was relatively small, although we obtained a response rate of 70%. The PRO feedback was accessible only to patients completing the questionnaire online, which limits the generalizability of the results to the total lymphoma population, as patient characteristics are different for patients who participated online versus patients who participated on paper [40].

Conclusion

Future research should determine whether this kind of feedback could also increase empowerment and possibly improve HRQoL.

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CHAPTER 5

LYMPHOMA INTERVENTION [LIVE] – PATIENT-REPORTED OUTCOME FEEDBACK AND A WEB-BASED SELF-MANAGEMENT INTERVENTION FOR PATIENTS WITH LYMPHOMA: STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL



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ABSTRACT

Background

Patients with lymphoma are at risk of experiencing adverse physical and psychosocial problems of their cancer and its treatment. Regular screening of these symptoms by use of patient reported outcomes (PROs) could increase timely recognition and adequate symptom management. Moreover, self-management interventions intend to enhance knowledge and skills and empower patients to better manage their disease and related problems. The objective of the Lymphoma InterVention (LIVE) trial is to examine whether feedback to patients on their PROs and access to a web-based self-management intervention named *Living with lymphoma* will increase self-management skills and satisfaction with information, and reduce psychological distress.

Methods

The LIVE randomized controlled trial consists of three arms: 1) standard care, 2) PRO feedback, and 3) PRO feedback and the *Living with lymphoma* intervention. Patients who have been diagnosed with Hodgkin lymphoma, non-Hodgkin lymphoma, including chronic lymphocytic leukemia as registered in the Netherlands Cancer Registry in various hospitals will be selected for participation. Patients are invited via their haemato-oncologist 6 to 15 months after diagnosis. The PRO feedback includes a graphical overview of patients' own symptom and functioning scores and an option to compare their scores with other patients with lymphoma and a normative population of the same age and sex. The *Living with lymphoma* intervention is based on cognitive-behavioral therapy components and includes information, assignments, assessments, and videos. Changes in outcomes from baseline to 16 weeks, 12 and 24 months post-intervention will be measured. Primary outcomes are self-management skills, satisfaction with information, and psychological distress. Secondary outcomes are health-related quality of life, illness perceptions, fatigue, and health care use.

Discussion

The results of the LIVE trial will provide novel insights in whether access to PRO feedback and the *Living with lymphoma* intervention will be effective in increasing self-management skills and satisfaction with information, and reducing distress. The LIVE trial is embedded in a population-based registry, which provides a unique setting to ascertain information on response, uptake and characteristics of patients with lymphoma in web-based intervention(s). When effective, PRO feedback and *Living with lymphoma* could serve as easily and widely accessible interventions for coping with lymphoma.

INTRODUCTION

Due to advances in treatment, the 20-year prevalence of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) in the Netherlands is expected to increase by 5% to 6300 and 32,000 patients in 2020, respectively [1,2]. As a result of their cancer and its treatment, patients with lymphoma are at risk of experiencing adverse physical and psychosocial problems, such as fatigue, neuropathy, cognitive and emotional problems [3-6]. Patients who report adverse problems have a lower health-related quality of life (HRQoL) and visit their physician more often [7-9]. In addition, up to a quarter of patients with lymphoma experience persistent levels of anxiety, depressive feelings and fears, also called psychological distress [7-10].

Patient-reported outcomes (PROs) intend to evaluate the impact of a disease and its treatment from the perspective of the patient [11]. PROs are being increasingly recognized to be important in daily practice [12-13]. Regular screening of physical and psychosocial symptoms by use of PROs could increase awareness and recognition of symptoms and can contribute to adequate symptom management [11,14-17]. Moreover, the greater the resources available for coping with symptoms and stress, the lower the risk for psychological distress [18]. Interventions using cognitive behavioral therapy (CBT) components, such as psychoeducation and coping skills, can reduce persistent psychological distress and physical problems and improve HRQoL [8].

As the number of patients surviving lymphoma continues to grow, interventions need to be easily accessible and without increasing the burden on health services. Self-management interventions can be effective in strengthening the role of patients, by increasing patient engagement in care, and limit the burden on health services [19,20]. Self-management interventions aim to empower patients to have an active role in the management of their disease and its symptoms and consequences, including treatment, physical, psychosocial and lifestyle changes [21,22]. Web-based technologies are particularly suitable for self-management interventions, since they are easily accessible, can reach a large number of patients [19,23], and provide more anonymity compared to face-to-face interventions [24]. Therefore, web-based interventions have the potential to eliminate barriers to psychosocial care for patients with cancer. However, it is important that such interventions should be evidence-based and empirically tested [25].

The Lymphoma InterVEntion (LIVE) trial consists of two interventions: 1) feedback to patients on their PROs, and 2) a web-based self-management intervention named *Living with lymphoma*. Patients will be randomized to: 1) standard care, 2) standard care plus access to PRO feedback, or 3) standard care plus access to PRO feedback and the *Living with lymphoma* intervention. PRO feedback enables patients to monitor their symptoms and compare them with outcomes among other patients. This may help to either reassure that what they experience is 'normal' or may empower them to take action. The *Living with lymphoma* intervention is based on CBT components and is an adaptation from the evidence-based BREast cancer e-healTH (BREATH) intervention [26]. By using the *Living with lymphoma* intervention, patients will receive psychoeducation and learn coping skills, which they can apply as self-management skills in daily life.

METHODS AND DESIGN

Objectives and hypotheses

The objective of the LIVE trial is to examine whether PRO feedback and the *Living with lymphoma* intervention will increase self-management skills and satisfaction with information and reduce psychological distress. In concordance with the stress-coping model of Lazarus and Folkman (1984), psychological adjustment after cancer is determined by the balance between stress and resources [18]. Therefore, it is hypothesized that patients with access to PRO feedback and/or the *Living with lymphoma* intervention will report increased self-management skills and satisfaction with information (greater resources available for coping), and lower levels of psychological distress compared to patients receiving standard care. Moreover, it is expected that patients with access to both PRO feedback and the *Living with lymphoma* intervention will benefit most..

Study design

The LIVE-trial is designed as a non-blinded randomized controlled trial with three arms. For an overview of the design of the trial, see Figure 1. Standard care plus the access to PRO feedback and the *Living with lymphoma* intervention (arm 3) will be compared to standard care plus access to PRO feedback (arm 2) and standard care (arm 1). Patients with lymphoma from various hospitals in the Netherlands will be included and asked to complete questionnaires at four points in time: baseline (T0; 6 to 15 months after diagnosis), after 16 weeks (T1; post-intervention), after 12 months (T2), and after 24 months (T3).

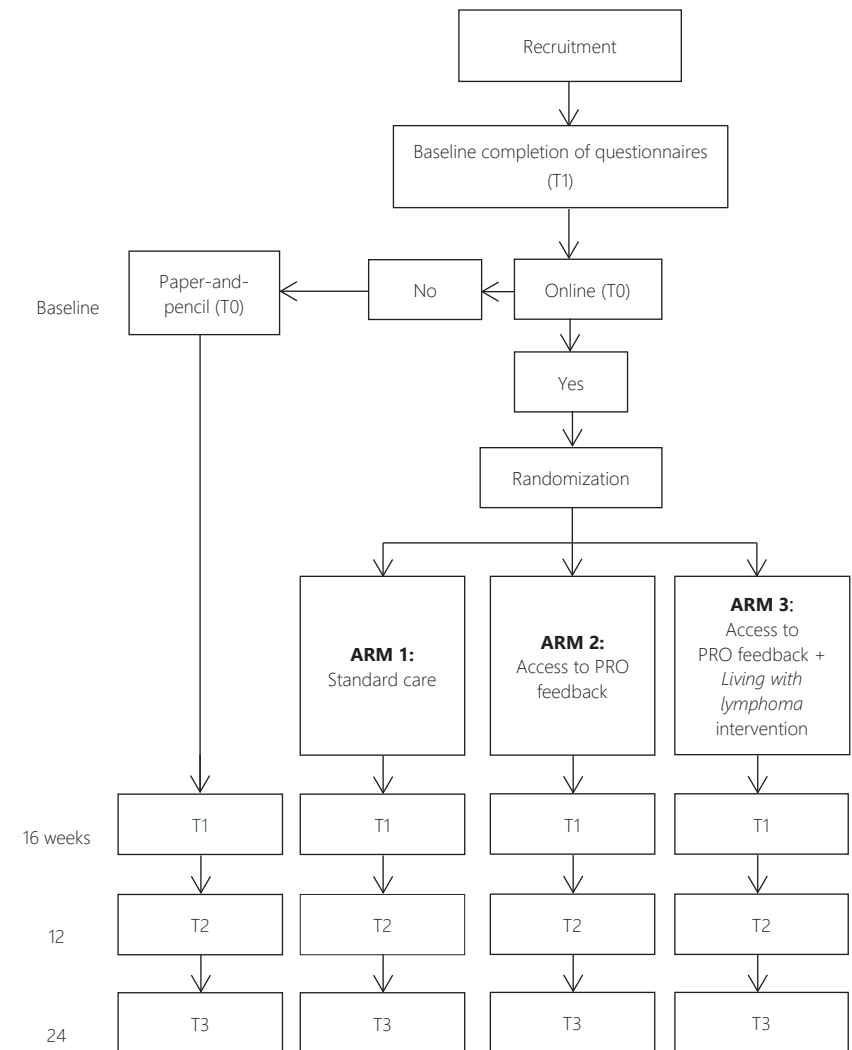


Figure 1. Overall study design of the Lymphoma InterVEntion (LIVE) trial

Study population

All patients who have been diagnosed with HL or NHL, including chronic lymphocytic leukemia (CLL) as defined by the International Classification of Diseases for Oncology-3 codes (ICD-O-3) [27], in the participating hospitals will be selected for participation via the Netherlands Cancer Registry (NCR). Patients must be aged 18 years or older at time of diagnosis. Patients who have problems with the Dutch language, patients with severe psychopathology or dementia, and patients in transition to terminal care will be excluded from the study.

Setting

LIVE-trial will be conducted within the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) registry [28]. PROFILES is a tool that enables data collection management; from inviting patients to participation in studies, to collecting PRO data via web-based or mailed questionnaires and linking these data with clinical data. Since this trial is embedded in the population-based PROFILES lymphoma registry, we have access to information on response, uptake and user characteristics of patients with lymphoma in a web-based intervention.

Recruitment

The population-based NCR of the Netherlands Comprehensive Cancer Organisation (IKNL) will be used to select all patients in the participating hospitals who meet the inclusion criteria. The NCR registers all newly diagnosed cancer patients within six months after diagnosis. After excluding deceased patients, the treating haemato-oncologists are asked to verify the patients' study eligibility. All eligible patients will be invited for participation by their own haemato-oncologist. The haemato-oncologists will provide the eligible patients with an invitation package, including an invitation letter and leaflet to inform them about the study, a postcard, and two informed consent forms (i.e., one for the researchers and one for the patient). The letter explains the study objectives and includes a link and password to a secure website, so that patients can complete questionnaires online. If patients prefer paper-and-pencil participation, they can complete the postcard and return it by mail to the study manager. Patients will then receive paper-and-pencil questionnaires and a pre-stamped envelope within one week of receipt of the postcard. Patients are informed that paper-and-pencil participation automatically means that they will not be able to participate in the LIVE-trial and only participate in the observational PROFILES lymphoma registry, as both PRO

feedback and the *Living with lymphoma* intervention are web-based. If the questionnaire is not completed within three weeks, a reminder will be sent by the treating haemato-oncologists. After obtaining informed consent, the subsequent communication to the patients will be addressed via PROFILES. To guarantee anonymity, questionnaires only contain a study number.

Randomization

Patients who complete the baseline questionnaire online and consent to participate in the LIVE-trial, will be automatically randomized in an equal ratio (1:1:1) to one of the three study arms: 1) standard care, 2) standard care plus access to PRO feedback, or 3) standard care plus access to PRO feedback and the *Living with lymphoma* intervention. This randomization will be performed using block randomization. The randomization will be performed by a computer randomization program, which will ensure a balance in sample size across groups over time [29].

Interventions versus standard care

Arm 1: Standard care

For patients randomized to arm 1, the haemato-oncologist provides standard care. Most haemato-oncologists give their patients leaflets regarding the diagnosis and treatment they receive. Most information is given during the initial treatment phase, and some of the haemato-oncologists give additional information during follow-up, for ad-hoc referrals if needed by the patient. Patients who receive standard care can use information about lymphoma on the internet, but do not have access to PRO feedback or the *Living with lymphoma* intervention.

Arm 2: PRO feedback

Patients randomized to arm 2 and 3 have access to PRO feedback, including general HRQoL, physical, emotional, cognitive and social functioning, fatigue, neuropathy (only for patients with high-grade NHL), anxiety and depressive symptoms. Patients can compare their scores to mean scores of other patients with lymphoma (same sex and age group) and/or a normative population (same sex and age group) to find out whether their scores are average or not (using a traffic light model). A detailed description of how to interpret the scores is added to assist patients in understanding the graphs. Mean scores of the lymphoma sample are extracted from data of our previous research on HRQoL among 856 patients with lymphoma³⁰. The normative population was selected from a reference cohort of

1859 individuals from the general Dutch population (CentERpanel). This cohort is representative for the Dutch-speaking population in the Netherlands [31]. Individual scores will be integrated into graphical displays with colored bar-charts [32,33]. The colors of the bar-charts are related to clinically relevant mean differences of the evidence-based guidelines of the EORTC QLQ-C30 [34]. A score that differs less than the minimal medium clinically relevant difference from the mean score is considered 'average' (amber). A score that differs as much as or more than the minimal medium clinically relevant difference from the mean score is considered 'above average' (green) or 'below average' (red). The interpretation of anxiety and depressive symptoms is according to the published scoring algorithm: 0-7 indicating no or mild symptoms (green), 8-10 indicating moderate symptoms (amber), and ≥ 11 indicating severe symptoms (red) [35]. Patients with a score in the red part of the chart are advised to contact their general practitioner. For an example of PRO feedback, see Figure 2.

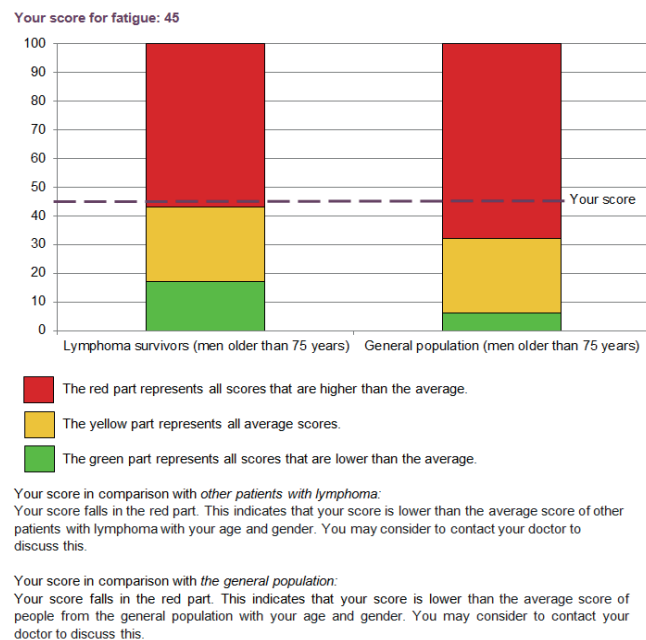


Figure 2. An example of patient-reported outcome feedback.

To review the PRO feedback, patients have to click on the 'feedback' tab after completing the questionnaire. Patients can decide not to review their PRO feedback as they prefer not to.

Arm 3: PRO feedback + 'Living with lymphoma' intervention

In addition to PRO feedback, patients randomized to arm 3 get access to the *Living with lymphoma* intervention. This web-based self-management intervention is an adaptation of the evidence based BREATH intervention for breast cancer survivors [26,26]. The content of the intervention is adapted to warrant its relevance for patients with lymphoma. Symptoms that are typically common in patients with lymphoma, such as neuropathy, infections and infertility, have been added.

One key feature of the intervention is the 'work space' that includes four phases: 1) 'looking back', 2) 'emotional processing', 3) 'strengthening', and 4) 'looking ahead'. For a screenshot of the 'work space', see Figure 3. The intervention is based on CBT techniques, such as psychoeducation, to enhance patients' knowledge and skills, for instance by providing tailored advices based on patients' input. Working ingredients of the four phases include information, assignments, assessments, and videos. The information part provides patients with knowledge on various subjects, such as adverse physical and psychological problems, work, sexuality, and lifestyle. Assignments are for example writing tasks, social engagement or conversation tasks and aim to increase skill-building [26]. Assessments include tests that could be used by patients as a screening instrument of potential problems and are followed by automated feedback. Videos are clips extracted from recorded interviews with patients with lymphoma. Another feature of the intervention is the library with background and additional information on subjects from the four phases (e.g., work, sexuality, lifestyle). For a screenshot of the library, see Figure 4. The library also contains links to additional health care services (e.g., psychologists, physiotherapists, dieticians).

The advised intervention usage is one part per week, with a duration of approximately one hour. However, it is up to the patients how and to what extent they use the intervention. From the BREATH intervention it is known that patients use the website quite diverse [37]. The intervention is fully-automated and non-guided and is delivered without professional support of a therapist. Support for content or technical assistance is available by the study manager.

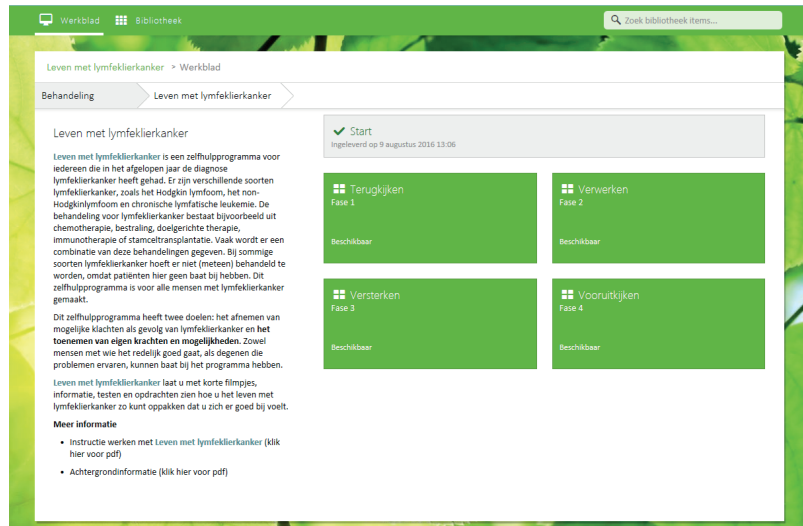


Figure 3. Screenshot from the 'work space' of the *Living with lymphoma* intervention with phase structure (in Dutch).

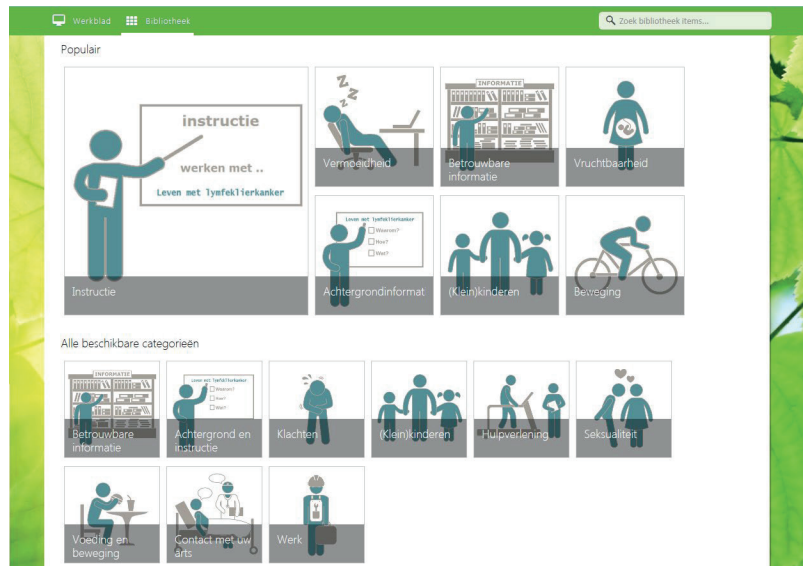


Figure 4. Screenshot from the library of the *Living with lymphoma* intervention (in Dutch).

Study outcomes measures

Patient demographics and clinical information will be available from the NCR that routinely collects data on among other things patients' age and sex, date of cancer diagnosis, histological classification, stage, treatment and comorbidity. Information on marital status, educational level, and employment status are gathered by self-report using questionnaires.

Primary outcomes

Self-management skills are measured by the Health Education Impact Questionnaire (heiQ) [38]. The heiQ contains 40 items across eight scales: positive and active engagement in life, health-directed activities, skill and technique acquisition, constructive attitudes and approaches, self-monitoring and insight, health service navigation, social integration and support, and emotional distress. Each item will be scored on a four-point Likert-scale. The scale scores are obtained by computing the mean of respective items. Higher scores indicate better status or self-management, except for emotional distress, in which higher scores indicate higher distress [38]. The heiQ has high construct validity [38]. Five scales of the heiQ are validated among patients with cancer [39].

Psychological distress will be assessed by the 14-item Hospital Anxiety and Depression Scale (HADS) [35]. A sum score is obtained by adding the items. Its rating system is based on a four-point format and asks how the patient has felt in the past week. Higher scores indicate higher levels of psychological distress. The HADS has shown good reliability and validity in oncology settings [40,41].

Satisfaction with information will be measured by an adapted version of the 9-item Information Satisfaction Questionnaire (ISQ) [42]. The ISQ has been widely used to assess overall information satisfaction and the need for involvement in decision making. The original measure demands patients to categorize themselves into one of three groups: those who would like 1) all available information and to be involved in decisions about the illness; 2) only positive information about the illness; and 3) only limited information and prefer the doctor to make the decisions. However, Fallowfield suggests that there is a distinction between the desire for information and involvement in decision making [43]. Therefore, we divided that question in two items, one assessing the desire for information and one assessing the desire for involvement in decision making. Patients are furthermore asked to rate their level of satisfaction with the information they have received about their illness, treatment, and lifestyle. Each of these questions will be scored on a five-point Likert

scale. The English version of the ISQ was translated into Dutch by forward-backward translation procedures. Questions about desire for more or less information, helpfulness of information, and the use of internet (to search for information) were added to the questionnaire.

Secondary outcomes

Health-related quality of life—general will be assessed using the Dutch validated European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) [44]. This 30-item questionnaire includes 5 functional scales, 3 symptom scales, a global health and quality of life scale, and several single-item symptom measures. All items will be scored on a 4-point Likert scale, except for the global health and quality of life scale that is scored on a 7-point linear analogue scale. After linear transformation, all scales and single item measures range in score from 0-100. Higher scores on functional and health and quality of life scales indicate better functioning or HRQoL, whereas higher scores on symptom scales indicate more complaints.

Health-related quality of life—lymphoma specific will be assessed with the EORTC disease specific modules, i.e. QLQ-HL27 for HL, QLQ-NHL-HG29 for high-grade and QLQ-NHL-LG20 for low-grade NHL, and QLQ-CLL17 for CLL [45]. The modules are divided in multi-item subscales including symptom burden, physical condition/fatigue, worries/fears, health and functioning, emotional impact, and neuropathy (only in the NHL-HG29 module). Items are scored on a 4-point Likert scale. After linear transformation, all scales range in score from 0-100, whereby a higher score reflects more problems [45].

Self-efficacy with regard to symptoms (in this study as a result of lymphoma) will be measured with the self-efficacy scale (SE28) [46-48]. This scale consists of seven items, which will be scored on a four-point Likert scale. A higher score reflects more sense of control. This scale had previously been used to assess self-efficacy concerning post-cancer fatigue [49].

Adjustment to cancer will be assessed using the 40-item Mental Adjustment to Cancer Scale (MAC) [50]. Items are rated on a four-point Likert scale. The summary scales (i.e., summary positive adjustment scale, summary negative adjustment scale) can be used to identify general adjustment styles for cancer. The summary positive adjustment scale includes 17 items and scores range from 17-68 (cut-off ≥ 47), whereas the summary negative adjustment scale includes 16 items with

scores ranging from 16-64 (cut-off ≥ 36) [51]. Summary scales are scored through addition of the items.

Illness perceptions will be assessed using the validated Brief Illness Perception Questionnaire (BIPQ) [52]. This scale has 9 items, measuring cognitive representations, emotional representations, and illness comprehensibility. Items are scored on a continuous linear 0-10 point scale. A higher score reflects a more threatening view of the illness. The BIPQ has previously cross-culturally adapted into the Dutch Language Version (Brief IPQ-DLV), with acceptable face and content validity [53].

Fatigue will be assessed with the 20-item validated Multidimensional Fatigue Inventory (MFI) [54]. The MFI covers five scales: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. Each scale contains 4 items, with 2 items formulated in a positive (e.g., I feel fit) and 2 formulated in a negative direction (e.g., I feel fatigued). All items are scored on a 5-point Likert scale. The negative formulated items must be recoded before adding up scores. Higher sum scores correspond with more acute levels of fatigue. The MFI is reliable and valid to assess fatigue in patients with cancer [54].

Health care use will be assessed by single-items: 'How often did you contact a general practitioner in the past 12 months?', 'How many of these visits were related to cancer or the consequences of your cancer?', 'How often did you visit a medical specialist in the past 12 months?', 'How many of these visits were related to cancer or the consequences of your cancer?'. These questions were asked in a similar way as by Statistics Netherland [55] (<http://statline.cbs.nl/>). Three questions are asked about follow-up appointments (whether or not receiving follow-up appointment, the frequency of follow-up appointments and satisfaction with this frequency). Furthermore, patients are asked whether they visited a psychologist, psychiatrist or social worker and the last question was 'Did you receive care after the treatment of your cancer?' To answer this question, patients could either choose 'No' or 'Yes' and then choose multiple additional care services from a list: sexologist, pastoral care, dietician, physical therapist, oncological rehabilitation, creative therapy, oncology nurse, or contact with other cancer survivors.

Covariates

Comorbidity at the time of survey will be assessed with the adapted Self-administered Comorbidity Questionnaire (SCQ) [56]. Patients will be asked to identify comorbid conditions developed since diagnosis.

Personality will be assessed using the Big Five Inventory (BFI) [57]. The BFI is a 44-item inventory designed to measure the Big Five dimensions: extraversion, agreeableness, conscientiousness, neuroticism and openness to experience. Items are scored on a 5-point Likert scale. Scale scores will be created by averaging the items for each domain. The Dutch BFI has good psychometric quality [58].

Usage statistics

In addition to the standardized questionnaires, technical data on the use of the intervention, such as frequency, duration and activity, will be evaluated.

Sample size calculation

Sample size calculation was performed using G*Power version 3.1.9.2 for Windows. Based on the three primary outcomes of this trial, effect on patient level is defined as increased self-management skills or satisfaction with information (as measured by the heiQ and the ISQ, respectively) or reduced psychological distress (as measured with the HADS). Therefore, effectiveness of LIVE is demonstrated when one of the three effects is statistically significant. Significance level of the sample size calculation was adjusted to $P \leq .167$ to keep the overall chance for type-I errors at 5%.

Clinically important differences will be determined with Norman's 'rule of thumb', whereby a difference of $\approx 0,5$ SD indicates a threshold of discriminant change in quality of life scores of a chronic illness [59]. To detect a clinically important difference with 90% power, a sample size of 222 patients with lymphoma (74 in each group) is needed. This sample size calculation is based on a medium effect size of 0.25 for repeated measures ANOVA with two measurements, since at least two measurements are necessary to compare pre-intervention and post-intervention outcomes. We take into account a response rate of 70% as observed in earlier studies (of them 60% is expected to complete the questionnaires online) and a study drop-out rate of 25%, based on a systematic review on adherence in internet interventions for anxiety and depression [60]. This results in 663 patients with lymphoma that need to be invited for participation.

Statistical analyses

All statistical analyses will be performed using Statistical Analyses Software (SAS; version 9.4 for Windows, SAS Institute Inc., Cary NC, USA). Analyses on effectiveness of the intervention will be primarily done according to intention-to-treat methodology. Second, per protocol analysis will be performed to analyze the efficacy of the intervention. All statistical tests will be two-sided and considered significant if $P < .05$.

Missing outcome data will be assumed to be 'missing at random' (MAR), conditional on key predictors of 'missingness' (in particular baseline values of the outcome variables of interest, and study arm).

Patients' sociodemographic and clinical variables will be compared at baseline between the three study arms using chi-square analyses for categorical variables and ANOVA for continuous variables and will be analyzed as covariates.

Repeated measures analysis using generalized estimating equations, which account for the intra-patient dependency of the repeated measures, will be used to analyze the effect of the intervention on the outcome variables. We will investigate differences in effect of the two intervention arms and the arm receiving standard care at the different time points. Differential effects of the intervention arms by age, cancer subtype and baseline levels of the outcomes of interest will be assessed for the outcome measures by adding terms for the interaction between age, cancer subtype, baseline levels and care arm to the regression models.

Routinely collected data from the population-based NCR on patient and tumor characteristics will enable us to compare paper-and-pencil respondents with online respondents, as well as respondents with non-respondents and patients with unverifiable addresses in order to determine the external validity of the results and answer our second study objective.

DISCUSSION

Regular screening of symptoms by use of PROs and access to resources for coping skills could help to detect and/or manage symptoms that up to a quarter of patients with lymphoma are experiencing. The results of the LIVE-trial will provide

novel insights in whether access to PRO feedback and the *Living with lymphoma* intervention will be effective in increasing self-management skills and satisfaction with information, and reducing psychological distress. Since one-third of patients will be randomized to solely access to PRO feedback and not to the *Living with lymphoma* intervention, it will be possible to investigate the superiority of access to PRO feedback as well as the superiority of access to PRO feedback and the *Living with lymphoma* intervention compared to standard care.

The LIVE-trial is embedded in the population-based PROFILES lymphoma registry, which provides a unique setting to ascertain information on response, uptake and characteristics of patients with lymphoma in web-based intervention(s). This information is important with respect to the generalizability of results and moreover, it demonstrates which patients subgroups will benefit most from PRO feedback and the *Living with lymphoma* intervention. Patients will not be selected based on their symptoms or distress level prior to study entry and it is up to patients themselves how and to what extent they use the intervention(s). When effective, access to PRO feedback and the *Living with lymphoma* intervention could serve as easily and widely accessible interventions for coping with lymphoma in the Netherlands.

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CHAPTER 6

IMPACT OF PATIENT-REPORTED OUTCOME FEEDBACK AND A WEB-BASED SELF-MANAGEMENT INTERVENTION AMONG UNSELECTED PATIENTS WITH LYMPHOMA: RESULTS OF THE LIVE TRIAL



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ABSTRACT

Purpose

Based on patients' wishes to get insight in their own patient-reported outcomes (PRO) data, the Lymphoma InterVention [LIVE] trial was conducted to examine the effects of PRO feedback to patients and a web-based self-management intervention – *Living with lymphoma* – on psychological distress, self-management, satisfaction with information, and healthcare use in population-based setting.

Methods

PRO feedback included comparison with age- and sex-matched peers and was built in the PROFILES registry. *Living with lymphoma* was an adaptation of an evidence-based intervention for breast cancer survivors. Patients with lymphoma were randomized equally to 1) care as usual (CAU), 2) PRO feedback, and 3) PRO feedback and *Living with lymphoma*. Patients completed questionnaires 9 to 18 months after diagnosis (T0; N=227) and 4 months later (T1; N=192). Outcomes were psychological distress (HADS), self-management (heiQ), satisfaction with information (ISQ), and healthcare use.

Results

No effects of PRO feedback with or without *Living with lymphoma* was observed on psychological distress, self-management, satisfaction with information provision, and healthcare use. PRO feedback was viewed by 77% of those with access. Of those with access to *Living with lymphoma*, only 36% accessed and registered and only 16 patients opened at least one part of the intervention.

Conclusion

No effects of PRO feedback on psychological distress, self-management skills, satisfaction with information provision, or healthcare use were found. As PRO feedback meets patients' wishes to gain insight in their PROs and does not negatively impact their well-being, it might be implemented in daily clinical practice. Since the uptake and adherence of *Living with lymphoma* was very limited, no definite conclusions about the effectiveness of *Living with lymphoma* in a population-based sample can be drawn yet. More research is needed to investigate the optimal format and delivery of *Living with lymphoma*.

INTRODUCTION

About 25% of patients with lymphoma experiences persistent levels of anxiety, depressive symptoms and fears [1], also known as psychological distress. As psychological well-being is determined by the balance between stress and the resources available for coping [2,3], psychological distress may exaggerate when the right information and support is not available [4,5] and may lead to increased healthcare use [6]. Prior research showed that one third of patients with lymphoma are not satisfied with the information provision and would have liked more information, for example about supportive care [7].

Based on the wishes of patients to get access to their own patient-reported outcome (PRO) data [8], an application has been developed to provide patients with feedback. PRO feedback enables patients to monitor their functioning, compare their scores with peers [8], and to be aware of and recognize symptoms. Subsequent steps, such as self-management interventions may be necessary to actually improve health outcomes [9]. Self-management interventions intend to enhance patients' knowledge and skills and empower patients to play an active role in the management of their disease and its consequences [10,11], which is needed to keep up a good health-related quality of life (HRQoL). Increased self-management may limit the burden on health services [12,13], which is desirable as the number of lymphoma survivors continues to grow.

The Lymphoma InterVention [LIVE] trial consists of two interventions [14]: (1) PRO feedback to patients, including comparison with peers, and (2) a web-based self-management intervention: *Living with lymphoma*. *Living with lymphoma* is based on psychoeducation and cognitive behavioural therapy (CBT), components shown to be effective in coping with cancer [15]. Although beneficial effects have been demonstrated among patients with breast cancer [16], little is known about the effects of such interventions in a population-based setting with unselected patients with cancer.

The primary aim of the LIVE randomized controlled trial (RCT) is to examine the effects of PRO feedback to patients with or without access to *Living with lymphoma* on self-management, satisfaction with information, and psychological distress in a population-based setting [14]. We hypothesized PRO feedback with or without *Living with lymphoma* to increase self-management and satisfaction with

information provision, while reducing psychological distress. Based on new insights that psychologically distressed patients reported increased healthcare use [6], we added an additional aim to investigate the effects of PRO feedback with or without *Living with lymphoma* on healthcare use.

METHODS

Design and participants

The RCT was embedded in the population based Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) registry [17], that enables PRO data collection management and linking these data to clinical data from the Netherlands Cancer Registry (NCR).

Between October 2015 and February 2019, patients diagnosed with lymphoma (i.e., Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), or chronic lymphocytic leukemia (CLL)), as defined by the International Classification of Diseases for Oncology-3 codes (ICD-O-3) [18], from thirteen hospitals in the Netherlands were selected for participation 9 to 18 months after diagnosis. The NCR registers all newly diagnosed patients with cancer in the Netherlands within the first year after diagnosis and routinely collects detailed data on sociodemographic and clinical characteristics (e.g., patients' age and sex, date of cancer diagnosis, cancer type, and primary treatment). Treating hemato-oncologists were asked to verify patients' eligibility. Eligible patients were invited to participate in the RCT and complete a questionnaire. Patients were informed that completion of the web-based questionnaire resulted in RCT enrolment with automatic randomization to one of the three study groups, whereas paper respondents were only observationally followed within the PROFILES lymphoma registry. A reminder mail was sent after three weeks. All respondents received a follow-up questionnaire four months after the baseline questionnaire. The RCT was centrally and locally approved by a Medical Research Ethics Committee [14].

Randomization

Randomization was performed using block randomization to ensure a balance in sample size across groups over time [19]. Participants were randomized equally to: 1) care as usual (CAU), 2) CAU plus access to PRO feedback, or 3) CAU plus access to PRO feedback and *Living with lymphoma*.

Interventions versus CAU

Group 1: CAU

In arm 1, patients received CAU from their healthcare providers (e.g., hemato-oncologists, oncology nurses). Most healthcare providers provided verbal information to their patients and gave them leaflets regarding the diagnosis and treatment they received.

Group 2: PRO feedback

In group 2 and 3, after patients completed the web-based questionnaire, PRO feedback was automatically generated. Patients could choose to either click on the 'feedback' button to review the PRO feedback or not.

Detailed information about the PRO feedback has been described elsewhere [8,14]. In short, PRO feedback was provided on patients' general HRQoL, physical, emotional, cognitive and social functioning, fatigue, neuropathy, anxiety and depressive symptoms [14]. Individual scores were integrated into graphical displays with colored bar-charts [20,21]. Patients had the opportunity to compare their scores to mean scores of other patients with lymphoma [7] and/or an age- and sex-matched normative population without cancer [22] to discover whether their scores were average or not. The colors of the bar-charts were related to clinically relevant mean differences of the evidence-based guidelines of the EORTC QLQ-C30 [23] and considered 'average' (amber); 'above average' (green); or 'below average' (red). Patients with above average scores on symptoms were advised to contact their general practitioner.

Group 3: PRO feedback + *Living with lymphoma*

In addition to PRO feedback, patients in arm 3 had access to a web-based self-management intervention: *Living with lymphoma*. A detailed description of *Living with lymphoma* has been previously described elsewhere [14]. *Living with lymphoma*, an adaptation of the BREATH intervention for breast cancer [16,24], was based on psychoeducation and CBT techniques to enhance patients' knowledge and skills. The intervention also includes a library with background and additional information on various subjects (e.g., work, sexuality, lifestyle) and links to additional healthcare services (e.g., psychologists, physiotherapists). It was left to the discretion of the patients how and to what extent they used the intervention. The intervention was fully-automated, non-guided and was delivered without professional support of a therapist.

Measures

Sociodemographic and clinical information were obtained from the NCR. NCR data were available for both RCT participants and nonparticipants. Among RCT participants, information about education, partner and comorbid conditions was assessed in the questionnaire.

Self-management skills were assessed with the Health Education Impact Questionnaire (heiQ) including 40 items across 8 scales [25]. Each item was scored on a 4-point scale. Scale scores were obtained by computing the mean of respective items. Higher scores indicate better status or self-management, except for emotional distress, where higher scores indicate higher distress [25].

Satisfaction with information was assessed with an adapted version of the 9-item Information Satisfaction Questionnaire (ISQ) [26]. Patients were asked to categorize themselves into those who would like (1) all available information; (2) only positive information about the illness; and (3) only limited information. In addition, patients had to categorize themselves into those who would like (1) to be involved in decisions about the illness; (2) prefer the doctor to make the decisions. Patients were furthermore asked to rate their level of information satisfaction about their illness, treatment, and lifestyle. Questions were scored on a five-point scale.

Psychological distress was assessed with the 14-item Hospital Anxiety and Depression Scale (HADS) [27]. Higher sum scores indicate higher levels of psychological distress [28]. Patients with a HADS sum score ≥ 13 were categorized as "distressed" [29].

Two open questions were asked to assess healthcare use: 1) "How often did you contact a general practitioner (GP) in the past 12 months?" and 2) "How often did you visit a medical specialist in the past 12 months?".

Statistical analyses

All statistical analyses were performed with SAS version 9.4 (Cary, NC, USA). With more than 74 participants per study group, the study had 90% power to detect an effect size of .50 with a two-tailed *P* value set at .05 [30]. Baseline characteristics between the study groups were compared using analysis of variance and chi-square tests. If at least half of the items from a subscale have been completed,

missing items were replaced by the average of those that are present for the participant.

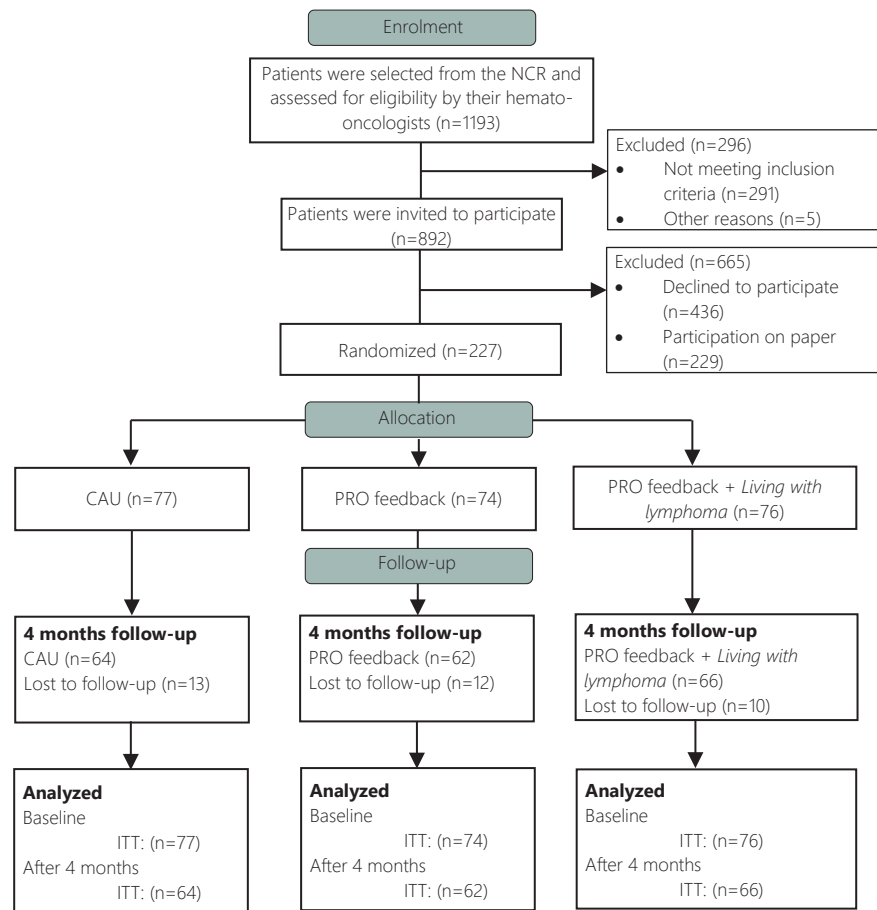
To model between-group difference in change from baseline to follow-up, mixed-effect models were used with an unstructured covariance structure and a restricted maximum likelihood solution [31]. A random intercept on the patient-level was included in the model to adjust for the inter-dependency between repeated measures. The CAU-group (group 1) was assigned as the reference group. The *P* value for overall model effects was set at .05 and for specific contrasts at .01, lowering the risk of type I errors as a result of multiple testing. In the iterative process of variable selection, a priori selected covariates (i.e., age, sex, cancer type, treatment) were removed from the as they were non-significant and non a confounder. We adjusted for baseline psychological distress in all analyses (when this was not our outcome variable), since participants in the group 1 seemed somewhat more often psychologically distressed (22%) than those in group 2 (12%) and group 3 (11%, $P=.10$, data not shown).

Group difference from baseline to follow-up in mean change were accompanied by Cohen's ES. Cohen's ES was calculated by dividing the difference in mean change scores between the control and intervention group by the pooled baseline standard deviation. An ES of .20 was considered small, .50 moderate, and .80 large. An ES of approximately .50 was considered to be clinically relevant [30,32]. All analyses were conducted on an intention-to-treat basis.

RESULTS

Baseline characteristics of RCT participants

In total, 1,193 patients were selected from the NCR. After verifying eligibility, 892 patients were invited to participate. Forty-nine percent declined to participate ($n=436$) and 229 patients completed the questionnaire on paper and were excluded. As depicted in the CONSORT diagram (Figure 1), both patient who declined participation and those who responded on paper were considered nonparticipants [33].



Note. CAU=care as usual; ITT=Intention To Treat analyses, comparing all respondents in both intervention groups to all respondents in the CAU group; NCR=Netherlands Cancer Registry; PRO=Patient-Reported Outcome.

Figure 1. CONSORT Flow diagram of the progress of the patients with lymphoma through the phases of the LIVE trial

Two-hundred and twenty-seven patients provided written informed consent, completed the first questionnaire online, and were randomly assigned to the PRO feedback with access to *Living with lymphoma* group (n=77), the PRO feedback group (n=74), or the CAU group (n=76). The completion rate of the follow-up questionnaire was 85% (n=192) and did not differ significantly among groups.

RCT participants were younger than nonparticipants (60.7 vs 65.3 years, $P < .01$), and more often men (71% vs 57%; $P < .01$). RCT participants were on average 14.0 months after diagnosis. The majority of RCT participants had a partner (84%). Seventy-one percent received active treatment, whereas 23% was on active surveillance and did not receive active treatment (Table 1). All baseline sociodemographic and clinical characteristics were balanced across groups.

Intention-to-treat analyses

Results of the intention-to-treat analyses indicated no significant group-by-time interaction for psychological distress, all self-management skills, satisfaction with information provision, and healthcare use ($P > .05$, Table 2). Differences on outcome variables did not seem to depend on the intervention patients received, which ensured that we should not look further at specific contrasts.

Use of the *Living with lymphoma* intervention

In total, 76 patients were randomized to group 3 and had access to *Living with lymphoma*, of whom 27 patients (36%) accessed and registered. No differences were observed in baseline sociodemographic and clinical characteristics between those who accessed and who did not. Of those who accessed *Living with lymphoma*, 16 patients (59%) opened at least one part of the intervention and were therefore assessed as users. In addition, various items from the library were viewed by the users: 'Reliable information' was opened 12 times, 'Fatigue', 'Emotional counselling', and 'Nutrition and cancer' were opened 6 times, 'Exercise' was opened 5 times and 'Physical counselling', 'Sexuality', and 'Reintegration' were opened twice.

As we observed that adherence was very low, we asked patients about reasons for nonadherence and they indicated they felt well and still had regular appointments with their hemato-oncologist, and therefore were not in need of an intervention.

Table 1. Baseline sociodemographic and clinical characteristics of participants (n=227) and nonparticipants (n=666).

	Total participants (N=227)	Nonparticipants (N=666)	P
	n(%)	n(%)	
Sociodemographic characteristics			
Age in years: mean (SD)	60.7 (13.4)	65.3 (15.7)	<.01
Sex			<.01
Male	161 (71)	377 (57)	
Female	66 (29)	289 (43)	
Marital status			
Partner	190 (84)	N/A	
No partner	37 (16)	N/A	
Educational level [#]			
Low	6 (3)	N/A	
Medium	106 (47)	N/A	
High	114 (50)	N/A	
Clinical			
Months since diagnosis: mean (SD)	14.0 (3.2)	14.0 (3.5)	.80
Cancer type			.95
HL	27 (12)	75 (11)	
NHL-HG	125 (55)	359 (54)	
NHL-LG	56 (25)	169 (25)	
CLL	19 (8)	63 (9)	
Treatment			.13
Active treatment	172 (76)	458 (69)	
No active treatment	53 (23)	199 (30)	
Unknown	2 (1)	9 (1)	
No. of comorbid conditions	1.1 (1.1)	N/A	

Note. The numbers may not always add up to 100, because percentages have been rounded off to whole numbers.

Abbreviations: CLL, chronic lymphocytic leukemia; HL, Hodgkin lymphoma; NHL-HG, high-grade non-Hodgkin lymphoma, NHL-LG, low-grade non-Hodgkin lymphoma; SD, standard deviation.

[#] For education, low indicates none/primary school; medium, lower general secondary education/vocational training; and high, pre-university education/high-level vocational training/university.

Table 2. Between group differences in mean change from baseline to follow-up

	T0		T1		Between group-difference T0-T1		
	N	Mean	SD	N	Mean	SD	Mean change SE P ES*
Outcome and group							
Psychological distress							
HADS total (p=.989 [†])							
PRO feedback + Living with lymphoma	76	5.75	5.03	63	5.87	4.98	0.09 0.63 .883 .01
PRO feedback	74	6.59	5.26	60	6.43	6.21	0.06 0.64 .922 .01
CAU †	77	7.03	7.10	62	6.98	7.48	
The Positive and Active Engagement in Life							
HeiQ positive and active engagement in life (p=.587 [†])							
PRO feedback + Living with lymphoma	76	3.22	0.44	63	3.26	0.52	0.07 0.07 .330 .12
PRO feedback	74	3.22	0.46	62	3.23	0.50	0.01 0.07 .839 .02
CAU †	77	3.16	0.52	62	3.16	0.52	
Health Directed Behavior							
HeiQ health directed behavior (p=.473 [†])							
PRO feedback + Living with lymphoma	76	3.22	0.58	63	3.24	0.66	0.09 0.08 0.262 .15
PRO feedback	74	3.27	0.53	62	3.29	0.59	0.08 0.08 0.326 .12
CAU †	77	3.34	0.62	62	3.28	0.56	
Skill and Technique Acquisition							
HeiQ Skill and Technique Acquisition (p=.723 [†])							
PRO feedback + Living with lymphoma	76	2.97	0.53	63	2.94	0.51	-0.05 0.08 .532 -.09
PRO feedback	74	2.94	0.44	61	2.98	0.43	0.01 0.08 .902 .03
CAU †	76	2.94	0.44	62	2.97	0.46	

(continued on following page)

Table 2. Between group differences in mean change from baseline to follow-up (continued)

	T0			T1			Between group-difference T0-T1			
	N	Mean	SD	N	Mean	SD	Mean change	SE	P	ES*
Constructive Attitudes and Approaches										
HeiQ Constructive Attitudes and Approaches (p=.138 [†])	76	3.33	0.43	63	3.30	0.49	0.08	0.07	0.227	.17
PRO feedback + <i>Living with lymphoma</i>	74	3.27	0.51	61	3.30	0.49	0.13	0.07	0.048	.26
CAU ‡	77	3.26	0.52	62	3.16	0.51				
Self-Monitoring and Insight										
HeiQ Self-Monitoring and Insight (p=.477 [†])	76	3.00	0.43	63	3.05	0.38	0.06	0.06	0.311	.15
PRO feedback + <i>Living with lymphoma</i>	74	3.05	0.39	62	3.11	0.40	0.07	0.06	0.277	.15
CAU ‡	77	3.08	0.45	62	3.07	0.32				
Health Services Navigation										
HeiQ Health Services Navigation (p=.658 [†])	76	3.22	0.49	63	3.19	0.50	0.05	0.06	0.468	.10
PRO feedback + <i>Living with lymphoma</i>	74	3.27	0.39	61	3.26	0.40	0.05	0.06	0.398	.13
CAU ‡	76	3.30	0.45	62	3.22	0.44				
Social Integration and Support										
HeiQ Social Integration and Support (p=.535 [†])	76	3.22	0.47	63	3.21	0.47	0.06	0.07	0.324	.13
PRO feedback + <i>Living with lymphoma</i>	74	3.12	0.46	61	3.12	0.50	0.07	0.07	0.341	.15
CAU ‡	76	3.15	0.57	62	3.07	0.54				

(continued on following page)

Table 2. Between group differences in mean change from baseline to follow-up (continued)

	T0			T1			Between group-difference T0-T1			
	N	Mean	SD	N	Mean	SD	Mean change	SE	P	ES*
Emotional Wellbeing										
HeiQ Emotional Wellbeing (reversed scale) (p=.662 [†])	76	1.71	0.48	63	1.71	0.51	-0.06	0.07	0.404	-.12
PRO feedback + <i>Living with lymphoma</i>	74	1.83	0.52	62	1.82	0.53	-0.05	0.07	0.468	-.10
CAU ‡	76	1.82	0.62	62	1.88	0.65				
Satisfaction with information provision										
ISQ total information provision (p=.179 [†])	76	3.86	0.80	64	3.69	0.94	-0.002	0.12	0.986	-.002
PRO feedback + <i>Living with lymphoma</i>	74	3.91	0.72	62	3.95	0.71	0.19	0.12	0.110	.22
CAU ‡	76	3.86	0.78	63	3.73	0.79				
Contacts general practitioner past 12 months										
GP contacts (p=.154 [†])	76	4.89	4.32	64	3.36	3.27	0.10	0.55	0.857	.03
PRO feedback + <i>Living with lymphoma</i>	74	4.78	4.17	62	4.40	4.97	0.98	0.55	0.080	.43
CAU ‡	74	4.70	3.91	63	3.16	2.58				
Contacts medical specialist past 12 months										
Medical specialist contacts (p=.779 [†])	74	10.46	7.18	62	7.40	5.41	0.34	1.09	0.757	.05
PRO feedback + <i>Living with lymphoma</i>	74	10.42	6.72	61	6.70	4.73	-0.43	1.09	0.691	-.07
CAU ‡	76	10.10	6.27	63	7.00	4.12				

Table 2. Between group differences in mean change from baseline to follow-up (continued)

Note: Reported means, standard deviations and effects sizes are model-based. In the analysis, contrasts were based on the between group differences in mean change from baseline to follow-up (i.e. differences between the control group and the two intervention groups in mean change from T0 to T1). Abbreviations: CAU, care as usual; GP, general practitioner; HADS, Hospital Anxiety and Depression Scale (ranging from 0-42, higher scores indicate more psychological distress; HeiQ, Health Education Impact Questionnaire (ranging from 1-4, higher scores indicate higher levels of self-management ability, except for emotional distress, where higher scores indicate more distress); ISQ, Information Satisfaction Questionnaire (ranging from 1-5, higher scores indicate more satisfaction with perceived information); PRO, patient-reported outcome; SD, standard deviation; SE, standard error; T0, baseline assessment; T1, short term follow-up assessment at 16 weeks post-randomization.

* Effect size, based on the between group-difference in mean change and pooled SD of the intervention and control groups (.20 is considered small, .50 moderate/clinically significant, and .80 large)

* P value of the overall time by group interaction.

‡ Control group is reference category.

Access to PRO feedback

In total, 150 patients were randomized to group 2 or 3 and had access to PRO feedback, of whom 115 patients (77%) actually viewed the PRO feedback. Thirty-six patients (31%) viewed the feedback once, whereas the remainder viewed it more than once. Thirteen patients (13%) viewed the PRO feedback more than five times. Those who viewed the PRO feedback were more recently diagnosed (15.0 months vs 13.6 months, $P=.03$) and more often wanted to receive all available information about the disease than those who did not (59% vs 29%, $P<.01$).

Ninety-two patients (80%) wanted to compare their scores to both other patients with lymphoma and a normative population without cancer, 13 patients (11%) only to other patients with lymphoma, and 1 patient only to a normative population. In addition, 9 patients (8%) only viewed their own scores.

DISCUSSION

The results of this RCT did not support our hypothesis that PRO feedback, with or without access to *Living with lymphoma*, has a beneficial effect on psychological distress, self-management skills, satisfaction with information provision, and healthcare use among patients in a population-based setting. Although no beneficial effects were observed, we have not found any negative effects of PRO feedback, with or without access to *Living with lymphoma* on patients' well-being either.

The majority (77%) of those with access, actually viewed the PRO feedback, of whom two-thirds viewed it more than once. Nevertheless, as up to a quarter was not interested in viewing PRO feedback, it is important that patients can decide for themselves whether or not they want to view the feedback. It is known that PRO feedback may particularly be effective in identifying problems, but intervening steps are necessary to actually improve outcomes [34].

In contrast to the BREATH intervention that was found to be effective in reducing psychological distress and increasing self-efficacy among breast cancer survivors [16], we did not find an effect of *Living with lymphoma* on our outcome variables. To prevent patients from being dependent on healthcare providers to identify problems and refer them for intervention, we chose to make the intervention available to all patients with lymphoma, without prior screening. Although meta-

analyses demonstrated greater uptake of interventions aiming to reduce psychological distress among unselected patients compared to pre-screened patients [35,36], uptake and adherence rates in this sample were very low. Only 36% of those with access, actually accessed the intervention and registered. Sixteen patients of those who registered, opened at least one part of *Living with lymphoma* and were assessed as users. There is evidence that unguided self-management interventions to reduce psychological distress could be more effective when targeted to those with the greatest need of an intervention, such as low-distress patients [16,37]. In our sample only 15% of participants were psychologically distressed, which is significantly lower than the 25% that was previously observed among a similar group of patients [1]. This might suggest that the need for intervention in our sample may be low and we may have not reached the right sample. However, our aim was explicitly to investigate effectiveness of the intervention in an unselected group of patients with lymphoma. In addition, timing of the intervention may not have been optimal, as participants were on average 14 months post diagnosis and mostly finished primary treatment. Patients on treatment more frequently reported psychological distress compared with short- and long-term survivors [38]. Interventions closer to diagnosis or during active treatment may be more effective, as patients are especially vulnerable to psychological distress in that specific time frame.

Some other limitations of this RCT should be noted. Participants were not representative of the lymphoma population, as they were younger, more often male, and more often highly educated [33]. More research is needed to understand why underrepresented patients were not reached and how they could be reached in the future. Furthermore, low uptake and adherence rates for *Living with lymphoma* limited its potential impact. Supporting intervention adherence by someone who guides patients through the intervention, with weekly email or telephone calls providing guidance, may be necessary to increase usage and completion of relevant modules of the web-based intervention.

In conclusion, no effects of PRO feedback on psychological distress, self-management, satisfaction with information, or healthcare use were found. As PRO feedback meets patients' wishes to gain insight in their PROs and does not negatively impact their well-being, it might be implemented in daily clinical practice. No definite conclusions about the effectiveness of *Living with lymphoma* in a population-based sample can be drawn yet because the uptake and

adherence of *Living with lymphoma* was very limited. More research is needed to investigate the optimal format and delivery of *Living with lymphoma*.

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CHAPTER 7

WEB-BASED SELF-MANAGEMENT FOR PATIENTS WITH LYMPHOMA: ASSESSMENT OF THE REACH OF INTERVENTION OF A RANDOMIZED CONTROLLED TRIAL



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ABSTRACT

Background

Randomized controlled trials (RCTs) often provide accurate estimates of the internal validity of an intervention but lack information on external validity (generalizability). We conducted an RCT on the effectiveness of a self-management intervention among patients with lymphoma in a population-based setting. The objectives of the current study were to describe the proportion of RCT participants compared to all patients invited to participate, and compare sociodemographic and clinical characteristics of RCT participants with all respondents, all patients invited to participate, and all patients selected from the Netherlands Cancer Registry (NCR) to determine the reach of the intervention. An additional objective was to assess differences on RCT outcome variables between RCT and paper respondents.

Methods

Patients with lymphoma or chronic lymphocytic leukemia ≥ 18 years old at diagnosis from 13 hospitals in the Netherlands were selected from the population-based NCR, which routinely collects data on sociodemographic and clinical characteristics. Eligible patients were invited to participate in an RCT and complete a questionnaire. Web-based completion determined RCT enrollment, whereas paper respondents were followed observationally.

Results

A total of 1193 patients were selected from the NCR, 892 (75%) of whom were invited to participate in the trial by their hematologist after verifying eligibility. Among those invited, 25% completed the web-based questionnaire and were enrolled in the RCT. The RCT participants were younger and there was a higher proportion of men than non-participants. In addition, 26% of those invited opted to participate in the paper-based observational follow-up study. Compared with paper respondents, RCT participants were younger, with a higher proportion of men, and had higher education levels. RCT participants more often wanted to receive all available information on their disease, whereas paper respondents reported higher levels of emotional distress.

Conclusions

From a population-based sample of eligible patients, the participation rate in the RCT was approximately 25%. RCT participants may not be representative of the target population because of different sociodemographic and clinical characteristics. Since RCT participants represent a minority of the target population, RCT results should be interpreted with caution as patients in the RCT may be those least in need of a self-management intervention.

INTRODUCTION

Randomized controlled trials (RCTs) are widely considered to be the gold standard for evaluating the effects of an intervention in behavioral and psycho-oncological research [1,2]. In contrast to the effects of interventions that are most often examined extensively in RCTs [3], much less attention has been paid to the proportion of patients who participate in these interventions and whether those who choose to participate are representative of the target population in terms of sociodemographic and clinical characteristics [2,4]. Thus, RCTs often provide accurate estimates of the internal validity (i.e., effect of an intervention for the sample enrolled in the RCT), but do not typically provide information about the external validity or generalizability (i.e., effect of an intervention in the target population) [5-7].

The reach of an RCT provides information on the absolute number, proportion and representativeness of the sample that participates in the trial [8]. The absolute number and proportion of RCT participants are relatively easy to assess and are therefore most often reported. However, few studies report the representativeness of the sample enrolled in an RCT, which is a much more challenging metric to assess [8,9], since it requires sociodemographic information, and preferable psychosocial, clinical or case mix information on RCT participants as well as non-participants. It is particularly challenging to collect information on non-participants who typically do not consent to be included in the research [8].

Interventions with promising effects in RCTs have been implemented in daily practice without specific knowledge of the generalizability of the results. Therefore, more attention should be paid to providing information related to the representativeness of the sample enrolled in an RCT. Lack of representativeness may occur as a result of inadequate selection procedures (i.e., sampling bias) or when the probability of non-participation in the study is related to the object of research (i.e., non-response bias) [10,11].

To fill this gap, the aim of the current study was to address the reach of a web-based self-management intervention within the context of the Lymphoma InterVEntion [LIVE] trial, whose objectives have been described elsewhere [12]. For the LIVE-trial, patients were selected from the population-based Netherlands Cancer Registry (NCR) that routinely collects data on sociodemographic and

clinical characteristics. This can provide unique insight into the characteristic differences between RCT participants and non-participants to estimate the reach of this intervention. The primary objectives were to (1) describe the proportion of RCT participants compared to all patients invited to participate, and (2) compare sociodemographic and clinical characteristics of RCT participants with those of all respondents (i.e., patients who completed a web-based or paper questionnaire), all patients invited to participate, and all patients selected from the NCR. In addition, as patients had the option of completing a web-based questionnaire (i.e., enrollment in the RCT) or a paper-based questionnaire (i.e., no enrollment in the RCT, observational cohort), a secondary objective was to assess baseline differences in psychological distress, self-management skills, and satisfaction with information provision (i.e., RCT outcome variables) between the two groups.

METHODS

Study design

Baseline data were collected from an RCT embedded in a population-based registry [13] as an observational cross-sectional dataset without information on the effectiveness of the intervention. In short, the LIVE-trial examines the effectiveness of feedback on patient-reported outcomes and a web-based self-management intervention on self-management skills, satisfaction with information provision, and psychological distress among patients with lymphoma [12].

Participants and recruitment procedure

From October 2016 to February 2019, patients who were diagnosed with lymphoma (i.e., Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), or chronic lymphocytic leukemia (CLL)), as defined by the International Classification of Diseases for Oncology-3 codes (ICD-O-3) [14], from 13 hospitals in the Netherlands were selected for participation via the NCR. The NCR registers all patients newly diagnosed with cancer in the Netherlands within the first year after diagnosis and routinely collects detailed data on sociodemographic and clinical characteristics (e.g., patient age and sex, date of cancer diagnosis, cancer type, and primary treatment). Patients had to be 18 years or older at time of study invitation. Treating hematologists were asked to verify the patients' eligibility for the study and to exclude patients who were deceased, had severe psychopathology, were too ill, were not able to complete a questionnaire in Dutch, or had severe cognitive impairment. All eligible patients were invited by mail to participate by their own

hematologist. Patients had the option to complete a web-based or paper-based questionnaire. Patients were informed that completion of the web-based questionnaire automatically resulted in enrollment in the RCT with randomization to one of the study arms, whereas completion of a paper questionnaire resulted in participation in the observational Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) lymphoma registry [13] but not enrollment in the RCT. To address the primary objective of the current study – describing the proportion of RCT participants compared to all patients invited to participate – paper respondents were assessed as nonparticipants as they did not participate in the RCT.

Measures

Sociodemographic and clinical measures

Sociodemographic characteristics (age and sex) and detailed clinical information (date of diagnosis, cancer type, primary treatment) were available from the NCR. Information on education level and marital status was assessed from the questionnaire (data only available for respondents). Comorbidities at the time of questionnaire completion were assessed using an adapted version of the Self-Administered Comorbidity Questionnaire [15]. Patients were asked to identify comorbidities present within the past 12 months, including heart disease, hypertension, arthritis, stroke, lung disease, diabetes, stomach disease, kidney disease, liver disease, anemia, thyroid disease, and rheumatoid arthritis. Positive responses were summed to a total score ranging from 0 to 12 (data only available for respondents).

Personality traits

Personality traits were assessed with the Big Five Inventory, a 44-item inventory designed to measure the Big Five dimensions of personality: extraversion, neuroticism, conscientiousness, agreeableness, and openness to experience [16]. Each item was scored on a 5-point scale. Scale scores were obtained by averaging all items for each domain ranging from 0 to 5. Each trait is assumed to represent a continuum from high to low on the specific attribute and is partnered with a trait on the opposite pole of the spectrum [17,18].

Information preferences

One question from an adapted version of the Information Satisfaction Questionnaire was used to measure information preferences [19]. Patients had to categorize themselves into one of three groups: those who would like (1) *all*

available information, (2) only positive information about the illness, and (3) only limited information. Patients were further asked whether they use the internet (yes/no).

Psychological distress, self-management skills, and satisfaction with information provision

Primary outcomes to assess the effectiveness of the intervention were psychological distress, self-management skills, and satisfaction with information provision.

Psychological distress was assessed with the 14-item Hospital Anxiety and Depression Scale (HADS) [20]. Each item is rated on a 4-point scale from 0 to 3. The total score was obtained by adding all item scores and ranged from 0 to 42, in which higher scores indicate higher levels of psychological distress [21]. Patients with a HADS total score ≥ 13 were categorized as “psychologically distressed” [22].

Self-management skills were assessed with the Health Education Impact Questionnaire (heiQ) that contains 40 items across 8 scales: positive and active engagement in life, health-directed activities, skill and technique acquisition, constructive attitudes and approaches, self-monitoring and insight, health service navigation, social integration and support, and emotional distress [23]. Each item is scored on a 4-point scale. Scale scores were obtained by averaging all items for each domain and ranged from 1 to 4. Higher scores indicate better status or self-management, except for emotional distress in which higher scores indicate greater distress [23].

Satisfaction with overall information provision was assessed with one item from an adapted version of the Information Satisfaction Questionnaire [19]. Patients were asked to rate their level of satisfaction for overall information provision on a scale from 1 (“very unsatisfied”) to 5 (“very satisfied”).

Statistical analyses

The proportion of RCT participants (i.e. participation rate) was calculated by dividing the number of patients who were enrolled in the RCT by the total number of eligible patients who were invited to participate. Sociodemographic and clinical characteristics of RCT participants were compared with those of all respondents (i.e., patients who completed a web-based or paper-based questionnaire), all patients invited to participate, and all patients selected from the population-based

NCR. In addition, personality traits and information preferences of RCT participants were compared with those of all respondents. Differences on sociodemographic and clinical characteristics between RCT participants and non-participants were compared using analysis of variance for continuous variables and chi-square tests for categorical variables. Differences in baseline psychological distress, self-management skills, and satisfaction with information provision (i.e., RCT outcome variables) between RCT participants and paper respondents were compared using analysis of variance for continuous variables and chi-square tests for categorical variables. All statistical analyses were performed with SAS version 9.4 (Cary, NC, USA). $P \leq .05$ indicated statistically significant differences.

RESULTS

Patients selected from the NCR

As shown in Figure 1, a total of 1193 patients with lymphoma or CLL who were ≥ 18 years old at diagnosis from 13 hospitals were selected from the population-based NCR. The basic characteristics of the invited patients are summarized in Table 1. The majority of patients were men, were diagnosed with high-grade NHL, and were actively being treated, with chemotherapy as the most common treatment.

Patients invited to participate

A flowchart of the patient selection process is shown in Figure 1. Of all selected patients, 25% (296/1193) were excluded after verifying eligibility by their treating hematologists for the following reasons: deceased, severe psychopathology, too ill, insufficient proficiency of the Dutch language, and cognitive impairment. In addition, 156 patients were not eligible for other reasons, including 36 patients who received treatment or follow-up in another hospital and 20 patients for whom the ultimate diagnosis did not meet our inclusion criteria (e.g., myelodysplastic syndrome, acute lymphoblastic leukemia). The remaining 100 patients were excluded by the hematologists for unknown reasons. Furthermore, five patients were excluded as they declined participation in previous studies within the PROFILES registry. After exclusion of these patients, 892 patients (75%) were invited to participate and completed a questionnaire. Patients invited to participate did not significantly differ from all patients selected from the NCR in terms of age ($P = .38$) and sex ($P = .07$) (Table 1).

Table 1. Baseline characteristics of patients selected from the NCR according to participation

	Patients selected from the NCR (N=1193) n(%)	Patients invited to participate (N=892) n(%)	Respondents (N=456) n(%)	RCT participants (N=227) n(%)
Sociodemographic characteristics				
Age in years: mean (SD)	64.7 (15.6)	64.1 (15.3)	64.5 (13.5)	60.7 (13.4)
Sex				
Male	725 (61)	537 (60)	291 (64)	161 (71) ^{+,‡}
Female	468 (39)	355 (40)	165 (36)	66 (29)
Education level #				
Low	N/A	N/A	33 (7)	6 (3)
Medium	N/A	N/A	260 (58)	106 (47)
High	N/A	N/A	159 (35)	114 (50)
Partner (yes)	N/A	N/A	355 (79)	190 (84)
Clinical characteristics				
Months since diagnosis: mean (SD)	13.9 (3.5)	14.0 (3.4)	14.2 (3.3)	14.0 (3.2)
Cancer type				
HL	120 (10)	102 (11)	46 (10)	27 (12)
NHL-HG	676 (57)	484 (54)	260 (57)	125 (55)
NHL-LG	280 (23)	224 (25)	114 (25)	56 (25)
CLL	116 (10)	82 (9)	36 (8)	19 (8)
Primary treatment				
Active surveillance	315 (26)	252 (28)	113 (25)	53 (23)
CT alone	522 (44)	405 (45)	222 (48)	109 (48)
RT alone	80 (7)	70 (8)	31 (7)	11 (5)
CT + RT	103 (9)	90 (10)	51 (11)	29 (13)
SCT ± CT ± RT	30 (3)	25 (3)	20 (4)	16 (7)
Other	56 (5)	39 (4)	16 (4)	7 (3)
Unknown	87 (7)	11 (1)	3 (1)	2 (1)
Number of comorbidities: mean (SD)	N/A	N/A	1.3 (1.2)	1.1 (1.1)
Personality traits				
Openness	N/A	N/A	3.4 (0.6)	3.5 (0.6)
Conscientiousness	N/A	N/A	3.7 (0.5)	3.7 (0.4)
Extraversion	N/A	N/A	3.5 (0.6)	3.5 (0.6)
Agreeableness	N/A	N/A	3.8 (0.5)	3.8 (0.4)
Neuroticism	N/A	N/A	2.5 (0.7)	2.4 (0.6)

(continued on following page)

Table 1. Baseline characteristics of patients selected from the NCR according to participation (continued)

	Patients selected from the NCR (N=1193) n(%)	Patients invited to participate (N=892) n(%)	Respondents (N=456) n(%)	RCT participants (N=227) n(%)
Information preferences				
All available information	N/A	N/A	211 (47)	126 (56)
Only positive information	N/A	N/A	65 (15)	23 (10)
Limited information	N/A	N/A	170 (38)	78 (34)
Internet use (yes)	N/A	N/A	370 (82)	220 (97)

Abbreviations: CLL, chronic lymphocytic leukemia; CT, chemotherapy; HL, Hodgkin lymphoma; NHL-HG, high-grade non-Hodgkin lymphoma; NHL-LG, low-grade non-Hodgkin lymphoma; RCT, randomized controlled trial; RT, radiotherapy; SCT, stem-cell transplantation; SD, standard deviation.

The groups in columns are not mutually exclusive; RCT participants are also included in the groups of the other 3 columns.

For education, low indicates none/primary school; medium, lower general secondary education/vocational training; and high, pre-university education/high-level vocational training/university.

⁺ Statistically significantly different from all patients selected from the NCR ($p < 0.05$).

[‡] Statistically significantly different from all patients invited to participate ($p < 0.05$).

Respondents

Among the 892 invited patients, 456 patients (51%) responded and completed either a web-based or paper questionnaire. The mean age of all respondents (Table 1) was comparable with that of non-respondents (63.8 years, $P = .43$), and the majority of the respondents were also men. Respondents did not differ from all patients selected from the NCR in terms of age ($P = .81$) and sex ($P = .26$). Respondents were more often actively treated than non-respondents (75% vs 66%, $P = .01$). Half of the respondents completed a paper questionnaire ($N = 229$), whereas the other half completed a web-based questionnaire and were enrolled in the RCT ($N = 227$). Nearly half of the respondents (47%) stated that they would like to receive all available information, with a lower proportion preferring limited information (38%), and even less indicating that they would like to receive only positive information about the illness (15%) (Table 1). Approximately 82% of all respondents reported using the internet.

RCT participants

A quarter of all invited patients (227/892) participated by completing a web-based questionnaire, which resulted in a participation rate of the RCT of 25%. The mean

age of RCT participants was slightly lower than that of non-participants (i.e., non-respondents and paper respondents; $N=665$, 65.3 years, $P<.001$) with a slightly higher mean time since diagnosis, and comprised a higher proportion of men (71% vs 57%, $P<.001$). The proportion of patients who were actively treated were comparable between RCT participants and non-participants (76% vs 69%, $P=.13$). In addition, RCT participants were significantly younger than respondents, patients invited to participate, and patients selected from the NCR (all $P<.001$). Furthermore, there was a higher proportion of men among RCT participants compared with all patients invited to participate and all patients selected from the NCR (both $P<.001$).

RCT participants vs paper participants

RCT participants were younger than paper respondents (60.7 vs 68.3 years, $P<.001$). In addition, RCT participants were more often male (71% vs 57%, $P=.002$), more highly educated (50% vs 20%, $P<.001$) and more often had a partner (84% vs 75%, $P=.02$). No significant differences were found between RCT and paper respondents regarding cancer type or primary treatment ($P=.54$ and $P=.06$, respectively). RCT participants also reported fewer comorbidities than paper respondents (1.1 vs 1.4, $P=.02$).

Concerning personality traits, RCT participants had lower scores on neuroticism (2.4 vs 2.6, $P=.003$) and higher scores on openness to experience (3.5 vs 3.4, $P=.002$) than paper respondents, although effect sizes were small (Cohen $d=.29$ and $.28$, respectively). With respect to information preferences, the majority of RCT participants stated a preference for receiving all available information, whereas only 39% of paper respondents indicated this preference ($P=.001$). Conversely, paper respondents more often preferred receiving limited information (42% vs 34%, $P=.001$). Furthermore, RCT participants more often used the internet (97% vs 66%, $P<.001$).

Emotional distress, as measured with the heiQ, was significantly lower among RCT participants compared with the score of paper respondents (Table 2), although the effect size was small (Cohen $d=.25$).

No significant differences were observed regarding other self-management skills between the RCT and paper groups. In addition, no significant differences were observed in the proportion of patients with psychological distress between RCT participants and paper respondents, although paper participants seemed to have

higher mean scores. Furthermore, no differences were observed between RCT participants and paper respondents regarding satisfaction with overall information provision (Table 2).

Table 2. Differences in RCT outcome variables at baseline between RCT participants ($N=227$) and paper respondents ($N=229$)[‡].

	RCT participants ($N=227$)	Paper respondents ($N=229$)	<i>P</i>	Cohen's <i>d</i>
	n(%)	n(%)		
Psychological distress (yes)	34 (15)	45 (20)	.18	
Psychological distress: mean (SD) [#]	6.5 (5.9)	7.5 (6.1)	.06	.18
Self-management skills: mean (SD)[†]				
Health-directed behavior	3.3 (0.6)	3.2 (0.6)	.12	.14
Positive and active engagement in life	3.2 (0.5)	3.1 (0.5)	.05	.18
Self-monitoring and insight	3.0 (0.4)	3.1 (0.4)	.62	.05
Constructive attitudes and approaches	3.3 (0.5)	3.3 (0.5)	.66	.04
Skill and technique acquisition	2.9 (0.5)	3.0 (0.5)	.33	.09
Social integration and support	3.2 (0.5)	3.2 (0.5)	.77	.03
Health services navigation	3.3 (0.4)	3.3 (0.4)	.54	.06
Emotional distress	1.8 (0.5)	1.9 (0.6)	.01	.25
Satisfaction with overall information provision			.29	
Very unsatisfied	1 (0)	2 (1)		
Unsatisfied	9 (4)	8 (4)		
Neither	49 (22)	41 (18)		
Satisfied	126 (56)	143 (63)		
Very satisfied	41 (18)	27 (12)		

Abbreviations: RCT, randomized controlled trial; SD, standard deviation.

[#] scale 0-42; higher score indicates more psychological distress

[†] scale 1-4; higher scores indicate better status or self-management, except for emotional distress, in which higher scores indicate higher distress

DISCUSSION

Principal findings

This reach analysis among RCT participants within a population-based sample showed a selective reach with an underrepresentation of older patients, women, and those with a medium to low level of education. In addition, our RCT

participants may represent individuals with relatively better psychological well-being as scores for emotional distress were lower in this group.

Approximately a quarter of the population-based sample of patients with lymphoma and CLL were assessed to be not eligible for the study for various reasons (e.g., deceased, severe psychopathology or cognitive impairment, a different diagnosis was ultimately made). Among the eligible patients who were invited to participate, 51% responded and completed a questionnaire, half of whom completed the web-based questionnaire and were enrolled in the RCT, resulting in a participation rate of 25%. This means that only one in four of all eligible patients actually participated in the RCT. This participation rate was lower compared with that of an RCT on the fully automated electronic health (eHealth) application Oncokompas that supports cancer survivors in their self-management (48%) [24]. Patients in the Oncokompas RCT were selected from the population-based NCR. However, cancer survivors in the Oncokompas RCT were first invited in an online survey study on supportive care and eHealth to assess internet use. Their participation rate was calculated as the number of RCT participants divided by the number of eligible respondents of the survey (access to the internet and email address). Thus, their group of eligible respondents was more selective compared with our sample. In our sample, only 82% of all respondents used the internet, and this percentage may be even lower among all patients invited to participate.

The results of the current study demonstrate that the RCT participants were younger, more often men, and more often actively treated compared to non-participants. Thus, the sample of RCT participants may not be representative of the target population. Therefore, even though the sample size reached the required number of patients [12], this sample may not be reliable for drawing conclusions about the target population. Furthermore, the effects of the intervention on the target population may be different from the effects that were found in the RCT sample [10,25].

These results also provide information about the response rate of observational research, which was 51%. This is comparable with response rates from other population-based studies on quality of life among lymphoma survivors in Germany (54.7%) [26] and the United States (54.8%) [27]. However, the current response rate is lower compared with that reported from earlier observational research within our study group at approximately 80%, despite similar patients and

recruitment procedures [28]. This might be explained by the knowledge that the more information that is disclosed about the study – which is inherently more for an RCT than for observational research – the higher the proportion of non-respondents [29]. Patients received abundant information along with the invitation, especially about participation in an RCT and randomization. The amount of information, as well as the knowledge of being randomized when completing a web-based questionnaire may have deterred patients from participating. In addition, the type of intervention may have influenced the participation rate, as the majority of patients did not have problems with adjustment to cancer and therefore may have been less interested in a self-management intervention. Another explanation may be related to the fact that participation and response rates for health-related research have been declining over the past several years [30,31], and potential participants are faced with an increasing number of requests to participate in studies. This may result in patients refusing to participate in all studies [32].

We further compared characteristics of RCT participants with those of paper respondents. RCT participants, who completed the web-based questionnaire, were younger, more often men, and more highly educated than the paper respondents, which is similar to the characteristics from previous observational studies within our study group [33,34]. Highly educated patients more often display prosocial behavior than patients with lower levels of education, and therefore the former group may be more likely to participate in an RCT for altruistic reasons [35]. In addition to differences in sociodemographic characteristics, RCT participants reported lower scores related to neuroticism and higher scores related to openness than paper respondents. In addition, information preferences slightly differed between RCT and paper respondents, as RCT participants more often wanted to receive all available information on their disease. RCT participants also more often reported using the internet. To complete a web-based questionnaire, and subsequently be enrolled in a web-based self-management intervention RCT, patients must not only be able to use a computer but also be sufficiently skilled in browsing the internet [33]. Although there seems to be a trend of older individuals becoming more active online [33,36], there is still a subgroup of patients who do not use the internet and thus have no access to a web-based questionnaire or internet-based intervention.

Despite these various differences between RCT participants and paper participants, baseline scores on self-management skills, satisfaction with information provision and psychological distress appeared to be comparable between these groups, although scores for emotional distress were slightly lower among RCT participants.

Strengths

The strengths of this study include its unique setting. As patients were recruited from the population-based NCR, we had information on sociodemographic and clinical characteristics of both RCT participants and non-participants. In addition, as the RCT was embedded in the PROFILES registry, we were able to assess differences between RCT participants and paper respondents on sociodemographic and clinical characteristics, in addition to personality traits, information preferences, and baseline psychological distress, self-management skills, and satisfaction with information provision (i.e., RCT outcome variables). This information provided the opportunity to determine both the reach and generalizability of the RCT sample.

Limitations

The current study has some limitations. Although information regarding sociodemographic and clinical characteristics of non-participants was available, we did not have information about non-participants' reasons for declining participation or their physical and psychological health. Therefore, it remains unclear whether the physical and psychological health of RCT participants is similar to that of non-participants. In a previous study that assessed the generalizability of the results of observational research among cancer survivors by comparing characteristics of participants and non-participants, sensitivity analysis demonstrated that quality of life might be lower among non-participants [34]. As RCT participants may have a systematically higher quality of life, or report fewer symptoms, compared to non-participants, observed outcomes may represent a group of healthier patients with better outcomes. This may lead to circumspection in generalizing the results of an RCT to the target population. It is important to keep this in mind when interpreting RCT results that may only represent a minority of the target population.

Conclusions

The participation rate in the RCT was 25%. RCT participants may be not representative of the target population owing to different sociodemographic and

clinical characteristics. RCT results should be considered with caution, as RCT participants represent a minority of the target population, and may actually be those least in need of the intervention.

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CHAPTER 8

GENERAL DISCUSSION



GENERAL DISCUSSION

In this chapter, the main findings of the studies described in this thesis are discussed in a broader context. In addition, methodological considerations and implications for clinical practice and future research are discussed.

The first objective of this thesis was to make an inventory of factors that are associated with psychological distress (**Part I**). We started with investigating factors associated with an increased risk of psychological distress among patients with lymphoma (**Chapter 2**). We observed that neuroticism was the greatest factor associated with psychological distress. The association between neuroticism and psychological distress, however, was partially explained by passive coping strategies including anxious preoccupation and helplessness/hopelessness. In addition, younger age and comorbid conditions were associated with psychological distress. Next, we investigated the impact of lymphoma and psychological distress on the use of healthcare services (**Chapter 3**). Lymphoma survivors reported more medical contacts (i.e., contacts with the general practitioner (GP) or medical specialist) compared to a normative population without cancer. In addition, psychologically distressed survivors had even more medical contacts than those without psychological distress and received psychosocial care more often.

The second part of this thesis focused on the development, evaluation, and reach of an intervention for patients with lymphoma to reduce psychological distress and increase satisfaction with information provision and self-management skills: the Lymphoma InterVEntion [LIVE] (**Part II**). We started this part with investigating whether patients with lymphoma wished to receive feedback on their patient-reported outcomes (PROs), *how* they would like to receive this feedback, and how this feedback was evaluated (**Chapter 4**). The majority of patients (80%) wished to receive feedback on their PROs, of whom almost all patients wished to compare their scores with other patients with lymphoma. In addition, patients rated the PRO feedback as useful.

Next, the rationale and study design of the LIVE randomized controlled trial (RCT) were presented (**Chapter 5**). The RCT consisted of two interventions: 1) feedback to patients on their PROs, and 2) a web-based self-management intervention named *Living with lymphoma*. These interventions aimed to reduce psychological

distress, and increase self-management skills and satisfaction with information provision. Hereafter, the main effects of the PRO feedback and *Living with lymphoma* were described (**Chapter 6**). Neither positive, nor negative effects of PRO feedback with or without the use of the *Living with lymphoma* intervention were observed on psychological distress, self-management skills, satisfaction with information provision, and healthcare use. Last, the reach of our web-based self-management intervention within the context of the LIVE trial was evaluated (**Chapter 7**). From a population-based sample of eligible patients, 51% completed the first questionnaire, of whom half completed a paper questionnaire and half completed a web-based questionnaire. Web-based completers were automatically randomized into one of the RCT arms, which resulted in an RCT participation rate of 25%. RCT participants were younger, more often male, and more highly educated compared to nonparticipants. Therefore, we cannot extrapolate the results of our RCT to all patients with lymphoma in the Netherlands.

Together, the studies in this thesis described the process from making an inventory of factors associated with psychological distress among lymphoma survivors (**Chapter 2 and 3**) to the development (**Chapter 4 and 5**), evaluation (**Chapter 6**) and reach (**Chapter 7**) of an intervention to reduce psychological distress and increase self-management skills and satisfaction with information provision: Lymphoma InterVEntion [LIVE]. This final chapter discusses the practical implications of the findings in more detail and some methodological considerations about the central approaches. At the end of this chapter, implications for clinical practice and future research, and an overall conclusion are presented.

MAIN FINDINGS

Factors associated with psychological distress

Sociodemographic and clinical factors

The results in this thesis indicate that sociodemographic, clinical, and psychological factors are associated with psychological distress among patients with lymphoma. We observed that younger age and the presence of comorbid conditions were associated with psychological distress. Our findings that younger age was associated with increased psychological distress was supported by an integrative review among hematological cancer survivors [1]. Various reasons can account for why psychological distress may be more prevalent among younger patients:

younger patients are more likely to receive aggressive lymphoma treatment [2], which is associated with greater side-effects and long-term late effects. In addition, younger patients may have more problems with adjustment to cancer because the disease and intensive treatment regimen can interfere substantially with their social and vocational needs [3], such as child care, missed work because of their cancer treatment or side effects, and lack of financial or employment stability. Furthermore, patients with more comorbid conditions had an increased risk of psychological distress. Previous studies showed that although the specific impact of cancer on psychological distress is smaller among patients with comorbid conditions than those without, each comorbid condition increases total psychological distress [3]. Thus, comorbid conditions interact with cancer to result in more symptoms and psychological burden.

Moreover, other sociodemographic and clinical factors including sex, education, cancer type, and active treatment showed no significant association with distress in patients with lymphoma.

Psychological factors

Personality reflects patients' characteristic patterns of thoughts, feelings, and behaviors [4] and it affects the way in which stressful situations are interpreted. It is recognized that substantial associations exist between personality and psychological distress [5]. The results of this thesis indicated that the personality trait of neuroticism – referring to stable tendencies to experience negative affects and to respond with negative emotions to threat, frustration, or loss [4] – was positively associated with psychological distress. A meta-analysis among adults in general demonstrated that neuroticism showed the strongest link to psychopathology [6], but several other traits showed substantial effects independent of neuroticism. Although personality traits are relatively stable and hard to change [7], they can be useful for identifying patients at risk for psychological distress [6].

In addition to the abovementioned factors, coping strategies have been considered important determinants of psychological distress in patients with cancer [8]. The results of this thesis revealed that passive coping strategies (i.e., 'Helplessness/Hopelessness', 'Anxious Preoccupation') were positively associated with psychological distress and showed substantial effects independent of personality, sociodemographic and clinical characteristics. These results were in line

with previous literature that demonstrated a positive association between passive coping strategies and psychological distress among patients with different cancer types [9-11]. Passive coping refers to a sense of helplessness in dealing with the stressor and relying on others to resolve the stressful event or situation [12,13]. A sense of lack of control and inability to have impact on the stressful situation reinforces negative adjustment to cancer and psychological distress. The reliance on external resources is opposite to active coping (e.g., 'Fighting Spirit'), in which patients rely upon their own resources to cope with the stressor. In literature, some inconsistencies exist about the association between active coping and psychological distress. Although some studies – including the findings in this thesis – did not reveal an association between active coping and psychological distress [9,10], others indicated that active coping was a protective factor for psychological distress [14-16].

Impact of psychological distress on healthcare use

In this thesis, it was observed that lymphoma survivors contacted their GP and medical specialist more often than an age- and sex-matched normative population without cancer. These results were in line with previous studies [17-21]. The number of GP contacts normalized over time, whereas the increased contacts with medical specialists persisted up to ten years after diagnosis. This may be due to the frequency of follow-up appointments as advised in the Dutch guidelines for treatment and follow-up of patients with lymphoma (www.hovon.nl). Furthermore, when looking at the impact of psychological distress on healthcare use, our results demonstrated that those who experienced psychological distress had even more contacts with their GP and medical specialist. It has been demonstrated that patients with psychological problems contact their GP almost twice as often – for both psychological and somatic problems – compared to those without psychological problems [22]. It is known that psychologically distressed patients are more likely to somatize, intensify their symptoms, and be more aware of bodily sensations, making them more likely to seek help from medical care services [23-26]. These results suggest that the presence of psychological distress may impact the way and frequency lymphoma survivors access healthcare.

The results in this thesis furthermore indicated that psychologically distressed patients not only had an increased use of medical services, but also received psychosocial care more often. Nevertheless, more than half of those scoring above the cutoff for psychological distress did not receive psychosocial care. Hence, many

survivors did not receive coping resources and psychosocial care services that may help to reduce psychological distress [27]. This is in line with previous literature [25,28-30]. It has been demonstrated that only one-third of patients scoring above the cutoff for psychological distress indicated a need for professional help with psychological distress [31]. There may be various reasons why psychologically distressed patients do not seek or engage in psychosocial care services. They may choose to rely on friends and family or prefer not to talk about their problems [32]. Moreover, it is known that lack of organizational and therapeutic integration of psycho-oncological services in routine oncology care may be a barrier to the use of psychosocial care services [33]. It has been demonstrated that those experiencing psychological distress and not receiving psychosocial care reported an increased use of medical care services [29]. Therefore, adequate recognition of psychological distress and appropriate care for those experiencing psychological distress may help to reduce the use of medical care services [25]. It is known that minimal psychosocial interventions may increase survivors' quality of life and reduce overall healthcare expenditures [34].

Interventions to reduce psychological distress

Psychological distress and other adverse problems may increase when the right information and support is not available [35,36]. This may subsequently lead to increased use of healthcare services [37]. Interventions that provide patients with psychosocial support and adequate information have the potential to reduce psychological distress.

Previous research showed that one third of lymphoma survivors were not (completely) satisfied with the information they received and would like to have more information, for example, about supportive care [38]. The results of this thesis indicate that approximately 75% of patients with lymphoma were satisfied with the information they received, which means that the proportion of patients who were not (completely) satisfied diminished to a quarter. Since information provision is often seen as a crucial tool for the support of cancer survivors – by facilitating their involvement in management of their health(care) [39] – it has been suggested that efforts are needed to improve the information provision for lymphoma survivors. Furthermore, as mentioned before, it is known that many survivors do not receive coping resources and psychosocial support services that may help them to reduce their psychological distress [27]. It has been suggested that an intervention that increases patients' own resources to cope with cancer may help to reduce

psychological distress. In this thesis, two interventions were developed that aimed to increase patients' self-management skills and satisfaction with information provision, and reduce psychological distress.

Impact of PRO feedback to patients and a web-based self-management intervention on patient reported outcomes

Based on the wishes of patients to get insight in their own PRO data, an application within the PROFILES registry has been developed to provide feedback on PROs directly to patients instead of via healthcare providers. PRO feedback directly to patients enables patients to self-monitor their physical and psychosocial functioning, which could increase awareness and early recognition (in changes) of symptoms. The findings in this thesis indicate that 80% of those in the pilot study and 77% of those with access to PRO feedback in the RCT consulted the PRO feedback. Survivors who consulted the PRO feedback had similar scores on psychological distress compared to those who did not. In addition, the results of this thesis indicate that lymphoma survivors considered the PRO feedback as useful, especially the option to compare their scores with other lymphoma survivors with the same age and sex. This may help them to either reassure that what they experience is 'normal' or may motivate them to take action and discuss their problems with a healthcare professional. These findings suggest that inclusion of PRO feedback directly to patients may increase patient involvement and help patients to feel more in control of their care.

No evidence of a beneficial effect of PRO feedback to patients on psychological distress, self-management skills, and satisfaction with information provision was found in this thesis. Moreover, the PRO feedback neither had adverse effects on these outcomes and thus not induces fears or anxiety compared to the control group. Early recognition and discussion of adverse problems with healthcare providers is important. Appropriate referral to psychosocial care in cancer survivors may subsequently contribute to decreased use of medical healthcare services.

Self-monitoring of symptoms may be a good first step for early symptom recognition. Providing PRO feedback to patients however may not be sufficient to ensure a reduction in psychological distress. Previous literature showed that providing feedback on PROs is particularly effective in the identification and creation of awareness of problems and unmet needs, but intervening steps may be necessary to actually improve health outcomes [40].

Nevertheless, face-to-face psychosocial interventions are costly and often associated with prolonged waiting periods for individuals in need for psychosocial care. These waiting periods are disadvantageous for both individuals seeking help as the healthcare system, as it has been demonstrated that those in need for help use more unspecific healthcare services [29]. Therefore, appropriate interventions should be offered to those unable to receive immediate professional psychosocial care. Web-based interventions can be applied flexibly, with comparably little time, and personnel resources [41,42]. The implementation of web-based self-help interventions may be a possibility to produce relief for those waiting for psychosocial care or those with symptoms that may be too mild to be considered for professional support.

Living with lymphoma is a web-based self-management intervention that aims to increase self-management skills and satisfaction with information provision, and reduce psychological distress. It is an adaptation from the evidence-based BREast cancer e-healTH (BREATH) intervention [43,44] and is based on psychoeducation and cognitive behavioral therapy (CBT). Previous research demonstrated that interventions based on CBT – that combine emotion, cognition, and behavior – may help patients to better cope with the stress of the cancer experience [45]. Although the efficacy of the web-based BREATH intervention for the reduction of mild psychological distress has been shown in a targeted sample of mild distressed breast cancer survivors, there is limited evidence for the effectiveness and acceptance of such an intervention in cancer care under ‘real world conditions’ [46].

Unfortunately, no evidence of a benefit of *Living with lymphoma* in an untargeted sample was found in this thesis. Access to *Living with lymphoma* did not increase self-management skills or satisfaction with information provision, and did not reduce psychological distress. The findings in this thesis thus differ from the findings regarding the BREATH intervention [43]. The major difference between the BREATH intervention and *Living with lymphoma* is the population to whom the intervention was offered. In this thesis, however, it was explicitly the aim to investigate the effects within a population-based setting without prior screening for distressed symptoms, as this format has the greatest potential to enable psychosocial care services to be delivered nationwide.

Regarding the uptake of the intervention, of those with access to *Living with lymphoma* only 36% actually signed up and even among them, the actual use of the intervention was minimal. Low intervention uptake rates (i.e., logging into the intervention) and low levels of adherence (i.e., completing modules of the intervention) are known to limit the potential impact of an intervention [47]. When patients were asked about their uptake and adherence, they indicated that they felt well and were not in need of an intervention. This corresponds to the small proportion of psychologically distressed patients within a web-based sample (15%). This percentage was significantly lower than observed within the previously investigated, observational lymphoma cohort (25%), suggesting that web-based participants may represent the more healthy patients with fewer adverse problems and not the patients who might be in need for an intervention to reduce psychological distress. On the other hand, a meta-analysis investigating the uptake and adherence of psychological interventions targeting psychological distress for cancer patients demonstrated that patients who were screened and identified as psychologically distressed were less likely to accept intervention than unselected patients [48]. Thus, the uptake was lower in studies that recruited patients scoring above the cutoff for psychological distress, compared to studies that recruited unselected patients. Although this suggests that unselected patients were more likely to accept such interventions, there is no evidence that greater intervention effects could be found among unselected patients. The results in this thesis, however, suggest that unguided web-based self-management interventions may not be effective in reducing psychological distress within a population-based, untargeted setting, but mainly in a targeted group. More research is needed to understand barriers to acceptance of psychosocial support, particularly since it has been demonstrated that uptake rates were lower for psychologically distressed patients [48].

Furthermore, our findings indicate that older, female, and medium or low educated patients were underrepresented in the web-based RCT sample. These findings suggest that results from the RCT may not be simply generalized to the target population. The representativeness of the sample and the generalizability of the results will be more extensively discussed in the next section of this chapter.

METHODOLOGICAL CONSIDERATIONS

The studies presented in this thesis have several methodological strengths and limitations, which have been previously described in the different chapters. In this section, the most important methodological considerations of the LIVE trial are discussed in more detail, and suggestions to advance future studies are provided.

RCT embedded within a population-based registry

In this thesis, an RCT was conducted to examine the effectiveness of PRO feedback with or without access to *Living with lymphoma* on psychological distress, self-management skills, and satisfaction with information provision. RCT participants were individually randomized to avoid bias by distributing the characteristics of patients that may influence outcome randomly between the three RCT arms⁴⁹: (1) standard care; (2) standard care plus PRO feedback; (3) standard care plus PRO feedback with access to the web-based self-management intervention *Living with lymphoma*.

In addition to a randomized controlled design, we chose for a pragmatic approach. As opposed to explanatory RCTs – which are designed to investigate the efficacy of an intervention under optimal, highly controlled conditions – pragmatic RCTs are designed to investigate the effectiveness of an intervention in a real-world setting [50,51]. In a pragmatic RCT it is important to align with clinical practice by the way in which you offer your intervention and without too many inclusion and exclusion criteria. Thus, exclusion criteria in our RCT were minimal, patients could use the interventions in the way they wanted to, and those in the standard care arm were not restricted regarding the way they searched for information about their disease and its consequences. Furthermore, our RCT was embedded within the population-based PROFILES registry [52], that enables PRO data collection management and linking these data to clinical data from the Netherlands Cancer Registry (NCR). In our RCT, the population-based NCR was used to select all patients who were diagnosed with lymphoma within a specific time frame in thirteen hospitals in the Netherlands and study eligibility was verified by their hematologists. Eligible patients were invited to participate and complete a questionnaire. Those who completed the web-based questionnaire participated in the RCT, whereas paper respondents were only observationally followed within the PROFILES lymphoma registry. The most important advantage of an RCT within a population-based setting is that the applicability and generalizability of the results

are maximized. As patients who participated in the BREATH trial – were *Living with lymphoma* was based on – were screened for psychological distress prior to the intervention, and the intervention was provided under slightly controlled conditions [43,44], it remained unclear what the effects of such intervention would be in a population-based setting. The population-based setting is essential for the evaluation of the effectiveness of PRO feedback and a web-based self-management intervention, as there is a lack of evidence that such interventions are applicable in daily clinical practice.

A pragmatic RCT however also has a number of methodological challenges that need to be considered. Pragmatic RCTs require access to more diverse clinical settings in order to increase the external validity and relevance of the outcomes [51]. In our RCT, patients were selected from thirteen – academic and community – hospitals throughout the Netherlands. Furthermore, both patients with aggressive and indolent lymphoma were invited to participate, so our RCT sample represents patients with curable lymphoma who have to cope with living *after* cancer, as well as patients with incurable lymphomas, who have to cope with living *with* cancer. Moreover, the interventions were designed in close and ongoing collaboration with relevant stakeholders [51] including psychologists, hematologist, researchers, and patients.

Response rates

This thesis reports data collected from two studies, namely a previously investigated, observational lymphoma cohort (**Chapter 3** and **4**) and the prospective longitudinal LIVE trial (**Chapter 2, 5, 6** and **7**). The response rate in the retrospective study was approximately 70%, which was relatively high. In the RCT the response rate was considerably lower, approximately 50%. Although similar patient groups were invited via comparable recruitment procedures, considerable differences in response rates exist. These differences may be explained by the knowledge that the more information is disclosed about a study – which is obviously more for an RCT than for an observational study – the greater the proportion of non-respondents [53]. Patients who were invited for the RCT received a lot of information, especially on participation in an RCT and randomization procedures. The amount of information, as well as the knowledge of being randomized when completing a web-based questionnaire may have deterred patients from participating. In addition, it is known that participation and response rates for health-related research in general have been declining over the

past years because potential participants are faced with an increasing number of requests to participate in studies [54-55]. This overload may result in patients refusing to participate in studies [56].

Another limitation with RCTs is loss to follow-up. Achieving a high response rate to follow-up questionnaires is important for study validity. However, in most longitudinal studies some loss to follow-up is considered to be inevitable. The findings in this thesis indicate that, after 4 months, approximately 85% of RCT participants completed the follow-up questionnaire, of whom 75% completed the follow-up questionnaire after one year, which is approximately 64% of the total RCT participants. This one year follow-up response rate was comparable with response rates of the previously investigated, observational lymphoma cohort for the second questionnaire, which varied between 50-67%. Furthermore, unequal loss of participants from different arms in an RCT results in attrition bias. Nevertheless, there was no difference among losses in the three arms in our RCT, decreasing the probability of attrition bias.

Generalizability of the results

As previously mentioned, pragmatic RCTs are designed to investigate the effectiveness of an intervention in a real-world setting [50,51]. Although all eligible patients from a population-based sample were selected and invited for participation, the findings in this thesis indicate that older, female, and medium or low educated patients were underrepresented in the RCT. While the RCT may yield accurate estimates of the effect of the interventions for those who participated in the RCT – mainly younger, male, and highly educated patients – it does not yield information about the effects in the target population and therefore, the findings in this thesis may not be simply generalizable to *all* patients with lymphoma. The results of this thesis indicate that it is difficult to recruit a sample that is representative of *all* patients with lymphoma, especially in an RCT for a web-based intervention. It is expected however that the RCT sample reflects the part of the population that is interested in engaging in a web-based intervention.

The findings in this thesis indicate that RCT participants were more often male (70% vs 60%), highly educated (50% vs 20%), and had a partner (84% vs 77%) than respondents of the previously investigated observational cohort study. It has been demonstrated that lower education was associated with a decreased willingness to participate in RCTs [57]. An explanation why we did not reach lower educated

patients within the RCT – as only 3% was lower educated – could be that those patients may not understand the information and therefore not participated in the RCT. The use of multimedia (e.g., video, audio, and graphics), for example, may allow complex information to be presented in a simple format comprehensible even to those with low literacy skills [58]. Another way to make the intervention better accessible to lowly educated individuals may be through commissioning someone who guides them through the intervention.

In addition, patients in the cohort study reported psychological distress considerably more often than patients who participated in the RCT (26% vs 15%, respectively). These findings suggest that the discrepancies between the previously investigated, observational cohort study and the RCT may be based on patient selection. It appears that especially those who may need the intervention the least, actually participated in the RCT. Furthermore, up to 20% of respondents of the prospective longitudinal study, in which the RCT was embedded, had no access to the Internet. As access to the Internet is necessary – but not sufficient – to benefit from web-based interventions, these findings suggest that not all patients who may benefit from psychological interventions could be reached via the Internet.

Moreover, as the findings in this thesis only reflect the effects of the intervention on patients with lymphoma, it remains unclear whether similar effects would be obtained among patients with different cancer types. Previous research indicated that perceived receipt of information differed for different cancer types [59], which may be explained by differences in, for example, age, sex, and severity of the disease. More research is needed to examine the impact of the interventions on patients with different cancer types.

Measures

All outcomes in this thesis were self-reported and thus subjective. While PROs are deemed essential in the evaluation of psychological interventions, it would also be valuable to have some more objective data. For example, as healthcare use was self-reported, it remains unclear how often and for what reasons healthcare services were really used. Similarly, comorbid conditions were self-reported by the patients. This way to collect health information only represents conditions known, memorized and openly reported by the patients [60]. Therefore, it remains unclear whether self-reported comorbid conditions may be under- or overreported. It

would be interesting to compare outcomes of self-reported data to more objective data, for example, from medical records or pharmacy data.

Furthermore, the outcome measures in the RCT were selected to investigate the effectiveness of the interventions, but not how patients anticipated on the extra information they received from the PRO feedback or self-management intervention. Although the results of this thesis indicated that patients who consulted the PRO feedback, reported more contacts with their GP, it remains unclear whether it was really the PRO feedback that motivated them to contact the GP. In line with the previous paragraph, it would be useful to ask patients for what reasons they contacted the GP. In addition, it would have been interesting to ask RCT participants how they felt after viewing the PRO feedback and what actions they have taken thereafter, in order to provide more information about the impact of the PRO feedback on patients.

Outcomes in both the cohort study and the RCT were furthermore generally very much focused on the negative effects of cancer and its treatment. In recent years, patients have regularly stated that they believe that our research focuses too much on the negative effects of cancer. The findings in this thesis suggest that most patients are able to cope with the disease and its consequences. This may be due to a high level of resilience, which refers to the ability to maintain or restore relatively stable psychological and physical functioning when confronted with stressful life events and adversities [61]. In addition, a cancer diagnosis can trigger positive life changes in survivors (e.g., a better appreciation for life or a better understanding what is most important in their life) [62,63]. These positive changes during the disease trajectory are commonly referred to as posttraumatic growth [64,65]. For future research, it would therefore be interesting to investigate factors related to resilience or posttraumatic growth among cancer survivors. This also provides patients with an opportunity to share more positive experiences of receiving a cancer diagnosis.

Clinical relevance

Measures of statistical significance quantify the probability that the study results are due to chance. Although statistical significance is of importance when the impact of an intervention is evaluated, it is also important to look at clinical relevance. Clinical relevance reflects whether a change makes a real difference to patients' well-being. While there are established, traditionally accepted values for

statistical significance testing, this is often lacking for evaluation clinical relevance [66]. However, for some questionnaires evidence-based guidelines have been developed to determine whether differences in scores are clinically relevant for patients [67]. When such guidelines are lacking, a cut-off of half a standard deviation (0.5 SD) can be used to determine clinically relevant differences [68]. When using this 'rule of thumb', there was no clinically relevant effect of the interventions observed in the RCT. Nevertheless, it is mostly the judgement of the patient which decides whether a result is clinically relevant or not. For example, I received a phone call from a young women who participated in the RCT and consulted the PRO feedback. She experienced some persistent symptoms and found out that her symptoms were above average. The PRO feedback made her more aware of her symptoms and motivated her to take action and contact an AYA outpatient clinic – intended for all adolescents and young adults who have had cancer at the age of 18 to 35 years – to discuss these symptoms with a healthcare provider. In addition, I spoke with another female patient who had an indolent NHL and received active surveillance. She had experienced reasonable fatigue for some time and was unsure whether this was normal for her disease. The PRO feedback demonstrated that fatigue was often experienced by patients with lymphoma. This reassured her and she told me she was no longer worried about her fatigue. It would have been interesting to ask an open question in the follow-up questionnaire about the evaluation of the interventions by the patients. Unfortunately, information about the evaluation is missing. Therefore, we were not able to make conclusive statements about the clinical relevance of the interventions on patients' well-being.

IMPLICATIONS FOR CLINICAL PRACTICE AND FUTURE DIRECTIONS

PRO feedback to patients

Previous research demonstrated that feedback from PROs could lead to improved symptom detection and increased dialogue about symptoms and problems between patients and healthcare providers [40,69-77]. In the majority of studies, PRO feedback however was provided to healthcare providers, such as physicians or nurse practitioners, and not directly to patients. In contrast, as it was the wish of patients to get insight in their own PRO data, we developed an application within the PROFILES registry to provide PRO feedback directly to patients and not to healthcare providers. Initially, healthcare providers were reluctant, as they expected patients to be increasingly worried if they scored high on symptoms, perhaps even

resulting in increased healthcare use. However, providing PRO feedback to patients may help them to either reassure that what they experience is 'normal' or may motivate them to take action and discuss their symptoms with a healthcare provider. Providing PRO feedback directly to patients may increase patient involvement and help patients to feel more in control of their care, as our patient-centered focus depends on patients actively communicating their concerns. This approach recognized that patients' and healthcare providers' perspectives regarding needs and symptoms can be meaningfully different [78-79]. In addition, although healthcare providers do not encourage an intervention that leads to an increase in the use of healthcare services, early recognition of adverse problems and appropriate referral to the right care services may eventually contribute to decreased use of medical healthcare services.

Thus, as PRO feedback meets the wishes of patients and appears not to increase patients' worries and fears, we would recommend implementing PRO feedback to patients with cancer in daily clinical practice, although substantial evidence of a benefit of PRO feedback on PROs is lacking. The PRO feedback application and algorithms have already been developed in our PROFILES system and therefore, it is relatively easy to adapt the feedback for patients with different cancer types. Nevertheless, it is important to take into account that there is sufficient normative data available to make comparisons with peers, as this comparison was evaluated as the most valuable part of the feedback intervention. At present, the PRO feedback has already been adapted for patients with colorectal, esophageal and stomach cancer. This allows all new patients with lymphoma, colorectal, esophageal, or stomach care who participate in observational studies to have access to their own PRO data. In addition, the PRO feedback for patients with lymphoma is already being used in daily clinical practice in specific hospitals.

In the best case, PRO feedback is shared with both patients and healthcare providers. For healthcare providers, a summary of PRO scores would be implemented in the electronic health record so that healthcare providers will be able to follow patients' functioning, symptoms, and emotional well-being jointly over time. Furthermore, rather than assessing outcomes after treatment, and using it primarily for research purposes, the goal would be to have PROs discussed with patients during their office visit. It can then be compared to normative values for similar conditions, and for patients and healthcare providers to use this data to inform clinical decision making consistent with patients' preferences and values

[80]. Completion of PRO measures when responses are fed back to healthcare providers can signal to the patient that they feel someone is interested in their feelings and gives them 'permission' to share or raise issues with healthcare providers [81]. Previous literature showed that both patients and healthcare providers express satisfaction with using PRO information in clinical care [82,83]. Thinking more broadly, shared PROs could be linked with other health data and aid in value-based initiatives [80], as in the era of value-based oncology care, stakeholders are increasingly interested in PRO findings as a guide for clinical, regulatory, and reimbursement decisions [84]. Future research should determine whether PRO feedback to both patients and healthcare providers has a beneficial effect on patients' symptoms and functioning, or may even have clinical benefits.

Moreover, the findings in this thesis suggest that almost a quarter of participating patients did not want access to their own PRO data. Those who did not access the PRO feedback appeared to be less self-efficacious. It has been demonstrated that those patients with low self-efficacy feel less confident in their abilities to make better decisions in face of potentially negative information and be less likely to obtain such information [85]. Therefore, it is of great importance that patients could decide for themselves whether or not they want to access the PRO feedback and whether or not they want to share their data with their healthcare provider. This helps to ensure that patients do not see the PRO feedback when they do not want to.

Web-based self-management interventions

Self-management has been proposed as a strategy to help patients with cancer optimize their health and well-being during survivorship. Previous literature demonstrated variable effects of self-management on various outcomes [86]. In addition, interventions that are self-directed or guided by patients may hold promise as they allow patients to engage with interventions as they need [87]. In its current form, we would however not recommend implementation of the web-based self-management intervention – *Living with lymphoma* – for all patients with lymphoma. First, the results of this thesis revealed no substantial evidence of a beneficial effect of the intervention. No differences were observed in psychological distress, self-management skills, and satisfaction with information provisions between patients who had access to *Living with lymphoma* and those who did not. Second, only one-third of patients logged into the intervention, of whom only a few completed some modules of the intervention. A prerequisite for exploiting the

potential of effective treatment is that individuals are willing to use the intervention [88]. Low uptake and low levels of adherence not only limited the potential impact of the intervention, but also suggest that patients are unwilling to use such interventions. Although previous literature showed that uptake rates of web-based psychosocial interventions implemented in real-life settings under less-structured and monitored conditions are known to be limited [88], it has also been demonstrated that the uptake of psychosocial interventions to reduce psychological distress was higher among unselected patients, compared to patients scoring above the cutoff for psychological distress [48]. Supporting intervention adherence through weekly email or telephone calls providing guidance may be necessary to increase usage and completion of relevant modules of the web-based intervention. In addition, web-based interventions may need to be accompanied by counseling, as talking and interpersonal factors could be important in psychosocial interventions. Nevertheless, interventions that are unguided rather than requiring professional facilitation may hold promise as they may be cost-effective to deliver, allow the patient to engage with the intervention as they are ready and may also overcome geographical barriers [87]. Therefore, in clinical practice, interventions that need human assistance however may be more difficult to integrate into standard care given the required resources. Third, the timing of the intervention may be not optimal. Previous literature demonstrated that patients on treatment more frequently reported psychological distress compared with short- and long-term survivors [89]. Although our research typically focused on patients who were on average 14 months after diagnosis – and mostly finished primary treatment – interventions may be more effective closer to diagnosis or during active treatment, as patients are especially vulnerable to psychological distress in that specific time frame. Early intervention for reducing or preventing the development of psychological distress may improve patients' quality of life throughout the treatment period [90]. Therefore, a web-based self-management intervention for psychological distress may be more appropriate as a population-level intervention as part of a stepped care approach. A stepped care approach has the potential to improve the efficiency of psychosocial care. The central idea underpinning a stepped care approach is that patients with mild psychological problems are offered low intensity interventions including psychoeducation, self-help, counseling, or problem-solving treatment. For those who not respond to these approaches, or for those with more severe problems, more intensive treatment options may be appropriate [91]. More research is needed to investigate the optimal format, and delivery of a web-based self-

management intervention, before conclusions can be drawn about the effectiveness of *Living with lymphoma* within a population-based setting.

Moreover, when effective, web-based self-management interventions have the potential to be highly cost-effective, as they can be delivered at scale across large populations, with relatively low additional costs per additional user [92]. Although, we have not formally studied cost-effectiveness of the intervention, it was an important issue in our considerations of whether or not to implement the intervention. Two types of costs are related to the intervention: those incurred during the development of the intervention; and those related to ongoing delivery and maintenance of the intervention. The developmental costs, although considerable, are unlikely to be repeated if the intervention would be adopted in routine care. Conversely, if the intervention were to be widely implemented into routine care, costs of delivery, maintenance and updating of the intervention would be required on an on-going basis. The findings in this thesis suggest that the costs of implementation of the intervention into routine care would be much higher than the potential benefits, as no beneficial effects of the intervention were observed. It is important to keep cost-effectiveness in mind when large scale implementation of the interventions that are only suitable for a very small proportion of patients is considered.

CONCLUDING REMARKS

Based on the wishes of patients to get insight in their own data, we developed an application to provide feedback on PRO directly to patients. The findings in this thesis demonstrated that providing PRO feedback directly to patients did not have adverse effects on patients' well-being and may be a useful tool to increase symptom detection and motivate patients to discuss their symptoms with a healthcare provider, as PRO feedback increased the number of GP contacts. Hence, we would recommend both expansion of the PRO feedback to other cancer types as well as implementation in daily clinical practice. Moreover, the results of this thesis showed that an unguided web-based self-management intervention, with low uptake and low levels of adherence, did not have beneficial effects on patients' well-being. At present, we would therefore not recommend implementation of *Living with lymphoma* in routine care, as first more research is needed to investigate the optimal format and delivery of a web-based self-

management intervention, before conclusions can be drawn about the effectiveness of *Living with lymphoma* within a population-based setting.

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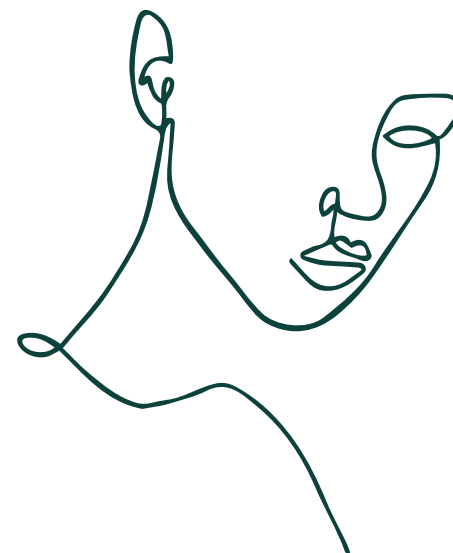
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CHAPTER 9

SUMMARY



SUMMARY OF RESULTS

The current thesis describes the process from making an inventory of factors associated with psychological distress among lymphoma survivors to the development and evaluation of an intervention that aims to increase self-management skills, satisfaction with information provision, and ultimately reduce psychological distress. In this chapter, the main findings of the studies described in this thesis are summarized.

Part I Inventory: factors associated psychological

The first part of this thesis consists of an inventory of sociodemographic, clinical and psychological factors that are associated with psychological distress among lymphoma survivors (**Chapter 2**). Four hundred and fifty-six patients participated in this study. We observed that, besides age and comorbid conditions, both personality traits, in particular neuroticism, and coping strategies including anxious preoccupation, helplessness/hopelessness, and avoidance were significantly associated with psychological distress. Although neuroticism was the greatest factor associated with psychological distress, this association was partially explained by coping strategies. The regression model, in which personality traits and coping strategies were added to sociodemographic and clinical characteristics, explained half of the total variance in psychological distress among patients with lymphoma. Education, cancer type and active treatment were not associated with psychological distress.

Next, we compared the use of healthcare services by lymphoma survivors with that of an age- and sex-matched normative population. In addition, we compared the use of healthcare services between those with and without psychological distress (**Chapter 3**). It was observed that lymphoma survivors (N=1,444) reported more medical contacts (i.e., contacts with the general practitioner (GP) or medical specialist) compared to an age- and sex-matched normative population without cancer (N=563). In addition, we observed that those who experienced psychological distress (N=345) had even more contacts with their GP and medical specialist. Furthermore, we observed that psychologically distressed patients not only had an increased use of medical services, but also received psychosocial care more often. Nevertheless, more than half of those scoring above the cutoff for psychological distress did not receive psychosocial care. Especially among older lymphoma survivors psychosocial care seemed suboptimal. Although older

survivors seemed more often psychologically distressed, they received psychosocial care somewhat less often.

Part II Intervention: Lymphoma InterVENTion [LIVE]

The second part of the current thesis is about the development and evaluation of an intervention that aims to increase self-management skills and satisfaction with information provision and reduce psychological distress. We started to investigate whether patients with lymphoma wished to receive feedback on their patient-reported outcomes (PROs), including the option to compare their PRO summary scores with those of their peers, and how this feedback was evaluated (**Chapter 4**). We invited 64 patients participating in a lymphoma cohort who were eligible for a follow-up questionnaire and gave them the option to receive PRO feedback. Of the responding patients (N=45), approximately 80% wished to receive feedback on their PROs. The vast majority (94%) compared their scores with those of a lymphoma reference cohort, whereas approximately 64% compared their scores with those of a normative population without cancer. All patients wished to receive feedback on their general health-related quality of life, while 81-92% of the patients wished to receive feedback on their functioning scores (i.e., physical, emotional, cognitive, social), fatigue, neuropathy, anxiety, and depressive symptoms. Approximately 97% of the patients who received feedback on their PROs assessed the feedback as a useful tool, with reassurance and knowledge about their own functioning in relation to what is "normal" being the most frequently mentioned reasons.

In **Chapter 5**, the rationale and study design of the Lymphoma InterVENTion (LIVE) trial were presented. The LIVE trial was conducted to increase self-management skills and satisfaction with information provision and reduce psychological distress. The LIVE trial consists of two interventions: 1) feedback to patients on their PROs, and 2) a web-based self-management intervention named *Living with lymphoma*. The PRO feedback enabled patients to monitor their symptoms and compare their scores with those of their peers, which could have either reassured them that what they experienced was 'normal' or could have empowered them to take action. The *Living with lymphoma* intervention is based on psycho-education and cognitive behavioral therapy components and is an adaptation from the evidence-based BREast cancer e-health (BREATH) intervention. The LIVE trial was designed as a non-blinded randomized controlled trial with three arms. Care as usual (CAU) plus access to PRO feedback and the *Living with lymphoma* intervention (arm 3) and

CAU plus access to PRO feedback (arm 2) were compared to CAU (arm 1). The LIVE trial was embedded within the Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship (PROFILES) registry that enables PRO data collection management and linking these data to clinical data from the Netherlands Cancer Registry (NCR). Patients with lymphoma from various hospitals in the Netherlands were included and asked to complete questionnaires at four points in time: baseline (T0; 6 to 15 months after diagnosis), after 16 weeks (T1; post-intervention), after 12 months (T2), and after 24 months (T3). Primary outcomes were defined as self-management skills, satisfaction with information provision, and psychological distress. Based on new insights that psychologically distressed patients reported increased healthcare use, healthcare use was added as primary outcome.

The main effects of feedback to patients on their PROs and access to a web-based self-management intervention named *Living with lymphoma* on patients' self-management skills, satisfaction with information provision, psychological distress, and healthcare use were described in **Chapter 6**. No effects of PRO feedback on psychological distress, self-management skills, satisfaction with information provision, and healthcare use were found. However, the PRO feedback also had no negative impact on patients' well-being. Nevertheless, the PRO feedback meets the wishes of patients to gain insight in their PROs. The PRO feedback was viewed by 77% of those who had access to it. The uptake of *Living with lymphoma* was relatively low. Only 36% of those with access, actually registered and accessed the intervention, and 16 patients opened at least one part of the intervention. Because the uptake and adherence of *Living with lymphoma* was very limited, no definite conclusions about the effectiveness of *Living with lymphoma* in a population-based sample can be drawn yet.

The reach of a web-based self-management intervention within the context of the LIVE trial was examined in **Chapter 7**. Patients were recruited from the population-based Netherlands Cancer Registry (NCR) that routinely collects data on sociodemographic and clinical characteristics, which provided a unique insight into characteristic differences between trial participants and non-participants in order to address the reach of this intervention. Patients who completed the web-based questionnaire were automatically enrolled in the RCT, whereas paper questionnaire completers were observationally followed in the PROFILES registry. A total of 1193 patients with lymphoma were selected from the NCR, of which 892 (75%) patients

were invited for participation after hematologist verified their eligibility. From the total population-based sample of eligible patients who were invited to participate, 25% participated in the RCT (N=227). RCT participants were younger, more often male, and more highly educated than nonparticipants. Therefore, RCT participants may represent a minority of the target population, which may limit external validity of RCT results and translation to routine care.

Methodological considerations and implications for clinical practice and future research

The methodological considerations of the studies, as well as implications for clinical practice and future research were outlined in **Chapter 8**. Although the LIVE trial was designed to investigate the effectiveness of PRO feedback and the *Living with lymphoma* intervention in a real-world setting, it was observed that older, female and lower educated patients were underrepresented, which limits the generalizability of our results. More research is needed into reasons why some patients were not reached, and how they could be reached in the future. In addition, as uptake and adherence rates were relatively low, more research is needed to investigate the optimal format and delivery of *Living with lymphoma*, before conclusions can be drawn about its effectiveness within a population-based setting. Therefore, at present, we would not recommend implementation of *Living with lymphoma* in routine care. Conversely, as PRO feedback meets the wishes of patients and appears not to increase patients' worries and fears, we do recommend implementation of PRO feedback to patients with cancer in daily clinical practice.

Conclusions

Providing PRO feedback directly to patients meets patients' wishes to have insight in their own PROs and did not increase worries or fears. PRO feedback can be a useful tool to increase symptom detection and motivate patients to discuss their symptoms with a healthcare provider, as PRO feedback increased the number of GP contacts. In addition, no beneficial effects of an unguided web-based self-management intervention – *Living with lymphoma* – in a population-based setting were observed. The uptake and adherence of such an intervention in a population-based sample, however, were relatively low and may limit the effectiveness of the intervention.

SAMENVATTING

(SUMMARY IN DUTCH)

Dit proefschrift beschrijft het proces van het inventariseren van factoren die samenhangen met psychologische stress bij (ex-)patiënten met lymfeklierkanker tot de ontwikkeling en evaluatie van een interventie die gericht is op het vergroten van de zelfmanagementvaardigheden, tevredenheid van informatievoorziening, en het verminderen van psychische stress. In dit hoofdstuk worden de belangrijkste bevindingen uit dit proefschrift samengevat.

Deel I Inventarisatie: factoren die samenhangen met psychologische stress

Het eerste deel van dit proefschrift bestaat uit een inventarisatie van factoren die samenhangen met psychologische stress bij (ex-)patiënten met lymfeklierkanker. In **hoofdstuk 2** worden sociodemografische, klinische en psychologische factoren gepresenteerd die samenhangen met psychologische stress. In totaal namen 456 (ex-)patiënten met lymfeklierkanker deel aan dit onderzoek. De gemiddelde leeftijd van de deelnemers was 65 jaar, 64% was man en 17% had te maken met psychologische stressklachten. We constateerden dat een jongere leeftijd en de aanwezigheid van comorbiditeit – het hebben van een andere ziekte naast kanker, zoals suikerziekte of hart- en vaatziekten – samenhangen met meer psychologische stress bij (ex-)patiënten met lymfeklierkanker. Ook vonden we dat persoonlijkheid en copingstijlen samenhangen met psychologische stress. Zo kwam naar voren dat mensen die hoog scoren op neuroticisme meer psychologische stress ervoeren en zagen we dat copingstijlen die gekenmerkt werden door hulpeloosheid en angstige preoccupatie samenhangen met meer psychologische stress, terwijl vermijding gerelateerd leek aan minder psychologische stressklachten.

In **hoofdstuk 3** hebben we het zorggebruik van patiënten met lymfeklierkanker vergeleken met dat van een normpopulatie zonder kanker. Tevens hebben we gekeken naar de verschillen in zorggebruik tussen patiënten met en zonder psychische stress. Er deden in totaal 1,444 (ex-)patiënten met lymfeklierkanker mee aan deze studie. De normpopulatie bestond uit 563 personen. We vonden dat (ex-)patiënten met lymfeklierkanker gemiddeld meer medische contacten hadden (d.w.z. contacten met de huisarts of medisch specialist) dan de normpopulatie zonder kanker. Ook zagen we dat patiënten met psychologische stress meer medische contacten hadden dan zij die geen psychologische stress ervoeren. Patiënten met psychologische stress maakten niet alleen meer gebruik van

medische zorg, maar ontvingen ook meer psychosociale zorg. Desondanks ontving meer dan de helft van de patiënten met psychologische stress geen psychosociale zorg. Vooral onder ouderen leek de psychosociale zorg niet optimaal. Hoewel oudere patiënten in dit onderzoek vaker psychologische stress ervoeren, ontvingen zij minder vaak psychosociale zorg.

Deel II Interventie: Lymphoma InterVention [LIVE]

Het tweede deel van dit proefschrift bestaat uit de ontwikkeling en evaluatie van een interventie die gericht is op het vergroten van zelfmanagementvaardigheden en de tevredenheid met de informatievoorziening, en het verminderen van psychologische stress. In **hoofdstuk 4** begonnen we met onderzoeken of patiënten met lymfeklierkanker een terugkoppeling zouden willen ontvangen van hun patiëntgerapporteerde uitkomsten, inclusief de optie om hun scores te vergelijken met anderen, en hoe deze terugkoppeling werd geëvalueerd. We hebben voor dit onderzoek 64 (ex-)patiënten met lymfeklierkanker uitgenodigd die reeds deelnamen aan een lopend studiecohort en in aanmerking kwamen voor een vervolgvragenlijst. Zij kregen de optie om een terugkoppeling van hun patiëntgerapporteerde uitkomsten – zoals kwaliteit van leven, functioneren en symptomen – te ontvangen. Van de 64 uitgenodigden namen 45 patiënten deel aan dit onderzoek, van wie ongeveer 80% een terugkoppeling van hun uitkomsten wilde ontvangen. De meerderheid (94%) wilde zijn of haar scores vergelijken met die van andere patiënten met lymfeklierkanker en 64% koos voor een vergelijking met de normpopulatie zonder kanker. Alle patiënten, die een terugkoppeling van hun scores wilden ontvangen, wilden inzicht in hun scores op algehele kwaliteit van leven, terwijl 81% tot 92% van de patiënten een terugkoppeling wilde ontvangen van hun scores op functioneren (lichamelijk, emotioneel, cognitief, sociaal), vermoeidheid, neuropathie (tintelingen en/of doof gevoel in handen en voeten), angst en depressieve symptomen. Ongeveer 97% van de patiënten die een terugkoppeling van zijn of haar patiëntgerapporteerde uitkomsten had ontvangen, vond de terugkoppeling nuttig. De terugkoppeling van hun uitkomsten stelde hen gerust of gaf hen kennis over het eigen functioneren in relatie tot wat 'normaal' is.

In **hoofdstuk 5** worden de aanleiding voor en de opzet van de Lymphoma InterVention [LIVE] studie gepresenteerd. De LIVE studie werd opgezet om zelfmanagementvaardigheden en de tevredenheid met de informatievoorziening te verbeteren en psychologische stress te verminderen. De LIVE studie bestaat uit

twee interventies: 1) een terugkoppeling aan patiënten van hun patiëntgerapporteerde uitkomsten en 2) een online zelfmanagementinterventie *Leven met lymfeklierkanker*. De terugkoppeling stelde patiënten in staat hun symptomen monitoren en hun scores te vergelijken met die van andere patiënten of een normpopulatie zonder kanker. Dit zorgde voor geruststelling dat wat ervaren werd 'normaal' was, of stelde hen in staat actie te ondernemen. De online zelfmanagementinterventie *Leven met lymfeklierkanker* is gebaseerd op psycho-educatie en onderdelen uit de cognitieve gedragstherapie. *Leven met lymfeklierkanker* is een aanpassing vanuit de online zelfmanagementinterventie *Op adem na borstkanker*, die reeds effectief is gebleken in het verminderen van milde psychologische stress bij patiënten met borstkanker. De LIVE studie is opgezet als een gerandomiseerde gecontroleerde studie met drie studiearmen. Gebruikelijke zorg plus toegang tot terugkoppeling van patiëntgerapporteerde uitkomsten én de *Leven met lymfeklierkanker* interventie (arm 3) en gebruikelijke zorg plus toegang tot terugkoppeling van patiëntgerapporteerde uitkomsten (arm 2) werden vergeleken met gebruikelijke zorg (arm 1). De LIVE studie was ingebed in PROFIEL-studie, een infrastructuur die het mogelijk maakt om gegevens te verzamelen over patiëntgerapporteerde uitkomsten en deze gegevens te koppelen aan de klinische gegevens uit de Nederlandse Kankerregistratie (NKR). Patiënten met lymfeklierkanker uit verschillende ziekenhuizen in Nederland werden uitgenodigd en gevraagd om vragenlijsten in te vullen op vier tijdstippen: direct na de uitnodiging, na 16 weken (na de interventie), na 12 maanden en na 24 maanden. De primaire uitkomstmaten werden gedefinieerd als zelfmanagementvaardigheden, tevredenheid met de informatievoorziening en psychologische stress. Op basis van nieuwe inzichten, waarin naar voren kwam dat patiënten met psychologische stress meer zorg gebruikten dan patiënten zonder psychologische stress, werd zorggebruik als primaire uitkomstmaat toegevoegd.

In **hoofdstuk 6** worden de resultaten met betrekking tot de effecten van de terugkoppeling van patiëntgerapporteerde uitkomsten en de online zelfmanagementinterventie *Leven met lymfeklierkanker* op zelfmanagementvaardigheden, tevredenheid met de informatievoorziening, psychologische stress en zorggebruik van (ex-)patiënten met lymfeklierkanker beschreven. We vonden geen effecten van de terugkoppeling van patiëntgerapporteerde uitkomsten op psychologische stress, zelfmanagementvaardigheden, tevredenheid met de informatievoorziening en zorggebruik. Tevens vonden we dat het terugkoppelen van patiëntgerapporteerde uitkomsten geen negatieve invloed had op het welzijn

van patiënten. De terugkoppeling komt tegemoet aan de wensen van patiënten om inzicht te krijgen in hun eigen patiëntgerapporteerde uitkomsten. De terugkoppeling van patiëntgerapporteerde uitkomsten werd door 77% van de patiënten bekeken. Het gebruik van *Leven met lymfeklierkanker* was veel lager. Slechts 36% van de patiënten die toegang hadden, hebben zich aangemeld en 16 patiënten hebben tenminste een onderdeel van de interventie geopend. Omdat het gebruik van de interventie relatief laag was, kunnen we nog geen harde conclusies trekken over de effecten van *Leven met lymfeklierkanker* op psychologische stress, zelfmanagementvaardigheden, tevredenheid met de informatievoorziening en zorggebruik. Hiervoor is eerst vervolgonderzoek nodig.

In **hoofdstuk 7** wordt het bereik van een online zelfmanagementinterventie binnen de context van de LIVE studie onderzocht. Patiënten werden geworven via de Nederlandse Kankerregistratie (NKR), waarin structureel sociodemografische en klinische gegevens worden verzameld van mensen die kanker hebben (gehad) in Nederland. Dit gaf een uniek inzicht in de verschillen tussen patiënten die wel deelnamen aan de gerandomiseerde gecontroleerde studie en patiënten die niet deelnamen en gaf ons de mogelijkheid om het bereik van de interventie te bepalen. Patiënten die de vragenlijst online invulden namen automatisch deel aan de gerandomiseerde gecontroleerde studie, terwijl patiënten die de vragenlijst op papier invulden enkel observationeel gevolgd werden. In totaal werden 1193 patiënten met lymfeklierkanker geselecteerd uit de NKR. Nadat de betreffende hematologen akkoord hadden gegeven voor het benaderen van hun patiënten, werden 892 (75%) patiënten uitgenodigd voor deelname aan de studie. Uiteindelijk vulden 227 patiënten (25%) de vragenlijst online in en namen deel aan de gerandomiseerde gecontroleerde studie. Deze patiënten waren jonger, vaker man en hoger opgeleid dan mensen die de vragenlijst op papier of helemaal niet invulden en dus niet deelnamen aan de gerandomiseerde gecontroleerde studie. Dit wees erop dat de patiënten in de gerandomiseerde gecontroleerde studie slechts een minderheid van de totale doelgroep vertegenwoordigden, wat mogelijk de externe validiteit of generaliseerbaarheid van de resultaten kan beperken, alsook de mogelijkheid om de resultaten te vertalen naar de dagelijkse klinische praktijk.

De methodologische overwegingen en de implicaties voor de klinische praktijk en toekomstig onderzoek worden beschreven in **hoofdstuk 8**. De LIVE studie werd opgezet om de effectiviteit van een terugkoppeling van patiëntgerapporteerde uitkomsten en de online zelfmanagementinterventie *Leven met lymfeklierkanker* in

de echte wereld te onderzoeken. Echter vonden we dat ouderen, vrouwen en lager opgeleide patiënten niet voldoende vertegenwoordigd waren in de studie, wat de generaliseerbaarheid van de onderzoekresultaten beperkt. Er is meer onderzoek nodig naar de redenen waarom sommige patiënten niet werden bereikt en naar hoe deze patiënten in de toekomst wel kunnen worden bereikt. Tevens is meer onderzoek nodig naar de optimale manier van het aanbieden van *Leven met lymfeklierkanker*, voordat er duidelijke conclusies kunnen worden getrokken over de effectiviteit van de interventie in de echte wereld, daar het gebruik slechts minimaal was. Er wordt daarom (nog) niet aangeraden de online zelfmanagement-interventie *Leven met lymfeklierkanker* te implementeren in de dagelijkse klinische praktijk. Aan de andere kant kan de terugkoppeling van patiëntgerapporteerde uitkomsten worden geïmplementeerd in de dagelijkse klinische praktijk, daar het tegemoet komt aan de wensen van patiënten zonder dat het de zorgen en angsten rondom de ziekte lijkt te vergroten.

Conclusie

Het aan patiënten aanbieden van een terugkoppeling van patiëntgerapporteerde uitkomsten komt tegemoet aan hun wensen om meer inzicht te krijgen in hun uitkomsten zonder de zorgen en angsten rondom de ziekte te vergroten. De terugkoppeling van patiëntgerapporteerde uitkomsten kan een nuttig hulpmiddel zijn om symptomen beter te kunnen detecteren en patiënten te motiveren om hun symptomen met een zorgverlener te bespreken. Er werden geen effecten van de online zelfmanagement interventie *Leven met lymfeklierkanker* gevonden. Echter was het gebruik van de interventie relatief laag, wat de effectiviteit van de interventie kan hebben beperkt.

APPENDICES



A

“At times, our own light goes out and is rekindled by a spark from another person. Each of us has cause to think with deep gratitude of those who have lighted the flame within us.”

– *Albert Schweitzer*

DANKWOORD

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Op 15 februari 2015, op carnavalsmaandag, startte mijn ritje in de achtbaan die promoveren wordt genoemd. Het waren uitdagende en interessante jaren, met ups en downs. Nu is het einde van de rit nabij: mijn proefschrift is klaar! Tijd om terug te kijken op vijf super leerzame en enerverende jaren, waarbij soms mijn vlammetje voor het doen van onderzoek eventjes leek te doven. Gelukkig had ik veel fijne mensen om me heen die er mede voor hebben gezorgd dat dat vlammetje steeds weer ging branden. Ik wil daarom graag iedereen bedanken die heeft bijgedragen aan deze bijzondere periode en mijn proefschrift.

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Lindy
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Lindy Arts was born in Grave on March 20th, 1992. After graduating pre-university education at the Stedelijk Gymnasium Nijmegen in 2009, she did a bachelor Psychology at the University of Tilburg, with a research internship at the Center of Research on Psychology in Somatic Diseases (CoRPS) on the sexual functioning and quality of (sexual) life of patients with colorectal cancer and their partners. After graduating her bachelor's degree in 2013, she did a Master in Psychology and Mental Health with Track Mental Health of Adults at the University of Tilburg. In 2014, she completed her master with merit. Subsequently, she started her PhD research at the Netherlands Comprehensive Cancer Organisation (IKNL) in collaboration with the University of Tilburg. Her research focused on psychological distress for patients with lymphoma. Currently, she is working as a psychologist at Revalis - a rehabilitation clinic for patients with chronic pain and/or fatigue – in 's-Hertogenbosch.