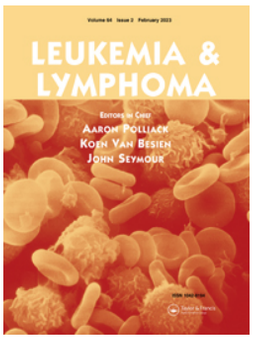

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ORIGINAL ARTICLE

Health-related quality of life and chronic fatigue in long-term survivors of indolent lymphoma – a comparison with normative data

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ABSTRACT

The aims of this study are to describe health-related quality of life (HRQoL, SF-36) and fatigue in long-term indolent lymphoma survivors, compared to normative data, and to examine factors related to impaired HRQoL among the survivors. The participants ($N = 136$, median follow-up after first line therapy 9.8 years) were included from a follow-up study of two clinical trials, with chemo-free first-line therapy. The present survey included questionnaire based data. Compared to the normative data, the mean total fatigue score were higher, and HRQoL lower in 4 of 8 domains among the lymphoma survivors. Among the survivors, somatic comorbidities, not being in paid work and chronic fatigue were significantly associated with reduced physical HRQoL. Anxiety and depressive symptoms were associated with reduced mental HRQoL. Our findings highlight the need for awareness of HRQoL and fatigue in long term follow up in lymphoma survivors, as there are treatments and rehabilitation options.

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Indolent lymphoma; health-elated quality of life; fatigue; long-term survivors; survivorship

Introduction

Follicular lymphoma is an indolent form of non-Hodgkin lymphoma. The disease is typically diagnosed by enlarged lymph nodes in otherwise asymptomatic individuals. For most patients, this is a chronic, indolent disease with long overall survival approaching two decades. More than 80% of the patients are alive 10 years after diagnosis, leading to a considerable number of patients living with the disease [1]. For asymptomatic patients with low tumor burden 'wait and watch' is considered a valid strategy. Sooner or later, however, the disease will progress and the patient will need therapy. There is no international consensus regarding treatment, but usually a variant of systemic immuno-chemotherapy (rituximab + chemotherapy) will be prescribed. In addition, simple rituximab based therapy become an accepted alternative with the benefit of avoiding the side-effects of chemotherapy [1]. Still, most follicular lymphoma patients relapse and require multiple lines of treatment and are considered incurable.

Health-related quality of life (HRQoL) has been defined as 'the extent to which one's usual or expected physical, emotional or social wellbeing is affected by a medical condition or its treatment,' and is increasingly recognized as an important outcome in cancer patients [2]. Cancer survivors may have ongoing health problems affecting their HRQoL long after their treatment has been completed [3]. Long-term survivors of follicular lymphomas might have impaired HRQoL due to distress related to the protracted course of the disease, but also due to late effects after treatment. However, few studies have assessed HRQoL among long-term survivors of follicular lymphoma. One study reported significantly lower scores on several domains of HRQoL in survivors after non-Hodgkin lymphoma compared to controls up till 10 years after diagnosis [4]. Another study comparing survivors of indolent and aggressive non-Hodgkin lymphoma, found similar HRQoL in these two groups [5]. Among the survivors of indolent lymphoma, the HRQoL was significantly better among long term

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compared to short term survivors (≥6 years *versus* < 6 years post diagnosis).

Fatigue is characterized by tiredness, lack of energy, and subjective cognitive problems. Chronic fatigue (defined as fatigue scored above a defined level and lasting for ≥6 months) is one of the most common late effects after treatment for lymphoma [6]. A prevalence of about 25–28% has been found in survivors after Hodgkin and aggressive subtypes of non-Hodgkin lymphoma [7,8]. Few studies have focused on fatigue in long-term survivors of follicular lymphoma. In a previous study by our group of 233 male lymphoma survivors, we found a prevalence of chronic fatigue of 11% among 35 survivors of indolent lymphomas at a median of 16 years from diagnosis [8]. Another study found significantly higher levels of fatigue in non-Hodgkin lymphoma survivors compared to a normative population up till 10 years after diagnosis, with no difference between survivors of indolent or aggressive non-Hodgkin lymphoma [4].

The Nordic lymphoma group has performed two randomized clinical trials in patients with symptomatic indolent lymphoma evaluating the efficacy and safety of chemotherapy-free first-line treatment [9,10]. A long-term follow-up survey was performed in 2016, addressing post-trial therapy, transformations, infections, secondary malignancies, and survival [11]. In addition, the participants were invited to complete a questionnaire addressing HRQoL, fatigue, and other relevant symptoms and variables. In this study, we use data from these questionnaires. Our objectives were to examine HRQoL and fatigue among long term survivors after treatment for indolent non-Hodgkin lymphoma and see if there was any difference as compared to the general Norwegian population. Furthermore, we wanted to identify factors related to the disease, treatment or other factors that are associated with impaired HRQoL among the survivors.

Methods

Participants

To be eligible for the follow-up study, participants had to be enrolled in one of the two Nordic clinical trials (accrual 1998–99 and 2002–8, respectively), including symptomatic patients with advanced, indolent CD20+ lymphoma, performance status 0–2, and adequate organ function [9,10]. Patients were randomized to either rituximab monotherapy or to rituximab combined with interferon alpha-2a (IFN). The treatment consisted of 4 weekly doses of rituximab (375 mg/m^2) and in case of IFN, 3 mill IU subcutaneously daily week 1, and 4.5 mill IU subcutaneously weeks 2 – 5. For patients responding to this first cycle, a second cycle was planned. The total duration of this first-line treatment was maximum 6 months.

Survivors included in the clinical trials were invited to participate in a follow-up study at the hospital where they had received their treatment [11]. Patient data were retrieved from the monitored databases of the clinical trials and from medical records during long-term follow-up and eventual relapse and lymphoma treatment after study medication was recorded.

Questionnaires

Norwegian and Swedish participants in the follow-up study were invited to a cross-sectional questionnaire survey including HRQoL, fatigue, socio-demographics including work-life issues, anxiety and depression, comorbidities, and lifestyle. The questionnaire was administered on paper to patients at the time of last follow-up, or for some Swedish patients sent to their home address by regular mail.

The Short Form 36 (SF-36) is considered a reliable and valid assessment of self-reported generic HRQoL [12]. SF-36 version 1 was used in Norwegian and Swedish translations and consists of 36 items grouped into 8 multi-item scales (4 physical and 4 mental) [13]. All dimensional scores were converted from 0 to 100 with higher scores representing better HRQoL. The physical and mental composite scales (PCS and MCS) of SF-36 were calculated by T-transformations, and the mean score was 50 and the standard deviation (SD) 10 based on the Norwegian normative data [14]. Besides comparisons with normative findings, we used the PCS and MCS scores as dependent variables in univariable and multivariable linear regression analyses.

The Fatigue Questionnaire (FQ) measures fatigue severity and contains questions concerning mental (4 items) and physical fatigue (7 items) for the last 4 weeks [6]. Each item is rated from 0 (as before) to 3 (very much worse). The total fatigue score ranges from 0 to 33 with higher scores signifying more fatigue. An additional item covers the duration of the fatigue experience. Concerning chronic fatigue, a dichotomized score for each response alternative (0 = 0, 1 = 0, 2 = 1, and 3 = 1) was used, and chronic fatigue was defined as a dichotomized sum score of ≥4 with duration of ≥6 months [7]. In our cohort internal consistency measured by Cronbach's was 0.92.*The Hospital Anxiety and Depression Scale (HADS)* comprises seven items each on the anxiety (HADS-A) and depression

(HADS-D) sub-scales rated for the last week [15]. The item scores range from 0 (not present) to 3 (highly present), and the sub-scale scores range from 0 (low) to 21 (high), with higher scores indicating more symptoms. Cutoff score for eventual cases of anxiety disorder or depression is a total score $\geq$8 on both subscales. Cronbach's alpha was 0.86 for HADS-A and 0.84 for HADS-D.

Current work ability was compared to the lifetime best on a continuous 10-point scale from 0 ('Currently not able to do work') to 10 ('Work ability as previous life-time best') from the *work ability index* (WAI) instrument [16,17].

Socio-demographic: Current paired relation was rated as present or absent. Level of education was dichotomized into low ($\leq$12 years) and high (>12 years). *Work status* was classified as either in paid work, on disability pension, or on retirement pension.

Comorbid somatic diseases included self-report of stroke, hypertension, lung diseases, diabetes, gastrointestinal ulcer, diseases of the kidneys or the liver, anemia or other blood diseases, thyroid diseases, arthrosis, rheumatic disorders, and heart diseases. The sum of comorbidity was classified as none, 1–2, and 3–5. *Dental health* was dichotomized as good or poor. *Cognitive problems* were present if either concentration or memory problems were rated as 'quite a bit' or 'very much' by the survivors.

Life style: Daily *smoking* concerned any number of cigarettes. Body mass index (BMI) was calculated as weight in kilos/(height in meters)^2, and *obesity* was defined as BMI $\geq$ 30. *The Godin-Shephard Leisure-Time Physical Activity Questionnaire* ratings was used to calculate the proportion of patients meeting the guidelines for physical activity per week [18].

Comparators

The comparison of fatigue was performed by extraction of data from a recently performed study on fatigue and depressive symptoms in the general Norwegian population [19]. From the SF-36 published national database ($N = 2118$) we at random draw 5 controls for each patient in our sample ($N = 680$) [20].

Outcomes

Outcomes of this study is HRQoL as the 8-dimensional scores and the two summary scores of the SF-36 (MCS and PCS), the prevalence of chronic fatigue and levels of fatigue.

Statistical analyses

The comparisons with the normative sample on the SF-36 subscales were done with independent sample t-tests. The effect sizes of the comparisons were made with Cohen's coefficient *d*, and *d* values $\geq$0.30 were considered as clinically significant [21]. The internal consistencies were examined with Cronbach's coefficient alpha. Associations between independent variables and SF-36 MCS and PCS scores as dependent variables were examined with univariable and multivariable linear regression analyses. The strength of associations was expressed as unstandardized beta (B)-values. Variables included in the multivariable analysis were tested for multicollinearity. For PCS, we omitted depression in the multivariable analyses, as this is known to have high correlation to chronic fatigue [19]. The *p* value was set as <0.01 and all tests were two-sided. The statistical software applied was SPSS version 24 for PC (IBM Corporation, Armonk, NY).

Ethical approval

The Regional Committees for Medicine and Health Research Ethics (REK) of South-Eastern Norway (REK number #2013/634) and Stockholm, Sweden (number 2014/1771-31/4 with amendment 2015/2018-32) approved the study. All participants gave informed consent.

Results

Participants characteristics

A total of 136 survivors were included in this study, with a median of 9.8 years (range 0.1–18.8 years) since randomization in the clinical trials. The non-Hodgkin lymphoma survivors consisted of 45% men and 55% women with a mean age of 55 years, while the normative group consisted of 46% men and 54% women with a mean age of 56 years ($p = 0.85$ and 0.28, respectively).

The characteristics of our study population are displayed in Table 1. A total of 57% ($n = 78$) of the participants had received chemo- or immune-chemotherapy after the study medication due to progressive disease, 16% ($n = 22$) had experienced a transformation of their lymphoma, and 15% ($n = 21$) had been treated with high dose chemotherapy with autologous stem cell transplantation. At the time of follow-up the majority reported one or more somatic comorbidities (73%, $n = 99$).

Table 1. Description of the sample ($N = 136$).

Variables	$N = 136$
Sex, n (%)	
Men	61 (45)
Women	75 (55)
Country, *n* (%)	
Sweden	84 (62)
Norway	52 (38)
Median age (range)	56 (23–79)
Types of lymphomas, *n* (%)	
Follicular lymphoma grade 1	57 (42)
Follicular lymphoma grade 2	59 (43)
Follicular lymphoma grade 3a	5 (4)
MZL	9 (7)
Low-grade lymphoma NOS	6 (4)
Stage at inclusion in the clinical trials, *n* (%)	
II	9 (7)
III	48 (35)
IV	78 (57)
Not known	1 (1)
Chlorambucil pre-inclusion	14 (10)
Radiotherapy pre-inclusion	16 (12)
Treatment after first-line trial therapy, *n* (%)	
Chemotherapy/immune-chemotherapy	78 (57)
+Allo-SCT	3 (2)
+Auto-SCT	21 (15)
Transformation after first-line trial therapy, *n* (%)	22 (16)
Another cancer later on, *n* (%)	16 (12)
Anemia, Hb < 120 g/L	21 (15)
Somatic comorbidity at survey*, *n* (%)	
No comorbidity	37 (27)
One comorbidity	53 (39)
Two–five comorbidities	46 (34)
Poor dental health, *n* (%)	42 (31)
Cognitive problems, *n* (%)	83 (61)
Civil status, *n* (%)	
Partner	104 (77)
Non-partner	32 (23)
Level of education, *n* (%)	
$\leq$12 years	90 (66)
$\geq$13 years	45 (33)
Work status at survey, *n* (%)	
Paid work	56 (42)
Sick-leave, sick pension	12 (9)
Retirement pension	67 (49)
Work ability, mean ± sd	
At diagnosis	7.7 (3.3)**
At survey	6.7 (3.0)
Fatigue	12.9 (5.2)
Total fatigue score, mean ± sd	24 (18)
Chronic fatigue cases, *n* (%)	
HADS anxiety case, *n* (%)	17 (13)
HADS depression case, *n* (%)	11 (8)
Obesity (BMI $\geq$ 30), *n* (%)	14 (10)
	$N = 119$
Fulfill physical activity recommendations, *N* (%)	49 (36)

*Self-reported at survey, **Paired sample *t*-test at diagnosis versus at survey $p = 0.010$.
MZL:marginal zone lymphoma, NOS: not otherwise spesified, Allo-SCT: allogeneic stem cell transplantation, Auto-SCT: autologous stem cell transplantation, Hb: hemoglobine, HADS: Hospital Anxiety and Depression Scale, BMI: Body Mass Index

HRQoL and fatigue in survivors versus normative group

The non-Hodgkin lymphoma survivors reported statistically significantly lower levels in 4 of the 8 SF-36 dimensions (physical function, role physical, general health, and role emotional) compared to the normative group, with clinically significant effects sizes (0.30–0.53) (Table 2). The highest effect sizes were found for physical function and general health (0.53 and 0.44).

The non-Hodgkin lymphoma survivors had statistical and clinical significantly lower level of the physical HRQoL composite score (PCS) compared to the normative group (44.8 *versus* 48.5, $p < 0.001$, effect size 0.37). There was no statistical significant difference in the mental HRQoL composite score (MCS) between the survivors and the normative group.

The mean total fatigue score (12.9 *versus* 11.5, $p = 0.001$, effect size 0.33) were statistical and clinical significant higher among the survivors compared to the normative group.

Factors associated with impaired HRQoL in survivors

Table 3 shows the uni- and multivariable analyses with statistical significant associations with levels of PCS in bold types. In the multivariable analyses having somatic comorbidities or chronic fatigue, and not being in paid work remained statistical significantly associated with reduced PCS among the survivors.

Table 4 shows the uni- and multivariable analyses with statistical significant associations with levels of MCS in bold types. In the multivariable analysis anxiety and depressive symptoms remained statistical significantly associated with reduced MCS.

There were no differences between genders regarding PCS and MCS. In addition, receiving therapy after study medications were not statistically significant associated with neither PCS nor MCS.

Discussion

In this study, we found that survivors of indolent lymphoma with a median follow-up of 9.8 years after first-line therapy reported higher fatigue level, and significantly lower HRQoL in 4 of 8 domains, compared to normative groups. The SF-36 PCS, but not the MCS, was statistically significant lower among the survivors compared to the normative group. Multivariable analyses revealed that somatic comorbidities, not being in paid work and chronic fatigue were significantly associated with reduced PCS, whereas anxiety and depressive symptoms were significantly associated with reduced MCS among survivors.

Our findings of lower scores on several domains of HRQoL among the non-Hodgkin lymphoma survivors compared to the normative group are comparable to results by Oerlemans et al. [4]. Even though different

Table 2. Comparison of patients and NORMs of the SF-36 dimensions and Fatigue Questionnaire (FQ).

SF-36 dimensions	Patients ($N = 136$) Mean (SD)	NORMs ($N = 680$) Mean (SD)	p Value	Effect size
Physical function	78.7 (21.1)	88.2 (17.3)	**<0.001**	**0.53**
Role physical	65.8 (40.3)	78.5 (35.7)	**0.002**	**0.35**
Bodily pain	70.8 (25.9)	68.7 (24.7)	0.367	0.08
General health	64.7 (23.8)	74.1 (20.7)	**<0.001**	**0.44**
Vitality	64.1 (22.2)	60.8 (20.1)	0.086	0.16
Social function	85.1 (23.4)	89.0 (19.4)	0.039	0.19
Role emotional	82.8 (34.7)	90.8 (24.6)	**0.001**	**0.30**
Mental health	82.3 (18.1)	82.2 (13.7)	0.942	0.01
PCS	44.8 (10.5)	48.5 (10.0)	**<0.001**	**0.37**
MCS	54.7 (10.1)	53.6 (8.1)	0.167	0.13
Fatigue				
Mental fatigue	4.3 (1.7)	4.1 (1.5)	0.166	0.13
Physical fatigue	8.6 (4.0)	7.7 (3.1)	**0.003**	0.28
Total fatigue	12.9 (5.2)	11.5 (4.1)	**0.001**	**0.33**
Chronic fatigue, *N* (%)	24 (18)	74 (11)	0.031	**NA***

*NA not applicable.
p-value <0.01 considered statistically significant. Effect size values > 0.29 considered clinically significant.

Table 3. Uni- and multivariable linear regression analyses of independent variables and SF-36 PCS as dependent variable ($N = 136$).

	Univariable analyses		Multivariable analysis	
Variables	B*	p Value	B*	p Value
Age at survey	−0.18	0.04	0.026	0.78
Supplementary treatment	−3.28	0.11	–	–
Second cancer	−4.88	007	–	–
Comorbidities	–	–	–	–
None (reference)	–	–	–	–
1-2	−7.68	**<0.001**	−6.1	**0.01**
3 +	−10.81	**<0.001**	−9.1	**<0.001**
Females (males reference)	−0.49	0.79	–	–
Non-paired relationship	−0.99	0.64	–	–
Low basic education	−4.68	**0.01**	−1.9	0.25
Not in paid work	−2.66	**0.006**	−6.0	**0.003**
Chronic fatigue case	−12.94	**<0.001**	−10.9	**<0.001**
Anxiety score	−0.56	0.02	–	–
Depression score	−1.21	**<0.001**	–	–
Poor dental health	2.04	0.30	–	–
Cognitive problems	−2.46	0.18	–	–

B*= unstandardized beta.

Table 4. Uni- and multivariable linear regression analyses of independent variables and SF-36 MCS as dependent variable ($N = 136$).

	Univariable analyses		Multivariable analysis	
Variables	B*	p Value	B*	p Value
Age at survey	0.20	0.02	0.09	0.07
Supplementary treatment	1.52	0.43		
Second cancer	1.61	0.54		
Comorbidities				
None (reference)				
1-2	−3.38	0.12		
3 +	−1.26	0.57		
Females (males reference)	−0.87	0.62		
Non-paired relationship	−5.02	**0.01**	**−0.37**	**0.77**
Low basic education	−0.45	0.81		
Not in paid work	1.40	0.13		
Chronic fatigue case	−2.21	0.32		
Anxiety score	−2.13	**<0.001**	**−1.61**	**<0.001**
Depression score	−1.95	**<0.001**	**−0.73**	**<0.001**
Poor dental health	−3.73	0.05		
Cognitive problems	−3.36	0.06		

B* = unstandardized beta.

measures was used (SF-36 and EORTC QLQ C30), we found impairment of the similar domains of HRQOL [4]. However, both are generic measures of HRQoL and are widely used for assessment of cancer patients and survivors.

Oerlemans et al. included participants with shorter observation time (mean 4.2 years from diagnosis) than in our patient population. This might suggest that impairment of HRQoL remains over time among survivors, maybe due to long lasting adverse effects of treatment. A recent publication reported a worsening of QoL in patients with newly diagnosed indolent non-Hodgkin lymphoma and chronic lymphatic leukemia in active surveillance compared to patients receiving cancer directed treatment when followed one year [22]. A limited number of patients were included ($n = 64$) and the majority were in the active surveillance group. Nevertheless, the finding suggest that active surveillance might have negative impact on patients' QoL, which might be due to distress related to not having treatment for a diagnosed malignancy. To what degree this might influence QoL in long-term survivors, is not known, but emphasize the importance of focus on symptoms and HRQoL in the follow-up during the whole disease trajectory.

This study supports results from other group of lymphoma survivors finding reduced physical HRQoL but not mental HRQoL compared to reference populations [23]. The impaired physical HRQoL among survivors is considered to be related to the burden of late

adverse effects [24]. In line with our findings, late effects and comorbidities have been shown to substantially affect HRQoL in cancer survivors [25–27]. Our group have previously reported negative associations between chronic fatigue, psychological late effects, and peripheral neuropathy on HRQoL among lymphoma survivors [26,28,29]. However, these issues have to a limited degree been explored among survivors of follicular lymphoma, except for this study. Also in studies from the general population, medical conditions and comorbidities have been shown to significantly affect HRQoL [30].

Few studies have assessed fatigue in long-term survivors of indolent lymphomas and none in patients with chemo-free therapy in a clinical first line trial. The finding of a prevalence of chronic fatigue of 18% seem to be higher than in our previous study including 35 male survivors of indolent lymphomas (11%) [8]. However, it was somewhat lower compared to what is found in long-term survivors after Hodgkin and aggressive non-Hodgkin lymphoma [7,8]. Significantly higher levels of fatigue have been reported in non-Hodgkin lymphoma survivors compared to a normative population up till 10 years after diagnosis [4]. That study did, however, not find significant difference in fatigue between survivors of indolent or aggressive non-Hodgkin lymphoma, which has also been reported in a more recent study measuring fatigue at diagnosis and at 5 years follow-up [31]. The latter study reported 18.7% of the survivors having persistent fatigue, which is similar to our results. However, these findings are somewhat difficult to compare, as different questionnaires for measurement of fatigue was used and the time point for evaluation was much later in our study. Moreover, the therapy in our cohort of indolent lymphoma included no chemotherapy first line. Even though fatigue persists for years after completion of treatment for many cancer survivors, some variations and fluctuations over time might appear [31,32]. In addition, in the Dutch study the group of indolent lymphomas also survivors of chronic lymphocytic leukemia were included [4].

Strenghts and limitations

Strength of the study is the inclusion of survivors of indolent lymphomas treated first line in a clinical trial and with a long-term follow-up. We used validated questionnaires on fatigue and HRQoL widely used among cancer patients and survivors and we could explore associations to relevant explanatory variables. Moreover, we had normative data for comparisons.

One limitation is the cross-sectional design which hampers investigation of causal relationship between variables. In addition, we do not have information on for example depressive symptoms during interferon therapy, which could be useful to elucidate the relation to long-term depressive symptoms. Our study also included a limited number of patients, which limits the number of analyses of explanatory variables to be performed.

Conclusion

Our findings highlight the importance of awareness of HRQoL and fatigue on long-term follow-up of survivors of indolent lymphoma, in particular among those with comorbidities, and psychological late effects such as anxiety and depressive symptoms, as there are treatments and rehabilitation options for these conditions. As overall survival in lymphoma patients continues to improve, related long-lasting clinical needs will become of even greater importance in the future.

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No potential conflict of interest was reported by the authors.

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