

Adolescent and young adult (AYA) lymphoma survivors report lower health-related quality of life compared to a normative population: results from the PROFILES registry

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Running title: Quality of life in young adult lymphoma survivors

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Abstract

Background: Trying to simultaneously achieve developmental milestones and cope with a life-threatening disease may place adolescents and young adults (AYAs) at risk for impaired health-related quality of life (HRQoL) later in life. The aim of this study was to examine differences in HRQoL between AYA lymphoma survivors and a normative population and to determine sociodemographic, clinical and long-term symptom-related factors associated with HRQoL.

Material and methods: This study was part of a longitudinal, population-based survey among lymphoma survivors diagnosed between 1999-2012. The AYA survivor sample (18-39 years at time diagnosis) was compared to a sex- and age-matched normative population on HRQoL (EORTC QLQ-C30) and psychological distress (HADS). Multiple linear regression analyses were conducted to determine factors associated with HRQoL among survivors.

Results: One hundred ninety-eight AYA lymphoma survivors (58%) responded to the study invitation. Compared to an age- and sex-matched normative population (N=380), significantly and clinically relevant poorer HRQoL was observed for AYA lymphoma survivors in seven specific domains of HRQoL: physical, role, cognitive, emotional, social functioning, fatigue and financial difficulties (all $p < .05$). In addition, AYA lymphoma survivors less often had a spouse/partner and more often had a lower educational level compared to the normative population. Linear regression analyses showed that being unemployed, female gender, having one or more comorbid conditions, high levels of fatigue and psychological distress were most strongly associated with HRQoL.

Conclusions: These findings identify specific domains of life in which cancer has a significant and long-term impact for AYA lymphoma survivors. Future investigations are needed to identify and test administrations and timing of psychosocial support interventions having potential to reduce long-term late effects in specific HRQoL domains and promote function and adaptability after cancer treatment.

Keywords: Adolescent and young adult cancer; lymphoma; psychological distress; (health-related) quality of life

Background

In The Netherlands, each year approximately 4,000 people are diagnosed with Non-Hodgkin lymphoma (NHL) and 450 with Hodgkin lymphoma (HL)[1]. Nearly 4% of the NHL and 38% of the HL patients are diagnosed within the adolescent and young adult (AYA) age range of 18-39 years. Lymphoma is one of the most common cancers diagnosed at AYA age, affecting both males and females [2]. Advances in early cancer detection, diagnosis, and treatments have noticeably improved survival rates of patients with lymphoma[3]. Epidemiological data from the United States, however, suggest that 5-year survival rates have not improved to the same extent in AYAs as in children or older adults for several cancers including lymphoma[4]. Three potential explanations are a patient and doctors delay in diagnosis; cancers diagnosed at AYA age may be biologically distinct from those diagnosed at older or younger ages; and clinical trial participation is extremely low in this age group[5]. Although the improvement in survival of AYAs with cancer lags behind, the 5-year overall survival is still 95% for HL and 76% for NHL[4].

Adolescence and young adulthood is a challenging period of physical, emotional, cognitive and social development[6]. Important and complex age-related developmental tasks need to be achieved, such as forming one's own identity and a healthy body image, establishing autonomy, responsibility and independence, finishing education and starting a career, getting a relationship and having children[6]. A cancer diagnosis may have profound effects on the lives of AYAs, interfering with the attainment of these normal developmental milestones. Cancer-related issues such as premature confrontation with mortality, changes in physical appearance, increased dependence on parents, disruptions of social life and school/employment because of treatment, and potential loss of reproductive capacity may become particularly distressing and could negatively impact their health-related quality of life (HRQoL) [6]. Understanding HRQoL outcomes among AYA lymphoma survivors is important to identify who is at risk for poor outcomes and to determine potential relevant services and resources required to serve them. This population-based study aims to (1) assess HRQoL in AYA lymphoma survivors and compare it to an age- and sex-matched normative population; and (2) identify sociodemographic, clinical and long-term symptom-related factors associated with HRQoL for this aged-defined population.

Methods

Setting and population

This study is part of a dynamic, longitudinal, population-based survey of lymphoma patients registered in the Netherlands Cancer Registry (NCR). The NCR records data on all patients who are newly diagnosed with cancer in the Netherlands. The NCR was used to select all survivors who were diagnosed with indolent (including Chronic Lymphocytic Leukemia) and aggressive B-cell non-Hodgkin lymphoma (NHL) or Hodgkin lymphoma (HL), as defined by the International Classification of Diseases for Oncology-3 codes (ICD-O-3), between 1/1/1999 and 1/6/2012. Patients from 18 hospital locations and 2 large radiotherapy institutes in the southern part of the Netherlands, an area with 2.3 million inhabitants, were selected. Survivors who had cognitive impairment or were too ill at time of the study (according to advice from (former) treating specialist) or died prior to the start of the study (according to the NCR, hospital records, and the Central Bureau for Genealogy) were excluded. Ethical approval for the study was obtained from the local certified Medical Ethics Committee of the Maxima Medical Centre Veldhoven.

For this study we only used data of patients aged 18-39 years at time of diagnosis as this is the AYA age range in The Netherlands.

Data collection

Data collection was done within PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). PROFILES is a registry for the study of the physical and psychosocial impact of cancer and its treatment from a dynamic, growing population-based cohort of both short and long-term cancer survivors. PROFILES contains a large web-based component and is linked directly to clinical data from the NCR. Details of the data collection method were previously described[7].

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 1/6/2012 were subsequently invited to participate.

Study measures

Health-related quality of life - EORTC-QLQ-C30

HRQoL was measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30)[8]. This 30-item HRQoL questionnaire consists of five functional scales (physical, role, cognitive, emotional and social), a global quality of life scale (overall health and overall quality of life during the past week), three symptom scales and a number of single items assessing common symptoms and perceived financial impact of the disease. After linear transformation, all scales and single item measures range in score from 0-100. A higher score on the functional scales and global QoL means better functioning and HRQoL, whereas a higher score on the symptom scales means more complaints. Clinically important differences were determined according to the guidelines of the EORTC Quality of Life Group[9]. This size effect as measured by the EORTC QLQ-C30 is divided into four size classes: large (one representing unequivocal clinical relevance), medium (likely to be clinically relevant, but to a lesser extent), small (subtle but, nevertheless, clinically relevant) and trivial (circumstances unlikely to have any clinical relevance or where there was no difference).

Psychological distress (anxiety and depression) – HADS

Psychological distress was assessed with the Hospital Anxiety and Depression Scale (HADS), with seven items each for assessing symptoms of anxiety and depression [10]. All items were scored on a 0- to 3-point scale, with higher scores indicating more symptoms. Clinically relevant differences were determined according to Norman's rule of thumb = 0.5 standard deviation[11].

Socio-demographic and clinical characteristics

Clinical information was available from the NCR that routinely collects data on tumour characteristics, including date of diagnosis, tumour grade, histology, Ann Arbor stage, primary treatment and patients' background characteristics, including sex and date of birth. Comorbidity at the time of survey was categorized according to the Self-administered Comorbidity Questionnaire, assessing the prevalence of 14 comorbidities including heart disease, stroke, high blood pressure, COPD/asthma, diabetes, stomach disease, kidney disease, liver disease, anemia, depression, thyroid disease, osteoarthritis, back pain, and rheumatoid arthritis. Self-designed questions on educational level (high/intermediate/low), partnership (yes/no) and occupation(yes/no) were added to the questionnaire.

Normative population

Normative population data was obtained from CentERpanel, an online household panel that is representative for the Dutch population. The process of the annual data collection, which started in 2009 by our study group, has been described elsewhere[12]. The data wave in 2011 included assessment of HRQoL. From the 2,040 (82%) respondents ≥ 18 years, a normative sample (n=380) was matched on age at time of questionnaire completion and sex.

Statistical analyses

Differences in sociodemographic and clinical characteristics between respondents and non-respondents or survivors with unverifiable addresses, and between AYA lymphoma survivors and an age- and sex-matched normative population, were examined with t-tests or analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables, where appropriate.

The same analytical techniques were used to determine differences in HRQoL and distress between the AYA lymphoma survivors and an age- and sex-matched normative population.

Hierarchical linear regression models were conducted to identify associations of demographic and clinical characteristics, long-term symptoms and psychological distress with HRQoL among AYA lymphoma survivors. The models were composed as follows: 1) demographics+clinical variables; 2) demographics+clinical variables+long-term symptoms (fatigue, pain, insomnia, financial difficulties); 3) demographics+clinical variables+psychological distress (anxiety, depression). All statistical tests were two-sided and considered significant if $p < 0.05$. All analyses were conducted using SPSS version 22.0 (Statistical Package for Social Sciences, Chicago, IL, USA).

Results

Patient and tumor characteristics

Of the 360 survivors selected from the NCR, 18 were excluded because of death or too ill at time of study. The questionnaire was completed by 198 survivors (58%). No differences were found between respondents, non-respondents (n=63; 18%) and survivors with unverifiable addresses

(n=81; 24%) with regard to age, sex, time since diagnosis, primary treatment, lymphoma type and disease stage (data not shown).

AYA lymphoma survivors differed from the age- and sex-matched normative population in that AYA lymphoma survivors less often had a partner ($p<0.01$) and more often had a lower educational level ($p<0.01$) at time of questionnaire completion (n=380; Table 1).

Differences in HRQoL and psychological distress between AYA lymphoma survivors and normative population

AYA lymphoma survivors scored significantly worse on role, cognitive, social (all small to medium clinical importance), physical and emotional functioning (both trivial clinical importance) compared to the age- and sex-matched normative population (Figure 1). No significant differences were found for global quality of life.

AYA lymphoma survivors had significantly more symptoms of fatigue and reported more financial difficulties (respectively of small and medium clinical importance) compared to the normative population (Figure 1).

No statistically significant difference between survivors and the normative population was found for psychological distress.

Factors associated with HRQoL of AYA lymphoma survivors

Model 1 of the hierarchical regression analyses showed that age at cancer diagnosis was negatively associated with cognitive and social functioning (Table 2). Female sex was negatively associated with physical, role, cognitive and social functioning. Being unemployed and having one or more comorbid conditions were negatively associated with all scales, except social functioning for comorbid conditions. Explained variances ranged from 0.19 to 0.33.

In model 2 we added fatigue which was independently, negatively associated with all functioning scales and global quality of life. Pain was negatively associated with physical functioning and global quality of life. Insomnia was negatively associated with emotional functioning and positively associated with social functioning, whereas financial difficulties were negatively associated with physical and social functioning. Explained variances ranged from 0.48 to 0.63.

Adding anxiety in model 3 showed that anxiety was independently, negatively associated with physical, emotional and cognitive functioning, whereas depression was negatively associated

with all functioning scales and global quality of life. Explained variances ranged from 0.34 to 0.64.

Discussion

In this study, AYA lymphoma survivors reported a considerably lower HRQoL compared to an age- and sex-matched normative population, with the largest differences for cognitive, role and social functioning, fatigue and financial difficulties. Our results are in line with those of two previously conducted studies among heterogeneous groups of AYA survivors in terms of tumor types[13, 14]. Data from the Adolescent and Young Adult Health Outcomes and Patient Experience (AYA HOPE) study, a population-based cohort of 523 AYA cancer patients 6 to 14 months post diagnosis at study entry showed that AYA cancer survivors reported significantly worse HRQoL across both physical and mental scales of the Short Form-12 (SF-12) compared to population norms[14]. This study found the greatest deficits for AYA cancer survivors in limitations to physical and emotional roles, physical and social functioning and general health. A German study among 117 AYA cancer survivors within the first five years after diagnosis, using the EORTC QLQ-C30 to assess HRQoL, found that AYA cancer survivors reported poorer outcomes on all scales (physical, role, emotional, cognitive and social functioning) compared to a normative population [13]. The highest point differences were found for social, role and emotional functioning.

Poorer functioning among AYA lymphoma survivors may mirror the cumulative effects of normal developmental challenges in AYAs (e.g., education, work, relationships, starting families) while dealing with the aftermath of cancer and its treatment. Our finding that AYA lymphoma survivors less often had a partner, more often a lower educational level and more financial problems compared to an age- and sex-matched normative population, may indicate that relationships, school/work and finances are negatively impacted and sustained over time by a diagnosis of and treatment for lymphoma.

Although we did not find a significant difference in employment status between AYA lymphoma survivors and the normative population, not having a job was strongly associated with all

HRQoL functioning scales. It could be that reasons for unemployment are more often disease or disability related among AYA cancer survivors compared to controls[15]. Not having a job could reflect a higher severity and impact of the disease. A recent study showed that AYA cancer survivors who reported their cancer treatment was “very intensive” and those who had quit work/school after being diagnosed were more likely to report that cancer negatively affected their work/school after diagnosis, with more than half reporting problems with memory and attention[16], indicating problems with cognitive functioning. Those who remain employed during treatment or reenter shortly after treatment have probably less troubles to maintain normalcy and social reintegration with friends, peers, and others, which minimizes life disruption and optimizes social functioning[17]. Furthermore, a lymphoma diagnosis could significantly impact work plans. Not all AYA lymphoma survivors are able to get the type of job or do the kind of work they would have liked to do and need to adjust their goals as a result of their cancer, which by itself could negatively affect HRQoL. This is illustrated by a study reporting that AYA cancer survivors felt “left behind” in their career or job trajectories compared with their peers[18].

Problems with getting back to work or finding a job after cancer may also be related to the higher financial difficulties experienced by AYA lymphoma survivors. In addition, there may be financial strains related to the cost of treatment and loss of pay resulting from time off from work, but AYA cancer survivors often also have lower earnings as they are in the beginning stages of work and vocational development. Financial independence is considered a hallmark of adulthood, AYA cancer survivors may need to rely on significant others for financial support, which can result in feelings of dependency and loss of control[18].

Interference with work or school and financial difficulties can both result in psychological distress. Our finding that fewer AYA lymphoma survivors had a partner compared to the normative population could indicate high relationship concerns. On the one hand a negative body image, infertility concerns, or feelings of “abnormality” as a result of cancer and its treatment may lead to troubles with starting a serious relationship[19], on the other hand emotional stress and financial burdens of cancer can negatively impact AYA lymphoma survivors’ relationship with their partner. Relationship concerns by itself can lead to higher levels of psychological distress[19]. In our study psychological distress was strongly associated with HRQoL, however distress levels were not higher compared with population norms. Still our findings indicate the

importance of age-appropriate psychosocial support to reduce distress and help AYA lymphoma survivors adjust to their illness.

Next to factors related to developmental milestones, age and gender were also associated with HRQoL. Older AYA lymphoma survivors had worse scores on cognitive and social functioning, which may have to do with higher work-related and social demands at time of diagnosis. Female gender was associated with lower HRQoL. Women in general have the tendency to report more problems and express emotions more easily compared to men[13]. Therefore, the association that we found, should not lead to the conclusion that male patients need less psychosocial support. Another noteworthy observation was the lack of differences in HRQoL between short- and long-term AYA lymphoma survivors. This is an interesting finding because it is an indication that deteriorated HRQoL scores do not improve over time. No other clinical factors (type of lymphoma, disease stage) were related to HRQoL. This is in congruence with the current state of research suggesting that subjective appraisals of cancer's impact on one's life may be more salient as contributors to HRQoL than objective cancer-related clinical factors (e.g., time since diagnosis, type or severity of treatment)[20]. This research suggests that survivors who report subjective appraisals, perceptions or experiences of how cancer has negatively affected their lives experience worse HRQoL[20]. Given that perceptions are malleable and change over time, cognitive and behavioral interventions that reframe perceptions may have the potential to enhance survivors' HRQoL. On the other hand, we found that long-term symptoms such as fatigue were strongly associated with several functioning scales, suggesting that post-treatment symptom management would be helpful to diminish debilitating symptoms and improve functioning[14].

Despite the lower functioning scores of AYA lymphoma survivors, no difference in global quality of life between AYA lymphoma survivors and the normative population was found. One possible but not yet well investigated explanation could be that some AYA cancer survivors experience posttraumatic growth post-treatment[21]. It will be interesting for future research to identify factors that may underpin the emergence of these positive psychological outcomes to help development of interventions for AYA lymphoma survivors who continue to report symptoms psychological distress.

Limitations

This study has several limitations that should be mentioned. First, the cross-sectional design limits the determination of changes over time in AYA lymphoma survivors' HRQoL. Longitudinal studies are needed to assess within-person changes in HRQoL to identify risk groups for persistent lower levels of HRQoL for whom interventions are most needed. Second, detailed follow-up treatment and relapse data was lacking because the NCR registers only the primary diagnosis and treatment procedures. Third, although the CentERpanel is designed to be representative for the Dutch population, due to selective response on our questionnaire we have included a somewhat higher educated population. Fourth, we did not make use of an AYA cancer specific HRQoL measure, because there is a relative lack of measures developed or validated in this population[22]. Qualitative research highlights the need for tools measuring domains, such as cognition, sexual and reproductive health and social relationships[23]. An AYA specific HRQoL instrument in research and clinical practice will be instrumental in the objective evaluation of the new psychosocial and supportive care interventions that minimize or prevent long-term deleterious effects of cancer but also promote positive adaptation, resilience, and the achievement of age-specific developmental tasks. Fifth, because lymphoma is a very heterogeneous disease with respect to subtypes and treatment, our study can only answer the question how a lymphoma diagnosis at AYA age influenced HRQoL. However, the homogeneous study sample with respect to tumor type could also be mentioned as strength of this study. Compared to other studies among more heterogeneous groups of AYA cancer survivors, we were able to show sex differences in HRQoL not related to tumor type.

Future perspectives

Overall, our findings support research into (early) psychosocial interventions for AYA lymphoma survivors as well as the need to manage long-term symptoms, provide financial support and facilitate AYA lymphoma survivors' involvement in work and/or school. Due to the still relatively small number of AYA survivors implementing age-appropriate interventions might be a challenge. Nevertheless, the recent developments of AYA-specific programs with multidisciplinary care teams to approach this area of need will provide new opportunities[24]. In addition, new media can facilitate AYA lymphoma survivors' participation in their own care and

may become new modes of delivering cost-effective and easy to disseminate psychosocial support[25].

Conclusion

AYA lymphoma survivor report lower HRQoL scores compared with the normative population. Although overall global quality of life scores are good, impairments are experienced in the domains of role, cognitive and social functioning, fatigue and financial problems. Employment status, gender, comorbid conditions, fatigue and psychological distress were most strongly associated with HRQoL. Future intervention studies should explore ways to timely address poor functioning.

Conflict of interest

None declared.

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Table 1. Sociodemographic and clinical characteristics of AYA lymphoma patients compared to normative population

	AYA cancer patients N=198 N (%)	Normative population N=380 N (%)	p-value
Sex (Male)	112 (57%)	204 (54%)	0.47
Age at time diagnosis – M (SD)	30.4 (6.4)	NA	
Age at time diagnosis		NA	
18-25 years	55 (28%)		
26-39 years	143 (72%)		
Age at time survey* – M (SD)	34.7 (7.4)	35.2 (8.0)	0.50
Age at time survey*			0.20
18-29 years	45 (23)	83 (22)	
30-35 years	59 (30)	85 (22)	
36-40 years	45 (23)	104 (27)	
≥41 years	49 (25)	108 (28)	
Years since diagnosis – M (SD)	4.2 (2.7)	NA	
Years since diagnosis		NA	
<2 years	54 (27%)		
2-5 years	69 (35%)		
>5 years	75 (38%)		
Tumor type		NA	
Hodgkin Lymphoma	89 (45%)		
Non-Hodgkin Lymphoma	109 (55%)		
Stage[#]		NA	
I	43 (22%)		
II	84 (42%)		
III	31 (16%)		
IV	34 (17%)		
Unknown	6 (3%)		
Primary treatment		NA	
Wait and see	15 (8%)		
Chemotherapy alone	85 (43%)		
Radiotherapy alone	9 (4%)		
Stem cell transplantation	1 (1%)		
Radiotherapy and chemotherapy	82 (41%)		
Other therapies	5 (3%)		
Missing	1 (1%)		
Number of comorbid conditions[^] – M (SD)	1.3 (3.0)	0.6 (1.3)	<0.01
Number of comorbid conditions			0.01
None	122 (62%)	246 (65%)	
One	36 (18%)	90 (24%)	
Two or more	40 (20%)	44 (12%)	
Partner (yes)	137 (69%)	312 (82%)	<0.01
Job (yes)	132 (75%)	301 (79%)	0.22
Educational level			<0.01
Low	53 (27%)	10 (3%)	
Middle	112 (58%)	219 (58%)	
High	29 (15%)	149 (39%)	

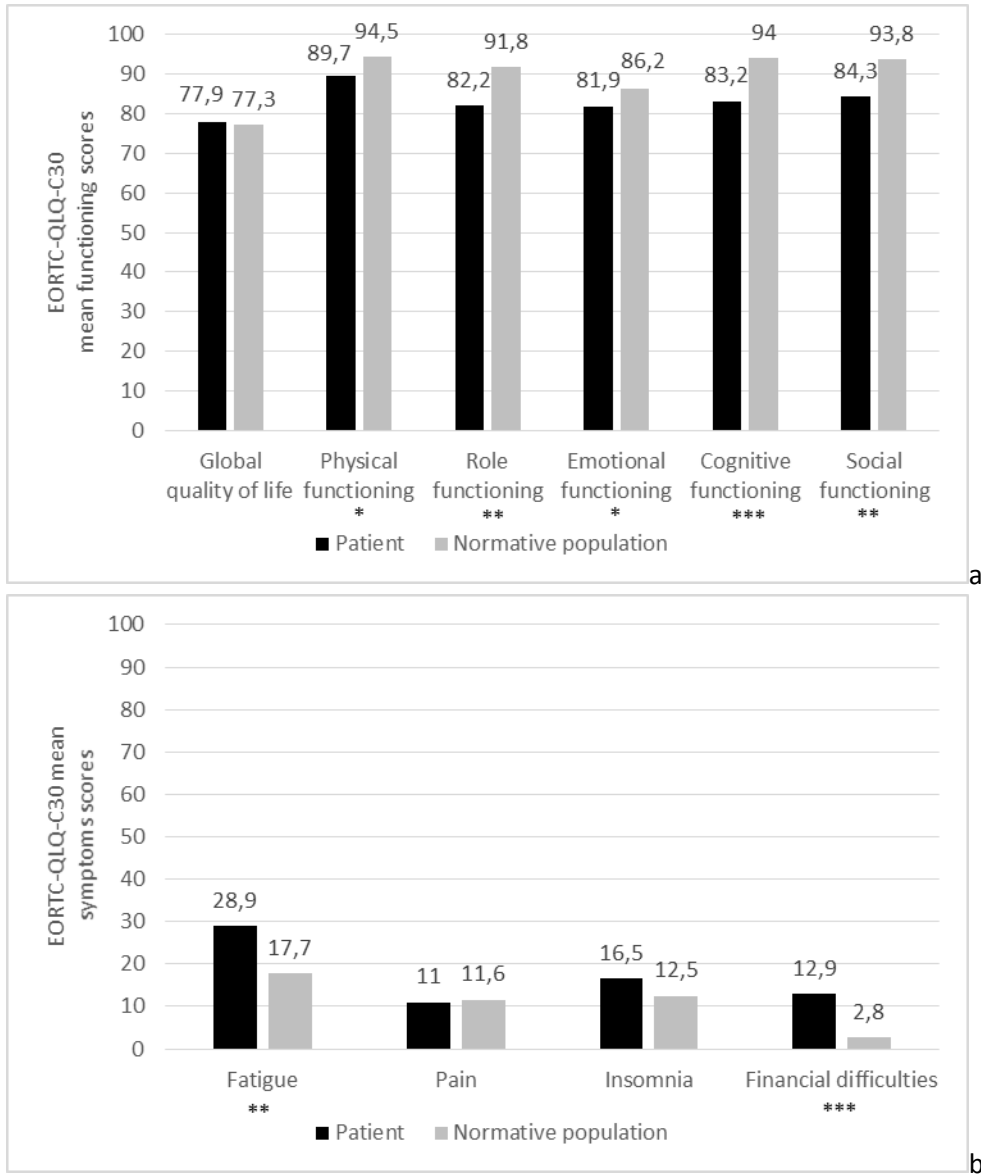
*Matching was based on age at questionnaire completion and sex

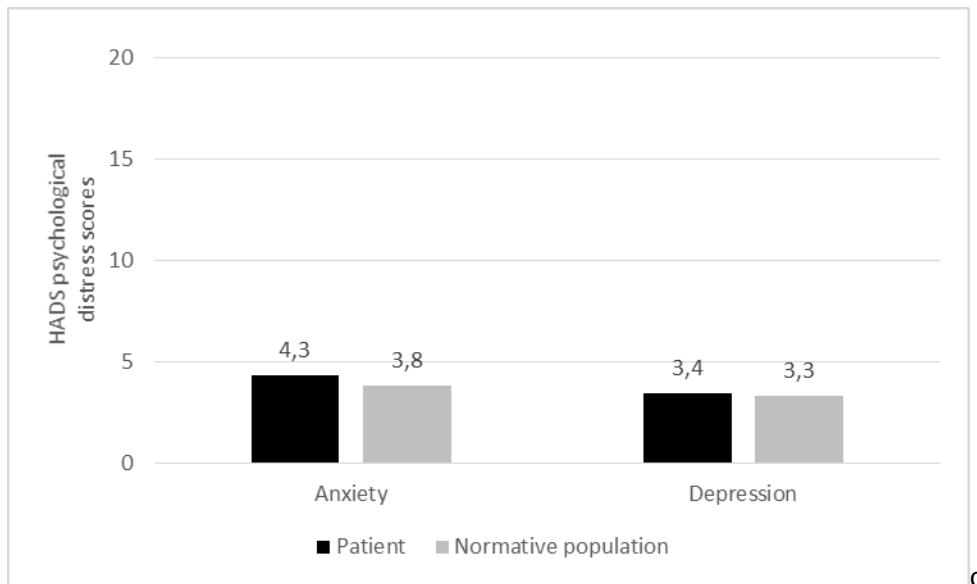
Disease stage was not available for some indolent Non-Hodgkin Lymphoma patients

~22 patients had indolent Non-Hodgkin Lymphoma and 87 had aggressive Non-Hodgkin Lymphoma

^Comorbid conditions that were assessed included heart disease, stroke, high blood pressure, lung disease (e.g. COPD, asthma), diabetes, ulcer, kidney disease, liver disease, anemia, thyroid disease, depression, rheumatism, back pain, osteoarthritis,
NA = not applicable
M=mean; SD=standard deviation

Figure 1 Comparison of HRQoL (a), long-term symptoms (b) and psychological distress scores (c) between patients and normative population





Note: * $p < .05$ and trivially clinically important difference; ** $p < .05$ and small clinically important difference; *** $p < .05$ and medium clinically important difference.

- a. Scores can range from 0-100 with higher scores implying a better HRQoL.
- b. Scores can range from 0-100 with higher scores implying more symptoms
- c. Scores can range from 0-21 with higher scores implying more psychological distress

Table 2: Standardized betas of hierarchical multiple linear regression analyses evaluating the association of demographic and clinical characteristics, symptoms and psychological distress with HRQoL among AYA lymphoma patients

	Global quality of life Beta	Physical functioning Beta	Role functioning Beta	Emotional functioning Beta	Cognitive functioning Beta	Social functioning Beta
Model 1: Demographics and clinical variables						
Age time diagnosis <i>≥26 years (ref 18-25 years)</i>	-0.09	-0.12	-0.06	-0.10	-0.21**	-0.16*
Sex <i>Females (ref males)</i>	-0.04	-0.24**	-0.16*	-0.04	-0.21**	-0.22**
Education <i>High vs. medium</i> <i>High vs. Low</i>	-0.06 -0.05	-0.01 -0.03	-0.12 -0.05	0.09 0.05	-0.06 -0.02	-0.08 -0.03
Partner <i>Partner (ref no partner)</i>	-0.04	-0.01	0.04	0.13	0.03	0.11
Job <i>No (ref yes)</i>	-0.34**	-0.35**	-0.25**	-0.21**	-0.23**	-0.16*
Time since diagnosis	-0.06	0.03	0.12	0.02	0.12	0.05
Tumor type <i>HL (ref NHL)</i>	0.01	-0.05	0.07	0.07	-0.02	0.07
Stage <i>1 vs. 2</i> <i>1 vs. 3</i> <i>1 vs. 4</i> <i>1 vs. missing</i>	-0.15 -0.13 -0.14 -0.04	0.08 -0.08 -0.03 -0.03	-0.05 0.01 -0.03 -0.09	-0.16 -0.10 -0.04 -0.06	-0.08 -0.04 -0.11 -0.04	-0.15 -0.09 -0.14 0.02
Comorbid conditions <i>0 vs. 1</i> <i>1 vs. 2 or more</i>	-0.10 -0.19*	-0.17* -0.20**	-0.12 -0.21**	-0.14 -0.34**	-0.18* -0.17*	-0.14 -0.12
R ²	0.23	0.33	0.24	0.26	0.25	0.19
Model 2: Model 1 + long-term symptoms						
Fatigue	-0.40**	-0.41**	-0.66**	-0.41**	-0.50**	-0.43
Pain	-0.25**	-0.25**	-0.13	-0.05	-0.01	0.01
Insomnia	-0.07	0.05	0.01	-0.28**	-0.08	0.17*
Financial problems	-0.15	-0.17*	-0.06	-0.08	-0.05	-0.47**
R ²	0.56	0.63	0.63	0.55	0.48	0.55
Model 3: Model 1 + psychological distress						
Anxiety	-0.15	-0.23**	-0.15	-0.51**	-0.31**	-0.12
Depression	-0.52**	-0.18*	-0.30**	-0.27**	-0.29**	-0.40**
R ²	0.50	0.45	0.36	0.64	0.47	0.34

*p<0.05; **p<0.01