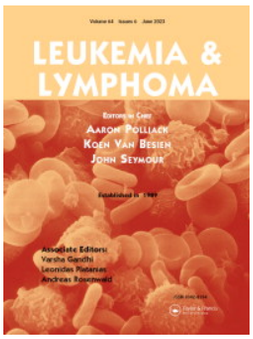

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ORIGINAL ARTICLE

Health-related quality of life, depressive symptoms, and chronic fatigue in long-term survivors of Hodgkin lymphoma

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ABSTRACT

High-dose chemotherapy with autologous stem cell transplantation (HDT-ASCT) is the preferred treatment option in relapsed or refractory Hodgkin lymphoma (HL). We analyzed the association between treatment intensity and health-related quality of life (HRQoL), depressive symptoms, and chronic fatigue (CF) in long-term survivors of HL (HLS), identified in two population-based national cross-sectional studies on late adverse effects. We included 375 HLS treated between 1987 and 2006, 264 with conventional therapy only, and 111 with HDT-ASCT. Despite similar differences to the matched general population, when controlling for other imbalances between the groups, use of HDT-ASCT was not associated with poorer outcome in multivariable analysis. However, work participation, family income, comorbidities, and lifestyle factors had stronger associations with aspects of HRQoL, depressive symptoms, and CF. Our data suggest that better rehabilitation to work participation and adequate income as well as follow-up for comorbidities may reduce differences in long-term outcome after treatment for HL.

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Introduction

Hodgkin lymphoma (HL) is one of the most common cancer diagnoses in adolescents and young adults with an annual incidence of 2–3 cases per 100,000 in developed countries. Currently, the probability of surviving 5 years after diagnosis is 85%–90% with best results in younger age groups [1]. There are now more than 3000 Hodgkin lymphoma survivors (HLS) in Norway [2].

Contemporary treatment for HL consists of combination chemotherapy supplemented with radiotherapy in a proportion of patients [1,3]. In case of progressive disease on first-line treatment or relapse of HL, most young and fit patients are considered for salvage treatment with curative intent, followed by high-dose chemotherapy with autologous stem cell transplantation (HDT-ASCT) [4,5].

As the patients are young and the cure rate is high, long-term HLS are at risk of experiencing adverse effects (AEs) of treatment. For HLS such AEs include somatic, psychological, and social impairments such as heart disease, reduced sexual function and infertility, secondary malignancies, depression, chronic fatigue (CF), and social problems, and might affect health-related quality of life (HRQoL) [6,7]. Many late AEs seem closely related to specific components of treatment, such as occurrence of secondary malignancies after large radiotherapy fields or infertility associated with cumulative doses of alkylating agents and procarbazine [6,8,9]. Contemporary risk- and response-adapted treatment for HL aims to avoid over-treatment and prevent long-term AEs in survivors [3]. However, any reduction in therapy may be associated with an increased risk of treatment failure as reported in studies evaluating response-adapted use of radiotherapy in early stages or comparing chemotherapeutic regimens of different intensities for advanced

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disease [10–12]. Any treatment decision for patients with newly diagnosed HL will therefore have to balance the likelihood of cure and the risk of long-term complications. Since a large proportion of patients who fail first-line treatment will be candidates for HDT-ASCT, knowing the long-term complications after intensive second-line treatment is an integral part of this equation.

In two national population-based surveys, we have characterized the long-term outcome of HLS after contemporary risk-adapted treatment and those after salvage treatment including HDT-ASCT [13–15]. Combining data from these surveys, the aim of this study was to determine (1) how treatment intensity of HL is associated with HRQoL, depressive symptoms, and CF in long-term survivors after conventional treatment and HDT-ASCT and (2) differences between the HLS and their age- and gender-matched controls regarding these outcomes. The present study is, to the best of our knowledge, the first study to compare HRQoL, depressive symptoms, and CF in two large, population-based cohorts after either conventional treatment only or additional HDT-ASCT. The results may help decision making and guiding of patients at different steps of the treatment trajectory.

Materials and methods

Study sample

HLS were recruited through two population-based national multicenter studies. During 2012–2014, a cross-sectional study at all four Norwegian university hospitals responsible for HDT-ASCT identified all lymphoma survivors who had undergone this treatment as adults between 1987 and 2008 and were alive and tumor-free in 2012 [14,15]. From this study, referred to as HL-HDT-12, only HLS were included. During 2017–2019, a national cross-sectional study on late effects, referred to as HL-17, included survivors treated for HL between 1997 and 2006 who were alive and in remission in 2016 [13]. Survivors from three regional health authorities (South-Eastern, Central, and Northern Norway) were identified through the Norwegian Cancer Registry. The number of eligible HLS from the two studies, those invited and those responding, are shown in Figure 1. In HL-17, non-responding survivors were more likely men ($p < 0.001$) and younger at diagnosis and survey (both with $p < 0.01$), compared to respondents, whereas no such differences in attrition were seen in HL-HDT-12. For all consenting HLS, data concerning diagnosis and treatment were extracted from hospital records.

Questionnaires

The mailed questionnaire in both studies was similar and contained identical study-specific items on sociodemographic factors (education, household income, education level, and marital status), and lifestyle variables (weight, height, smoking habits, and alcohol consumption). Self-reported comorbidity was captured according to the Self-Administered Comorbidity Questionnaire [16].

For generic HRQoL, both surveys used the Short Form 36 (SF-36), containing 36 items in eight

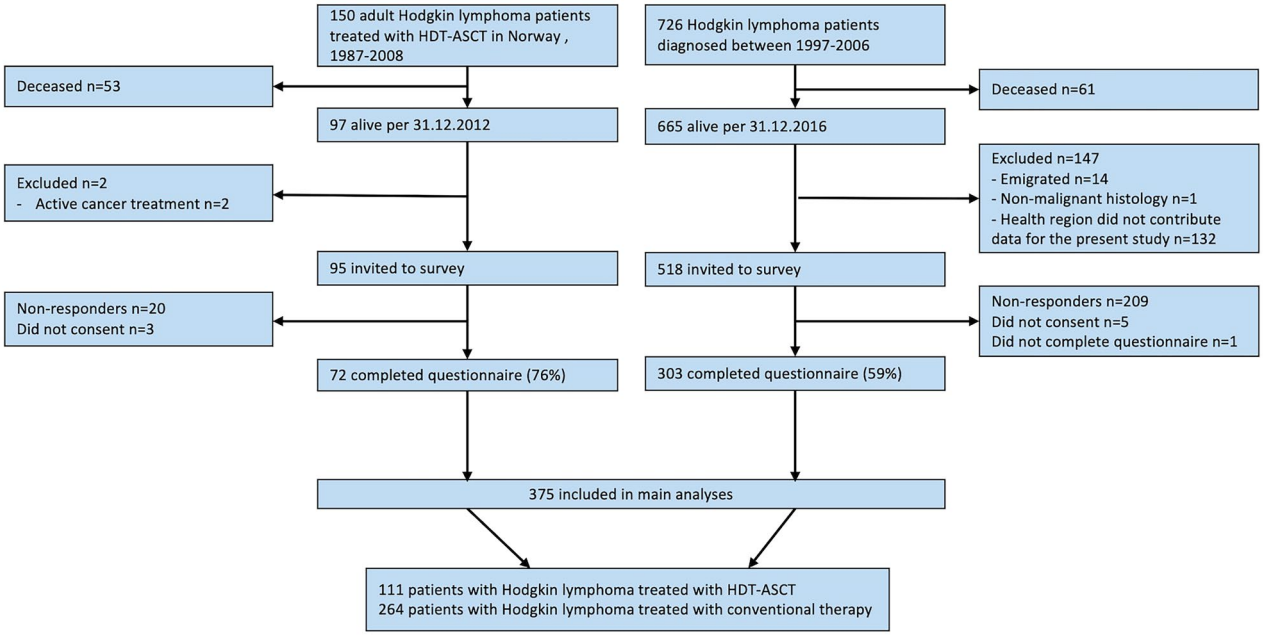

Figure 1. Flow chart of study participants. HDT-ASCT: high-dose therapy with autologous stem cell transplantation.

dimensions (four mental and four physical) and summarized into physical (PCS) and mental (MCS) composite scores. Responses were transformed into a 0–100 score, where lower scores imply lower HRQoL [17].

The two surveys used different questionnaires to assess depressive symptoms. HL-HDT-12 included the Hospital Anxiety and Depression Scale–Depression Subscale (HADS-D) which covers depressive symptoms last week and consists of seven items [18]. The subscale ranges from 0 (low) to 21 (high) with higher scores indicating more symptoms. HL-17 applied Patient Health Questionnaire-9 (PHQ-9) concerning symptoms during the last 2 weeks and provides a 0–27 severity score, with higher scores indicating more symptoms [19]. For both instruments, cutoff values indicating the presence of clinically relevant levels of depression have been published, and cutoff scores of ≥8 for HADS-D and ≥12 for PHQ-9 were used in the present report [20].

Both surveys used the Fatigue Questionnaire (FQ) which covers the last 4 weeks and contains 11 items assessing mental and physical fatigue, each on a scale from 0 to 3. Total fatigue ranges from 0 to 33 with higher scores representing more fatigue. To calculate the prevalence of CF, each of the 11 items was dichotomized (0 and 1 scored as 0, and 2 and 3 scored as 1). Sum scores ≥4 for the dichotomized responses with a duration of 6 months or longer were defined as CF [21].

Reference population

Controls were identified through the Nord-Trøndelag Health Study for HADS-D [22] and a Norwegian population study, 'Normstudien 2015' for PHQ-9, SF-36, and FQ [23,24]. The controls were matched 1:3 with respect to gender and age within 10-year age groups.

Statistical analyses

Categorical data are presented as numbers and percentages, and continuous data with median and range for skewed data. Comparison of categorical and continuous data was done with chi-square and Mann–Whitney *U* tests, respectively. Effect size (ES) for chi-square tests was expressed by phi (2 × 2) or Cramer's *V* (>2 × 2) and for Mann–Whitney *U* test by estimated *r*. ES interpretations were small (ES 0.1–0.3) medium (>0.3–0.5) and large (>0.5 large). Factors associated with HRQoL were analyzed by linear regression and logistic regression was used to estimate factors associated with either depressive symptoms above threshold or CF. Along with type of treatment, conventional only versus HDT-ASCT, other variables with *p* values ≤0.1 in univariate analysis or those considered clinically relevant were included in multivariable analysis. The strength of associations was expressed as unstandardized regression coefficient for linear regression and odds ratio (OR) for logistic regression, all with 95% confidence intervals (CI). Missing data were treated as missing. Tests for significance were two-sided and *p* values <0.05 were considered statistically significant. The assumptions for linear and logistic regression were met. Statistical analyses were performed using SPSS Version 26 (IBM Corp, Armonk, NY).

Results

Survivor characteristics

From the two surveys, 375 long-term HLS were included (Figure 1 and Table 1). They had either received conventional treatment only ($n = 264$) or additionally undergone HDT-ASCT for refractory or relapsing disease ($n = 111$). For survivors after conventional treatment only, 51.5% were men and median age at diagnosis and survey were 28.5 years (range 8–50) and 44.5 years (range 21–70), respectively. For survivors after HDT-ASCT, 54.1% were men and median age at diagnosis and survey were 31 years (range 10–64) and 46 years (range 24–76). Survivors after HDT-ASCT more often had higher stage or B-symptoms at diagnosis and more often had received chemotherapy or radiotherapy as part of their treatment (comparisons with *p* values <0.1). 25 (22.5%) of HLS after HDT-ASCT had completed primary treatment and 7 underwent HDT-ASCT before 1997, whereas all survivors after conventional treatment received it from 1997 and beyond ($p < 0.001$). First-line chemotherapy was anthracyline-based without the alkylating agents, such as cyclophosphamide and procarbazine in 81 survivors in the HDT-ASCT group and 196 in the conventional treatment group, and alkylator-based regimens were used as first-line treatment in 22 survivors after HDT-ASCT and 46 after conventional treatment only, with no significant difference between the groups (Table 1). Median time from diagnosis to survey was 16 years (range 10–21) after conventional treatment only, compared to 14 years (range 4–34) in the HDT-ASCT group ($p = 0.01$).

Health-related quality of life

Results for HRQoL in survivors after conventional treatment only or additional HDT-ASCT are shown

Table 1. Characteristics of responding Hodgkin lymphoma survivors.

	Survivors after conventional therapy only (*N* = 264)	Survivors after HDT-ASCT[a] (*N* = 111)	*p* value
Sociodemographic factors			
Sex, *n* (%[b])			0.65
Females	128 (48.5)	51 (45.9)	
Males	136 (51.5)	60 (54.1)	
Median age at diagnosis, years (range)	28.5 (8–50)	31 (10–64)	0.38
Median age at survey, years (range)	44.5 (21–70)	46 (24–76)	0.81
Median time from diagnosis to survey, years (range)	16 (10–21)	14 (4–34)	**0.01**
Marital status, *n* (%)			
In paired relationship			0.16
Not in paired relationship	214 (81.1)	82 (74.5)	
Education level, *n* (%)	50 (18.9)	28 (25.5)	
≤16 years			**0.1**
>16 years	214 (81.4)	98 (88.3)	
Annual household income, *n* (%)	49 (18.6)	13 (11.7)	
≤600,000 NOK[c]			**<0.001**
>600,000 NOK	75 (28.8)	54 (50.5)	
Current work participation, *n* (%)	185 (71.2)	53 (49.5)	
Yes	248 (96.9)	91 (82.7)	**<0.001**
No	8 (3.1)	19 (17.3)	
Lymphoma and treatment			
Ann Arbor stage, *n* (%)			**<0.001**
I–II	199 (75.4)	63 (56.8)	
III–IV	65 (24.6)	48 (43.2)	
B-symptoms, *n* (%)			**0.07**
No B-symptoms	183 (69.3)	66 (59.5)	
B-symptoms	81 (30.7)	45 (40.5)	
Chemotherapy, *n* (%)			**0.06**
Yes	247 (93.6)	111 (100)	
No	17 (6.4)	0	
Primary treatment[d], *n* (%)			**0.21**
Anthracyline-based	196 (74.2)	81 (74.3)	
Alkylator-based	46 (17.4)	22 (20.2)	
Other	0	1 (0.9)	
Radiotherapy only	22 (8.3)	5 (4.6)	
Radiotherapy, *n* (%)			**0.02**
Yes	201 (76.1)	96 (86.5)	
No	63 (23.9)	15 (13.5)	
Treatment period, *n* (%)			**<0.001**
1989–1996	0	25 (22.5)	
1997–2008	264 (100)	86 (77.5)	
Self-reported comorbidity, *n* (%)			
Stroke	3 (1.3)	2 (2.1)	0.59
Hypertension	44 (19)	15 (15)	0.38
Lung disease	34 (14.5)	21 (21.4)	0.12
Diabetes	14 (6)	4 (4.2)	0.51
Thyroid disease	68 (28.9)	56 (55.4)	**<0.001**
Depression	59 (25.4)	36 (35.6)	**0.06**
Secondary malignancy	20 (7.6)	16 (14.4)	**0.04**
Heart disease	40 (15.2)	26 (23.4)	**0.06**
Lifestyle variables			
BMI[e], median (range)	25.7 (17.3–42.5)	25.1 (15.4–50.3)	**0.09**
Smoking, *n* (%)			0.53
Never	131 (49.6)	59 (53.2)	
Previous or current	133 (50.4)	52 (46.8)	
Alcohol, median number of units[f] weekly (range)	1.5 (0–28)	1 (0–12)	**0.05**
Patient-reported outcome measures			
SF-36[g], median (range)			
MCS[h]	51 (13.8–71.7)	51.9 (13.7–67.4)	0.34
PCS[i]	49.5 (15.8–63.2)	47.1 (16–66.4)	0.1
PHQ-9[j], *n* (%)			
≥12	25 (10.5)	7 (20.0)	
≤11	213 (89.5)	28 (80.0)	
HADS-D[k], *n* (%)			
≥8		16 (22.2)	
≤7		56 (77.8)	
Depressive symptoms above threshold[l]			**<0.01**
Yes (*n* = 48)	25 (10.5)	23 (21.5)	
No (*n* = 297)	213 (89.5)	84 (78.5)	

Table 1. (Continued).

	Survivors after conventional therapy only ($N = 264$)	Survivors after HDT-ASCT[a] ($N = 111$)	p value
Chronic fatigue, *n* (%)			0.82
Yes	105 (40.4)	45 (41.7)	
No	155 (59.6)	63 (58.3)	

[a]High-dose chemotherapy with autologous stem cell transplantation.
[b]Percentage indicated for respondents with valid answer.
[c]Norwegian krone.
[d]Anthracyline-based: doxorubicin, bleomycin, vinblastine/vincristine, and dacarbazine [ABVD/ABOD] in 257 and 15; other combinations in 5. Alkylator-based: chlorambucil/mustargen, vincristine, procarbazine and prednisolone [LVPP or MOPP] containing combinations in 11; vincristine, etoposide/procarbazine, prednisolone, doxorubicin with cyclophosphamide, vincristine, procarbazine, and prednisolone (OEPA/OPPA-COPP) in 26; bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone [BEACOPP] in 18, cyclophosphamide, doxorubicin, vincristine, and prednisolone [CHOP]-like combinations in 13. Radiotherapy only as first-line treatment in 27. One patient received a high-dose methotrexate-based combination for a misdiagnosis of non-Hodgkin lymphoma. Primary treatment data missing in 2. Comparison based on groups with anthracyline-based or alkylator-based chemotherapy or radiotherapy only.
[e]Body mass index (kg/m^2).
[f]One unit corresponding approximately to 12–15 g of ethanol.
[g]Short Form 36.
[h]Mental composite summary.
[i]Physical composite summary.
[j]Patient Health Questionnaire-9.
[k]Hospital Anxiety and Depression Scale–Depression Subscale.
[l]Symptom severity dichotomized according to suggested cutoffs, HADS-D ≥ 8 or PHQ-9 ≥ 12.
Significant p values below 0.05 and medium and large are given in bold.

in Table 1 and Figure 2. Survivors after conventional treatment only reported a median PCS of 49.5 (range 15.8–63.2) and median MCS of 51 (range 13.8–71.7). Survivors after HDT-ASCT reported a median PCS of 47.1 (range 16–66.4) and median MCS of 51.9 (range 13.7–67.4). Neither in univariate nor multivariable analysis, adjusting for imbalances between the cohorts, did HRQoL differ between the two groups (Table 2).

In multivariable analyses, education level ≥16 years, a higher annual household income, current work participation and increasing weekly numbers of units of alcohol remained significantly associated with higher PCS values (Table 2). Increasing body mass index (BMI), the presence of thyroid- and heart disease remained significantly associated with lower PCS. For MCS, only annual household income above 600,000 Norwegian kroner remained significantly associated with higher MCS.

Survivors reported significantly lower HRQoL compared to the Norwegian general population. For survivors after conventional therapy, controls reported PCS of 52.9 (range 16.1–65.6, $p < 0.001$) and MCS of 54.1 (range 4.5–70.0, $p < 0.001$). The controls matched with survivors after HDT-ASCT reported PCS 53.6 (range 16.5–65.6, $p < 0.001$) and MCS 54.2 (range 16.8–67.4, $p = 0.05$; Figure 2). Differences in PCS and MCS compared to controls were small for both groups of survivors, all with ES below 0.1 (Table 3).

Depressive symptoms

With HADS-D scores ≥8 or PHQ-9 scores ≥12 chosen as indicators of clinically relevant depression, 48 of all 345 responding survivors had depressive symptoms above threshold (Table 1). The prevalence of clinically relevant depression was significantly higher after HDT-ASCT than conventional therapy only (21.5% vs. 10.5%, $p < 0.01$). In multivariable analysis, this difference was however not significant (Table 2). Use of radiotherapy and a higher annual household income remained significantly associated with the risk of depression in multivariable analysis.

A total of 10.5% of survivors after conventional therapy only reported depressive symptoms above threshold using PHQ-9, compared to 6.1% for the normal population ($p = 0.03$; Figure 2). In survivors after HDT-ASCT, 20.0% and 22.2% of the survivors reported depressive symptoms above PHQ-9 or HADS-D thresholds, compared to 5.1% and 8.3% ($p < 0.01$; Figure 2) in the relevant matched normal population, respectively. These differences between HLS and controls all had a small ES below 0.3 (Table 3).

Chronic fatigue

The prevalence of CF was similar in both treatment groups with 40.4% after conventional treatment and 41.7% (Table 1). In multivariable analysis, increasing BMI was the only significant factor associated with CF (Table 2).

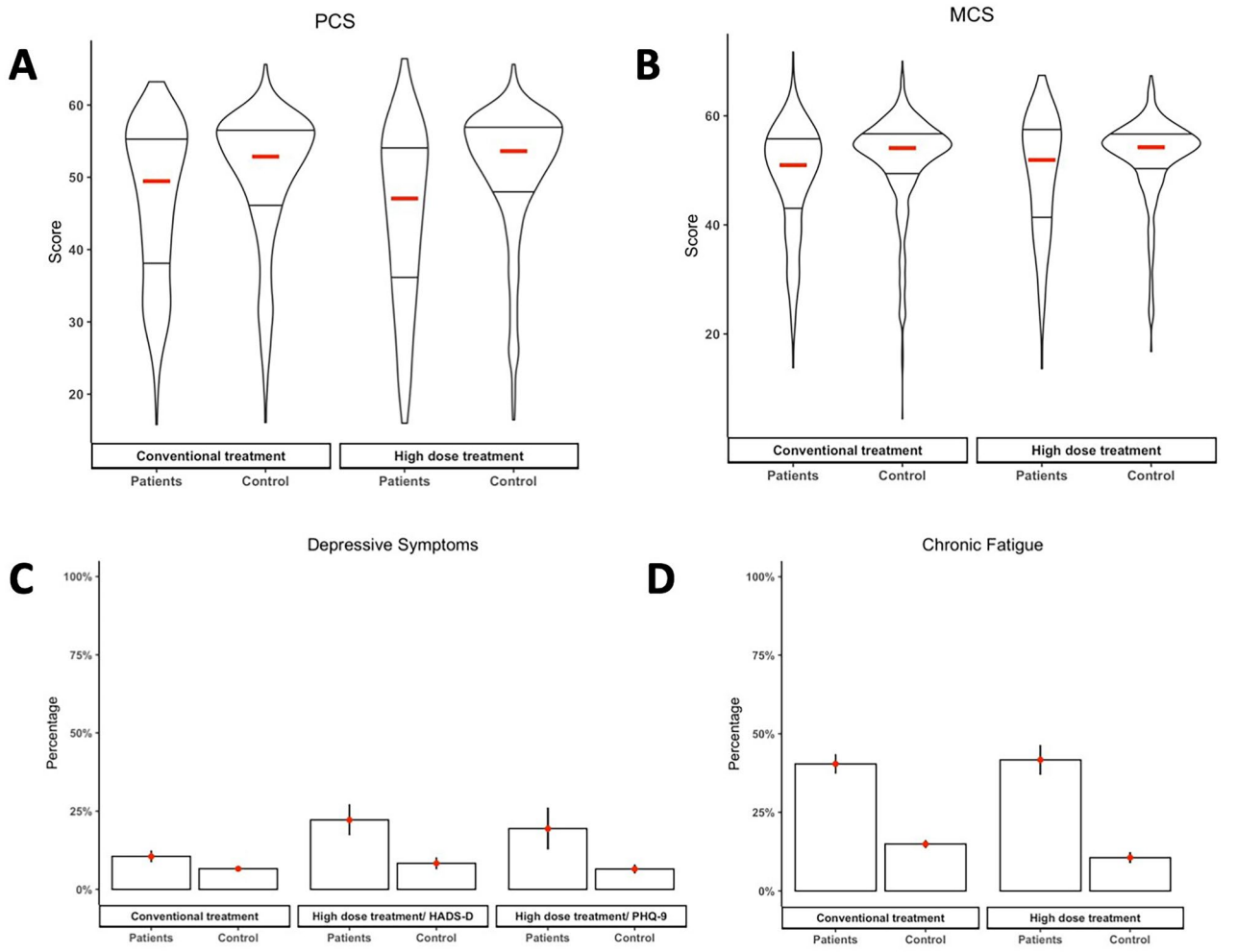

Figure 2. Health-related quality of life, depressive symptoms, and fatigue in survivors and matched controls. Beanplots for physical component score (A) and mental component score (B) with median (red horizontal line) and quartile width (black horizontal lines). Prevalence (red circles) and 95% confidence intervals (black vertical lines) of depression for Hospital Anxiety and Depression Scale-D and Patient Health Questionnaire-9 (C). Prevalence (red circles) and 95% confidence intervals (black vertical lines) of chronic fatigue (D).

Compared to the general Norwegian population, HLS reported approximately three times higher prevalences of CF, with 14.9% and 10.6% for the controls matched for the two treatment groups ($p < 0.001$; Figure 2(D)). The comparison for prevalence of CF had an ES of 0.27 for HLS after conventional treatment only and 0.35 for HLS after HDT-ASCT, values close to or just above the level of moderate effects (Table 3).

Discussion

We analyzed differences in HRQoL, depressive symptoms, and CF in two large, population-based cohorts of Norwegian HLS after either conventional treatment only or additional use of HDT-ASCT for relapsed or refractory disease. When controlling for other relevant variables differing between the groups, neither HRQoL, the prevalence of depression nor CF was significantly associated with treatment intensity. Differences in health, especially comorbidities, and socioeconomic parameters seemed more closely related to the outcomes studied. HLS, irrespective of type of treatment, reported lower HRQoL, higher rates of depression and were more often fatigued than the age- and sex-matched normal population.

HDT-ASCT is still recommended as the preferred treatment for most patients with relapsed or refractory HL [5,25]. However, the two randomized trials comparing HDT-ASCT to second-line conventional treatment are old and small [26,27]. Also, the fear of excessive short- and long-term toxicity, may defer clinicians or patients from choosing this option. Our study was therefore designed to compare important

Table 2. Multivariable analysis of factors associated with health-related quality of life, depression, and chronic fatigue.

	Mental composite summary			Physical composite summary			Depression			Chronic fatigue		
	B[a]	95% CI[b]	*p*	*B*	95% CI	*p*	OR[c]	95% CI	*p*	OR	95% CI	*p*
Sociodemographic factors												
Education level ≥16 years (ref. <16)				**3.48**	**0.57; 6.39**	**0.02**	0.48	0.14; 1.68	0.25	0.67	0.35; 1.30	0.24
Higher annual household income[f]	**3.27**	**0.95; 5.60**	**0.006**	**2.97**	**0.51; 5.42**	**0.02**	**0.40**	**0.20; 0.79**	**0.009**	0.77	0.46; 1.30	0.33
Current work participation	2.71	−1.54; 6.95	0.21	**9.72**	**4.88; 14.55**	**<0.001**	0.37	0.13; 1.05	0.06	0.38	0.13; 1.13	0.08
Lymphoma and treatment												
HDT-ASCT[d]	1.90	−0.54; 4.35	0.13	0.90	−1.66; 3.45	0.49	1.37	0.67; 2.84	0.39	0.76	0.44; 1.33	0.34
Radiotherapy							**4.58**	**1.33; 15.75**	**0.02**	1.26	0.67; 2.34	0.48
Self-reported comorbidity												
Thyroid disease				**−4.34**	**−6.71; −1.98**	**<0.001**				1.61	0.93; 2.77	0.09
Heart disease				**−3.55**	**−6.54; −0.56**	**0.02**						
Lifestyle variables												
BMI[e]				**−0.38**	**−0.61; −0.15**	**0.001**	1.05	0.98; 1.11	0.15	**1.06**	**1.01; 1.11**	**0.03**
Weekly number of units of alcohol[g]				**0.67**	**0.30; 1.03**	**<0.001**				0.92	0.84; 1.01	0.08

HDT-ASCT: high-dose chemotherapy with autologous stem cell transplantation.
Along with the type of treatment, HDT-ASCT versus conventional only, other variables unequally distributed between the groups and with *p* values ≤0.1 (presented in Table 1) were entered into the models. Next to treatment group, only factors univariately associated with the outcome at $p < 0.10$ were included in the multivariable analysis and only these variables are shown.
[a]Unstandardized regression coefficient beta.
[b]Confidence interval.
[c]Odds ratio.
[d]High-dose chemotherapy with autologous stem cell transplantation.
[e]Body mass index (kg/m2).
[f]>600,000 NOK (ref. ≤600,000).
[g]One unit corresponding approximately to 12–15 g of ethanol.
Variables with significant associations to a level of $p < 0.05$ are shown in bold.

Table 3. Comparison with age- and sex-matched controls for the general population.

	Health-related quality of life						Depression[e]						Chronic fatigue[f]		
	Mental component score/median (range)			Physical component score/median (range)			PHQ-9[a]/number of cases (%)			HADS-D[b]/number of cases (%)			Number of cases (%)		
	N		*p* value (ES[c])	*N*		*p* value (ES)	*N*		*p* value (ES)	*N*		*p* value (ES)	*N*		*p* value (ES)
Survivors after conventional treatment only	253	51.0 (13.8–71.7)	**<0.001**	253	49.5 (15.8–63.2)	**<0.001**	238	25 (10.5)	**0.03**				260	105 (40.4)	**<0.001**
Controls	771	54.1 (4.5–70.0)	(0.02)	771	52.9 (16.1–65.6)	(0.01)	684	42 (6.1)	(0.07)				776	116 (14.9)	(0.27)
Survivors after HDT-ASCT[d]	109	51.9 (13.7–67.4)	**0.05**	109	47.1 (16.0–66.4)	**<0.001**	35	7 (20)	**0.008**	72	16 (22.2)	**0.002**	108	45 (41.7)	**<0.001**
Controls	327	54.2 (16.8–67.4)	(0.01)	327	53.6 (16.5–65.6)	(0.06)	99	5 (5.1)	(0.23)	216	18 (8.3)	(0.19)	331	35 (10.6)	**(0.35)**

[a]Patient Health Questionnaire-9.
[b]Hospital Anxiety and Depression Scale–Depression Subscale.
[c]Effect size for chi-square tests expressed by phi (2×2) or Cramer's *V* (>2×2) and for Mann–Whitney *U* test by estimated *r*.
[d]High-dose chemotherapy with autologous stem cell transplantation.
[e]Symptom severity dichotomized according to suggested cutoffs, HADS-D ≥ 8 or PHQ-9 ≥ 12.
[f]Chronic fatigue versus no chronic fatigue.

Significant p values below 0.05 and medium and large ES are given in bold.

subjective outcomes in long-term survivors that had been cured with either conventional treatment alone or after additional HDT-ASCT. Interestingly, given that you survive HL and potentially fatal complications or treatment, we found that treatment intensity does not seem to have a major impact on HRQoL, depressive symptoms, and CF after many years of follow-up.

We are aware of only one previous study that has attempted to compare QoL outcomes in HLS after either conventional treatment or additional HDT-ASCT [28]. In this smaller single-institutional study with 98 HLS, the median follow-up for the 37 survivors after HDT-ASCT was 11 years, compared to the 3.5 years for 61 patients after conventional treatment. The authors found a tendency toward reduced QoL after more intensive treatment in all three main dimensions of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30. However, these differences were not significant except for dyspnea, the latter possibly related to the use of carmustine in the conditioning regimen prior to ASCT. Also, a Dutch study has suggested that aspects of QoL may improve with time since treatment [29], maybe leading to an underestimation of QoL differences. Our study, with a longer and more balanced time of follow-up in the two treatment groups and a larger sample size, addresses the two important limitations of the study by Brandt et al. Most of our patients had received carmustine as part of their conditioning regimen, but we did not include specific questions related to dyspnea. Our study, however, extends the comparison to include rates of depression and CF. Of interest, a more recent longitudinal study by the German Hodgkin Study Group compared different conventional treatment strategies in randomized trials of HL and reported little effect of intensity on long-term QoL [30,31].

Any excessive impact of HDT-ASCT on long-term QoL and other patient-reported outcome measures (PROMs) are best addressed in randomized trials. We are not aware of such results from the randomized studies on HDT-ASCT that were done more than 20 years ago [26,27]. We therefore believe our strategy is a reasonable approach. Using population-based data, we compared two balanced groups, albeit differing in terms of some pretreatment, such as stage and B-symptoms, treatment without chemotherapy, use of radiotherapy, or treatment period. Brandt et al. observed some of the same differences between the groups regarding sex, age, and stage [28]. Higher stage and B-symptoms are known negative prognostic factors in HL, and patients with these characteristics are more likely to suffer progression and relapse [32]. A minority of patients in our cohort were treated with surgery only for nodular-lymphocyte predominant HL and more patients needed radiotherapy at progression or relapse. The biology of HL may therefore explain these imbalances in our two cohorts. In multivariable analysis, none of these appeared to impact on neither HRQoL, depression nor CF.

Time since diagnosis is similar, but slightly shorter in the HDT-ASCT than in the conventional group, with a median of 14 versus 16 years. Even if QoL may improve in HLS during the first years after treatment, we are not aware of studies showing improvement beyond the first decade. Similarly, a Danish population-based study found that the use of psychotropic drugs, mostly antidepressants and anxiolytics, after a transient elevation, returned to the level observed in the normal population 5 years into survivorship of HL [33]. Correspondingly, time since diagnosis was not an independent significant predictor in any of the adjusted models. Substituting with time since treatment in these models gave identical results (data not shown).

In direct comparison, survivors after HDT-ASCT have a higher rate of depression as judged either by HADS-D or PHQ-9. This difference is however more closely associated with the use of radiotherapy and a lower household income at survey. How radiotherapy would influence the rate of depression more than a decade later is difficult to explain. Also, HRQoL expressed as PCS or MCS and CF, seems more closely associated with socioeconomic variables and somatic comorbidities than treatment intensity. Our study shows this for annual household income (associated with PCS, MCS, and depressive symptoms above threshold), current employment (associated with PCS), and the presence of certain comorbidities such as heart and thyroid disease and obesity (associated with PCS, obesity also with CF). Having to undergo HDT-ASCT may disturb survivors' education and work–life to a greater extent than conventional treatment. In line with our observation, patients surviving relapse or progression are shown to be at higher risk of work loss [34]. Also, survivors of HDT-ASCT are generally at higher risk of somatic comorbidities than those with lower burden of therapy [14,35]. Therefore, HDT-ASCT may indirectly contribute to poorer outcomes in terms of HRQoL, depression, and CF. On the other hand, many of these associated factors are amenable to interventions. Preventing and correcting these associated factors through improved medical and psychosocial rehabilitation may improve outcomes. Improving outcomes beyond cure itself holds promise for HLS after conventional and HDT-ASCT alike, emphasizing the need

for long-term follow-up and supporting the use of PROMs in care plans [36].

CF has previously been shown to be an important contributor to work–life and financial difficulties experienced by HLS, and to correlate with depression in lymphoma survivors [15,37,38]. In recent years, cognitive impairment has attracted interest as possible adverse long-term outcome in survivors of both HL and other lymphomas [39–41]. We have not formally assessed cognitive function, but FQ also covers the mental aspects of CF, symptoms probably experienced by many patients as cognitive dysfunction.

We compared our two HLS cohorts with age- and sex-matched controls from the general population to reduce the risk of underestimating the effect of HDT-ASCT on the outcomes of interest. In general, the differences from the general population for all outcomes were significant, confirming the findings by Brandt et al. [28]. Moreover, the differences from the matched population were similar for the cohorts after conventional and intensive treatment, mostly with small ES, only reaching moderate ES for the comparison of CF.

We used data from two separate cross-sectional studies and differences in time of diagnosis or time of survey may result in unapparent imbalances between the cohorts. All HLS responded to PROMs with similar time spans from diagnosis or treatment; therefore, both cohorts are probably affected by recall bias in a similar way. Due to the cross-sectional design and lack of PROMs from diagnosis or earlier time points after treatment, we cannot conclude any causative relationships.

A curious finding was the association of higher PCS with higher consumption of alcohol (Table 2). Alcohol consumption in our two cohorts is low, with a median of 1 and 1.5 weekly units in the HDT-ASCT and conventional groups, respectively, and lower than the mean number of 3 units/week in the Norwegian population [42]. HLS with reduced PCS may be less likely to attend social settings where alcohol is consumed.

High response rates of 76% (HL-HDT-12) and 59% (HL-17) in the two population-based surveys combined in our analysis and the use of validated PROMs are strengths in this study. There are, however, limitations. For comparison with norm data, we used generic instruments, but cancer-specific questionnaires may have more sensitively captured differences between the two treatment groups. In attrition analyses, younger and male HLS were underrepresented in the HL-17 study, but the study contributed respondents to both treatment groups, reducing any potential bias for the comparison of outcome after conventional treatment only or HDT-ASCT. With all outcomes studied known to be in part related to age and sex, the true prevalence of symptoms may be under- or over-estimated. Due to financial restrictions on the academic use of the HADS questionnaire, our study group changed to PHQ-9 in the years between the two surveys, clearly limiting the direct comparison of depressive symptoms across instruments. We have relied on cutoff values published to compare clinically relevant depression in cancer patients [20]. Using these cutoff values, the prevalence of depression in HLS was 20% (using PHQ-9) and 22% (using HADS-D) after HDT-ASCT, indicating that the difference between them may be small. The surveys were done at different time points approximately 6 years apart, but it is well documented that HRQoL has remained relatively stable in Norway from 1996 to 2015 [24]. Despite all survivors after HDT-ASCT being diagnosed after 1989 and 25 before 1997, there were no significant differences in the choice of regimens for primary treatment, as anthracycline-based treatment, mainly in the form of ABVD, was introduced in Norway in the early 1990s.

In conclusion, work participation, household income, and somatic comorbidities have stronger associations with HRQoL, depressive symptoms, and CF in long-term HLS than treatment intensity. Our data suggest that better psychosocial rehabilitation to work participation, assistance in attaining adequate income levels and improved prevention or treatment of comorbidities may be important to improve, beyond cure, long-term outcome after treatment for HL.

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