Total late effect burden in long-term lymphoma survivors after high-dose therapy with autologous stem-cell transplant and its effect on health-related quality of life

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Received: November 25, 2021.
Accepted: April 15, 2022.
Prepublished: April 28, 2022.

https://doi.org/10.3324/haematol.2021.280413

Abstract

Lymphoma survivors after high-dose therapy with autologous stem-cell transplant (HDT-ASCT) are at risk of several late effects, which might impair their health-related quality of life (HRQoL). We assessed the total late effect burden in this population, and how it affects HRQoL. All lymphoma survivors treated with HDT-ASCT as adults in Norway between 1987 and 2008 were identified, and 271 (68%) attended both a comprehensive clinical assessment and completed a questionnaire. Severity of 45 conditions in 12 organ-system categories were graded as mild, moderate, severe or life-threatening, according to a modified version of CTCAEv4.03. At a median of 8 years after HDT-ASCT, 98% of survivors had at least one moderate or more severe late effect and 56% had severe or life-threatening late effects. Fourteen percent had low, 39% medium and 47% high late effect burden, defined as having moderate or more severe late effects in 0-1, 2-3 and >3 organ-systems, respectively. Female sex, increasing age, B-symptoms at diagnosis and >1 treatment line prior to HDT-ASCT were independently associated with having high late effect burden. The survivors had significantly poorer physical and mental HRQoL assessed by the Short Form-36 compared to age- and sex-matched controls. The prevalence of poor physical and mental HRQoL increased with higher late effect burden (both $P<0.001$), and the low burden group had better physical HRQoL than controls ($P<0.001$). In conclusion, lymphoma survivors after HDT-ASCT have impaired HRQoL, seemingly driven by a high late effect burden. This highlights the importance of prevention, regular assessments for early detection and treatment of late effects and modifiable risk factors.

Introduction

High-dose therapy with autologous stem-cell transplantation (HDT-ASCT) has been a potentially curative treatment option for selected lymphoma patients for decades and its use is still increasing.[1,2] More than 60% of patients with Hodgkin lymphoma[3] and 50% of those with non-Hodgkin lymphoma[4] are alive 10 years after HDT-ASCT, and for patients who survive the initial 2-5 years after HDT-ASCT, reported long-term survival is up to 90%, approaching the average life expectancy.[3-5] Consequently, there is a growing population of long-term survivors at increased risk of late effects of the cumulative treatment received with radiotherapy, conventional chemotherapy and the HDT-ASCT itself. We and others have shown that lymphoma survivors in general, and those after HDT-ASCT, are

at increased risk of a wide range of late effects such as secondary cancers, cardiovascular disease, respiratory impairments, peripheral neuropathies, hormonal disturbances, sexual dysfunction, chronic fatigue and mental distress.[3,4,6-17] However, most of these studies have focused on a single late effect, were based on self-reports only or did not encompass the severity of the late effects. While several studies have described total burden of late effects in childhood cancer survivors,[18-22] a comprehensive assessment of the total late effect burden with systematic severity grading in adult lymphoma survivors or after HDT-ASCT specifically have, to the best of our knowledge, not previously been done.

Health-related quality of life (HRQoL) has been defined as: "the extent to which one's usual or expected physical, emotional or social well-being is affected by a medical condition or its treatment".[23] A recent meta-analysis, including 64 studies, found that HRQoL continues to be significantly impaired in long-term cancer survivors 2-26 years after diagnosis.[24] Among lymphoma survivors cardiopulmonary late effects, neuropathy, chronic fatigue and psychological late effects have been associated with impaired HRQoL.[25-27] To what degree the total burden, i.e. the number and severity, of late effects affects HRQoL in adult lymphoma survivors after HDT-ASCT is not known.

Our primary aim was to assess the total burden of late effects, including severity grading, in a national cohort of real-world adult lymphoma survivors treated with HDT-ASCT. Second, we examined factors associated with having a high late effect burden, and explored to what extent the total burden of late effects is related to HRQoL.

Methods

The study was part of a national, multicenter, cross-sectional study performed in four centers from 2012 to 2014.[15] All survivors treated with HDT-ASCT for lymphoma in Norway from 1987 to 2008, aged ≥18 years at the time of transplantation, resident in Norway at the time of the survey and not currently undergoing systemic therapy for active malignancy were eligible (n=399). The survivors were identified through treatment records and registries at each participating center. Eligible survivors were invited by mail to complete a 125-item multi-instrument questionnaire, including the Short Form-36 (SF-36) for HRQoL, and attend an outpatient clinical examination. Details are provided in the *Online Supplementary Methods*.

For comparison of HRQoL, we randomly drew 871 controls matched 1:3 on sex and 5-year age group from a representative sample of 2,107 people from the general Norwegian population with SF-36 data collected in 2015.[28]

Based on the information available from the clinical examination, the patient's charts and questionnaire, the severity of all late effects were graded according to a modified version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03 developed for late-onset and long-term chronic health outcomes in pediatric cancer survivors in the St. Jude Lifetime Cohort Study,[20] or according to the original CTCAE v4.03, as applicable. In total 45 conditions were graded as mild (grade 1), moderate (grade 2), severe (grade 3) or life-threatening (grade 4) and then grouped into 12 organ-system categories: endocrine, cardiovascular, neuro-/musculoskeletal, pulmonary, genital/sexual, renal, hematologic, hearing, second cancer, hepatic, chronic fatigue and psychological, as described in *Online Supplementary Table S1*. As the study only included survivors alive at the time of the survey, grade 5 (death) was not included. If the information was insufficient to distinguish between two grades, the lower grade was assigned.

To evaluate the total late effect burden, the number of organ-system categories with grade 2 (moderate) or more severe late effect(s) were counted, and survivors with late effects in 0-1, 2-3 and >3 organ-systems were classified as having low, medium and high burden, respectively. Grade 1 conditions were excluded in the analyses of late effect burden as these by definition are mild or asymptomatic and therefore found less relevant.

Descriptive statistics and comparison of groups by *t*-tests, Mann-Whitney U tests, Kruskall-Wallis tests, χ^2 tests and Fisher exact tests were performed as appropriate. Logistic regression analyses were performed to identify variables associated with having high late effect burden (late effects in >3 organ-system categories as the dependent variable). Independent variables with a *P*-value <0.15 in univariate analyses were included in the multivariable model. High-dose regimen and cisplatin were excluded in the multivariable model because of their strong correlations with time since HDT-ASCT and number of treatment lines, respectively. Variables included in multivariable analyses were tested for multicollinearity, and the assumptions for logistic regression analysis were met. The significance level was set at 0.05, and all tests were two-sided. Analyses were performed using IBM SPSS statistics version 26.

The study was approved by the South East Regional Committee for Medical and Health Research Ethics (n. 2011/1353). All participants gave written informed consent to the study.

Results

Study population and attrition analysis

Of 399 eligible survivors, 271 (68%) completed both the questionnaire and attended the clinical examination (*Online Supplementary Figure S1*). Age at the time of the sur-

vey, gender, time from HDT-ASCT, lymphoma type and HDT regimen did not differ between participants and non-participants (*data not shown*). Among participants, 167 (62%) were men (Table 1). The median age at the time of the sur-

Table 1. Patient, disease and treatment characteristics of the study population and according to late effect burden groups.

	Total (N=271)	Low-medium burden (N=142)	High burden (N=129)	*P*
Sociodemographics				
Age at diagnosis in years, median (range)	42 (10-65)	40 (13-65)	45 (10-64)	**0.04**
Age at HDT-ASCT in years, median (range)	46 (19-67)	43 (19-66)	48 (19-67)	**0.02**
Age at survey in years, median (range)	56 (24-77)	53 (24-73)	59 (24-77)	**0.001**
Time diagnosis to survey in years, median (range)	12 (3-34)	11 (3-31)	13 (4-34)	**0.03**
Time HDT-ASCT - survey in years, median (range)	8.5 (3-25)	8 (3-25)	9.5 (3-25)	**0.04**
Female sex, N (%)	104 (38)	46 (32)	58 (45)	**0.03**
In a relationship[a], N (%)	199 (74)	104 (74)	95 (74)	0.98
Education <13 years, N (%)	140 (52)	75 (53)	65 (51)	0.69
Unemployed, N (%)	68 (25)	23 (16)	45 (35)	**<0.001**
Household income low[b], N (%)	145 (54)	66 (47)	79 (62)	**0.01**
Lymphoma and treatment				
Lymphoma type Hodgkin lymphoma, N (%) Aggressive non-Hodgkin lymphoma[c], N (%) Indolent non-Hodgkin lymphoma[d], N (%)	 61 (23) 182 (67) 28 (10)	 29 (20) 101 (71) 12 (9)	 32 (25) 81 (63) 16 (12)	0.32
Stage III-IV at diagnosis, N (%)	186 (69)	96 (68)	90 (70)	0.77
B-symptoms at diagnosis, N (%)	95 (36)	38 (27)	57 (45)	**<0.01**
High-dose regime Total body irradiation, N (%) BEAM, N (%)	 38 (14) 233 (86)	 14 (10) 128 (90)	 24 (19) 105 (81)	**0.04**
>1 treatment lines prior to HDT-ASCT, N (%)	191 (71)	91 (64)	100 (78)	**0.02**
Radiotherapy, N (%)	174 (64)	82 (58)	92 (71)	**0.02**
Radiotherapy to mediastinum, N (%) >30 Gy to mediastinum, N (%) Gy to mediastinum, median (range)	99 (37) 37 (14) 29.75 (13-67)	45 (32) 20 (14) 30 (13-65)	54 (42) 17 (13) 26 (13-67)	0.08 0.83 0.12
Radiotherapy below diaphragm, N (%)	97 (36)	44 (31)	53 (41)	0.08
Doxorubicin, mg/m^2, median (range)	300 (0-775)	300 (80-580)	300 (0-775)	0.67
Cyclophosphamide, gr/m^2, median (range)	4.5 (0-12.3)	4.5 (0-11.3)	4.5 (0-12.3)	0.55
Cisplatin, N (%)	11 (4)	3 (2)	8 (6)	0.08
Bleomycin, N (%)	34 (13)	16 (11)	18 (14)	0.51
Rituximab, N (%)	114 (42)	63 (44)	51 (40)	0.42
Relapse after HDT-ASCT, N (%)	59 (22)	28 (20)	31 (24)	0.39
Allogeneic transplantation, N (%)	17 (6)	10 (7)	7 (5)	0.58
Lifestyle				
Sedentary[e], N (%)	145 (54)	66 (47)	79 (62)	**0.01**
Smoking[f], N (%)	50 (19)	27 (19)	23 (18)	0.80
Unhealthy alcohol consumption[g], N (%)	15 (6)	4 (3)	11 (9)	**0.03**
Diet less than 5-a-day[h], N (%)	236 (87)	125 (88)	111 (86)	0.63

The late effect burden groups compared were low-medium burden (grade 2 or more severe late effect(s) in ≤3 organ-systems) *vs*. high burden (grade 2 or more severe late effect(s) in >3 organ-systems). *P*-values obtained by the χ^2-test for categorical variables and independent *t*-test or Mann-Whitney (skewed data) for continuous variables. Statistically significant *P*-values are indicated in bold. Missing values: in at relationship, n=1; education, n=2; income, n=4; stage, n=1; B-symptoms, n=4; sedentary, n=1; smoking, n=2, unhealthy alcohol consumption, n=4. [a]Married or cohabitant. [b]Low household income: <600,000 NOK/year (≈ €60,000). [c]Includes diffuse large B-cell lymphoma, n=60; mantle cell lymphoma, n=34; T-cell lymphomas, n=29; transformed lymphomas, n=28; lymphoblastic lymphoma, n=19; Burkitt lymphoma, other/not-specified non-Hodgkin lymphoma, n=2. [d]Includes follicular and other indolent lymphomas. [e]<150 min/week of moderate physical activity or <75 min/week of strenuous physical activity (WHO recommendation). [f]Smoking current or occasionally. [g]Alcohol consumption >6 or >12 alcohol units per week for women and men, respectively. [h]Three vegetables and two fruits per day. HDT-ASCT: high-dose therapy with autologous stem-cell transplantation; BEAM: carmustine, etoposide, cytarabine and melphalan

vey was 56 years, and the median observation time from lymphoma diagnosis and HDT-ASCT to survey was 12 and 8 years, respectively. HDT-ASCT was given after relapse in 70% of the survivors, while the remaining received HDT-ASCT in first remission. All but one patient had received doxorubicin, with a mean cumulative dose of 310 mg/m^2 (standard deviation [SD] 117), and 64% had also received radiotherapy.

Prevalence and grading of late effect

The frequencies and grades of the separate late effects within each organ-system category are given in *Online Supplementary Table S1*. All of the 271 survivors had late effect(s) in at least one of the 12 organ-system categories when including all grades. Ninety-eight percent (n=265) had at least one grade 2 or more severe late effect and 56% had severe or life-threatening (grade 3-4) late effect(s) (Figure 1). The endocrine system was most commonly affected, with dysfunction observed in 94% of survivors. Most of these late effects were grade 1-2 hypogonadism (n=129), hypothyroidism (n=129) and abnormal glucose metabolism (n=57), but grade 3-4 late effects were also present in 28% (mostly body mass index ≥30 and premature ovarian failure). The second most commonly affected category was the cardiovascular system with 86% of survivors having any grade late effects and 23% have grade 3-4 late effects. The types of late effects and severity were largely similar for patients with Hodgkin lymphoma or non-Hodgkin lymphoma (*Online Supplementary Figure S2*), with the endocrine and cardiovascular systems being the two most commonly affected for both.

Total late effect burden

The mean number of organ-system categories with grade 2 or more severe late effects per survivor was 3.5 (SD 1.7) (Figure 2). Thirty-seven (14%), 105 (39%) and 129 (47%) had low, medium and high burden, respectively. The proportions with high late effect burden among females and males were 55.8% and 42.5%, respectively (P=0.03). Survivors with a high late effect burden were also older (median 48 *vs*. 43 years [P=0.02] and 59 *vs*. 53 years [P=0.001] at the time of the HDT-ASCT and survey, respectively), and had a longer time from diagnosis to HDT-ASCT and from HDT-ASCT to survey (Table 1). The proportions of survivors with low income and unemployed were higher in the high late effect burden group.

Of lymphoma- and treatment-related factors, the high late effect burden group had higher proportions of survivors with B-symptoms at diagnosis, survivors treated with total body irradiation as the high-dose regimen or with radiotherapy given at any time, and survivors having received >1 treatment line prior to HDT-ASCT. In the high burden group, 62% and 9% had a sedentary life style and unhealthy alcohol consumption, respectively, compared with 47% and 3% of those with mild to medium burden.

Table 2 shows the factors associated with having high late effect burden with P<0.15 in univariate logistic regression analyses. In the multivariable analysis, female sex (odds ratio [OR]=1.76; 95% confidence interval [95% C]: 1.01-3.07; P=0.04), increasing age (OR=1.05; 95% CI: 1.02-1.07; P<0.001), B-symptoms at diagnosis (OR=2.56; 95% CI: 1.39-4.69; P<0.01) and >1 treatment line prior to HDT-ASCT (OR=2.09; 95% CI: 1.11-3.94; P=0.02) were associated with having high late effect burden.

Health-related quality of life and association with late effect burden

Mean physical (PCS) and mental (MCS) composite scale

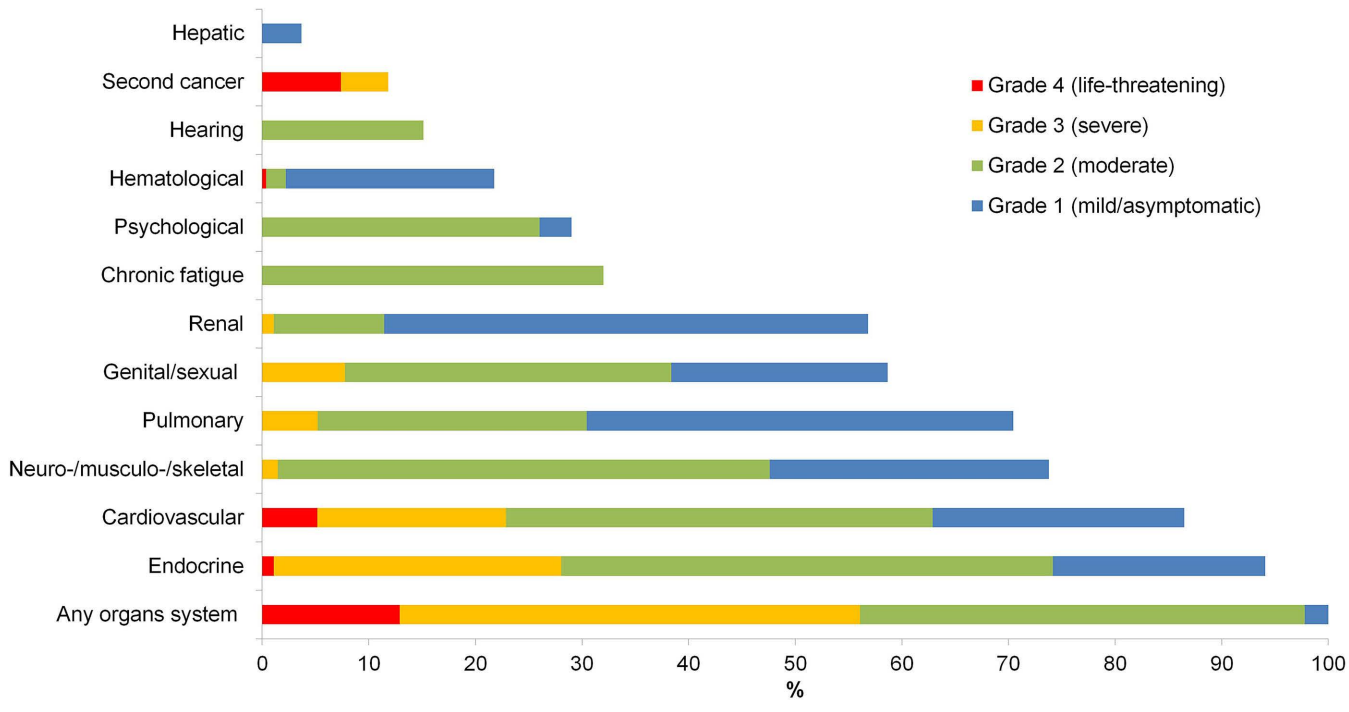

Figure 1. Maximum grade late effect per survivor for each organ-system category and for any organ system. Blue: grade 1 (mild/asymptomatic), green: grade 2 (moderate), orange: grade 3 (severe), red: grade 4 (life-threatening)

scores for all survivors were 44.9 (SD 10.9) and 51.8 (SD 10.0), respectively, compared with 48.5 (SD 10.5) (P<0.001) and 53.4 (SD 7.8) (P=0.02) in controls (Figure 3). The prevalence of poor physical HRQoL (PCS <40) and mental HRQoL (MCS <40) among survivors were 33% and 14%, respectively, compared with 20% and 7% in controls (P<0.001 for both). Survivors scored significantly lower on seven out of the eight SF-36 scales compared to controls (Figure 3E). Both PCS (P<0.001) and MCS (P<0.01) scores decreased and the prevalence of poor physical (P<0.001) and mental (P<0.001) HRQoL increased with higher late effect burden (Figure 3).

When assessing the late effect organ-system categories separately, survivors with chronic fatigue and those with psychological late effect(s) had both lower PCS and MCS, while survivors with cardiovascular, pulmonary and neuro-/musculoskeletal late effect(s) had lower PCS scores, but similar MCS scores. For the remaining late effects categories there were no statistically significant differences in mean PCS or MCS scores (Table 3).

Discussion

To our knowledge, this is the first study assessing late effect burden in adult lymphoma survivors, including severity grading based on a comprehensive clinical assessment combined with patient-reported outcomes. The prevalence of late effects in this unselected cohort of long-term lymphoma survivors after HDT-ASCT was high, with almost all (98%) having at least one moderate or more severe late effect and more than half having severe or life-threatening late effect(s). The vast majority had multiple organ-systems affected, with about half of survivors having a high late effect burden, defined as late effects in three or more of the 12 organ-system categories assessed. Both physical and mental HRQoL was reduced among survivors compared with that in the general population, and decreased with increasing late effect burden.

A high prevalence of late effects and high late effect burden among survivors after childhood cancer have previously been shown in several studies.[18-20] Among 112 long-term survivors after pediatric stem cell transplantation (including 32 HDT-ASCT) from the St. Jude Lifetime Cohort Study cohort, Eissa *et al.* reported a prevalence of 100% of any grade 1-4 conditions, and 67% of grade 3-4 for those treated with HDT-ASCT.[19] While their cohorts differ from ours in many aspects, in particular with regard to age at transplantation, attained age and follow-up time, the results are similar to ours (corresponding prevalence of 100% and 56%). Studies based on self-reports only have found lower prevalences of any grade and grade 3-4 late effects in survivors after hematopoietic stem cell transplantation both in adults (61% and 16%, respectively after HDT-ASCT)[29] and children.[30]

In line with previous findings, female sex, higher age and more treatment lines were associated with high late effect burden.[21,22,29-32] In addition, presence of B-symptoms at diagnosis was also statistically significant in multivariable analysis, an association consistently observed with chronic fatigue.[33] The reason for this is not clear, but could possibly be related to the intensity of primary treatment and/or to detrimental effects of inflammation. Supporting this, we found, in a previous study on this same cohort of

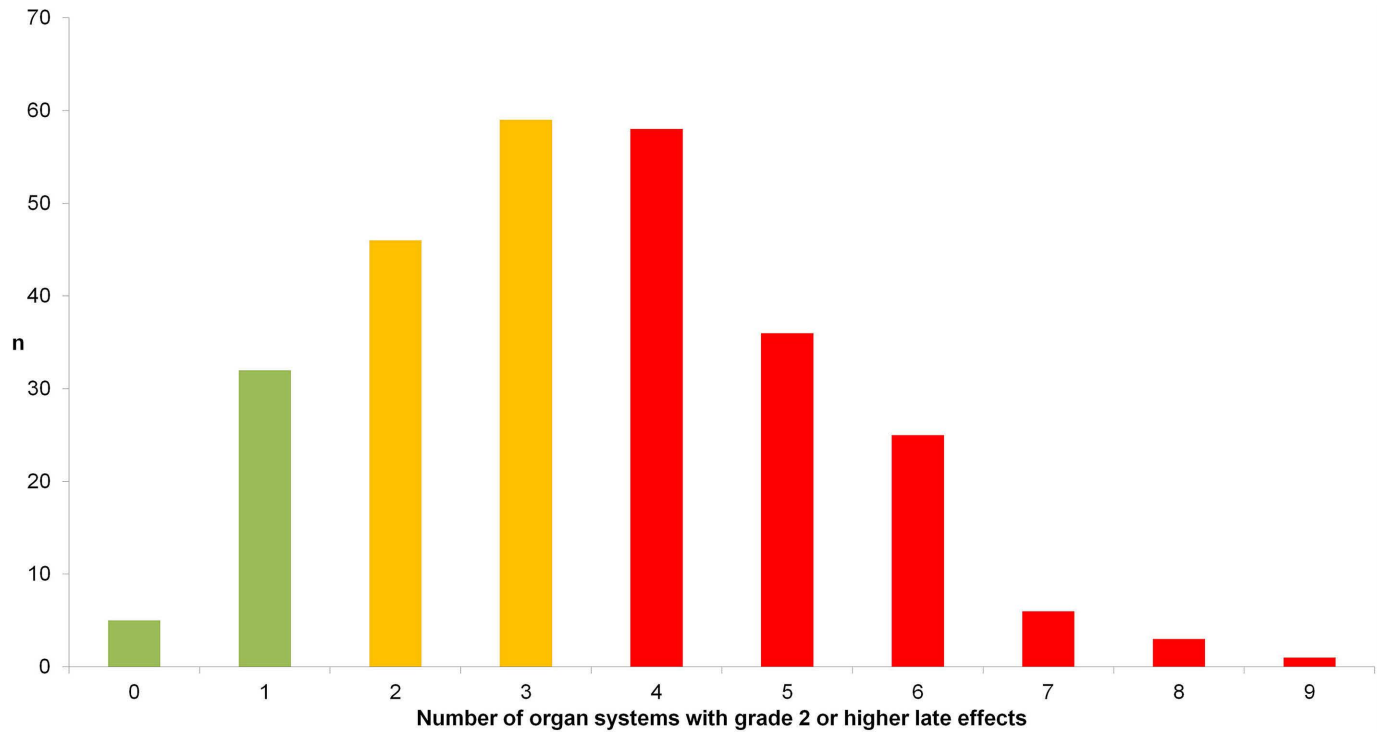

Figure 2. Number of organ-system categories with grade 2 or higher late effects per survivor. Green (0-1 organ system): low late effect burden (n=37); orange (2-3 organ systems): medium late effect burden (n=105); red (>3 organ systems): high late effect burden (n=129).

Table 2. Univariate and multivariable logistic regression analyses of potential factors associated with high late effect burden (n=129, 48%).

	Univariate			Multivariable		
	OR	95% CI	*P*	OR	95% CI	*P*
Female sex (ref. male)	1.71	1.04-2.79	**0.03**	1.76	1.01-3.07	**0.04**
Age at survey (years)	1.04	1.02-1.06	**<0.001**	1.05	1.02-1.07	**<0.001**
Time HDT-ASCT - survey (years)	1.05	1.00-1.10	**0.03**	1.02	0.96-1.07	0.58
Household income <600,000 NOK	1.85	1.13-3.10	**0.01**	1.59	0.92-2.75	0.10
B-symptoms at diagnosis	2.19	1.31-3.64	**<0.01**	2.56	1.39-4.69	**<0.01**
TBI high-dose regime (ref. BEAM)	2.10	1.03-4.24	**0.04**			
Radiotherapy	1.82	1.10-3.02	**0.02**	1.85	0.94-3.63	0.07
Infradiaphragmatic radiotherapy	1.55	0.94-2.56	0.08			
Mediastinal radiotherapy	1.55	0.94-2.55	0.08			
>1 treatment line prior to HDT-ASCT	1.93	1.13-3.31	**0.02**	2.09	1.11-3.94	**0.02**
Cisplatin	3.06	0.80-11.8	0.10			
Sedentary life style[a]	1.83	1.12-2.98	**0.02**	1.49	0.86-2.59	0.15
Unhealthy alcohol consumption[b]	3.33	1.03-10.7	**0.04**	1.51	0.41-5.60	0.54

High late effect burden is defined as grade 2 or more severe late effects in >3 organ-system categories. Variables with $P \leq 0.15$ in univariate analysis are shown. [a]Less than 150 min/week of moderate intensity or 75 min/week of vigorous intensity (WHO recommendation). [b]Alcohol consumption >6 or >12 alcohol units per week for women and men, respectively. OR: odds ratio; CI: confidence interval; HDT-ASCT: high-dose therapy with autologous stem-cell transplantation; NOK: Norwegian krones; TBI: total body irradiation; BEAM: carmustine, etoposide, cytarabine and melphalan

long-term lymphoma survivors, increased serum levels of the pro-inflammatory cytokines interleukin-6 and interleukin-1 receptor antagonist compared to the levels in controls from the general population, with an independent association with chronic fatigue.[8]

Our study supports previous reports of reduced physical HRQoL in long-term lymphoma survivors relative to controls from reference populations.[24,34-36] We also found significantly reduced mental HRQoL among the survivors, in line with the findings of some studies on other cancer survivor populations,[24] but in contrast to most reports on lymphoma survivors.[34-36] The negative effect on HRQoL seems to be driven by the late effect burden experienced by these survivors and, interestingly, even though all participating survivors had at least one late effect, those with the lowest burden reported better physical HRQoL than controls from the reference population. In contrast, in the high late effect burden group, the prevalences of poor physical and mental HRQoL were both two to three times higher than those in controls. Similarly, it has previously been shown that multi-morbidity is associated with poorer physical and mental HRQoL,[37,38] and that cancer survivors have better HRQoL than cancer-free patients with other chronic diseases.[39]

Different demographic and diagnosis- or treatment-related factors that have been associated with poor HRQoL in cancer survivors are largely non-modifiable. The individual survivor's late effect burden can, however, potentially be targeted by early detection and treatment of prevalent late effects of somatic, mental and psychosocial character and known risk factors. For example, exercise interventions are effective at reducing late effects such as chronic fatigue and cardiovascular disease[40,41] and can improve quality of life.[42] It has also been shown that improved survivorship care, including the use of survivorship care plans based on risk factors and treatment exposures, can improve HRQoL in stem cell transplant survivors.[43]

The high late effect burden we observed in this cohort and its consequences in terms of reduced HRQoL calls for development of structured follow-up programs for such heavily treated lymphoma survivors, including monitoring and management of late effects and modifiable risk factors. An important focus should be on patients' education, lifestyle measures and tertiary prevention, and such programs should preferably be done in prospective intervention studies to evaluate their effects. Besides physical activity, there is scarcity of studies documenting a positive impact of other lifestyle factors such as diet quality, weight loss and smoking cessation on late effects and HRQoL in lymphoma survivors.[41] Future research should also focus on identifying underlying mechanisms for different common late effects, to increase our understanding and help guide future treatment decisions.

The completeness of the study population is a major strength of this study, with all lymphoma survivors treated with HDT-ASCT in Norway until 2008 being accounted for

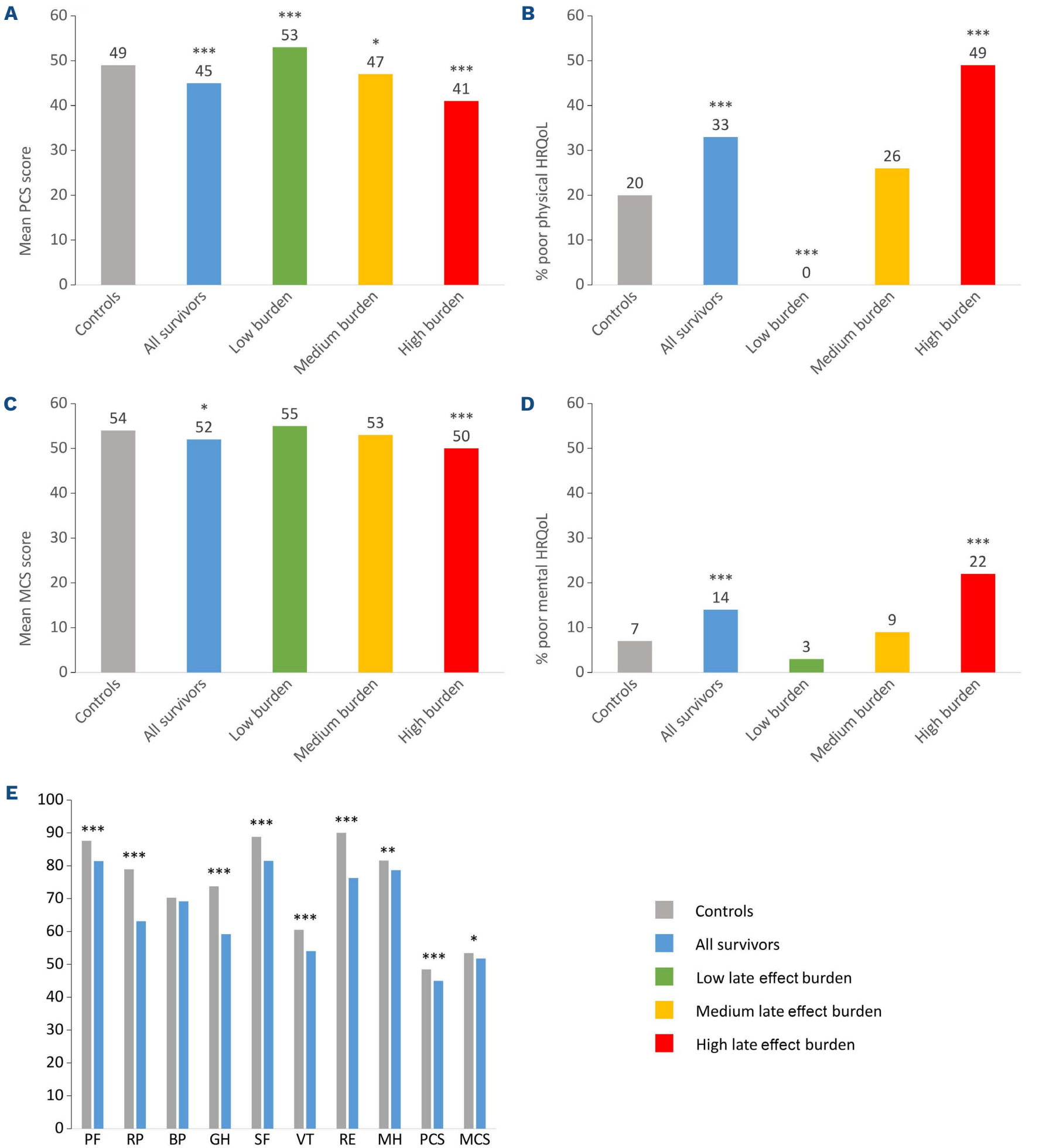

Figure 3. Health-related quality of life and its association with late effect burden. (A) Mean physical composite scale (PCS) scores. (B) Percentage with poor physical health-related quality of life (HRQoL) (PCS score <40). (C) Mean mental composite scale (MCS) scores. (D) Percentage with poor mental HRQoL (MCS score <40), (E) Mean Short Form-36 domain scores for controls (gray) compared with all survivors (blue) and survivors with low late effect burden (green): grade 2 or more severe late effects in 0-1 organ-system categories, medium late effect burden (orange): grade 2 or more severe late effects in 2-3 organ-systems and high late effect burden (red): grade 2 or more severe late effects in >3 organ systems. PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; SF: social functioning; VT: vitality; RE: role emotional; MH: mental health, PCS: physical composite score, MCS: mental composite score. Statistically significant differences compared to controls denoted as *P<0.05, **P<0.01 and ***P<0.001.

Table 3. Physical composite scale and mental composite scale scores according to the presence or not of grade 2 or more severe late effect(s) in each organ-system category.

	PCS, mean +/- SD			MCS, mean +/- SD		
	None	Present	*P*	None	Present	*P*
Endocrine	46.6 ± 10.3	44.4 ± 11.2	0.15	52.1 ± 10.7	51.7 ± 9.9	0.75
Cardiovascular	46.8 ± 9.8	43.8 ± 11.5	0.03	51.0 ± 10.3	52.2 ± 9.9	0.34
Neuro-/musculoskeletal	47.8 ± 9.9	41.8 ± 11.2	<0.001	51.6 ± 9.7	52.0 ± 10.4	0.31
Pulmonary	46.8 ± 9.6	39.6 ± 12.8	<0.001	52.2 ± 9.5	50.6 ± 11.4	0.41
Genital/sexual	45.7 ± 10.7	43.7 ± 11.3	0.17	51.7 ± 10.3	51.9 ± 9.7	0.93
Renal	45.3 ± 11.0	41.8 ± 10.5	0.12	51.5 ± 10.2	54.9 ± 8.6	0.26
Hematologic	45.1 ± 11.0	39.0 ± 9.6	0.18	52.9 ± 10.0	47.3 ± 11.1	0.27
Hearing	45.2 ± 10.9	43.6 ± 11.4	0.42	51.6 ± 10.2	52.9 ± 9.1	0.42
Second cancer	45.3 ± 10.9	42.3 ± 11.4	0.15	51.7 ± 10.0	52.1 ± 10.4	0.85
Chronic fatigue	48.9 ± 8.6	36.7 ± 10.9	<0.001	54.2 ± 8.3	46.5 ± 11.4	<0.001
Psychological	46.4 ± 10.5	30.4 ± 11.0	<0.001	55.3 ± 6.9	40.4 ± 11.0	<0.001

PCS: physical composite scale; MCS: mental composite scale score.

and invited to participate. Of the eligible survivors, 68% completed both the clinical examination and the questionnaire, and these individuals did not differ from non-participants in attrition analysis, strengthening the external validity and generalizability of our results. Furthermore, detailed and high quality real-world data from hospital records combined with objectively measured findings of clinical examinations and patient-reported outcome measures ensure a thorough assessment of most common late effects.

Having matched controls from the background population for comparison of SF-36 data collected at a similar time is another strength. Not having normative controls for the late effect burden, however, is a limitation. Prevalent late effects observed in this study are common conditions also in the general population. However, as only patients who are medically fit and without serious co-morbidities are considered eligible for HDT-ASCT, the participants would probably be healthier than the general population before their lymphoma diagnosis and treatment. This could also explain the better physical HRQoL seen in survivors than in controls. We have previously published more in-depth analyses on separate late effects in this same cohort of lymphoma survivors showing higher prevalences of chronic fatigue,[8] cardiac disorders,[13-15] pulmonary and cardiorespiratory fitness impairments[9,10,12] and sexual dysfunction[6,7] than seen in the general population. On the other hand, the prevalence of osteoporosis was similar[11] and the state of being overweight/obese was less prevalent than in matched normative controls.[44] With 57% of survivors having a body mass index >25, being overweight/obese was still the most common separate grade 2 or more severe condition observed. Another limitation of the study was the cross-sectional design, with lack of pre-diagnostic and pretreatment data, which precludes causal conclusions.

The time period over which the survivors received treatment and HDT-ASCT is extensive and lymphoma therapy has evolved considerably, including less use of radiotherapy, especially for Hodgkin lymphoma, and significant improvements in treatment strategies and supportive care, as well as changing indications and selection for HDT-ASCT. Total body irradiation was used as the high-dose regimen in the first period (1987-1995) only, when the role of HDT-ASCT was less defined and performed in clinical trials, with more stringent eligibility criteria. It is not possible to separate the contribution of total body irradiation itself from longer observation time, and both variables could not be included in the same multivariable analysis, but neither was significantly associated with high late effect burden when entered separately in the multivariable model. However, we have previously shown a significant association between total body irradiation/early treatment period with separate late effects, including second cancer[4] and cardiac repercussions.[13,15]

In conclusion, we present a comprehensive overview of the total late effect burden in a real-world complete national cohort of lymphoma survivors treated with HDT-ASCT. Most survivors have a significant late effect burden and experience several different moderate or more severe late effects, affecting their HRQoL. This highlights the importance of efforts to prevent and treat any late effect or chronic condition of somatic or psychosocial character experienced by heavily treated cancer survivors. This could include risk-stratified survivorship surveillance and survivorship care incorporating a focus on lifestyle and

health-related behaviors and enabling early detection and management of conditions amenable to interventions.

Disclosures

No conflicts of interest to disclose.

Contributions

KS, CEK, JHL, HH and SK: conception and design of the study; KS, UMF, HB, MJH, KM, MDL, OF, JSS, MBL, SK and CEK: data collection and assembly; KS, JHL, CEK, MBL and HH: data analysis and interpretation. All authors took part in writing the manuscript and reviewed and approved the final version.

Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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