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ORIGINAL ARTICLE

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ABSTRACT

Background: Chronic fatigue (CF), substantial fatigue for $\geq$ six months, can manifest as a late effect (LE) after cancer treatment, and may affect several aspects of life. In a Norwegian cohort of Hodgkin's lymphoma survivors (HLS), more than a decade after contemporary risk-adapted treatment regimens with limited use of radiotherapy (RT), we assessed: (1) Prevalence of, (2) factors associated with (3) and implications of CF on socioeconomic status (SES) and work ability (WA).

Material and methods: HLS treated between 1997–2006, aged 8–49 years at diagnosis, were invited to participate in a population-based cross-sectional study on late effects in 2018–2019. In a mailed questionnaire, HLS responded to a fatigue questionnaire (FQ), work ability score (WAS) and short-form health survey (SF-36). Disease- and treatment data were extracted from hospital records. Factors associated with CF were identified by uni- and multivariate analysis. To study the implications of CF on SES and WA, a multinomial regression analysis was performed.

Results: Invitations were extended to 518 HLS and 298 (58%) responded to FQ, of whom 42% had CF with mean (standard deviation [SD]) physical- and mental fatigue scores of 10.2 (4.3) and 5.5 (2.1) respectively. Median age at survey was 45 years, 47% were females. In multivariate analysis female sex ($p = 0.03$), lower education ($p = 0.03$), body mass index $\geq 30 \, \text{kg/m}^2$ ($p = 0.04$), and an increasing number of comorbidities ($p = 0.01$) were associated with CF. No association with disease stage, chemotherapy or RT was found. CF was associated with poorer WAS scores at survey ($p < 0.001$), unemployment ($p = 0.03$), and receiving disability pension ($p = 0.003$).

Conclusion: After risk-adapted treatment, CF is still a frequent LE among long-term HLS, without apparent association with disease or treatment-related parameters. CF is associated with reduced WA and SES. As no apparent risk reduction is seen with contemporary treatment, further studies should emphasize etiological factors of CF and treatment to alleviate this common LE.

Introduction

Hodgkin's lymphoma (HL) is a common malignancy in adolescents and young adults with a peak in incidence between 15–34 years of age [1]. For decades, HL has been highly curable with combinations of chemotherapy and/or radiotherapy, and current 5-year relative survival estimates are reported to be in excess of 90% [2]. HL patients who face the disease and undergo extensive treatment at a relatively young age, are at risk of developing late effects (LEs) after therapy, adverse outcomes that may impact on different aspects of their lives after cancer. Long-term LEs after HL, i.e. more than a decade after treatment, are best studied in patients treated before year 2000. Survivors face increased risks of several LEs, such as second cancers, cardiovascular disease, hormonal dysfunction, reduced fertility, and impaired health-related quality of life (HRQoL) [3–7].

Cancer-associated chronic fatigue (CF) is a common LE characterized by tiredness, lack of energy, and subjective cognitive problems, being defined as symptoms lasting for $\geq$ 6 months [8]. Depending on the definition of CF the reported prevalence amongst Hodgkin's lymphoma survivors (HLS), treated mainly before 2000 and with more than 10 years of follow-up, ranges from 26–37% [9–12].

The etiology of CF after cancer is not clear, but believed to be multi-factorial and associated with different known risk-factors: demographic, psychosocial, medical, and biological [13].

Over the last three decades, treatment regimens for HL have been modified, mainly to reduce the burden of LEs observed after older and now partly obsolete treatment strategies [3–7]. In line with changes implemented in most Western countries, Norway from 1997 introduced

risk-adapted modifications with a shift from alkylator-based chemotherapy regimens to ABVD (adriamycin, bleomycin, vinblastine, dacarbazine), BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) or OEPA/COPP (vincristine, etoposide, prednisone, doxorubicin/cyclophosphamide, vincristine, procarbazine, and prednisone) and restricted use of radiotherapy, with reduced field sizes (from extended to involved fields) and lower doses (from 40 to 20–30 Gy) [14–17]. Randomized controlled trials for both early and advanced stages of HL, provide evidence that these modifications have maintained or improved cure rates of HL [16,18,19].

Prevalence and implications of LEs in long-term HLS treated after the introduction of modern risk-adapted treatment are still scarcely studied. Still, US patients diagnosed with HL between 2000 and 2015 are at increased risk of non-lymphoma-related death, also beyond the first year after treatment [20]. Recent Scandinavian data show no excess risk of mortality, and limited, but not eliminated excess long-term morbidity in stage I-IIA HL treated with ABVD and limited-field radiotherapy [17,21,22].

In 2018–2019 we conducted a population-based survey of HLS treated with modern strategies from 1997–2006, to study the prevalence of LEs and other aspects of life, more than 10 years after diagnosis [23]. Even though short- and intermediate-term prevalence rates of CF have been studied also in cohorts of patients treated after year 2000 [24–26], to our knowledge, rates of CF and possible implications thereof in long-term HLS, >10 years after contemporary treatment, have not been reported.

In the aforementioned study population of long-term HLS, we wanted to study: (1) Prevalence of CF, (2) factors associated with CF (3) and possible implications of CF on work ability (WA) and socioeconomic status (SES).

Method

Study design and population

HL survivors treated between 1997–2006 and aged 8–49 at diagnosis were invited to participate in a Norwegian population-based cross-sectional study on LEs. Survivors were identified by the Cancer Registry of Norway, and those treated in the three participating health regions in Norway (South-East, Mid and North Norway) received a study invitation along with a written questionnaire during 2018–2019. Consenting survivors returned the completed questionnaire, with further possibility to consent to an outpatient clinical examination, including blood sampling and echocardiography. Non-responders received one written reminder.

Patient-reported outcome measures

The questionnaire covered sociodemographic factors (sex, age, marital status), SES (education, work status, WA, income, disability pension, and other benefits), lifestyle data (smoking and alcohol consumption), and data on health status (weight, height, and pain).

Survivors were asked whether they were diagnosed with one or more, out of 8 pre-specified medical conditions (diabetes, hypertension, cardiovascular disease, lung disease, thyroid disease, rheumatoid disease, arthritis, and cancer other than HL). Responses on medical conditions were analyzed separately, and as a summarized comorbidity score, with a possible score of 0–8.

The questionnaire included validated patient-reported outcome measures (PROMs):

Chronic fatigue (CF) was assessed with the Chalder fatigue questionnaire (FQ) [27], an 11-item tool assessing fatigue symptoms experienced during the last month. The questionnaire can be divided into two components; one measuring physical fatigue (7 items) and the other mental fatigue (4 items). Each item is rated from 0 ("less than usual") to 3 ("much worse than usual"), where higher scores represent a higher fatigue burden. The total fatigue score is generated by summarizing the scores of all 11 items, with a possible score of 0–33. A dichotomized score was generated for each item (0 = 0, 1 = 0, 2 = 1, 3 = 1), with a possible score of 0–11, where the cut-off score ≥4 and with symptom duration ≥6 months indicating the presence of CF [28].

Work ability score (WAS) is the first question in the Work Ability Index, and is a self-assessment of current WA compared to the time point in life one felt at best, with a range from 0–10 [29]. A higher score represents better WA and is categorized into poor (0–5 points), moderate (6–7), good (8–9) and excellent (10). Use of this single-item question for WA assessment has been validated [30].

Patient Health Questionnaire (PHQ-9) is a 9-item self-assessment questionnaire, exploring the severity of depressive symptoms experienced during the last 2 weeks [31]. Each item is scored from 0 (not at all) to 3 (nearly every day), with a possible sum score 0–27, where cutoff scores of 5, 10, 15, and 20 represents mild, moderate, moderately severe, and severe symptoms, respectively [31].

Short-form health survey (SF-36) is a 36-item questionnaire measuring health-related quality of life (HRQoL), with four physical and four mental basic health components, summarized into physical (PCS) and mental (MCS) composite scores. The sum scores were T-transformed, where lower scores imply lower HRQoL and the Norwegian general population mean scores equal 50 [32].

Treatment and disease data

Disease (histology, clinical stage, presence of B-symptoms) and treatment-related data were retrieved from medical files.

Reference data

Socioeconomic data related to the Norwegian general population in 2018 (level of education, employment status, income level and utilization of disability benefits) was extracted from Statistics Norway (SN) [33]. No statistical analysis of differences between the HLS and the general population was performed.

Table 1. Descriptive data.

Characteristics[a]	Total N = 298	CF n = 124 (42)	No CF n = 174 (58)	p Value	ES[c]
Sociodemographic data					
Gender, n (%)					
Female	141(47)	69 (56)	72 (41)		
Male	157 (53)	55 (44)	102 (59)	**0.02**	0.14
Age, years, median (range)					
At diagnosis	29 (8–50)	30 (9–50)	29 (8–50)	0.20	0.15
At survey	45 (21–70)	45.5 (21–67)	45 (25–70)	0.09	0.20
Observation time, years, median (range)	16 (10–22)	17 (11–21)	15 (10–22)	0.13	0.18
Marital status, n (%)					
Married or partner	240 (81)	99 (80)	141 (81)		
Alone	57 (19)	25 (20)	32 (19)	0.72	0.02
Education, n (%)	129 (43)				
Primary- and high school (≤12 years)	112 (38)	63 (51)	66 (38)		
University (13-16 years)	56 (19)	47 (38)	65 (38)		
Higher education (>16 years)		14 (11)	42 (24)	**0.01**	0.18
Hodgkin's lymphoma and treatment					
Primary diagnosis, n (%)					
Classical HL	267 (89)	112 (90)	155 (89)		
Nodular lymphocyte predominant HL	29 (10)	11 (9)	18 (10)		
Unclassified	2 (1)	1 (1)	1 (1)	0.89	0.03
Stage, n (%)					
I-IIA	182 (61)	77 (62)	105 (60)		
IIB-IV	116 (39)	47 (38)	69 (40)	0.76	0.02
B-symptoms, n (%)	99 (34)	38 (31)	61 (36)	0.41	0.05
Radiotherapy given, n (%)	230 (77)	103 (83)	127 (73)	**0.04**	0.12
Chemotherapy given, n (%)	281 (94)	116 (94)	165 (95)	0.64	0.03
Progression/relapse, n (%)	45 (15)	22 (18)	23 (13)	0.41	0.08
HDT-ASCT, n (%)	38 (13)	19 (15)	19 (11)	0.26	0.07
Socioeconomic data					
Income source at time of survey					
Full-time work	187 (63)	58 (47)	129 (74)		
Part-time work	19 (6)	9 (7)	10 (6)		
Disability benefits	57 (19)	37 (30)	20 (12)		
Unemployed	9 (3)	3 (2)	6 (3)		
State pension	7 (2)	2 (2)	5 (3)		
Other state benefits[d]	19 (6)	15 (12)	4 (2)	**<0.001**	**0.34**
Employed before HL diagnosis, n (%)					
Yes	218 (73)	96 (77)	122 (70)		
No	34 (11)	8 (7)	26 (15)		
No, student/army	46 (15)	20 (16)	26 (15)	0.08	0.13
Disability benefit, n (%)	57 (19)	37 (30)	20 (12)	**<0.001**	0.23
When gained:					
After HL treatment	47 (82)	32 (86)	15 (75)		
Before HL treatment	6 (11)	4 (11)	2 (10)		
Uncertain	4 (7)	1 (3)	3 (15)	0.22	0.23
Degree %:					
20–49	2 (4)	1 (3)	1 (5)		
50–99	20 (35)	14 (39)	6 (29)		
100	35 (61)	21 (58)	14 (67)	0.70	0.11
Unemployed at some time after HL, n (%)[b]	49 (21)	28 (28)	21 (15)	**0.01**	0.16
As a result of the disease:					
No	22 (45)	8 (29)	14 (67)		
Partly	15 (31)	10 (36)	5 (24)		
Mostly	12 (24)	10 (36)	2 (9)	**0.02**	**0.40**
WAS at diagnosis, mean (SD)	8.8 (2.7)	8.9 (2.6)	8.7 (2.8)	0.41	0.10
By category, n (%)					
0–5 Poor	36 (13)	10 (9)	26 (16)		
6–7 Moderate	8 (3)	4 (3)	4 (2)		
8–9 Good	32 (11)	18 (16)	14 (9)		
10 Excellent	205 (73)	84 (72)	121 (73)	0.12	0.15
WAS at survey, mean (SD)	7 (3.3)	5.1 (3.2)	8.3 (2.7)	**<0.001**	**1.09**
By category, n (%)					
0–5 Poor	78 (27)	59 (49)	19 (11)		
6–7 Moderate	47 (16)	27 (22)	20 (12)		
8–9 Good	74 (25)	28 (23)	46 (27)		
10 Excellent	92 (32)	7 (6)	85 (50)	**<0.001**	**0.54**
Expected yearly income, NOK					
0 – 200,000	20 (7)	10 (8)	10 (6)		
201,000 – 400,000	77 (26)	41 (34)	36 (21)		
401,000 – 600,000	101 (34)	40 (33)	61 (35)		
601,000 – 800,000	53 (18)	20 (17)	33 (19)		
>801,000	44 (15)	10 (8)	34 (20)	0.06	0.20

(continued)

Table 1. Continued.

Characteristics[a]	Total N = 298	CF n = 124 (42)	No CF n = 174 (58)	p Value	ES[c]
Health and lifestyle factors at the survey					
Fatigue score, mean (SD)					
Total fatigue score	15.7 (5.9)	20.9 (4.5)	12.0 (3.5)	**<0.001**	**2.26**
Mental fatigue score	5.5 (2.1)	6.9 (2.2)	4.4 (1.3)	**<0.001**	**1.42**
Physical fatigue score	10.2 (4.3)	13.9 (3.2)	7.5 (2.7)	**<0.001**	**2.21**
Self-reported comorbidity at survey, n (%)					
Diabetes	15 (5)	8 (7)	7 (4)	0.36	0.05
Cardiovascular disease	28 (9)	10 (8)	18 (10)	0.51	0.04
Hypertension	48 (16)	24 (19)	24 (14)	0.22	0.07
Lung disease	44 (15)	26 (21)	18 (11)	**0.01**	0.15
Thyroid disease	83 (28)	38 (31)	45 (26)	0.41	0.05
Arthritis	46 (16)	28 (23)	18 (11)	**0.006**	0.16
Rheumatism	50 (17)	31 (25)	19 (11)	**0.002**	0.18
Other cancer	29 (10)	15 (12)	14 (8)	0.25	0.07
Depression	68 (23)	41 (33)	27 (16)	**<0.001**	0.20
Comorbidity score[e], mean (SD)	1.1 (1.1)	1.5 (1.2)	0.93 (1.0)	**<0.001**	0.47
Smoking, n (%)					
Never or prior	254 (85)	104 (84)	150 (86)		
Current or occasionally	44 (15)	20 (16)	24 (14)	0.58	0.03
Alcohol units per week, mean (SD)	2.6 (0–28)	2.1 (3.4)	3.0 (3.0)	**0.01**	0.31
Body mass index at survey,					
kg/m^2, median (range)	25.7 (17.3–45.9)	27.5 (17.8–45.9)	25.7 (17.3–40.4)	**<0.001**	0.40
BMI ≥30 kg/m^2	57 (19)	33 (27)	24 (14)	**0.005**	0.16
Pain last 4 weeks					
None/Very little	144 (49)	35 (29)	109 (63)		
Little/Moderate/Strong	151 (51)	88 (77)	63 (37)	**<0.001**	0.34
PHQ-9 score					
mean (SD)	6.3 (5.0)	9.8 (4.9)	3.8 (3.4)	**<0.001**	**1.48**
≥10 score, n (%)	70 (24)	11 (6)	59 (48)	**<0.001**	0.48
HRQoL (SF-36), mean (SD)					
Physical functioning	86.0 (16.7)	77.2 (19.3)	92.4 (10.7)	**<0.001**	**1.02**
Role physical	64.8 (42.5)	36.8 (40.5)	84.9 (30.9)	**<0.001**	**1.36**
Social functioning	78.0 (25.2)	61.2 (25.8)	90.1 (16.3)	**<0.001**	**1.38**
Role emotional	77.2 (37.8)	60.6 (44.3)	89.0 (30.0)	**<0.001**	**0.80**
Bodily pain	67.9 (27.8)	55.1 (26.9)	77.0 (24.6)	**<0.001**	**0.85**
General health	61.0 (27.2)	43.0 (23.9)	73.9 (21.4)	**<0.001**	**1.37**
Vitality	48.2 (23.7)	30.4 (16.6)	60.9 (19.4)	**<0.001**	**1.67**
Mental health	74.3 (17.2)	66.5 (18.9)	79.9 (13.2)	**<0.001**	**0.85**
Physical composite score	46.4 (11.0)	39.7 (10.9)	51.2 (8.3)	**<0.001**	**1.21**
Mental composite score	48.8 (10.2)	44.3 (11.7)	52.0 (7.3)	**<0.001**	**0.82**

SD: Standard Deviation; HD-ASCT: High Dose Therapy with Autologous Stem Transplantation; HL: Hodgkin's lymphoma; WAS: Work Ability Score; CF: Chronic fatigue; FQ: Fatigue Questionnaire; PHQ-9: Patient Health Questionnaire;. HRQoL: Health Related Quality of Life; SF-36: Short Form survey.
[a]Valid numbers only, responses missing in between 1–17 cases.
[b]Where 61 responses were missing.
[c]ES, Effect size for chi-square test assessed by phi (2×2) or Cramer's V (>2×2), for two sample t-test by Hedges' g and for Mann–Whitney U test by estimated r. ES interpretation by Phi, Cramer's V and estimated r (0.1–0.3 small, >0.3–0.5 medium and >0.5 large) and Hedges' g (0.2–0.5 small, >0.5–0.8 medium and >0.8–large). Significant p values below 0.05 and medium and large ES given in bold.
[d]Work assessment allowance, sickness benefit, rehabilitation money.
[e]Comorbidity score, summarized number of 8 possible self-reported diagnoses listed in table, possible score 0–8.

Statistical analysis and ethics

Data was presented as absolute numbers and percentages if categorical, continuous data as mean and SD when normally distributed, otherwise as median and range. Groups of HLS with and without CF were compared using univariate analysis (Chi-square analysis, two-sample t-tests, and Mann–Whitney U tests). Effect size (ES) of differences between groups was calculated and interpreted according to general guidelines [34].

To predict associations with CF in binary logistic regression analysis, predictors with a significant association in univariate analysis (p < 0.05) were entered in the multivariate model, with the exception of pain, depressive symptoms and HRQoL, all factors are known to be highly correlated with each other and with CF.

To assess the implications of CF as an independent variable on work-related and socioeconomic variables, multinomial logistic regression analysis was performed with WAS and different factors of SES (income level, employment- and disability benefits status) as dependent variables. Models were adjusted for sex, age at diagnosis, BMI ≥30 kg/m^2 and comorbidities.

All tests were two-sided and p Values <0.05 considered significant. Statistical analysis was performed using International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) version 25 for PC (IBM Corporation, Armonk, USA).

The study was approved by the regional committee for medical and health research ethics South East (2016/2311).

Results

Sociodemographic and socioeconomic status of the study population

Of 518 invited HLS, 304 consented and returned the questionnaire, with 298 responding fully to the FQ, yielding a

Table 2. Factors associated with chronic fatigue in multivariate binary logistic regression analysis.

	Multivariate			
	N	OR	CI	p Value[b]
Descriptive data				
Gender				
Male	134	Ref.		
Female	149	1.78	1.05–3.01	**0.03**
Education				
Higher university degree	55	Ref.		
University/college	107	1.84	0.87–3.91	0.11
Primary/secondary school	121	2.32	1.10–4.90	**0.03**
Disease/treatment data				
Received radiotherapy				
No	217	Ref.		
Yes	66	1.50	0.80–2.79	0.21
Lifestyle				
Alcohol units per week		0.93	0.84–1.02	0.12
BMI ≥ 30 kg/m^2				
No	52	Ref.		
Yes	231	1.97	1.03–3.77	**0.04**
Comorbidity score[a]		1.38	1.08–1.75	**0.01**

OR: Odds Ratio; CI: Confidence Interval; BMI: Body Mass Index; HDT-ASCT: High Dose Therapy with Autologous Stem Cell Transplantation.
[a]Comorbidity score, summarized number of eight possible self-reported diagnoses listed in Table 1, possible score 0–8.
[b]Significant p-values below 0.05 given in bold.

Table 3. Chronic fatigue as a predictor of socioeconomic status and work ability in survivors.

		Chronic fatigue[a]		
Dependent variable[b]	N[c]	OR	CI	p Value
Payed work before treatment				0.14[d]
Yes	218	Ref.		
No	34	0.45	0.17–1.17	0.10
No, student/Army	45	1.17	0.50–2.77	0.71
Work status at survey				**<0.001[d]**
Employed	213	Ref.		
Unemployed	9	1.11	0.26–4.80	0.89
Disability and other benefits	76	3.78	2.10–6.84	**<0.001**
WAS at survey				**<0.001[d]**
Poor	77	Ref.		
Intermediate	47	0.44	0.19–0.98	**0.04**
Good	74	0.23	0.11–0.48	**<0.001**
Very good	92	0.03	0.01–0.08	**<0.001**
Unemployed after HL				
No	188	Ref.		
Yes	48	2.15	1.09–4.26	**0.03**
Disability benefits after HL				
No	250	Ref.		
Yes	47	2.88	1.42–5.81	**0.003**
Expected yearly income before tax, NOK				0.25[d]
0 – 200,000	20	Ref.		
201,000 – 400,000	76	1.19	0.42–3.38	0.74
401,000 – 600,000	101	0.78	0.28–2.16	0.63
601,000 – 800,000	53	0.78	0.26–2.35	0.66
> 801,000	44	0.44	0.13–1.45	0.18

[a]Odds ratios for survivors with chronic fatigue versus no chronic fatigue as independent variable, adjusted for sex, age at diagnosis, comorbidity score and BMI < vs ≥30 kg/m^2.
[b]Dependent variables analyzed in separate models.
[c]Number of survivors in regression analysis.
[d]First p-value of caseness of chronic fatigue in regression model, other p-values for individual comparisons. Significant p-values below 0.05 given in bold.
WAS: work ability score; NOK: Norwegian kroner.

response rate of 58%. There were 209 non-responders and 5 non-consensual. In attrition analysis, excluded survivors were more likely men ($p < 0.001$) and were younger at diagnosis and survey ($p = 0.01$ and $p = 0.004$ respectively), compared

to respondents, all differences with small differences between the groups (ES < 0.3).

Demographic, disease- and treatment-related, socioeconomic, work-related and health- and lifestyle-related data of all responding HLS and for those with or without CF are shown in Table 1.

Chronic fatigue - prevalence and associated factors

By use of FQ, 42% of the responders were classified as having CF. Mean (standard deviation [SD]) physical fatigue score was 10.2 (4.3) and the mean mental fatigue score 5.5 (2.1).

CF is associated with lower HRQoL, in all individual subdomains of SF-36 as well as in the MCS and PCS, and all with large ES (Table 1). Similarly, higher levels of depressive symptoms and pain were seen in HLS with CF, with large and small ES, respectively.

The multivariate binary logistic regression analysis, including as predictors all demographic, treatment-, health- and lifestyle-related factors significantly associated with CF, is shown in Table 2. Female sex (odds ratio [OR] 1.78, 95% confidence interval [CI]= 1.05–3.01, $p = 0.03$), educational level (lowest versus highest, 2.32, 1.10–4.90, $p = 0.03$), BMI ≥30 kg/m^2 (1.97, 1.03–3.77, $p = 0.04$) and higher number of comorbidities (1.38, 1.08–1.75, $p = 0.01$) retained a significant association with caseness of CF.

Implications of chronic fatigue on socioeconomic status and work ability

Of the responding HLS, 13% reported poor (score 0–5) WA at the time of HL diagnosis, a percentage that increased to 27% at the survey. This change corresponds to a reduction in WAS mean score (SD) from 8.8 (2.7) to 7 (3.3) in the whole group of HLS (mean difference −0.8, CI −0.1 −0.7, $p < 0.001$, Hedges' g 0.6). A larger reduction in WA was seen in HLS with CF (mean difference −1.6, CI −1.8 – −1.4, $p < 0.001$, Hedges' g 1.4), compared to the non-fatigued (mean – difference −0.25, CI −0.5 – −0.0, $p = 0.02$, Hedges' g 0.2).

To assess the implications CF might have on WA and socioeconomic variables, multinomial logistic regression analysis was performed with the presence of CF as an independent variable in several adjusted models. CF was significantly associated with lower current self-reported WAS, having experienced unemployment or been a recipient of disability benefits at some time after diagnosis and reporting disability or other state benefits at the time of the survey (Table 3). Although not statistically significant, there was a trend for CF to be associated with a lower income level in adjusted models.

Discussion

In long-term HLS after contemporary risk-adapted treatment approaches, we found CF in 42% of the responding population. CF was found to be associated with female sex, lower education, higher BMI, and an increasing number of comorbid conditions at the time of survey. No association to

disease- or treatment-related parameters was found. In univariate analysis, CF was also associated with lower HRQoL and a higher level of depressive symptoms, with a large ES for the differences between HLS with or without CF. Adjusting for other parameters associated with CF, chronically fatigued HLS reported lower WAS at the time of the survey and were more likely to have a history of unemployment and to receive disability benefits. There was a trend towards lower income levels among the HLS with CF.

As risk reduction of LEs has been a major motivation for the implementation of contemporary risk-adapted treatment approaches for HL, one would hope to see a lower prevalence of various LEs known to be associated with HL. Comparing the prevalence of CF across studies is challenging for several reasons, including differences in patient recruitment and study design, treatment eras, observation time, and use of different PROMs. However, at a median time since diagnosis of 16 years, with 42% of our cohort suffering from CF, there appears to be no obvious reduction in the prevalence of this ominous LE compared to studies in cohorts from previous periods using other treatment regimens. Using the same instrument, FQ, in HLS survivors treated in Norway before 1994, prevalence rates of 25% and 30%, at 12 and 16 years after diagnosis, have been described [9,10]. The cohort studied in the two latter studies is otherwise remarkably similar to the current study in terms of important parameters, such as sex, age and stage at diagnosis. During the same two decades, from 1996 to 2015, the prevalence of CF assessed by FQ in the Norwegian general population remained stable, with rates of 11.4% and 13.4% respectively [28]. Furthermore, our findings are comparable to other studies of CF in HLS after contemporary treatment, albeit with shorter follow-up. For instance, a Dutch study of HLS treated after 1999 and with a median follow-up of 4.6 years, reported a prevalence of 43% and 41%, when fatigue was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and Fatigue Assessment Scale, respectively [26]. Also using the EORTC-QLQ-30, but with a higher cutoff to indicate the caseness of CF, a longitudinal study from Germany found rates of severe fatigue at 2 and 5-year follow-up of 21% and 20%, respectively [25]. In the latter population, as in the current study, no treatment-related parameters that significantly predicted the development of severe fatigue persisting for 2 years or more were found [24]. Therefore, changes in the type and dose of chemotherapy or reduction in the use of radiotherapy implemented in most Western countries around the year 2000, may not have translated into improvements in fatigue burden.

Maybe an increased focus on LEs during the last decades is reflected in the high prevalence of CF, compared to previous studies. During the last decade, there has been increased focus on LEs after cancer treatment amongst governmental institutions [35,36], health professionals and patient organizations. In a study of Norwegian general practitioners in 2019, nearly all were familiar with at least some common LEs in HLS, including 92% who were aware of the risk of CF [37]. Although not comparable, this contrasts with the lower level

of awareness reported by lymphoma survivors after high-dose autologous stem cell therapy in a Norwegian cross-sectional survey from 2012–2014 [38]. Here, only 54% of the responding survivors recognized CF as a common LE after treatment. Surprisingly, a number of survivors reporting being fatigued, did not know about CF as a condition after lymphoma treatment. Just like the etiology of CF after cancer remains unknown, it is intriguing that most studies fail to identify disease- or treatment-related factors that predict the development of CF in survivors of HL [24,25,39]. Whereas some studies suggest disease-related factors to be associated with CF, such as B symptoms or advanced stage at diagnosis [9,10,40], this is not found by most others. As mentioned, a relationship with treatment-related factors is similarly difficult to find. In univariate analysis, our study found a higher risk of CF in patients that received radiotherapy, but this could not be substantiated in multivariable models.

In our study, a lower level of education at survey was associated with CF. Still, the level of education attained by the whole group of HLS at the time of questionnaire appeared to be higher than in the general Norwegian population [33]. At survey, 43% of the HLS had attained up to 12 years of education and 38% and 19% had a lower (13–16 years) or higher (>16 years) university degree. For 2018, in the general Norwegian population, the corresponding levels were 65.9%, 24.1% and 10% respectively [33]. HL appears to be a disease associated with indicators of higher SES of the patient and his or her family and higher educational level amongst HLS compared to the general population is described previously [9,39]. We cannot conclude the nature of the relationship between education and CF. Since the median age at diagnosis in our cohort was 29 years, younger HLS that develop CF at a young age may have more challenges successfully completing their planned professional education. Alternatively, HLS with higher education may cope better with the consequences of CF, adapt their professional and private life, and therefore relieve the symptom burden associated with CF.

With a relatively young patient group and excellent survival rates, one would hope for HLS to enter a long and productive work life. Therefore, we were particularly interested in the possible implications of CF on social reintegration and employment difficulties after treatment in HLS. At diagnosis, the vast majority of patients were either working, in professional education or in military service, with no difference between HLS with later development of CF and those without. However, we demonstrate that the presence of CF is independently associated with employment difficulties and the receipt of disability benefits. At survey, about half of the HLS with CF reported being employed full-time (47%) or part-time (7%), lower rates than in the non-fatigued survivors (74% and 6% respectively). Level of employment of HLS without CF was however higher than the Norwegian general population, where 68% of inhabitants aged 15–74 years were in any level of employment in 2018 [33]. Of HLS with CF, 30% received a disability pension, compared to 12% of those without CF, the latter being closer to the 10% of the general population reported by SN in 2018. The German Hodgkin

Study Group evaluating patients enrolled in large prospective treatment trials of HL, reached similar conclusions [25], with CF being a hindrance to successful reintegration into professional life after treatment. Our results in Norwegian HLS after modern treatment are also in line with a recent systematic literature review showing educational achievements and employment rates for HLS to be comparable to the general population, but with lower employment rates and an increase in disability benefits after diagnosis [41]. Our findings indicate that CF might be an added challenge for HLS on an individual and familial level, and cause societal costs due to loss of work productivity, increased work absenteeism and disability benefits.

HRQoL focuses on the physical, mental, and social effects of illness, and specifically on the impact of treatment on QoL [42]. Similar to other studies, we found HLS with CF scoring lower on all mental and physical components of HRQoL in SF-36, in addition to other health issues, such as increased depressive symptoms and more pain than the non-fatigued counterpart [26,43]. The magnitude of difference, expressed as ES, was large in most of these comparisons. There is considerable overlap in the content covered by PROMs addressing HRQoL, depressive symptoms and fatigue, and it is difficult to assess how these constructs impact on each other, i.e. whether CF is a major determinant of reduced HRQoL or higher burden of depressive symptoms reported by HLS with CF. This is also the reason why we chose not to include these items as explanatory variables in our multivariable models. The loss of HRQoL and a higher level of depressive symptoms however emphasizes the burden carried by HLS suffering from CF. In a large longitudinal study of HLS, impairments of most domains of HRQoL in EORTC QLQ C30 were observed at baseline amongst HL patients with all disease stages and were prognostic for long-term HRQoL of HLS [44]. Assessment of HRQoL in newly diagnosed HL patients could possibly support and prevent further impairments in HRQoL.

Strengths of the study include the representativity which included HLS identified from a large multicenter population-based study and a response rate of 58%. Female sex was associated with the development of CF, and male HLS were more likely not to be included in the survey, possibly overestimating the rate of CF. A more detailed attrition analysis was not possible, as access to individual data for non-consenting individuals was not permitted. Another strength of the study was the use of validated and well-known outcome measures.

We acknowledge weaknesses in our study design. The study is cross-sectional, and we do not have data on fatigue symptoms before treatment and the first years after treatment. Despite using hospital records for medical information, patient-reported outcome data is collected by a questionnaire at one-time point, with risk of recall bias. Furthermore, with a cross-sectional study we cannot conclude on causative factors for CF, only associations. A curious finding in our study was the association of CF with lower consumption of alcohol. The respondents overall appeared to consume less alcohol than the Norwegian general population [45] a finding that may be explained by fatigued HLS being less likely to attend social settings where alcohol is consumed. In FQ, only subjects with symptom duration ≥ 6 months are defined as having CF, thus excluding individuals with shorter periods of transient fatigue.

In conclusion, our analysis reveals a high prevalence of CF in HLS after contemporary risk-adapted therapy, possibly higher than seen in HLS treated in previous eras. No association with disease stage or cancer treatment was found. HLS as a whole have employment rates and income levels in line with the general population, but in sub-group analysis, we find HLS with CF to be disadvantaged socioeconomically and less integrated in work life.

With the high prevalence and unknown etiology of CF, emphasis should be put on studying etiopathological factors of CF. Being able to prevent and alleviate CF would probably be of immense benefit to HLS' health, HRQoL, work ability, and as such societal cost of survivorship.

Ethical approval

Ethics approval was granted by Regional committees for medical and health research ethics South East (2016/2311). The study was performed in accordance with the declaration of Helsinki.

Patient consent

Informed written consent from all participants in the study was obtained.

Author contributions

Study concept and design: K.S., C.K. and A.F.; acquisition of data: K.S., U.F., H.B. and V.S.; statistical analysis: S.E. and A.F.; interpretation of data: S.E., A.F., K.S. and C.K.; drafting of the paper: S.E. and A.F.; critical revision of the paper for important intellectual content: S.E, A.F, K.S., C.K., U.F., H.B and V.S.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

[1] Medeiros LJ, Greiner TC. Hodgkin's disease. Cancer. 1995;75(S1): 357–369.

[2] Cancer Registry of Norway. Cancer in Norway 2021 – Cancer incidence, survival, and prevalence in Norway; p. 17; 2022. [cited 2022 Jun 06]. Available from: https://www.kreftregisteret.no/globalassets/cancer-in-norway/2021/cin_report.pdf.

[3] Schaapveld M, Aleman BM, van Eggermond AM, et al. Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. N Engl J Med. 2015;373(26):2499–2511.

[4] Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for hodgkin lymphoma. Blood. 2007;109(5):1878–1886.

[5] Abrahamsen AF, Loge JH, Hannisdal E, et al. Late medical sequelae after therapy for supradiaphragmatic Hodgkin's disease. Acta Oncol. 1999;38(4):511–515.

[6] Loge JH, Abrahamsen AF, Ekeberg O, et al. Reduced health-related quality of life among Hodgkin's disease survivors: a comparative study with general population norms. Ann Oncol. 1999; 10(1):71–77.

[7] Haukvik UK, Dieset I, Bjøro T, et al. Treatment-related premature ovarian failure as a long-term complication after Hodgkin's lymphoma. Ann Oncol. 2006;17(9):1428–1433.

[8] Kiserud CE, Dahl AA, Fosså SD. Kreftoverlevere - ny kunnskap og nye muligheter i et langtidsperspektiv [Cancer survivors – new knowledge and new opportunities in a long-term perspective]. 3rd. ed. Oslo: Gyldendal; 2019.

[9] Hjermstad MJ, Fosså SD, Oldervoll L, et al. Fatigue in long-term Hodgkin's disease survivors: a follow-up study. J Clin Oncol. 2005; 23(27):6587–6595.

[10] Loge JH, Abrahamsen AF, Ekeberg Ø, et al. Hodgkin's disease survivors more fatigued than the general population. J Clin Oncol. 1999;17(1):253–253.

[11] Ng AK, Li S, Recklitis C, et al. A comparison between long-term survivors of Hodgkin's disease and their siblings on fatigue level and factors predicting for increased fatigue. Ann Oncol. 2005; 16(12):1949–1955.

[12] Daniëls LA, Oerlemans S, Krol AD, et al. Persisting fatigue in Hodgkin lymphoma survivors: a systematic review. Ann Hematol. 2013;92(8):1023–1032.

[13] Bower JE. Cancer-related fatigue – mechanisms, risk factors, and treatments. Nat Rev Clin Oncol. 2014;11(10):597–609.

[14] Viviani S, Bonadonna G, Santoro A, et al. Alternating versus hybrid MOPP and ABVD combinations in advanced Hodgkin's disease: ten-year results. J Clin Oncol. 1996;14(5):1421–1430.

[15] Dörffel W, Rühl U, Lüders H, et al. Treatment of children and adolescents with Hodgkin lymphoma without radiotherapy for patients in complete remission after chemotherapy: final results of the multinational trial GPOH-HD95. J Clin Oncol. 2013;31(12): 1562–1568.

[16] Diehl V, Franklin J, Pfreundschuh M, et al. Standard and increased-dose BEACOPP chemotherapy compared with COPP-ABVD for advanced Hodgkin's disease. N Engl J Med. 2003; 348(24):2386–2395.

[17] Lagerlöf I, Holte H, Glimelius I, et al. No excess long-term mortality in stage I-IIA Hodgkin lymphoma patients treated with ABVD and limited field radiotherapy. Br J Haematol. 2020;188(5):685–691.

[18] Aleman BM, Raemaekers JM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. N Engl J Med. 2003; 348(24):2396–2406.

[19] Fermé C, Eghbali H, Meerwaldt JH, et al. Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med. 2007;357(19):1916–1927.

[20] Dores GM, Curtis RE, Dalal NH, et al. Cause-specific mortality following initial chemotherapy in a population-based cohort of patients with classical Hodgkin lymphoma, 2000–2016. J Clin Oncol. 2020;38(35):4149–4162.

[21] Lagerlöf I, Fohlin H, Enblad G, et al. Limited, but not eliminated, excess long-term morbidity in stage I-IIA Hodgkin lymphoma treated with doxorubicin, bleomycin, vinblastine, and dacarbazine and limited-field radiotherapy. J Clin Oncol. 2022;40(13):1487–1496.

[22] Biccler JL, Glimelius I, Eloranta S, et al. Relapse risk and loss of lifetime after modern combined modality treatment of young patients with Hodgkin lymphoma: a nordic lymphoma epidemiology group study. J Clin Oncol. 2019;37(9):703–713.

[23] Eikeland SA, Smeland KB, Mols F, et al. Chemotherapy-induced peripheral neuropathy after modern treatment of Hodgkin's lymphoma; symptom burden and quality of life. Acta Oncol. 2021;60(7):911–920.

[24] Kreissl S, Mueller H, Goergen H, et al. Cancer-related fatigue in patients with and survivors of Hodgkin's lymphoma: a longitudinal study of the German Hodgkin Study Group. The Lancet Oncol. 2016;17(10):1453–1462.

[25] Behringer K, Goergen H, Müller H, et al. Cancer-Related fatigue in patients with and survivors of Hodgkin lymphoma: the impact on treatment outcome and social reintegration. J Clin Oncol. 2016; 34(36):4329–4337.

[26] Daniëls LA, Oerlemans S, Krol AD, et al. Chronic fatigue in Hodgkin lymphoma survivors and associations with anxiety, depression and comorbidity. Br J Cancer. 2014;110(4):868–874.

[27] Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a fatigue scale. J Psychosom Res. 1993;37(2):147–153.

[28] Dahl AA, Grotmol KS, Hjermstad MJ, et al. Norwegian reference data on the fatigue questionnaire and the patient health questionnaire-9 and their interrelationship. Ann Gen Psychiatry. 2020; 19:60.

[29] de Zwart BC, Frings-Dresen MH, van Duivenbooden JC. Test-retest reliability of the work ability index questionnaire. Occup Med2;52(4):177–181.

[30] Ahlstrom L, Grimby-Ekman A, Hagberg M, et al. The work ability index and single-item question: associations with sick leave, symptoms, and health – a prospective study of women on long-term sick leave. Scand J Work Environ Health. 2010;36(5):404–412.

[31] Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–613.

[32] Ware JE. SF-36 health survey update. Spine. 2000;25(24):3130–3139.

[33] Statistics Norway; 2018 [Internet]. Available from https://www.ssb.no/en.

[34] Lenhard WL. Computation of effect sizes: Psychometrica; 2016 [Internet]. Available from: http://www.psychometrica.de/effect_size.

[35] Helse- og omsorgsdepartementet. Leve med kreft – Nasjonal kreftstrategi 2018–2022. [Ministry of Health and Care Services. Living with cancer – National cancer strategy 2018–2022]. Helse. og omsorgsdepartementet; 2018.

[36] Helsedirektoratet. Seneffekter etter kreftebehandling. [The Norwegian Directorate of Health. Late effects after cancer treatment]. Helsedirektoratet; 2020. 2nd ed.; p.1–83.

[37] Eikeland SA, Smeland KB, Brekke MK, et al. Late-effect awareness and follow-up of cancer in general practice. Scand J Prim Health Care. 2022;40(3):360–369.

[38] Simensen VC, Smeland KB, Kiserud CE, et al. Survivors' knowledge of their diagnosis, treatment and possible late adverse effects after autologous stem cell transplantation for lymphoma. Acta Oncol. 2019;58(9):1315–1322.

[39] Calaminus G, Dörffel W, Baust K, et al. Quality of life in long-term survivors following treatment for hodgkin's disease during childhood and adolescence in the German multicentre studies between 1978 and 2002. Support Care Cancer. 2014;22(6):1519–1529.

[40] Heutte N, Flechtner HH, Mounier N, et al. Quality of life after successful treatment of early-stage Hodgkin's lymphoma: 10-year follow-up of the EORTC-GELA H8 randomised controlled trial. Lancet Oncol. 2009;10(12):1160–1170.

[41] Pálmarsdóttir R, Kiesbye AØ, Severinsen MT, et al. Socioeconomic impact of Hodgkin lymphoma in adult patients: a systematic literature review. Leuk Lymphoma. 2019;60(13):3116–3131.

[42] Guyatt GH, Ferrans CE, Halyard MY, et al. Exploration of the value of health-related quality-of-life information from clinical research and into clinical practice. Mayo Clin Proc. 2007; 82(10):1229–1239.

[43] Hjermstad MJ, Oldervoll L, Fosså SD, et al. Quality of life in long-term Hodgkin's disease survivors with chronic fatigue. Eur J Cancer. 2006;42(3):327–333.

[44] Kreissl S, Müller H, Goergen H, et al. Health-related quality of life in patients with Hodgkin lymphoma: a longitudinal analysis of the German Hodgkin Study Group. J Clin Oncol. 2020;38(25):2839–2848.

[45] Bye E, Rossow I. Alkoholbruk i den voksne befolkningen [Alcohol consumption in the adult population]: Norwegian Institute of Public Health; 2022 [cited 2018 Oct 9]. Available from: www.fhi.no/nettpub/alkoholinorge/omsetning-og-bruk/alkoholbruk-i-den-voksne-befolkningen.