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Fatigue in male lymphoma survivors differs between diagnostic groups and is associated with latent hypothyroidism

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ABSTRACT

Background. Few studies have explored fatigue in different groups of lymphoma survivors and the association with hormonal dysfunctions. The aims were to analyze associations between fatigue and thyroid and gonadal function in male lymphoma survivors. In addition, the impact of chronic fatigue on work situation and daily functioning were explored.
Patients and methods. This cross-sectional study included male lymphoma survivors diagnosed in 1980–2002, aged ≤ 50 years at diagnosis and > 18 years at survey in 2007. The participants ($n = 233$, median age at survey: 48 years, median observation time: 15 years) completed questionnaires assessing levels of fatigue, chronic fatigue (duration ≥ 6 months), mental distress, daily functioning and work situation. Levels of thyroid and gonadal hormones were assessed. The participants were grouped according to diagnosis: Hodgkin lymphoma (HL, $n = 131$), aggressive/very aggressive non-Hodgkin lymphoma (NHL) ($n = 67$) and indolent NHL ($n = 35$). Thyroid hormones were categorized as normal ($n = 174$) or latent hypothyroidism (elevated thyroid stimulating hormone, $n = 59$). Gonadal hormones were categorized as normal ($n = 111$), elevated follicle stimulating hormone only ($n = 45$), primary ($n = 35$) or secondary hypogonadism ($n = 42$). Uni- and multivariate regression analyses were performed. A p value < 0.05 indicated the level of significance.
Results. The survivors of HL and aggressive/very aggressive NHL had similar fatigue levels and similar prevalence of chronic fatigue (HL: 31%, aggressive/very aggressive; NHL: 27%). Survivors of indolent NHL had lower fatigue levels and prevalence of chronic fatigue (11%). Latent hypothyroidism was associated with increased fatigue levels ($p = 0.042$). Gonadal function was not associated with levels of fatigue or chronic fatigue. Mental distress was associated with increasing fatigue levels and chronic fatigue ($p < 0.001$). We found negative associations between chronic fatigue, daily functioning and work status.
Conclusions. Fatigued lymphoma survivors should be investigated for thyroid function. The negative impact of chronic fatigue on daily functioning and work status emphasizes the importance of maintaining the effort in understanding the mechanisms behind fatigue.

Fatigue is a subjective experience of tiredness, exhaustion and lack of energy and is a common and distressing late effect after lymphoma [1,2]. In relation to lymphomas, fatigue has in particular been studied in Hodgkin lymphoma (HL) survivors [1–3]. A prevalence of chronic fatigue (elevated levels of fatigue for ≥ 6 months [4]) of 26–30% among HL survivors has been reported at a median of, respectively, 12 and 16 years after diagnosis, compared to 11% in the general population [2,5]. Fewer studies have addressed fatigue in survivors after non-Hodgkin's lymphoma (NHL) [6,7]. Compared to a normative population NHL survivors had higher levels of fatigue at a mean of 4.2 years after

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diagnosis, and persistent fatigue was reported among 44–54% of the survivors when measured at two time points separated by a year [7]. Despite differences in tumor biology and treatment intensity, fatigue scores did not differ between survivors of indolent and aggressive NHL [7].

Fatigue in long-term lymphoma survivors is associated with both somatic and psychological factors, whereas treatment intensity seems to have limited impact [1,5,8]. Patient-reported comorbid conditions, such as cardiac diseases and arthritis, have been shown to be associated with fatigue levels [6,9]. Still, few studies have explored the associations between fatigue and somatic diseases including somatic late effects [10–12]. The importance of studying fatigue in relation to somatic late effects was recently pointed to, based on a significant association between development of cardiopulmonary complications and decline in energy level among 273 HL survivors [13].

A few studies have explored the impact of hormonal dysfunction on fatigue among lymphoma survivors [10–12], but the only study investigating thyroid function found no association between the presence of biochemical hypothyroidism and levels of fatigue [10]. Further, fatigue levels did not differ between male survivors of lymphomas or hematological malignancies with mild Leydig cell dysfunction and survivors with normal gonadal hormones [12]. In contrast, another survey reported higher levels of fatigue in hypogonadal versus eugonadal male survivors mainly treated for germ cell tumors and malignant lymphomas [11].

Possible associations between fatigue and daily functioning have not been well studied [14]. In our view, the functional consequences of fatigue including work participation are of great importance as they indicate the burden of this symptom for the affected individual and for the society.

On this background, the aims of the present study among male lymphoma survivors were:

1. To assess levels of fatigue and prevalence of chronic fatigue in different diagnostic groups (HL, aggressive/very aggressive NHL and indolent NHL).
2. To analyze whether thyroid or gonadal dysfunction is associated with fatigue levels and chronic fatigue.
3. To assess the impact of chronic fatigue on daily living, i.e. work situation and patient-reported functioning.

Patients and methods

The present study is part of a broader cross-sectional follow-up survey among male lymphoma survivors performed in 2007. The survey included gonadal and thyroid hormone function, and questionnaires assessing symptoms relevant to explore in relation to hormonal dysfunctions, such as fatigue and sexual function. In addition, quality of life, sociodemographic factors and emotional distress were assessed. Previous reports have included the survivors' gonadal and sexual function [15,16].

Patients

Inclusion criteria were: male survivors ≤ 50 years at diagnosis; treated for HL or NHL at the Norwegian Radium Hospital (NRH), primary diagnosis between 1 January 1980 and 31 December 2002, with age > 18 years at the time of survey (n = 653). The present study includes participants with a completed fatigue questionnaire and assessments of gonadal and thyroid hormones (n = 233, 36%).

Treatment strategies for HL and NHL at the NRH in this period followed national and international guidelines. Data on disease and treatment were collected from the hospital's lymphoma database. Treatment details are previously described [15,16]. Survivors were categorized into three diagnostic groups: HL (n = 131), aggressive/very aggressive NHL (diffuse large B-cell lymphoma, transformed lymphoma, mature T-cell lymphoma, mantle cell lymphoma, Burkitt's lymphoma and lymphoblastic lymphoma, n = 67) or indolent NHL (low grad lymphoma, n = 35). Type of treatment was categorized into three: radiotherapy only (n = 32), chemotherapy only (n = 51) and radiotherapy and chemotherapy in combination (n = 150). Observation time was calculated from date of first diagnosis to January 1, 2007.

Questionnaires

The main outcomes of this study are levels of fatigue and chronic fatigue assessed by the Fatigue Questionnaire (FQ) (11 items) [4]. Responses are scored in two ways. Likert scoring (0, 1, 2, 3) is used for the construction of physical fatigue (7 items), mental fatigue (4 items), and total fatigue (all 11 items) by simple addition. Higher scores imply higher levels of fatigue. Two additional items cover the duration and extent of fatigue. A dichotomized (0, 0, 1, 1) score of the responses is used for case definition. Chronic fatigue is defined by a sum score of ≥ 4 of the dichotomized responses with duration of ≥ 6 months [4]. Internal consistency (Cronbach's alpha) was 0.89 for all the 11 items of the FQ.

The following variables were used as explanatory variables. Married or cohabiting men were classified as having a committed relationship versus those without such a relationship. Level of education were dichotomized into: ≤12 years (low level) versus >12 years (high level) of completed school years. The males were categorized as having a comorbid condition if they reported at least one of the following diseases: myocardial infarction, angina pectoris, stroke, diabetes, asthma, or hypertension (defined by use of antihypertensive medication). Body mass index (BMI) was calculated based upon the patients' report of weight and height.

Anxiety- and depression-symptoms were measured by The Hospital Anxiety and Depression Scale (HADS) consisting of 14 items, seven comprising the depression subscale and seven comprising the anxiety subscale [17]. Responses to each item have four alternatives scored from 0 to 3. Sumscores for the depression and anxiety scales were summed to a total HADS score, with higher scores implying more mental distress. Due to high correlation between fatigue and one of the depression items (Item: "I feel as if I am slowed down") (Pearson correlation: 0.54), this item was not included in the total HADS score. Cronbach's alpha was 0.89 for the total HADS score.

The impact of chronic fatigue on daily functioning was assessed as the associations between chronic fatigue and current work situation and the functional scales of the SF-36 (Short form 36). The functional scales are: physical functioning (PF), role limitations due to physical health problems (limitations in daily activities because of physical health problems, RP), social functioning (SF), role limitations due to emotional problems (limitations in daily activities because of emotional problems, RE). The scores of the SF-36 scales were calculated according to standard SF-36 algorithm (0 = worst health state, 100 = best health state) [18]. Current work situation was dichotomized into working (including full time work, part time work, occupational rehabilitation, students, retired due to age) and not working (sickness allowance, disability benefit).

Thyroid and gonadal hormones

Blood samples were drawn by the patients' general practitioners and mailed to the Department of Medical Biochemistry at Oslo University Hospital for the hormone analyses. The normal serum ranges for thyroid function were: thyroid stimulating hormone (TSH): 0.50–3.5 mU/L and fT4: 9.0–21.0 pmol/L [19]. Thyroid function was categorized as follows: *normal function:* normal levels of fT4 and TSH (n = 174) and *latent hypothyroidism:* TSH: ≥3.6 mU/L and fT4 > 9.0 pmol/L (n = 59). No survivors had primary overt hypothyroidism (TSH ≥ 3.6 mU/L and fT4 < 9.0 pmol/L) or secondary hypothyroidism (TSH < 0.5 mU/L and fT4 < 9.0 pmol/L). A total of 38 of the survivors reported to use thyroid hormone substitution.

Age-adjusted reference values were used for classification of gonadal function. Free testosterone index was calculated as testosterone (nmol/L)/sex hormone binding globuline (SHBG) (nmol/L) × 10, and dichotomized into normal versus low according to age groups (20–30 years: 4.8–13.6, 30–40 years: 3.8–11.0, 40–50 years: 3.1–9.1, 50–60 years: 2.7–7.7, 60–70 years: 2.3–6.5, 70–80 years: 2.1–5.5) [20]. Normal values for follicle stimulating hormone (FSH) were: 20–30 years: 2–10 IU/L, 30–50 years: 2–12 IU/L and > 50 years: 3–14 IU/L and for luteinizing hormone (LH) were: < 50 years: 2–10 IU/L and > 50 years: 2–12 IU/L [20]. Gonadal function was categorized in four groups based on our previous reports on gonadal function [15,16] : *normal gonadal function* (n = 111), *elevated FSH only* (elevated FSH, normal LH and normal free testosterone index) (n = 45), *primary hypogonadism* (elevated LH, normal or low free testosterone index) (n = 35) and *secondary hypogonadism* (low free testosterone index, normal LH) (n = 42).

Ethical considerations

The Regional Committee for Medical Research Ethics, Health Region South, Norway, approved the study. All participants provided written informed consent forms.

Statistics

Descriptive statistics were used including Student's t-test for continuous variables and χ^2-tests for categorical data. Non-parametric tests were used in case of skewed distributions.

Univariate and multivariate linear regression analyses were performed with the total fatigue score as the dependent variable. Explanatory variables significant in the univariate analyses ($p < 0.05$) were included in the multivariate model and the strengths of the associations were expressed as standardized β values. For analyses of variables associated with chronic fatigue, univariate and multivariate logistic regression analyses were performed with chronic fatigue as the dependent variable. Explanatory variables significant ($p < 0.05$) in the univariate analyses were included in the multivariate model and OR, 95% CI, and p-values are presented. As previous studies have shown an association between increasing age and fatigue [2], age at survey was included in both the multivariate models even though it was neither significantly associated with chronic fatigue nor the total fatigue score in univariate analyses.

The impact of chronic fatigue on daily functioning was analyzed using linear regression analyses with the functional scales of SF-36 (PF, RP, SF or RE) as the dependent variables and chronic fatigue as the independent variable adjusting for age at survey. A logistic regression analysis with current work situation as the dependent variable and chronic fatigue as independent variable adjusting for age at survey was performed to explore the association between chronic fatigue and work situation.

A p-value of 0.05 was considered statistically significant; all tests were two-sided. PASW version 18 was used.

Results

Patient characteristics

The participants were significantly older at survey compared to the non-participants [48 years vs. 46 years (median), $p = 0.03$], whereas no significant differences in age at diagnosis, observation time, or distribution of diagnosis was observed between the participants and non-participants.

Among the 233 participants the median age at survey was 48 years and the median observation time was 15 years (Table I). Compared to both groups of NHL survivors, the HL survivors were younger at diagnosis ($p < 0.05$), and the survivors of indolent lymphoma were older than survivors of HL and aggressive NHL at survey ($p = 0.004$).

Factors associated with levels of fatigue

Compared to HL survivors, survivors of indolent NHL had significantly lower physical and total fatigue scores ($p = 0.01$), whereas no significant difference between the lymphoma groups where observed for the mental fatigue score (Tables I and III). There was no significant difference between survivors of aggressive/very aggressive NHL and HL regarding the mental, physical or the total fatigue scores.

Further, latent hypothyroidism ($p = 0.045$), increasing observation time ($p = 0.002$) and increasing HADS score ($p < 0.001$) were significantly associated with increasing total fatigue score. Compared to those with normal gonadal function, survivors with primary hypogonadism had higher level of fatigue ($p = 0.039$). There was no significant association between increasing age and total fatigue score.

The multivariate analysis confirmed that survivors after indolent NHL had significantly lower total fatigue score compared to HL survivors ($p = 0.02$). Further, increasing HADS score ($p < 0.001$) and latent hypothyroidism ($p = 0.042$) remained significantly associated with increasing levels of fatigue.

Due to the significant association between primary hypogonadism and level of fatigue a separate multivariate model was performed including gonadal function, age at survey, observation time and diagnostic groups. Primary hypogonadism was not significantly associated with fatigue in the multivariate model ($p = 0.15$).

Factors associated with chronic fatigue

A total of 62 (27%) of the survivors had chronic fatigue and the prevalence was 31% among survivors of HL, 27% among survivors of aggressive/very aggressive NHL, and 11% among survivors of indolent NHL (Table II).

Compared to HL, the survivors of indolent NHL had significantly reduced risk of chronic fatigue (OR 0.29, 95% CI 0.1–0.89, $p = 0.03$) whereas the survivors of aggressive/very aggressive NHL had similar risk as the HL survivors (OR 0.84, 95% CI 0.43–1.61, $p = 0.59$). Increasing HADS score was significantly associated with chronic fatigue ($p < 0.001$), whereas neither thyroid nor gonadal function were significantly associated with chronic fatigue (Table IV).

In the multivariate analysis increasing HADS score ($p < 0.001$) and age ≥ 60 years at survey (OR 3.81, 95% CI 1.17–12.45, $p = 0.03$) were significantly associated with increased risk of chronic fatigue. The lower risk for chronic fatigue among survivors of indolent NHL compared to HL survivors were of borderline significance in the multivariate model (OR 0.30, 95% CI 0.09–1.04, $p = 0.058$). The survivors of aggressive/very aggressive NHL displayed similar risk for chronic fatigue as the HL survivors (OR 0.91, 95% CI 0.42–1.97, $p = 0.81$).

Impact of chronic fatigue on daily functioning and work situation

Chronic fatigue was significantly associated with lower levels of PF, RP, SF and RE ($p < 0.001$) when adjusting for age at survey (Table V). Compared to the survivors without chronic fatigue, those with chronic fatigue had increased risk for not working (OR 3.61, 95% CI 1.67–7.84, $p = 0.001$). Increasing age at survey (in years) was also associated with not working (OR 1.08, 95% CI 1.04–1.31, $p < 0.001$).

Discussion

In this study we demonstrate that male long-term survivors after aggressive/very aggressive NHL report similar levels of fatigue and prevalence of chronic fatigue as HL survivors. In contrast, male survivors of indolent NHL had lower fatigue levels compared to HL survivors. Latent hypothyroidism was significantly

Table I. Patients characteristics.

	Total N = 233	HL n = 131	NHL aggressive/very aggressive n = 67	NHL indolent n = 35	p-Value between groups
Age at diagnosis/years [median (range)]	32 (11–49)	29 (11–49)	36 (14–49)	38 (28–49)	p < 0.001***
Age at survey/years [median (range)]	48 (21–73)	46 (21–67)	48 (24–65)	56 (35–73)	p = 0.004***
Observation time/years [median(range)]	15 (4–28)	16 (4–28)	13 (5–24)	16 (5–25)	p = 0.006***
Stage	% within this group	% within this group	% within this group	% within this group	
I/II A	106 (46%)	65 (50%)	24 (36%)	17 (49%)	
I/II B	26 (11%)	21 (16%)	5 (8%)	0	
III/IV A	54 (23%)	22 (17%)	16 (24%)	16 (46%)	
III/IV B	41 (18%)	21 (16%)	18 (27%)	2 (6%)	
Missing	6 (3%)	2 (2%)	4 (6%)		
B symptoms at diagnosis					
Yes	67 (29%)	42 (32%)	23 (34%)	2 (6%)	p = 0.003**
No	160 (69%)	87 (66%)	40 (60%)	33 (94%)	
Missing	6 (3%)	2 (2%)	4 (6%)		
Relapse					
Yes	48 (20%)	20 (15%)	17 (25%)	11 (31%)	p = 0.057**
No	185 (80%)	111 (85%)	50 (75%)	24 (69%)	
Treatment					
Radiotherapy only	32 (14%)	20 (15%)	2 (3%)	10 (29%)	p = 0.002**
Chemotherapy only	51 (23%)	22 (17%)	20 (30%)	9 (26%)	
Chemotherapy + radiotherapy	150 (64%)	89 (68%)	45 (67%)	16 (46%)	
Supradiaphragmatic radiotherapy	111	83	20	8	
Infradiaphragmatoc radiotherapy	46	22	9	15	
Total body irradiation	16	0	14	2	
Other radiation fields	9	4	4	1	
Thyroid status					
Normal	174 (75%)	93 (71%)	56 (84%)	25 (71%)	p = 0.14**
Latent hypothyroidism	59 (25%)	38 (29%)	11 (16%)	10 (29%)	
Gonadal hormones					
Normal	111 (48%)	69 (53%)	27 (40%)	15 (43%)	p = 0.32**
Elevated FSH only	45 (19%)	18 (14%)	17 (25%)	10 (29%)	
Primary hypogonadism	35 (15%)	20 (15%)	10 (15%)	5 (14%)	
Secondary hypogonadism	42 (18%)	24 (18%)	13 (19%)	5 (14%)	
Current work situation					
Working	195 (84%)	109 (83%)	57 (85%)	29 (83%)	p = 0.94**
Not working	38 (16%)	22 (17%)	10 (15%)	6 (17%)	
Total HADS score (mean, SD)	7.33 (6.3)	7.73 (6.2)	7.31 (7.2)	5.85 (4.8)	p = 0.31****
SF-36 functional scales					
Physical functioning [median(range)]	95 (5–100)	95 (10–100)	95 (5–100)	95 (40–100)	0.95***
Role physical [median (range)][a]	100 (0–100)	100 (0–100)	100 (0–100)	100 (0–100)	0.49
Social functioning [median (range)]	100 (0–100)	100 (0–100)	100 (12.5–100)	100 (37.5–100)	0.34
Role emotional [median (range)][b]	100 (0–100)	100 (0–100)	100 (0–100)	100 (0–100)	0.39
Chronic fatigue					
Yes	62 (27%)	40 (31%)	18 (27%)	4 (11%)	p = 0.08**
No	171 (73%)	91 (69%)	49 (73%)	31 (89%)	
Total fatigue (mean, SD)	14.17 (4.7)	14.69 (5.0)	14.15 (4.8)	12.23 (3.0)	*****
Mental fatigue (mean, SD)	4.80 (1.5)	4.89 (1.6)	4.82 (1.4)	4.40 (1.2)	
Physical fatigue (mean, SD)	9.37 (3.8)	9.80 (4.0)	9.33 (4.0)	7.83 (2.4)	

*t-test ** χ^2-test ***Non-parametric tests****One-way ANOVA.
*****linear regression: p = 0.001 for total fatigue and physical fatigue scores NHL indolent HL reference, ns NHL aggressive/very aggressive versus HL.
[a]Role physical: limitations in daily activities because of physical health problems; [b]Role emotional: limitations in daily activities because of emotional problems.

associated with fatigue levels, but not with chronic fatigue. There was a significant association between primary hypogonadism and fatigue level in univariate analysis, but gonadal function was not associated with levels of fatigue in a multivariate model or with chronic fatigue. We found negative associations between chronic fatigue and daily functioning and work status.

Table II. Prevalence of chronic fatigue and levels of total fatigue score, descriptive statistics, univariate analyses.

	Chronic fatigue n = 62 n (%)	p-Value	Total fatigue score Mean (SD)	p-Value
Diagnostic groups				
HL, n = 131	40 (31)	0.08*	14.69 (5.0)	0.02**
NHL aggressive/very aggressive, n = 67	18 (27)		14.15 (4.8)	
NHL indolent, n = 35	4 (11)		12.23 (3.0)	
Thyroid function				
Normal, n = 174	42 (24)	0.14*	13.80 (4.4)	0.045**
Latent hypothyroidism, n = 59	20 (34)		15.24 (5.5)	
Gonadal function				
Normal, n = 111	25 (23)	0.60*	13.53 (4.4)	0.12**
Elevated FSH only, n = 45	13 (29)		14.00 (5.1)	
Primary hypogonadism, n = 35	11 (31)		15.43 (4.5)	
Secondary hypogonadism, n = 42	13 (31)		14.98 (5.4)	
Observation time				
4–10 years, n = 63	12 (19)	0.15*	12.56 (4.3)	0.001**
11–20 years, n = 122	33 (27)		14.30 (4.5)	
21–28 years, n = 48	17 (35)		15.96 (5.2)	
Age at survey				
21–39, n = 57	17 (30)	0.06*	14.12 (5.2)	0.48**
40–49, n = 67	12 (18)		13.58 (4.7)	
50–59, n = 85	22 (26)		14.34 (4.6)	
60–69, n = 24	11 (46)		15.29 (3.9)	

*Chi-square, **ANOVA/t-test.

In total, as much as 27% of the participants had chronic fatigue. Similar prevalence has been reported by breast cancer survivors [1,21]. In contrast, data from the general Norwegian population have reported a prevalence of chronic fatigue of 11% [2]. Overall, these figures underline the importance of studying this debilitating late effect of cancer treatment.

To our knowledge, this is the first study assessing levels of fatigue and prevalence of chronic fatigue including survivors of HL, aggressive/very aggressive NHL and indolent NHL with a very long observation time from diagnosis. The high prevalence of chronic fatigue and high fatigue levels among survivors of aggressive/very aggressive NHL is striking. In contrast to previous findings by Oerlemans et al. [7], we found that survivors of indolent NHL had lower levels of fatigue compared to HL survivors. The prevalence of chronic fatigue among the survivors of indolent NHL in our study is similar to what has been found among males of similar age from the general population [2]. The difference in observation time, 4.2 years (mean) in the study by Oerlemans et al. and 14.8 years (mean) in our study might explain the difference in results. We speculate whether fatigue in some groups of lymphoma survivors might decrease with time, whereas it is more constant in other groups. The study by Khimani et al. showed an association between decline in energy levels and self-reported new cardiopulmonary late effects among HL survivors [13]. One might hypothesize that survivors of HL and aggressive/very aggressive NHL have higher risk of developing somatic late effects than survivors after indolent NHL because of more intensive treatment strategies. This in turn might lead to higher fatigue levels and higher prevalence of chronic fatigue as time elapses. However, in our study, only a few survivors of indolent NHL were included and our findings need to be confirmed in larger follow-up studies. As type of lymphoma, disease stage and treatment are highly associated, analyses on the relations between fatigue and treatment type and, for instance specific chemotherapy regimens are difficult to perform in patient samples like ours. However, in a previous follow-up study from our group among HL survivors, chronic fatigue was found to be associated with presence of B symptoms at diagnosis and treatment before 1980, whereas no associations between total fatigue score and treatment intensity and modality were found [5]. This is in line with other reports [22], and suggests that other factors than the treatment itself is the major contributor to fatigue in long-term survivors. In addition, strong associations between various treatments, like radiotherapy to the neck and gonadotoxic chemotherapy, and hormonal disturbances like hypothyroidism and hypogonadism have been reported among lymphoma survivors [15,23]. The present study aimed to explore the associations between fatigue and these hormonal disturbances, and sug-

Table III. Univariate and multivariate linear regression analyses with total fatigue score as the dependent variable.

	Univariate analyses B	β	p-Value	Multivariate analyses B	β	p-Value
Diagnostic subgroups						
HL (n = 131)	Ref	Ref		Ref	Ref	
NHL indolent (n = 35)	− 2.47	− 0.186	0.006	− 1.75	− 0.131	0.02
NHL agressive/very agressive (n = 67)	− 0.55	− 0.052	0.439	0.032	0.003	0.96
Age at survey (years)						
21–39 (n = 57)	Ref	Ref		Ref	Ref	
40–49 (n = 67)	− 0.541	− 0.052	0.528	− 0.73	− 0.07	0.30
50–59 (n = 85)	0.218	0.022	0.788	− 0.23	− 0.02	0.73
60–69 (n = 24)	1.169	0.075	0.313	1.27	0.080	0.22
Observation time (cont. variable)	0.15	0.198	0.002	0.070	0.092	0.13
Stage						
I/II A (n = 106)	Ref	Ref				
I/II B (n = 26)	1.34	0.091	0.19			
III/IV A (n = 54)	− 0.51	− 0.046	0.52			
III/IV B (n = 41)	0.527	0.043	0.54			
B symptoms at diagnosis						
No (n = 160)	Ref	Ref				
Yes (n = 67)	1.01	0.099	0.137			
Relapse						
No (n = 185)	Ref	Ref				
Yes (n = 48)	0.63	0.054	0.414			
Gonadal function						
Normal (n = 111)	Ref	Ref				
Elevated FSH only (n = 45)	0.49	0.039	0.574			
Primary hypogonadism (n = 35)	1.90	0.143	0.039			
Secondary hypogonadism (n = 42)	1.45	0.117	0.092			
Thyroid function						
Normal (n = 174)	Ref	Ref		Ref	Ref	
Latent hypothyroidism (n = 59)	1.43	0.13	0.045	1.18	0.11	0.042
Treatment groups						
Radiotherapy only (n = 32)	0.28	0.04	0.57			
Chemotherapy only (n = 51)	− 0.52	− 0.05	0.51			
Radiotherapy+chemotherapy (n = 150)	Ref					
HADS total score – D4(cont. variable)	0.47	0.58	< 0.001	0.45	0.56	< 0.001
Comorbidity						
No (n = 169)	Ref	Ref				
Yes (n = 64)	0.91	0.086	0.19			
BMI						
< 25 (n = 81)	Ref	Ref				
≥ 25 (n = 130)	− 0.666	− 0.068	0.317			
Education						
≤ 12 years (n = 119)	Ref	Ref				
≥ 13 years (n = 99)	0.78	0.08	0.22			
Relationship status						
In paired relation (n = 179)	− 0.786	− 0.068				
Not in paired relation (n = 50)	Ref	Ref	0.314			

Ref: reference.

gests that these late effects of treatment to some degree contribute to fatigue in long-term survivors rather than the treatment itself.

As far as we know, only one previous study has explored the association between levels of thyroid hormones and fatigue among lymphoma survivors [10]. In contrast to our results, no association between hypothyroidism and fatigue was found. However, the data in Knobel et al.'s study were originally from two separate follow-up studies in HL survivors on late medical effects and patient-reported outcomes respectively, performed at different time points [2,23,24]. This weakens their conclusion compared to our study where the questionnaires and blood sampling were performed at the same time point. Interestingly, our study revealed an association between latent hypothyroidism and level of fatigue, but not with chronic fatigue, which is a dichotomized variable defined as clinically relevant level of fatigue with a duration ≥ 6 months [4]. Chronic fatigue is thus a rougher estimate than fatigue level. Further, the association between total fatigue score and latent

Table IV. Univariate and multivariate logistic regression analyses with chronic fatigue as the dependent variable.

	Univariate logistic regression analyses OR (95% CI)	p-Value	Multivariate logistic regression analyses OR (95% CI)	p-Value
Diagnostic subgroups				
HL (n = 131)	Ref		ref	
NHL indolent (n = 35)	0.29 (0.1–0.89)	0.03	0.30 (0.09–1.04)	0.058
NHL agressive/very agressive (n = 67)	0.84 (0.43–1.61)	0.59	0.91 (0.42–1.97)	0.81
Age at survey (years)				
21–39 (n = 57)	Ref		Ref	
40–49 (n = 67)	0.51 (0.22–1.19)	0.12	0.47 (0.18–1.22)	0.13
50–59 (n = 85)	0.82 (0.39–1.73)	0.61	0.74 (0.31–1.77)	0.50
60–69 (n = 24)	2.00 (0.75–5.32)	0.17	3.81 (1.17–12.45)	0.03
Observation time				
4–10 years (n = 63)	Ref			
11–20 years (n = 122)	1.58 (0.75–3.32)	0.23		
21–28 years (n = 48)	2.33 (0.98–5.53)	0.06		
Stage				
I/II A (n = 106)	Ref			
I/II B (n = 26)	1.83 (0.74–4.51)	0.19		
III/IV A (n = 54)	0.75 (0.34–1.66)	0.47		
III/IV B (n = 41)	1.21 (0.54–2.70)	0.64		
B symptoms at diagnosis				
No (n = 160)	Ref			
Yes (n = 67)	1.57 (0.84–2.94)	0.16		
Relapse				
No (n = 185)	Ref			
Yes (n = 48)	1.51 (0.76–3.00)	0.24		
Gonadal function				
Normal (n = 111)	Ref	0.		
Elevated FSH only (n = 45)	1.40 (0.64–3.06)	40		
Primary hypogonadism (n = 35)	1.58 (0.68–3.66)	0.29		
Secondary hypogonadism (n = 42)	1.54 (0.69–3.40)	0.28		
Thyroid function				
Normal (n = 174)	Ref			
Latent hypothyroidism (n = 59)	1.61 (0.85–3.06)	0.15		
Treatment				
Radiotherapy only (n = 32)	0.95 (0.37–2.41)	0.91		
Chemotherapy only (n = 51)	1.30 (0.64–2.61)	0.47		
Radiotherapy + chemotherapy (n = 150)	Ref			
HADS total score (–D4)	1.19 (1.12–1.27)	< 0.001	1.2 (1.13–1.28)	< 0.001
Comorbidity				
No (n = 171)	Ref			
Yes (n = 62)	0.89 (0.46–1.72)	0.91		
BMI				
< 25 (n = 84)	Ref			
≥ 25 (n = 137)	0.77 (0.42–1.40)	0.38		
Education				
≤ 12 years (n = 126)	Ref			
≥ 13 years (n = 102)	0.84 (0.47–1.53)	0.58		
Relationship status				
In paired relation (n = 179)	Ref			
Not in paired relation (n = 50)	1.44 (0.73–2.86)	0.29		

hypothyroidism was not very strong with the p-value being 0.042. This suggests that fatigue among male lymphoma survivors in general is not solely explained by latent hypothyroidism. More detailed analyses on the impact of hypothyroidism on fatigue could be interesting to perform, such as if the impact varies between the lymphoma groups, and the impact of substitution therapy on fatigue over time. However, our data are not sufficient to explore this.

It is known that fatigue/tiredness might be a symptom of overt hypothyroidism [25]. Although the symptoms of latent hypothyroidism are less well studied, tiredness has been reported as a symptom in one large population-based study [26]. However, Grabe et al. found no increase of fatigue in subjects with latent or even overt hypo- or hyperthyroidism in another population-based study [27]. Also, clinical benefits of thyroxine substitution in subject with

Table V. Linear regression analyses with Physical functioning, Role physical, Social functioning and Role emotional as the dependent variable, chronic fatigue and age at survey as independent variables.

	Median (range)	Mean (SD)	B	β	p-Value
Physical functioning					
Chronic fatigue			Ref	Ref	
No	95.0 (25–100)	90.8 (13.7)	−14.42	−0.36	< 0.001
Yes	80.0 (5–100)	75.4 (21.8)	−0.47	−0.28	< 0.001
Age at survey (cont)					
Role physical[a]					
Chronic fatigue			Ref	Ref	
No	100.0 (0–100)	81.5 (34.4)	−42.73	−0.46	< 0.001
Yes	25.0 (0–100)	37.5 (41.2)	−0.62	−0.15	0.008
Age at survey (cont)					
Social functioning					
Chronic fatigue			Ref	Ref	
No	100.0 (25–100)	91.0 (16.2)	−24.77	−0.48	< 0.001
Yes	75.0 (0–100)	66.1 (27.6)	−0.07	−0.03	0.61
Age at survey (cont)					
Role emotional[b]					
Chronic fatigue			Ref	Ref	
No	100 (0–100)	92.9 (21.2)	−31.5	−0.43	< 0.001
Yes	100 (0–100)	61.8 (44.7)	0.19	0.061	0.31
Age at survey (cont)					

[a]Role physical: limitations in daily activities because of physical health problems; [b]Role emotional: limitations in daily activities because of emotional problems.

latent hypothyroidism have been difficult to demonstrate [28]. Elevated TSH levels have been shown to be associated with increased risk for thyroid carcinoma [29] and often precede overt hypothyroidism [30]. Based on this and on our data we think even though the conflicting effects of thyroxine treatment in subjects with latent hypothyroidism, that thyroxine treatment should be considered for fatigued lymphoma survivors with persistent elevated TSH if no contraindications exist. However, the symptomatic effect has to be evaluated.

There was a significant association between primary hypogonadism and levels of fatigue in univariate analysis, but this was not confirmed in the multivariate model, and we did not find association between gonadal function and chronic fatigue. This is similar to a previous report comparing male lymphoma or leukemia survivors with mild Leydig cell deficiency to a group with normal gonadal function [12]. In contrast, another study found higher levels of fatigue among young male cancer survivors mainly treated for lymphoma or germ cell tumors with low (testosterone $\leq$ 10 nmol/L) versus normal testosterone levels (testosterone $>$ 10 nmol/L) [11]. This discrepancy might reflect the individual variations regarding at what level testosterone deficiency results in clinical symptoms [31]. However, fatigue is shown to be related to testosterone levels in the general population [32]. In addition, there are methodological differences as these studies have used other questionnaires for assessment of fatigue. Testosterone levels show a diurnal variation with highest level in the morning and therefore blood sampling was generally performed in the morning in our study. Also in the study by Bjerner et al., which is the basis for our reference values, 75% of the blood sampling was performed before 9 a.m. in the morning [20]. We could not find any significant association between secondary hypogonadism and fatigue. This might be due to a more heterogeneous explanation for the low testosterone levels assessed in this group [15]. Even though the data among lymphoma survivors are conflicting, testosterone substitution might have symptomatic effect on fatigue and might be considered for fatigued male lymphoma survivors with persistent biochemical hypogonadism. However, data on the clinical effect of testosterone substitution for male cancer survivors are lacking.

The strong association between mental distress and fatigue is reported previously [8]. This finding emphasizes that also psychological factors contribute to fatigue among long-term lymphoma survivors and should be assessed in the evaluation of fatigue lymphoma survivors, as recently pointed out [33].

A recent review pointed to the importance of linking fatigue among cancer survivors to functional outcomes [14]. Our findings of negative associations between chronic fatigue, the functional scales of SF-36 and work situation underline the impact of fatigue on the affected survivors' daily functioning. Decreased quality of life among HL survivors compared to the general population, and in particular among the survivors with chronic fatigue has previously been reported by our group [34]. Other studies have shown that lymphoma survivors have reduced employment probability and difficulties in changing jobs [35,36]. In a prospective study including patients treated for various cancer types fatigue levels at six months from first day of sick leave predicted a prolonged sick leave period [37]. In total, these studies suggest that lymphoma survivors might be vulnerable regarding working ability due to late effects, especially in a hard labor marked.

The present study is restricted to male lymphoma survivors as this report is part of a broader follow-up study of males performed in 2007 [15,16]. Some previous studies have reported more fatigue among females than males, whereas other studies found no such relationship [3,7]. A similar association between latent hypothyroidism and fatigue and the lower prevalence of chronic fatigue among survivors after indolent NHL in females need to be confirmed.

Except for the increased risk for having chronic fatigue among males aged >60 years compared to the youngest age group, we found no significant associations between age and fatigue levels or prevalence of chronic fatigue. Compared to the previous report from our group among HL survivors [2], the total fatigue scores in the two samples is similar for the oldest age group (age >60 years at survey, total fatigue scores of 15.6 and 15.29, respectively). However, due to our sample size, the youngest age group in our sample included survivors from 21–39 years and presented a higher fatigue score than the youngest group in the study by Loge et al. (aged ≤ 29 years).

In this study analyses of both chronic fatigue and level of fatigue are included. Even though these two are correlated, the total fatigue score is, as a continuous variable, a more sensitive outcome compared to chronic fatigue which is a dichotomized variable. Other studies among lymphoma survivors have shown that there are changes in fatigue over time [5,13]. In addition, the hormone levels have only been assessed once, but might also fluctuate to some degree over time which makes analyses to level of fatigue more relevant than to chronic fatigue.

The present study includes multiple testing including a risk for type I error. However, as we consider this study to be hypothesis-generating, we preferred to keep the significance level at 0.05.

Altogether, the present study shows that fatigue is a frequent late effect among survivors after aggressive/very aggressive NHL. In the clinical evaluation of fatigued lymphoma survivors both somatic and psychological factors should be explored. Hormonal dysfunctions might for some fatigued survivors be an etiological and adjustable factor of the fatigue. The negative impact of chronic fatigue on daily function and work status emphasizes the importance of maintaining the effort in understanding the mechanisms leading to chronic fatigue to better prevent or treat this condition.

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