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The course of self-perceived cognitive functioning among patients with lymphoma and the co-occurrence with fatigue and psychological distress

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Abstract

Purpose To investigate the proportion of patients with lymphoma with persistent clinically relevant cognitive impairment, and its relation to treatment, fatigue, and psychological distress.

Methods Patients with diffuse-large-B-cell-lymphoma (DLBCL), follicular-lymphoma (FL), and chronic-lymphocytic-leukemia (CLL)/small-lymphocytic-lymphoma (SLL), diagnosed between 2004–2010 or 2015–2019, were followed up to 8 years post-diagnosis. Sociodemographic and clinical data were obtained from the Netherlands Cancer Registry and the Population-based HAematological Registry for Observational Studies. The EORTC QLQ-C30 was used to assess cognitive functioning and fatigue, and the HADS to assess psychological distress. Individual growth curve models were performed. Results were compared with an age- and sex-matched normative population.

Results A total of 924 patients were included (70% response rate). Persistent cognitive impairment was twice as high in patients (30%) compared to the normative population (15%). Additionally, 74% of patients reported co-occurring symptoms of persistent fatigue and/or psychological distress. Patients with FL (−23 points, $p < 0.001$) and CLL/SLL (−10 points, $p < 0.05$) reported clinically relevant deterioration of cognitive functioning, as did the normative population (FLnorm −5 points, DLBCLnorm −4 points, both $p < 0.05$). Younger age, higher fatigue, and/or psychological distress at inclusion were associated with worse cognitive functioning (all p's < 0.01). Treatment appeared less relevant.

Conclusion Almost one-third of patients with lymphoma report persistent cognitive impairment, remaining present up to 8 years post-diagnosis. Early onset and co-occurrence of symptoms highlight the need for clinicians to discuss symptoms with patients early.

Implications for Cancer Survivors Early recognition of cognitive impairment could increase timely referral to suitable supportive care (i.e., lifestyle interventions) and reduce (long-term) symptom burden.

Keywords Lymphoma · Cognition · Patient-reported outcome · Quality of life · Population-based registry

Introduction

About 20–40% of patients with lymphoma report self-perceived cognitive impairment [1, 2], including memory problems and inability to concentrate. These impairments can negatively affect patients' ability to function in daily activities and (return to) work [3, 4], and negatively impact patients' health-related quality of life (HRQoL) [5–7].

Several studies investigated the role of chemo-immunotherapeutic agents in relation to self-perceived and/or tested cognitive functioning among patients with lymphoma, with inconsistent results [7–9]. While some studies showed that higher doses of treatment resulted in worse cognitive functioning [9, 10], others showed no effect and/or demonstrated that cognitive impairment was related to factors of the cancer itself, fatigue and/or psychological distress [1, 2, 5, 6, 8, 11–13].

Large longitudinal studies of (long-term) cognitive functioning in a population-based setting among patients with

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lymphoma, including detailed treatment characteristics, are scarce [14]. So far, effects of cancer and cancer treatment on cognitive functioning have mostly been studied in relatively small samples of patients with lymphoma (i.e., maximum of 250 participants) [6, 8, 15, 16], or with a cross-sectional or short follow-up study design (i.e., maximum of 2 years after diagnosis) [1, 6, 12, 15–19]. No comparison with longitudinal changes in a normative population has previously been made to evaluate the unique effect of lymphoma and/or its treatment in addition to normal aging.

The aims of this study were (1) to identify the proportion of patients with persistent clinically relevant self-perceived cognitive impairment up to 8 years after diagnosis in a population-based setting, and (2) to study its association with treatment, and fatigue and/or psychological distress, and (3) to compare the results with an age- and sex matched normative population. We hypothesized that patients who underwent treatment with higher toxicity or a higher number of treatment lines or cycles, would have worse cognitive functioning. We furthermore expect that worse cognitive functioning will be strongly associated with fatigue and psychological distress, and that patients with lymphoma report worse cognitive functioning compared to a normative population.

Methods

Setting and population

Two longitudinal lymphoma cohorts from the PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship) registry were used and combined [20]. PROFILES is a registry investigating the physical and psychosocial impact of cancer and its treatment. PROFILES contains a large web-based component and is linked directly to clinical data from the population-based Netherlands Cancer Registry (NCR). Details of the data collection method have been previously described [20].

Both cohorts are embedded in the NCR, which was used to select patients diagnosed between 2004 and 2010 (cohort 1), and between 2015 and 2019 (cohort 2), with diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), chronic lymphocytic leukemia (CLL), or small lymphocytic lymphoma (SLL), as defined by the International Classification of Diseases for Oncology-3 codes (ICD-O-3) [21]. Patients with DLBCL, FL, and CLL/SLL were selected as these are the most common high-grade and low-grade types of non-Hodgkin lymphoma. Patients diagnosed during the time between these two cohorts could not be included, as they were not participating in a study of the PROFILES-registry. Patients 18 years and older at time of diagnosis were included. Patients who were deceased, in transition to terminal care, or who had severe cognitive impairment (i.e., dementia) were excluded.

Ethical approval for the study was obtained from a certified Medical Ethics Committee (Maxima Medical Centre in Veldhoven, the Netherlands; 0734).

Procedure

Patients were enrolled at different time points. In the first cohort, patients were included between May 2009 and July 2014. Patients diagnosed between January 2004 and January 2009 received the first questionnaire in May 2009. Each year newly diagnosed patients were subsequently invited to participate in this cohort until July 2014. All patients received yearly follow-up questionnaires starting from time of enrollment until the spring of 2019. The second cohort of patients was included between October 2015 and February 2019. Patients in this cohort were selected for participation 9–18 months after diagnosis and received follow-up questionnaires at 4, 12, and 24 months after inclusion. More details about the study design in this second cohort have previously been published [22].

Normative population

The normative population was selected from a reference cohort of 2040 individuals from the general Dutch population (CentER panel) [23]. This cohort is considered representative for the Dutch-speaking population in the Netherlands. Individual cases were matched based on age range (5 years below and 5 years above) and sex of each hematological malignancy (DLBCL, FL and CLL/SLL). Similar to patients with cancer, they received annual questionnaires between 2011–2015.

Study measures

Clinical data

The Population-based HAematological Registry for Observational Studies (PHAROS), an extension of the NCR, was used to retrieve detailed treatment information for patients diagnosed between 2004 and 2010. For patients diagnosed between 2015 and 2019, treatment information was embedded in the NCR.

If patients received more than one treatment line, the treatment category was based on the most toxic treatment prior to inclusion. Treatment categories per hematological malignancy are described in the Online Resource (Online Resource, Table 1). Additional clinical variables in the model were number of treatment lines, number of treatment cycles, stage of disease (Ann Arbor stage for DLBCL/FL and RAI for CLL/SLL), and time since diagnosis in years.

Questionnaires

Self-perceived cognitive functioning, hereafter referred to as "cognitive functioning," was measured using the cognitive functioning scale of the Dutch validated version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) [24, 25]. This scale consists of two items assessing inability to concentrate and memory problems. Fatigue was also assessed with the EORTC QLQ-C30. Evidence-based guidelines for interpretation of the EORTC QLQ-C30 were used to determine clinically important impaired cognitive functioning and fatigue [26], and clinically relevant changes in scores over time [27].

Psychological distress was assessed with the Hospital Anxiety and Depression Scale (HADS) [28]. A sum score was obtained by adding all items, with a higher score indicating more psychological distress [29]. Patients with a HADS sum score ≥ 13 were categorized as "psychologically distressed" [30]. The HADS was not included in the annual questionnaire among the normative population.

Comorbidity at the time of survey was categorized according to the adapted Self-administered Comorbidity Questionnaire (SCQ) [31]. Age, sex, marital status, and educational level were also assessed in the questionnaire.

Persistence of symptoms

For patients with at least two measurements, persistent symptoms were defined if more than half of their measurements were above the level of clinical importance [26]. For patients with two measurements, both scores had to be above the level of clinical importance. Patients with only one measurement were excluded from the analysis of persistent symptoms.

Statistical analyses

Statistical analyses were carried out using IBM SPSS Statistics for Windows, version 27 (IBM Corp., Armonk, N.Y., USA). Sociodemographic and clinical differences between respondents and non-respondents, and between respondents who completed one versus more than one questionnaire, were analyzed with a chi-square or t-test, where appropriate. p values of < 0.05 were considered statistically significant.

To assess the course of cognitive functioning, linear mixed model analyses were conducted. The rate of change (β) was calculated per year of survival [32]. Prior to analyzing the main effects of treatment, unconditional models were analyzed. Second, main effects of the a priori determined clinical (most toxic treatment regimen received before inclusion, comorbidities) and sociodemographic characteristics (age, sex, educational level, having a partner), as well as fatigue and psychological distress at inclusion, were included in the models. To ease interpretation of the results, age was centered by subtracting the mean age (DLBCL 65, FL 61 and CLL/SLL 67 years) [32]. To avoid overfitting, likelihood ratio tests were used to determine the inclusion of main effects for: stage of disease, number of treatment cycles and/or number of treatment lines, and interaction of main effects with time since diagnosis in years. The final model was obtained based on significant likelihood ratio tests and improved model fit based on a smaller Akaike information criterion (AIC) and Bayesian information criterion (BIC) value.

Analyses were carried out per hematological malignancy type (1) DLBCL, (2) FL, and (3) CLL/SLL.

Results

Characteristics of the study population

The study included 924 patients (70% response rate). Patients completed on average four measurements. At inclusion, mean age was 64.7 years, 62% were male and mean time since diagnosis was 2.1 years. Sixty-two percent reported one or more comorbid conditions, most frequently being high blood pressure (23%). Most patients had received one treatment line before inclusion (58%). Patients with DLBCL mostly received (R)-CHOP (84%; (R)-CHOP21 59% and (R)-CHOP14 25%), and patients with FL mostly received (R)-CVP (41%). Patients with CLL/SLL were mostly under active surveillance (61%) before inclusion (Table 1). Flow-charts of the data-collection in both cohorts are shown in Fig. 1.

The age- and sex-matched normative population ($N = 729$) had a mean age of 65.0 years at inclusion, 63% were male and 58% reported one or more comorbid conditions, most frequently being high blood pressure (29%).

Comparison between different groups of respondents of the questionnaires

Compared to respondents, non-respondents had a significantly shorter time since diagnosis. Non-respondents with DLBCL less often received "R-CHOP $14 > 6$ cycles" or "other chemo-immunotherapy," whereas non-respondents of FL or CLL/SLL were more often under active surveillance compared to respondents (data shown in Online Resource 2). Compared to patients who completed one questionnaire, patients with FL and CLL/SSL who completed more questionnaires were significantly more often higher educated. Patients with DLBCL who completed

Table 1 Characteristics of the study population at inclusion

Characteristic	Total cohort	DLBCL	FL	CLL/SLL	Normative population Total cohort	Normative population DLBCL	Normative population FL	Normative population CLL
	N = 924	*N* = 447	*N* = 210	*N* = 267	*N* = 729	*N* = 328	*N* = 187	*N* = 214
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Sex:								
Male	575 (62.2)	274 (61.3)	121 (57.6)	180 (67.4)	458 (62.8)	204 (62.2)	106 (56.7)	148 (69.2)
Female	349 (37.8)	173 (38.7)	89 (42.4)	87 (32.6)	271 (37.2)	124 (37.8)	81 (43.3)	66 (30.8)
Age: mean (SD)	64.7 (12.4)	64.7 (13.2)	61.3 (12.4)	67.5 (10.3)	65.0 (11.7)	64.4 (12.8)	61.0 (12.1)	66.7 (9.9)
Years since diagnosis: mean (SD)	2.1 (1.2)	2.1 (1.2)	2.1 (1.2)	2.2 (1.1)				
< 2 years	530 (57.4)	269 (60.2)	127 (60.5)	134 (50.2)				
2–5 years	364 (39.4)	166 (37.1)	76 (36.2)	122 (45.7)				
5–8 years	30 (3.2)	12 (2.7)	7 (3.3)	11 (4.1)				
Stage of the disease								
Ann Arbor/RAI		Ann Arbor	Ann Arbor	RAI				
I/0		123 (27.5)	49 (23.3)	83(31.1)				
II/1		100 (22.4)	32 (15.2)	37 (13.6)				
III/2		98 (21.9)	60 (28.6)	14 (5.2)				
IV/3		124 (27.7)	69 (32.9)	7 (2.6)				
/4				14 (5.2)				
Missing data	114 (12.3)	2 (0.4)	0 (0.0)	112 (41.9)				
Most toxic treatment before baseline QoL								
HDCT (+ SCT)	38 (4.1)	26 (5.8)	11 (5.2)	1 (0.4)				
(R)-CHOP14	119 (12.9)	110 (24.6)	5 (2.4)	4 (1.5)				
(R)-CHOP21	294 (31.8)	265 (59.3)	29 (13.8)	0 (0.0)				
(R)-CVP	122 (13.2)	3 (0.7)	86 (41.0)	33 (12.4)				
(R)-Chloorambucil	44 (4.8)	0 (0.0)	6 (2.9)	38 (14.2)				
Other CT[A]	61 (6.6)	31 (6.9)	5 (2.4)	25 (9.4)				
Radiotherapy	44 (4.8)	1 (0.2)	39 (18.6)	4 (1.5)				
Active surveillance/no treatment (yet)	195 (21.1)	4 (0.9)	29 (13.8)	162 (60.7)				
Missing data	7 (0.8)	7 (1.6)	0 (0.0)	0 (0.0)				
No. of chemo- immunotherapy treatment lines before baseline QoL questionnaire								
1 treatment line	539 (58.3)	365 (81.7)	105 (50.0)	69 (25.8)				
2 treatment lines	86 (9.3)	42 (9.4)	19 (9.0)	25 (9.4)				
≥ 3 treatment lines	33 (3.6)	14 (3.1)	12 (5.7)	7 (2.6)				
Active surveillance/radiotherapy mono	242 (26.2)	11 (2.5)	66 (31.4)	165 (61.8)				
Missing data	24 (2.6)	15 (3.4)	8 (3.8)	1 (0.4)				
No. of chemo- immunotherapy cycles before baseline QoL questionnaire: Mean (SD)	4.8 (6.0)	5.9 (2.4)	4.7 (4.4)	1.9 (3.1)				

Table 1 (continued)

Characteristic	Total cohort	DLBCL	FL	CLL/SLL	Normative population Total cohort	Normative population DLBCL	Normative population FL	Normative population CLL
	N = 924	*N* = 447	*N* = 210	*N* = 267	*N* = 729	*N* = 328	*N* = 187	*N* = 214
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
≤ 5 cycles	180 (26.4)	122 (28.0)	22 (15.3)	36 (35.3)				
6 cycles	172 (25.2)	121 (27.8)	27 (18.8)	24 (23.5)				
7–9 cycles	294 (43.1)	185 (42.4)	84 (58.3)	25 (24.5)				
> 9 cycles	8 (1.2)	1 (0.2)	4 (2.8)	3 (1.1)				
Maintenance treatment	3 (0.4)	0 (0.0)	2 (1.4)	1 (2.9)				
Missing data	25 (3.7)	8 (1.8)	4 (2.8)	13 (12.7)				
Radiotherapy before baseline QoL questionnaire (yes)	166 (18.0)	110 (24.6)	55 (26.2)	1 (0.4)				
Self reported comorbidity:								
No comorbidity	298 (32.3)	153 (34.2)	75 (35.7)	70 (26.2)	299 (41.0)	135 (41.2)	79 (42.2)	85 (39.7)
1 comorbidity	270 (29.2)	139 (31.1)	56 (26.7)	75 (28.1)	193 (26.5)	85 (25.9)	46 (24.6)	62 (29.0)
≥ 2 comorbidities	301 (32.6)	127 (28.4)	66 (31.4)	108 (40.4)	236 (32.4)	107 (32.6)	62 (33.2)	67 (31.3)
Missing data	55 (6.0)	28 (6.3)	13 (6.2)	14 (5.2)	1 (0.1)	1 (0.3)	0 (0.0)	0 (0.0)
Most frequent comorbidities:								
High blood pressure	216 (23.4)	101 (22.6)	47 (22.4)	68 (25.5)	209 (28.7)	91 (27.7)	52 (27.8)	66 (30.8)
Arthrosis	210 (22.7)	93 (20.8)	47 (22.4)	70 (26.2)	165 (22.6)	70 (21.3)	46 (24.6)	49 (22.9)
Heart diseases	165 (17.8)	82 (18.3)	30 (14.3)	53 (19.9)	114 (15.6)	51 (15.5)	33 (17.6)	30 (14.0)
Diabetes	95 (10.3)	35 (7.8)	23 (11.0)	37 (13.9)	60 (8.2)	31 (9.5)	13 (7.0)	16 (7.5)
Anemia	103 (11.1)	28 (6.3)	15 (7.1)	60 (22.5)	24 (3.3)	12 (3.7)	6 (3.2)	6 (2.8)
Educational level[B]:								
Low	126 (13.6)	57 (12.8)	25 (11.9)	44 (16.5)	32 (4.4)	15 (4.6)	6 (3.2)	11 (5.1)
Medium	519 (56.2)	252 (56.4)	118 (56.2)	149 (55.8)	373 (51.2)	160 (48.8)	102 (54.5)	111 (51.9)
High	253 (27.4)	126 (28.2)	57 (27.1)	70 (26.2)	320 (43.9)	151 (46.0)	78 (41.7)	91 (42.5)
Missing data	26 (2.8)	12 (2.7)	10 (4.8)	4 (1.5)	4 (0.5)	2 (0.6)	1 (0.5)	1 (0.5)
Partner (yes)	749 (81.1)	369 (82.6)	172 (81.9)	208 (77.9)	413 (56.7)	184 (56.1)	102 (54.5)	127 (59.3)

[A]Other chemo-immunotherapies consist of rituximab (mono), cyclofosfamide, fludarabine, vincristine, adriamycine, etoposide, mitoxantrone, methotrexaat, ifosfamide, dexamethason, (R)-PECC, R-DHAP, R-VIM, BEAM, alemtuzumab, cladribine, bendamustine, ofatumumab, zevalin, depocyte, interferon, pentostatin, OBL-FC. [B]Educational levels included low = no/primary school; medium = lower general secondary education/vocational training; or high = pre-university education/high vocational training/university

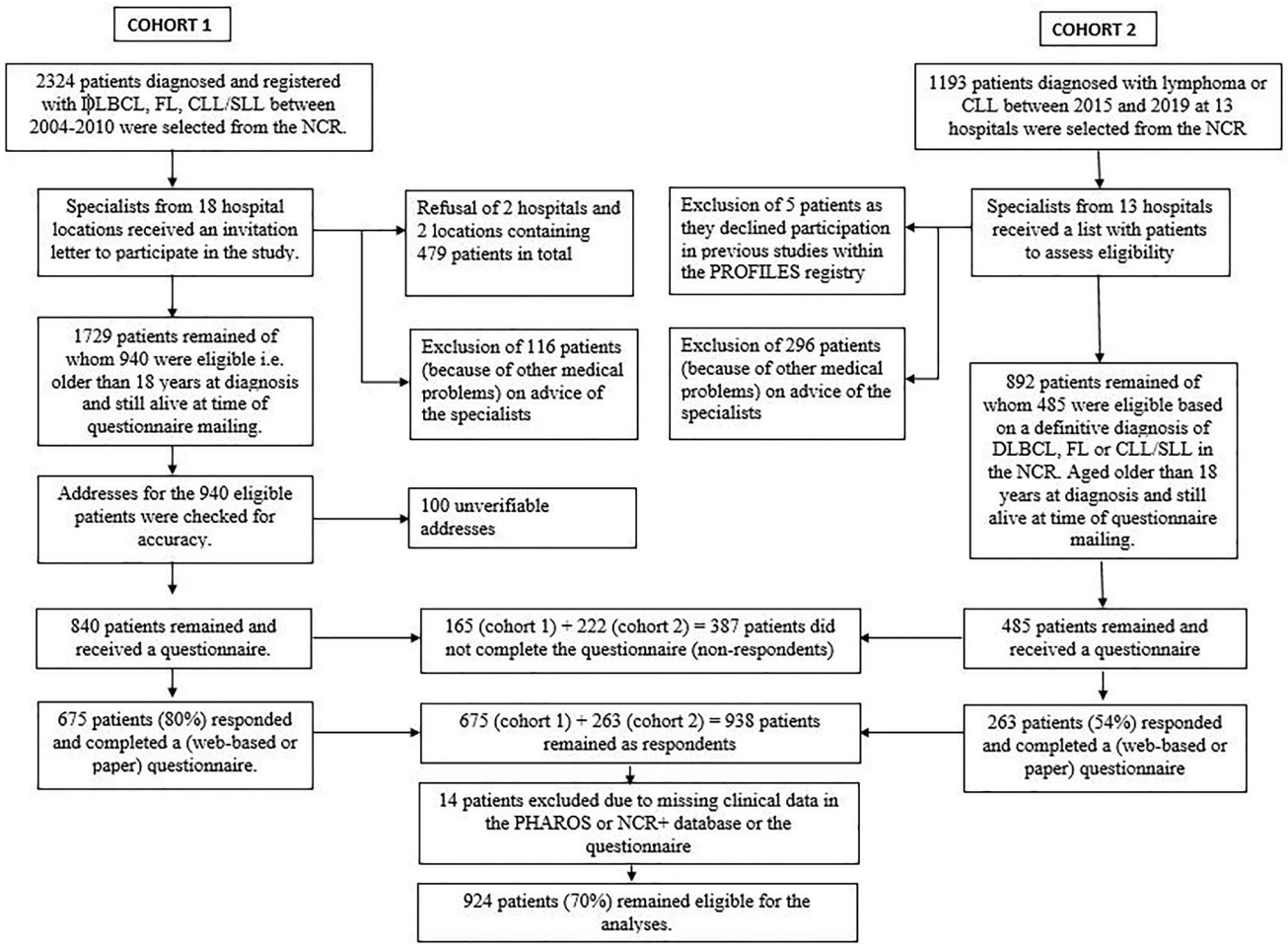


Fig. 1 Flowchart of the data collection

one questionnaire less often had a partner, and were more often psychologically distressed at inclusion (data shown in Online Resource 2).

Persistent cognitive impairment and the co-occurrence with fatigue and psychological distress

Of the total sample of patients who completed at least two measurements ($N=669$), 30% reported persistent cognitive impairment (DLBCL 30%, FL 33%, and CLL/SLL 26%). Among the normative population, 15% reported persistent cognitive impairment ($DLBCL_{norm}$ 14%, FL_{norm} 17%, and CLL/SLL_{norm} 14%).

Seventy-four percent ($N=147$) of patients with persistent cognitive impairment reported concurrent symptoms of persistent fatigue and/or persistent psychological distress: 23% in combination with persistent fatigue, 13% in combination with psychological distress, and 39% in combination with both persistent fatigue as well as persistent psychological distress (Fig. 2).

Fifty-three percent of all patients reported no persistent symptoms at all (DLBCL 56%, FL 46%, and CLL/SLL 54%).

The course of cognitive functioning

For patients with DLBCL and CLL/SLL, unconditional models showed that between 1 and 8 years after diagnosis, cognitive functioning scores remained relatively stable. For FL, a small clinically relevant deterioration (-6.8 points, $\beta=-0.90$ and $p<0.05$) was observed. Growth-curves for unconditional models are shown in Fig. 3.

Results of adjusted models are described in Table 2 (a full overview is reported in Online Resource , Tables 2, 3, 4).

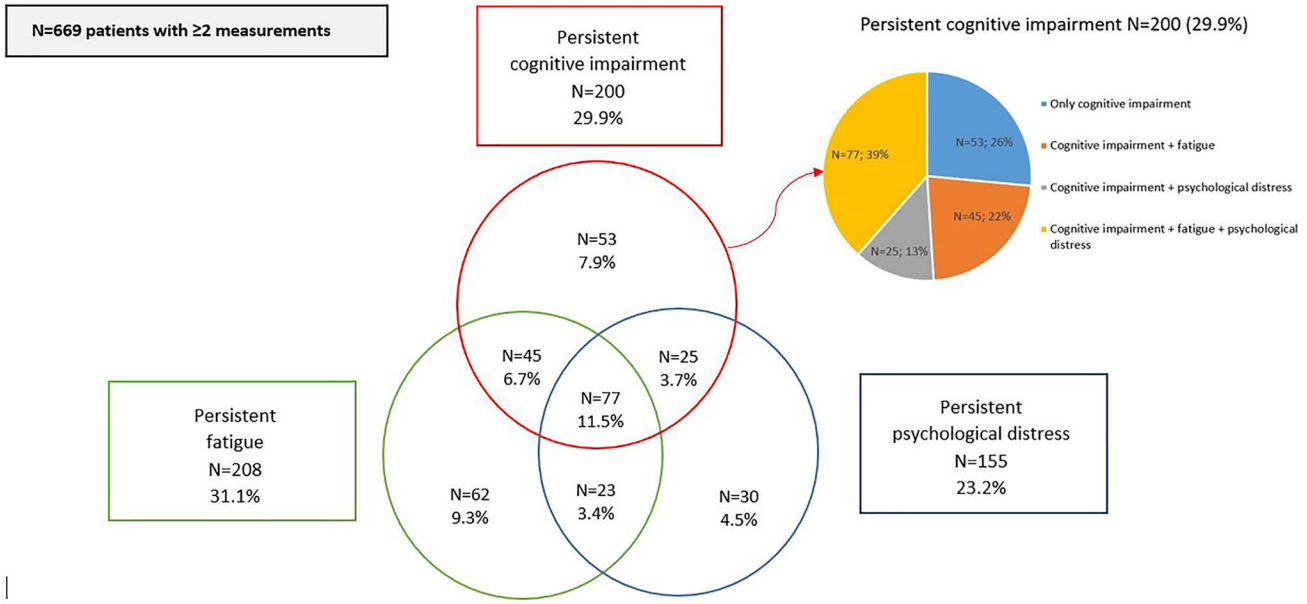


Fig. 2 Venn-diagram of the proportion of patients who reported persistent cognitive impairment, persistent fatigue and/or persistent psychological distress

DLBCL

Patients with DLBCL did not report any statistically significant or clinically relevant change of cognitive functioning over time. However, younger age ($\beta = 0.31$ and $p < 0.01$), having a partner ($\beta = -2.70$ and $p < 0.05$), two or more comorbidities ($\beta = -2.79$ and $p < 0.05$), higher fatigue at inclusion ($\beta = -0.26$ and $p < 0.001$), and/or more psychological distress at inclusion ($\beta = -0.96$ and $p < 0.001$) was associated with significantly worse cognitive functioning at inclusion. Over time, the negative impact of a younger age at inclusion diminished ($\beta = -0.06$ per year since diagnosis, $p < 0.01$).

FL

Patients with FL reported a statistically significant, and clinically relevant, deterioration of cognitive functioning over time of −22.6 points ($\beta = -2.82$ and $p < 0.001$). Cognitive functioning at inclusion was significantly worse for patients who had received more treatment cycles of chemo-immunotherapy ($\beta = -0.63$ and $p < 0.01$), and those who reported higher fatigue ($\beta = -0.29$ and $p < 0.001$), and/or more psychological distress ($\beta = -1.50$ and $p < 0.001$) at inclusion. Over time, the negative impact of psychological distress at inclusion diminished ($\beta = 0.15$ per year since diagnosis, $p < 0.05$).

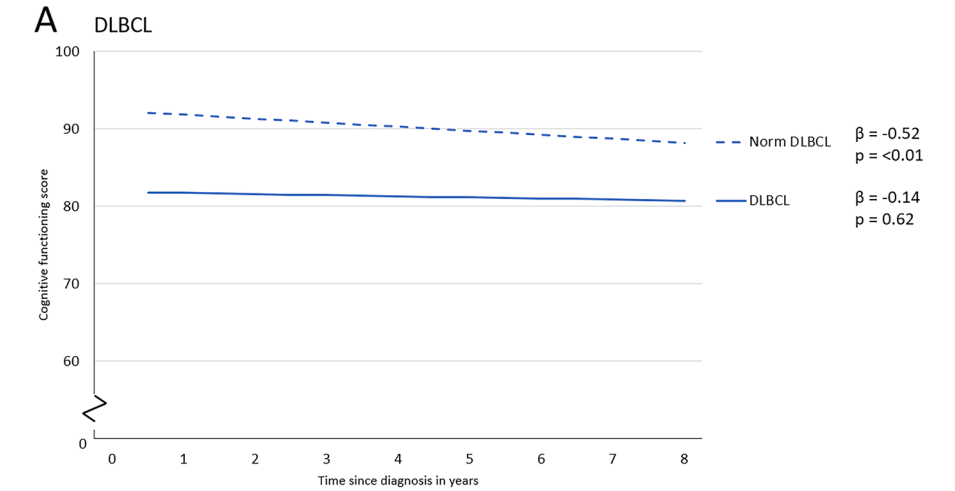
CLL/SLL

Patients with CLL/SLL reported a significant, and clinically relevant, deterioration of cognitive functioning over time of −10.1 points ($\beta = -1.26$ and $p < 0.05$). Among patients with CLL/SLL, men ($\beta = 3.91$ and $p < 0.05$), patients with a younger age ($\beta = 0.47$ and $p < 0.001$), a lower education ($\beta = 4.27$ and $p < 0.05$), higher fatigue at inclusion ($\beta = -0.46$ and $p < 0.001$), and/or more psychological distress at inclusion ($\beta = -0.44$ and $p < 0.001$) reported significantly worse cognitive functioning at inclusion. Over time, the negative impact of a younger age ($\beta = -0.09$ per year since diagnosis, $p < 0.05$), and higher fatigue at inclusion ($\beta = 0.03$ per year since diagnosis, $p < 0.05$) diminished.

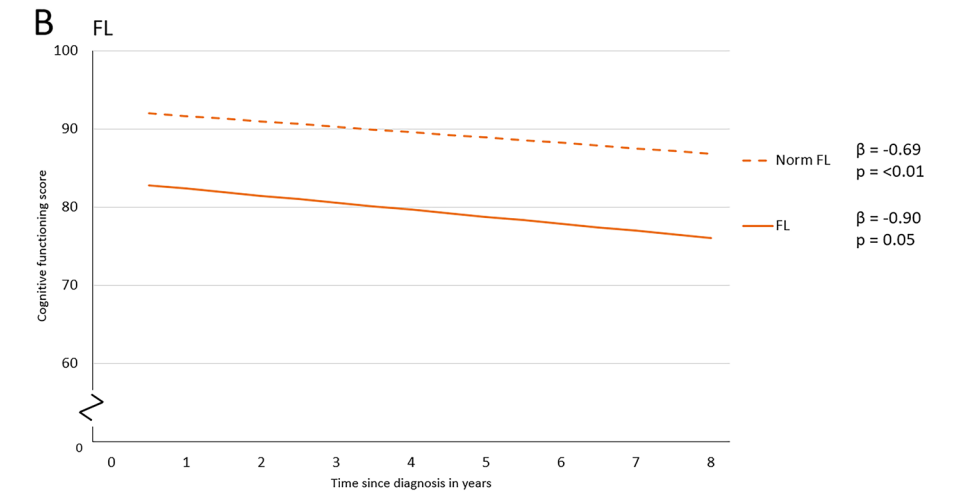
Comparison with the normative population

The normative population matched for FL and for DLBCL reported statistically significant and clinically relevant, deterioration of cognitive functioning over time (FL norm −4.8 points, $\beta_{normFL} = -0.60$, and $p < 0.05$. DLBCL norm −3.5 points, $\beta_{normDLBCL} = -0.44$, and $p < 0.05$).

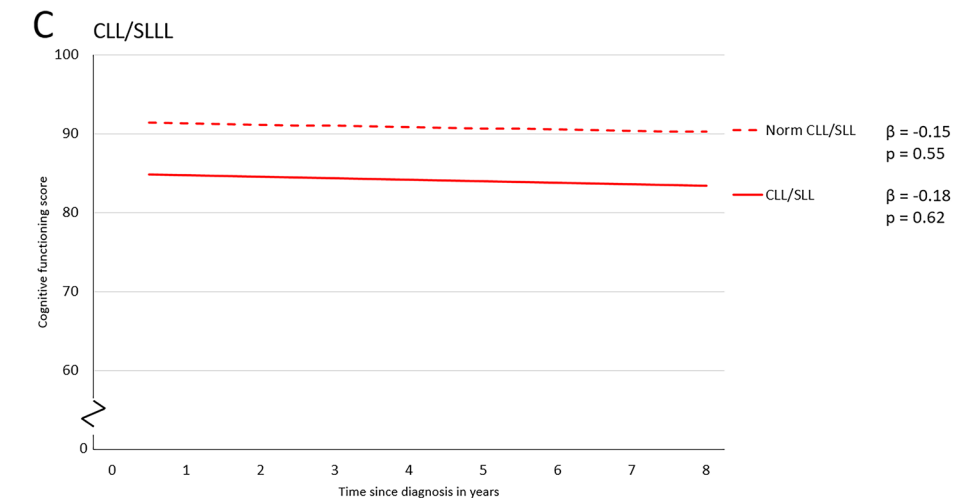
The score of cognitive functioning at inclusion, for patients with all types of lymphoma, is worse compared to the normative population. However, equally to patients, higher fatigue at inclusion in the normative population



T	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8
N DLBCL	57	363	326	194	135	107	90	88
N Norm DLBCL	34	171	228	235	220	177	93	41



T	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8
N FL	18	184	163	112	70	67	57	48
N Norm FL	16	108	137	132	128	99	45	22



T	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8
N CLL/SLL	23	186	220	127	88	73	53	49
N Norm CLL/SLL	16	100	152	158	138	121	66	31

Fig. 3 Unconditional growth curve of cognitive functioning per hematological malignancy and its comparison to the normative population

Table 2 Self-perceived cognitive functioning up to 8 years after diagnosis. Fixed effects of linear individual growth curve models

		DLBCL				FL				CLL/SLL			
		Final model patients		Final model normative population		Final model patients		Final model normative population		Final model patients		Final model normative population	
		N = 447		*N* = 328		*N* = 210		*N* = 187		*N* = 267		*N* = 214	
		Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Initial status		103.39***	3.41	93.93***	3.18	110.50***	5.71	98.27***	4.71	92.25***	3.32	89.91***	3.73
Linear growth: time since diagnosis in years		−0.18	0.27	−0.44*	0.22	−2.82***	0.78	−0.60*	0.30	−1.26*	0.49	−0.14	0.31
Sociodemographic variables													
Age (centered)		0.31**	0.10	−0.08	0.05	< −0.01	0.10	−0.12	0.07	0.47***	0.12	−0.25*	0.12
Sex (male = ref)		−0.50	1.64	0.46	1.28	−1.58	2.33	−1.22	1.70	3.91*	1.85	0.68	1.70
Education level	low	ref		ref		ref		ref		ref		ref	
	middle	0.98	1.87	2.88	2.85	4.76	3.19	3.11	4.58	4.27*	1.93	6.26	3.36
	high	−0.55	2.28	2.75	2.89	5.23	3.62	2.49	4.61	4.05	2.38	7.13*	3.38
	missing	−0.08	2.36	7.35	7.97	4.29	3.62	0.71	11.07	1.58	2.60	5.57	10.02
Partner (no = ref)		−2.70*	1.37	1.75	1.18	−3.61	2.13	−0.27	1.58	1.88	2.20	1.65	1.46
Age*Time since diagnosis in years[A]		−0.06**	0.02							−0.09*	0.04	0.05	0.03
Clinical variables													
Comorbidity	None	ref		ref		ref		ref		ref		ref	
	1	−1.63	1.27	−0.51	1.51	−1.47	2.13	−1.12	2.08	1.72	1.37	−1.70	1.79
	≥2	−2.79*	1.41	−1.29	1.55	−0.51	2.43	−2.45	2.18	−0.43	1.53	0.78	1.93
	missing	2.05	2.40	9.63	13.29	3.93	4.68	n/a	n/a	−1.03	2.41	n/a	n/a
Treatment regimen[B] DLBCL	(R) − CHOP21 < = 6cycles	ref											
	(R) − CHOP21 > 6cycles	0.58	2.06										
	(R) − CHOP14 < = 6cycles	2.46	2.79										
	(R) − CHOP14 > 6cycles	−1.69	2.34										
	HDCT(+SCT)	−2.33	5.48										
	Otherchemo − immunotherapy[C]	−4.84	3.00										
FL	WaitandSee/oth-erchemo − immunotherapy[D]					ref							
	Radiotherapy(mono)					−2.50	4.00						
	(R) − CVP/(R) − Chloorambucil					−2.32	3.65						
	RCHOP					−3.29	4.58						

Table 2 (continued)

		DLBCL				FL				CLL/SLL			
		Final model patients		Final model normative population		Final model patients		Final model normative population		Final model patients		Final model normative population	
		$N=447$		$N=328$		$N=210$		$N=187$		$N=267$		$N=214$	
		Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
CLL/SLL	WaitandSee/notherapy									ref			
	(R) – Chloorambucil									−4.06	2.84		
	Otherchemo – immunotherapy[E]									4.26	2.60		
Nr of treatment cycles[A]						−0.63**	0.21			0.02	0.14		
Nr of chemo-/immuno-therapy treatment lines[A]		−2.40	1.64			0.72	1.70			−1.91	1.51		
Nr of chemo-/immuno-therapy treatment lines*Time since diagnosis in years[A]						0.09	0.05						
Psychological variables													
Fatigue at first measurement		−0.26***	0.04	−0.29***	0.03	−0.29***	0.05	−0.38***	0.04	−0.46***	0.05	−0.37***	0.04
Psychological distress at first measurement		−0.96***	0.15			−1.50***	0.29			−0.45**	0.16		
Fatigue*Time since diagnosis in years[A]										0.03*	0.01		
Psychological distress*Time since diagnosis in years[A]						0.15*	0.07						
Fit statistics													
AIC		9562.41		9464.91		5169.56		5441.35		6300.63		6171.72	
BIC		9683.67		9546.65		5275.45		5509.69		6407.83		6246.67	

[A]Added based on significant likelihood ratiotest. [B]Patients might have received additional radiotherapy. [C]Other chemo-immunotherapies for DLBLC consist of (R)-CVP, (R)-chloorambucil, fludarabine, vincristine, adriamycine, etoposide, mitoxantrone, methotrexaat, ifosfamide, dexamethason, (R)-PECC, alemtuzumab, cladribine, bendamustine, ofatumumab, zevalin, depocyte. [D]Other chemo-immunotherapies for FL consist of interferon, FCR, rituximab (mono), cyclofosfamide, vincristine, adriamycine, etoposie, mitoxantrone, ifosfamide, dexamethason, methotrexaat, alemtuzumab, cladribine, bendamustatine, ofatumumab, zevalin, depocyte, (R)-PECC, R-DHAP, R-VIM, BEAM. [E]Other chemo-immunotherapies for CLL/SLL consist of (R)-CHOP, (R)-CVP, FCR, R-DHAP, rituximab (mono), alemtuzumab, bendamustine, cladribine, pentostatin, OBL-FC. *$p<0.05$, **$p<0.01$, ***$p<0.001$

was associated with worse cognitive functioning (DLBCL $\beta_{normDLBCL} = -0.29$ and $p < 0.001$. FL $\beta_{normFL} = -0.38$ and $p < 0.001$. CLL/SLL $\beta_{normCLL/SLL} = -0.37$ and $p < 0.001$). Among the normative population matched for CLL/SLL, significantly worse cognitive functioning at inclusion was also reported by participants with an older age ($\beta_{normCLL/SLL} = -0.24$ and $p < 0.05$) and/or a lower educational level ($\beta_{normCLL/SLL} = 7.13$ and $p < 0.05$). Additional associated characteristics that were observed among patients with lymphoma (i.e., sex, having a partner and/or comorbidities), were not associated with cognitive functioning in the normative population.

Discussion

This large population-based study showed that almost one-third of patients with lymphoma report persistent clinically relevant cognitive impairment, and almost three-quarter of these patients reported co-occurring symptoms of persistent fatigue and/or psychological distress. Treatment regimen seems to be less relevant in relation to cognitive functioning. The course over time is strongly associated with age and the presence of higher fatigue and/or more psychological distress at inclusion. Patients with FL and CLL/SLL reported a clinically relevant deterioration over time [27]. Similar rate of deterioration, and associations with non-clinical characteristics, were observed in the age- and sex-matched normative population.

The association between fatigue, psychological distress, and cognitive functioning was the most dominant and consistent factor among all groups, independent of cancer or its treatment. The co-occurrence of these symptoms might indicate the presence of a symptom cluster [33, 34].

Symptom clusters occur in various (mostly solid) types of cancer [34], as well as in patients with chronic diseases (i.e., long-COVID, chronic fatigue syndrome, or multiple sclerosis) [35, 36]. Although we hypothesized treatment toxicity to be associated with higher cognitive impairment, we did not observe that. Fatigue is one of the most central symptoms within a symptom network in patients with cancer, including lymphoma, and may play a driving role within this symptom cluster [37]. It might be that there are underlying mechanisms for these symptoms (i.e., higher inflammation levels, daily activity patterns, sleeping patterns, and/or diet) that need to be studied more extensively.

A growing number of research shows that symptoms tend to present early in hematological malignancies, and remain present for many years after diagnosis [11, 38, 39]. Identifying symptom onset and mapping symptom networks, in relation to clinically relevant cut-off points, is necessary to identify the patient population in need and to deliver more personalized (supportive) care for these patients [26, 40–43]. We therefore encourage clinicians to discuss symptoms of cognitive impairment, fatigue, and psychological distress with patients in the early stages of their disease. Awareness of the clustering of these symptoms and assessing the level and burden of them will improve early detection and symptom management [44, 45]. In addition, timely referral to supportive care (i.e., exercise or occupational therapy to manage energy and structure during the day) may prevent or slow down the worsening of symptoms [46–48].

Despite similarities in the course and co-occurrence of symptoms with age- and sex-matched counterparts, cognitive impairment is reported twice as much among patients with lymphoma. Younger FL patients also reported a larger negative impact on cognitive functioning compared to older DLBCL and CLL/SLL patients. Deterioration of cognitive functioning in younger patients may be related to the importance and necessity of cognitive functioning during the working life. At younger age, the effect of cognitive impairment most likely has a greater impact on daily life, working ability, and return to work [49]. As shown in the adjusted analyses, the difference in impact between younger and older patients diminished over time.

Several limitations of our study need to be acknowledged. First, as a result of including patients at different points in time after diagnosis, time since diagnosis at inclusion was not similar across all participants. Most patients had received one treatment line before inclusion. The cancer and its treatment might have already had an effect on symptoms such as fatigue or psychological distress at time of inclusion [11]. As a result of this, and based on the co-occurrence of symptoms, this may have led to an underestimation of the impact of treatment on cognitive functioning. Second, as patients were followed for a long time after diagnosis, we could only evaluate the longer-term outcomes of patients who survive, potentially introducing survivorship bias. As a result of this, and the fact that patients with poorer HRQoL drop out more often during follow-up, outcomes may represent the healthier patient, which may have led to an underestimation of the proportion of patients who experience cognitive impairment. A clinically relevant deterioration of cognitive functioning over time was not observed among patients with DLBCL. This might be because patients with DLBCL who dropped out after the first measurement reported significantly higher distress than patients who participated more than once. Also, treatment for DLBCL is relatively more often curative and/or of shorter duration, which may result in less distress and possibly fewer relapses/retreatment over time compared to FL and CLL/SLL. Survivorship bias in inevitable in longitudinal studies with patient-reported outcomes among cancer patients [50–52]. Third, cognitive functioning was measured with a 2-item subscale focusing only on concentration and memory. This may have led to an underestimation of patients reporting cognitive impairment. Future research

should include a scale that measures cognitive functioning in more detail.

Despite the limitations, the strengths of this study are its longitudinal population-based setting and the large number of participants in combination with the availability and use of detailed treatment information through the NCR and PHAROS. This rich amount of information allows for translating outcomes to the total population of patients with DLBCL, FL, and CLL/SLL.

In conclusion, one-third of patients with lymphoma report persistent cognitive impairment, remaining present up to 8 years after diagnosis. The co-occurrence with persistent fatigue and distress is substantial. Treatment regimen seems to be less relevant. Evidence for effective lifestyle interventions (i.e., exercising) is arising and is likely to be beneficial across outcomes of cognition, fatigue, and psychological distress [37, 46–48]. We encourage clinicians to discuss symptoms in the early stages of the disease. This will improve early detection and help to identify possible symptom clusters, allowing for the development of more tailored supportive care and treatment strategies for those in need.

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Data availability Since 2011, PROFILES registry data is freely available according to the FAIR (Findable, Accessible, Interoperable, Reusable) data principles for non-commercial (international) scientific research, subject only to privacy and confidentiality restrictions. Data is made available through Questacy (DDI 3.x XML) and can be accessed by our website (http://www.profilesregistry.nl). In order to arrange optimal long-term data warehousing and dissemination, we follow the quality guidelines that are formulated in the 'Data Seal of Approval' (http://www.datasealofapproval.org) document, developed by Data Archiving and Networked Services (DANS).

Declarations

Ethics approval Ethical approval for the study was obtained from a certified Medical Ethics Committee (Maxima Medical Centre in Veldhoven, the Netherlands; 0734).

Competing interests The authors declare no competing interests.

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