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ORIGINAL ARTICLE

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Reference values for the EORTC QLQ-C30 in patients with advanced stage Hodgkin lymphoma and in Hodgkin lymphoma survivors

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Abstract

Objectives: To provide reference values for the European Organisation for Treatment and Research of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) in advanced-stage Hodgkin lymphoma (HL) patients and 5-year HL survivors. The QLQ-C30 is the most widely used cancer-specific questionnaire to assess Health-Related Quality of Life (HRQoL).

Methods: The EORTC database was searched to identify HL RCTs in which patients' and survivors' HRQoL was assessed by the QLQ-C30. HRQoL mean scores were calculated and stratified by age and gender. Minimal important differences were used to assess the clinical relevance of the findings. Data from one RCT with HRQoL scores available at baseline (n = 343) and four RCTs with HRQoL scores available at follow-up (n = 1665) were analyzed.

Results: Patients reported worse HRQoL scores than survivors across most functioning scales and symptoms' scales. These scores varied as a function of gender but not age. Survivors' HRQoL reports were comparable to the ones of the general population.

Conclusions: These values provide an assessment framework for the comparison and interpretation of QLQ-C30 scores in advanced-stage HL. Our findings suggest that although HL patients' HRQoL scores are worse than the general population, HRQoL scores may normalize over long-term survival.

KEYWORDS

EORTC QLQ-C30, Hodgkin lymphoma - survivor, quality of life, reference values

Hugo Vachon and Justyna Mierzynska contributed equally to this work.

1 | BACKGROUND

Hodgkin lymphoma (HL) is a relatively rare malignancy located in the lymph nodes and the lymphatic system. Major advances in therapeutic approaches have made HL one of the most curable forms of cancer with a survival rate exceeding 80% in a relatively young patient group.[1,2] With increasing survival rates, patient-reported outcomes (PROs) become essential since they can inform whether the disease and treatment adversely impact patients' functioning, symptoms, and other health-related quality of life (HRQoL) issues.

Although HRQoL is increasingly recognized as an important outcome in cancer research[3] and care,[4] findings from HRQoL data are only relevant if they are interpreted in a clinically meaningful way.[5] Reference values address this need by providing information about HRQoL scores for specific cancer populations. Their value is recognized when designing randomized controlled trials (RCTs) and used as a benchmark for comparison and interpretation of cancer RCTs and interventions.[6]

The QLQ-C30 is one of the most commonly used PRO measures to assess HRQoL among cancer patients (eg,[7,8]). The QLQ-C30 includes 30 items, which are transformed into 15 scales according to a standardized scoring procedure.[9] The QLQ-C30 includes five functional scales (physical, role, emotional, cognitive, and social functioning); eight symptom scales or single items (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation and diarrhea); an item to assess financial difficulties; and one global health status scale (GHQ).[9] The main objective of this study was to establish the HRQoL reference values of HL patients and HL survivors using the QLQ-C30. Secondary objectives include comparing HRQoL scores among patients, survivors, and the general population normative data[110]. Finally, differences in reference values based on age and gender will be explored. When applicable, information regarding the clinical significance of the findings will be provided.

Summary Statements

1. This manuscript reports new reference values for the EORTC QLQ-C30 in patients with advanced-stage Hodgkin lymphoma and long-term Hodgkin lymphoma survivors.
2. The EORTC QLQ-C30 is one of the most widely used patient-reported outcome measures to assess quality of life in cancer research. Providing reference values is essential for interpreting the scores obtained through this measure in Hodgkin lymphoma patients and Hodgkin lymphoma survivors.
3. Reference values provide a framework for the interpretation and comparison of the EORTC QLQ-C30 scores in cancer clinical trials.

2 | METHODS

2.1 | Study selection

The EORTC database, which is a comprehensive database of all EORTC trials since 1977, was searched on March 2017 to select for trials including HL patients and survivors (Figure 1).

2.1.1 | Patients

The eligibility criteria for choosing the trials from the EORTC database were Phase II and III clinical trials with completed patient recruitment, involving HL patients for whom the baseline HRQoL was assessed using the EORTC QLQ-C30, version 3.0 (Appendix A), with a minimum sample size of 100.[2]

2.1.2 | Survivors

The eligibility criteria for choosing studies with HL survivors were studies that included HL patients treated in a Phase II and III EORTC clinical trial, and assessed HRQoL at long term using the EORTC QLQ-C30, version 3.0, with a minimum sample size of 200 (Table 1). In case several HRQoL assessments were available at follow-up, the most complete one was selected. If several fully completed assessments were available, then the most recent HRQoL assessment was used.

2.2 | Sample selection

2.2.1 | Patients

Eligibility criteria were as follows: histological diagnosis of HL (nodular lymphocyte predominant subtype of HL excluded), stage III or IV, previously untreated, International Prognostic Score ≥ 3, aged between 16 and 60, and WHO performance status between 0 and 2.

2.2.2 | Survivors

HL patients who participated in an EORTC trial and were alive after diagnosis and treatment of the disease ranging from 5 years onwards were considered as survivors.

2.3 | Data extraction

2.3.1 | Patients

HRQoL scores were collected at baseline. Baseline HRQoL assessment was defined as an assessment occurring 1 week before or after

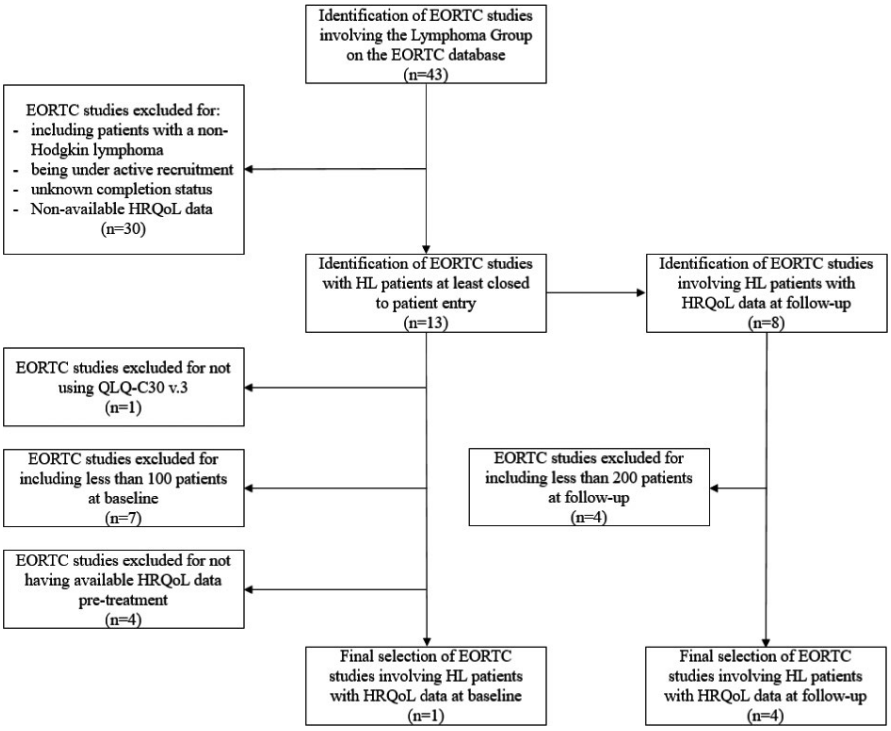

FIGURE 1 Flowchart of study inclusion protocol

randomization, and before treatment start. Sociodemographic and clinical data were collected.

2.3.2 | Survivors

HRQoL scores were collected at time of follow-up. Time at follow-up was defined as any assessment point after 5 years from diagnosis and treatment of disease. Sociodemographic and clinical data were also collected.

2.4 | Statistical analyses

Reference values are presented separately for patients and survivors, as well as a function of gender and age. To compare findings with the general population, the European general population norm data for the QLQ-C30 were extracted from Nolte et al.[10]

The scoring of the EORTC QLQ-C30 was performed according to the guidelines provided in the EORTC QLQ-C30 scoring manual.[11] Scale scores were calculated by averaging items within scales and by transforming linearly the average scores. A high scale score represents a higher response level. Thus, a higher score for a functional scale represents a better/healthier level of functioning, a higher score for the global health status/QoL represents a better QoL, but a higher score for symptom scale/item represents a more severe level of symptomatology/problems.[9] Findings were reported using mean scores and standard deviations. For the patients and survivors' reference values, proportions of responders reporting minimal and maximal scores were also reported. A threshold, derived from existing recommendations, was used to signify potential floor or ceiling effects,[12] where at least 15% of responders reporting the minimum score or the maximum score on a scale is considered a floor effect or a ceiling effect, respectively. Scoring of missing data from the QLQ-C30 was addressed according to the standard EORTC scoring manual.[11]

The interpretation of clinically meaningful important differences (MIDs) between scores was evaluated following Cocks et al's guidelines, where MIDs differed depending on the QLQ-C30 scales.[133] For each scale, MIDs were reported as the absolute difference between the HRQoL mean scores of a reference and a comparison sample (eg, patients vs survivors, male vs female), where the sign of the difference determined whether the reference sample reported higher (ie, Δ reference vs comparison = x) or lower (ie, Δ reference vs comparison=-x) HRQoL scores than the comparison sample.

Data preparation and statistical analyses were performed with SAS (version 9.4).[14]

3 | RESULTS

3.1 | Study selection

A search through the EORTC database (Figure 1) found five eligible EORTC phase III RCTs including HL patients with available HRQoL data: one RCT with HRQoL scores at baseline (HL patients)[15] and four RCTs with HRQoL scores at follow-up (HL survivors)[16-20] (Table 1). Ethics approvals were obtained for these trials from each local ethics committee, and patients were included in the trials if they provided written informed consent.

3.2 | Data extraction

Out of 550 HL patients from the available EORTC trial, 343 patients (62.4%) had valid baseline HRQoL assessment (HL patients). Maximum percentage of missing data for individual items were at 4.10% (item 28).

Out of 4798 HL patients from the four other EORTC trials, 1665 patients (34.7%) had a valid HRQoL assessment at follow-up (HL survivors). Maximum percentage of missing data for individual items were at 2.10% (item 27).

3.3 | Patient characteristics

Sociodemographic and clinical characteristics of patients at baseline and survivors at the time of follow-up are shown in Table 2.[4]

HL patients were fairly equally distributed across age categories (respectively, age < 25 = 29.2%, age[25-40] = 31.8%, and age > 40 = 39.1%) with a mean age of 36.1 (SD = 12.9), and were mostly male (75.5%). The majority of patients had extranodal disease (stage IV, 72.6%) with a WHO PS = 1 (48.7%) and had comorbidities (92.1%).

Most survivors were over 40 years of age (60.3%) with a mean age of 45.6 (12.2), and the sample was gender-balanced (female = 50.8%).

3.4 | Main findings

All of the scales and single-item measures of the EORTC QLQ-C30 range in score from 0 to 100. The reference values of HL patients and HL survivors for the QLQ-C30 are presented in Table 3.

3.4.1 | Patients

The highest mean score of the functional scales was for Cognitive Functioning (mean = 84.5, SD = 20.7) with 50.7% of patients reporting the maximum score. The lowest mean score was for Role Functioning (mean = 56.8, SD = 34.2) with 14.0% of patients reporting the minimum score.

Among all symptoms, the highest mean score was for Fatigue (mean = 50.0, SD = 27.2) with 8.2% of patients reporting the maximum score. The lowest mean score was for Diarrhea (mean = 9.2, SD = 20.0) with 78.4% of patients reporting the minimum score.

The Financial Difficulties score was 22.9 (SD = 33.7), and the GHQ mean score was 54.9 (SD = 23.1).

3.4.2 | Survivors

For the functional scales, the highest mean score was for Physical Functioning (mean = 87.3, SD = 16.8) with 41.9% of the survivors reporting the maximum score. The lowest mean score was for Emotional Functioning (mean = 76.0, SD = 24.1) with 1.6% of the survivors reporting the minimum score.

The highest mean level across symptoms was observed for Fatigue (mean = 29.9, SD = 26.5) with 3.1% of the survivors reporting the maximum score. The lowest mean score was for Nausea/Vomiting (mean = 3.8, SD = 11.6) with 85.6% of the survivors reporting the minimum score.

The Financial Difficulties score was 10.9 (SD = 24.9), and the GHQ mean score was 73.1 (SD = 20.5).

3.5 | Secondary findings

For the following comparisons, differences were only reported for MIDs defined as clinically significant (effect sizes ≥ small).[5]

3.5.1 | Comparison between HL patients, survivors, and general population

For the functional scales, patients reported lower mean scores than survivors and the general population for Physical Functioning, Role Functioning, and Social Functioning.

Across symptoms, patients reported higher levels than survivors and the general population for all symptoms but for Constipation and Diarrhea. Survivors reported lower mean scores than the general population for Pain.

For Financial Difficulties, patients reported higher scores than survivors and the general population.

For the GHQ, patients reported lower mean scores than survivors and the general population, whereas survivors reported higher mean scores than the general population.

3.5.2 | HRQoL of HL patients and survivors as a function of covariates

Age

Patients. For the functional scales, no consistent differences were observed across age categories.

Across the symptoms' scales, differences were observed for Constipation, which was higher in the older group while Insomnia was lower, whereas Appetite loss was higher in the younger group and Financial Difficulties and GHQ scores were similar across age categories.

Survivors. For the functional scales, Cognitive Functioning was consistently lower with age and Physical Functioning was lower in the older group. Role Functioning and Social Functioning were higher in the younger group.

For the symptoms' scales, Dyspnea and Insomnia were consistently higher with age, and all other symptoms, except Diarrhea, were lower in the younger group.

TABLE 1 Description of clinical trials included

Trial Numbers	Population	Disease stage	Population included in the trial/this RP (n)	Primary endpoint	QoL endpoint	Line of therapy	Median survival time
20 012 (BEACOPP) NCT00049595	Patients	Stage III/IV	549/343	Event-free survival	Secondary	BEACOPP versus ABVD	3.6 years (BEACOPP); 3.7 years (ABVD)
20 884 (H34) NCT00002462	Survivors	Stage IIIb/IV	739/242	Relapse-free survival and overall survival	Secondary	MOPP/ABV followed by no treatment or IFRT	7.7 years
20 881 (H7)	Survivors	Stage I/II supradiaphragmatic HL	831/253	Overall survival	Secondary	EBVP followed by IFRT versus STNI (favorable group) Or EBVP followed by IFRT versus MOPP/ABV hybrid + IFRT	6 years
20 931 (H8) NCT00379041	Survivors	Stage I/II supradiaphragmatic HL	1576/508	Failure-free survival and overall survival	Secondary	H8F: 3-MOPP/ABV + IFRT versus STNI. H8 U: 6-MOPP/ABV + IFRT versus 4-MOPP/ABV + IFRT versus 4-MOPP/ABV + STNI	7.8 years
20 982 (H9) NCT00005584	Survivors	Stage I/II supradiaphragmatic HL	1649/662	Failure-free survival and overall survival	Secondary	H9F: EBVP + IFRT versus EBVP followed with no adjuvant irradiation after chemotherapy. H9 U: 6-ABVD-IFRT versus 4-ABVD-IFRT versus BEACOPP-IFRT.	5 years

Abbreviations: ABV, chemotherapy regimen (adriamycin, bleomycin, vinblastine); ABVD, chemotherapy regimen (adriamycin, bleomycin vinblastine, dacarbazine); BEACOPP, chemotherapy regimen (bleomycin, etoposide, adriamycin, cyclophosphamide, oncovin, procarbazine, and prednisone); EBVP, chemotherapy regimen (epirubicin, bleomycin, vinblastine, and prednisone); IFRT, involved-field radiation therapy; MOPP, chemotherapy regimen (mustargen, oncovin, procarbazine, and prednisone); STNI, subtotal nodal irradiation.

TABLE 2 Sociodemographic and clinical characteristics of HL patients (baseline), HL survivors (follow-up), and the European general population normative data (GP)[a]

Sociodemographic and clinical characteristics	HL patients (n = 343)	HL survivors (n = 1665)	GP (n = 11 343)
	n (%)	n (%)	n (%)
Age			
Mean (SD)	36.1 (12.9)	45.6 (12.2)	53.6
Range	[16-60]	[24-84]	[18-99]
<25	100 (29.2)	9 (0.5)	/
[25-40]	109 (31.8)	652 (39.1)	/
>40	134 (39.1)	1004 (60.3)	/
Gender			
Male	259 (75.5)	819 (49.2)	5720 (50.4)
Female	84 (24.5)	846 (50.8)	5623 (49.6)
Disease stage			
III	94 (27.4)	/	/
IV	249 (72.6)	/	/
Comorbidity/other disease			
Absent	27 (7.9)	415 (24.9)	4204 (39.0)
Present	316 (92.1)	204 (12.2)	/
Missing	0 (0)	1046 (62.8)	486 (4.3)
WHO PS			
PS = 0	112 (32.7)	/	/
PS = 1	167 (48.7)	/	/
PS = 2[b]	64 (18.7)	/	/

[a]Data regarding GP are provided when available in Nolte et al 2019

[b]Only one patient reported a PS = 3 and was subsequently included in the PS = 2 group.

Financial difficulties scores were lower in the younger group.

GHQ mean scores were consistently lower with age increase (Table 4).

Gender[6]

Patients. For the functional scales, Cognitive Functioning and Social Functioning were lower in female patients.

Across symptoms, Fatigue and Appetite loss were higher in female patients.

Financial Difficulties scores and GHQ mean scores were higher in male patients.

Survivors. For the functional scales, no difference in mean scores was observed as a function of gender.

For the symptoms' scales, female survivors report higher scores for Fatigue, Insomnia, and Constipation.

Financial Difficulties scores and GHQ mean scores did not differ significantly as a function of gender (Table 5).

4 | DISCUSSION

Given the early incidence and improved survival rates of HL,[21] as well as the psychosocial burden and impact of this disease on the patients' daily life,[22] establishing a framework of comparison for the assessment of HRQoL in this clinical population is essential. This study provides reference values for the EORTC QLQ-C30 for patients with HL and survivors. These reference values are intended for regulators, clinicians, and researchers to a) perform comparisons with individual HL patients or groups with similar characteristics; b) increase familiarity with the distribution of QLQ-C30 scores in HL; and c) estimate the required sample size for future studies involving HL patients.[6] Furthermore, this study compares the HRQoL scores of HL patients with those of the survivors and the general population.[10]

4.1 | Main findings

Our findings corroborate previous research showing a deterioration of the quality of life of patients with HL.[22,23] Patients reported a low overall quality of life, reflected by an impaired functioning across most HRQoL subdomains and elevated symptomatic levels (Table 3). These results are in line with the report of a lower perceived physical functioning in cancer patients accompanied by an emotional distress and a deterioration of their role and social function in daily life.[23,24] These results also reflect the symptomatic

TABLE 3 Mean HRQoL scores (QLQ-C30) and proportions of floor/ceiling effects per domain for HL patients (n = 343), HL survivors (n = 1665), and European general population norm data (GP, n = 11 343)

	HL patients			HL survivors			GP
	Total	Floor effects	Ceiling effects	Total	Floor effects	Ceiling effects	Total
Domain	Mean (SD)	(%)	(%)	Mean (SD)	(%)	(%)	Mean (SD)
Function scales							
Physical function	77.3 (21.8)	0.3	22.7	87.3 (16.8)	0.1	41.9	85.1 (18.9)
Role function	56.8 (34.2)	14.0	23.6	85.5 (24.4)	2.4	64.6	84.3 (24.6)
Emotional function	66.5 (23.7)	2.0	8.7	76.0 (24.1)	1.6	27.7	74.2 (24.7)
Cognitive function	84.5 (20.7)	0.9	50.7	83.1 (21.9)	1.2	48.3	84.8 (21.3)
Social function	70.8 (30.2)	5.5	33.8	85.6 (23.7)	2.2	62.3	86.2 (24.1)
Symptom scales/items							
Fatigue	50.0 (27.2)	5.8	8.2	29.9 (26.5)	24.0	3.1	29.5 (25.5)
Nausea/vomiting	9.4 (17.6)	68.2	0.6	3.8 (11.6)	85.6	0.3	5.9 (16.0)
Pain	34.2 (32.2)	30.0	6.4	15.4 (24.7)	60.6	2.3	23.5 (27.1)
Dyspnea	32.0 (30.8)	37.0	7.3	18.3 (27.0)	60.7	4.0	15.9 (24.6)
Insomnia	49.4 (36.7)	22.7	25.1	26.0 (32.1)	51.3	8.0	26.6 (30.3)
Appetite loss	29.0 (33.1)	46.6	9.6	6.8 (18.0)	83.8	1.3	10.0 (21.6)
Constipation	15.4 (26.1)	67.3	4.1	10.8 (22.7)	76.2	2.4	12.5 (23.3)
Diarrhea	9.2 (20.0)	78.4	1.5	6.6 (17.5)	83.7	1.1	9.5 (20.9)
Financial difficulties	22.9 (33.7)	59.2	9.3	10.9 (24.9)	79.0	3.9	10.6 (23.6)
Global health/quality of life	54.9 (23.1)	2.0	5.2	73.1 (20.5)	0.3	15.4	66.1 (21.7)

landscape typically reported in this population, with worse scores for fatigue,[25] nausea,[26] dyspnea,[27] insomnia,[28] and pain.[29] On the contrary, the observation of a seemingly unaffected cognitive functioning may indicate that the long-term cognitive problems associated with the experience of HL or its related treatments[20] could be transitory[30] and/or affecting a minority of patients.[31] Alternatively, this finding may be driven by the larger proportion of early-stage HL patients included in the survivors' group and long-term cognitive deficits in patients with advanced-stage HL cannot be excluded.

HL survivors remain at increased risk for a variety of late effects after treatment,[32] which might negatively impact on their daily functioning and quality of life.[33] In line with identical observations in chronic lymphocytic leukemia survivors,[34] our results, however, did not support the potential long-term negative impact of HL on the survivors' quality of life. Indeed, no consistent clinically meaningful differences between the HRQoL scores of this group and the general population norm data were observed. This observation could support the idea that long-term cancer survivors, after all active treatment, experience a positive change in their view of life[35] or indicate a response shift[36] in the patients' reports. However, this finding should be interpreted cautiously as all HL patients included in the current study were diagnosed with advanced-stage HL and the majority of survivors (ie, 85.5%) with early-stage HL.

4.2 | Secondary findings

The secondary objectives of this study were to compare the HRQoL scores among HL patients, survivors, and the general population normative data and to explore the potential influence of age and gender on these HRQoL scores. Importantly, the use of MIDs allows for the interpretation of the clinical relevance of the observed between-group differences in HRQoL scores.

First, the comparisons between the HRQoL functioning scores of patients, survivors, and the general population support the main findings of this study. Patients reported clinically relevant lower GHQ and functioning across most HRQoL domains than survivors and the general population. As aforementioned, no clinically relevant differences were observed not only for the cognitive functioning domain, but also regarding emotional functioning despite seemingly large differences in HRQoL mean scores when compared to the other groups (Appendix C). However, the absence of well-defined minimal clinical important difference for this domain compelled the use of an arbitrary threshold, more conservative in comparison with the other MIDs used in this study,[13] which may have prevented the observation of relevant clinical differences. Regarding the HRQoL symptoms' scales, patients reported worse scores than survivors and the general European population across most scales. The effect of HL on the patients' HRQoL was large for GHQ and varying from small to moderate for the other domains (Appendix C).

TABLE 4 Mean HRQoL scores (QLQ-C30) per domain for HL patients and HL survivors stratified by age

	HL patients			HL survivors		
	Age < 25 (n = 100)	Age [25-40] (n = 109)	Age > 40 (n = 134)	Age < 25 (n = 9)	Age [25-40] (n = 652)	Age > 40 (n = 1004)
Domain	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Function scales						
Physical function	79.5 (20.0)	77.3 (23.8)	75.2 (21.2)	95.6 (7.5)	91.3 (14.4)	84.7 (17.8)
Role function	55.4 (33.3)	61.3 (34.7)	54.2 (34.4)	98.2 (5.6)	87.4 (23.3)	84.1 (25.1)
Emotional function	66.0 (24.0)	67.6 (22.9)	66.0 (24.3)	85.2 (27.3)	76.1 (24.1)	75.9 (24.0)
Cognitive function	86.0 (19.2)	84.4 (19.7)	83.5 (22.6)	92.6 (12.1)	85.8 (21.0)	81.3 (22.4)
Social function	72.2 (30.3)	69.1 (30.5)	71.2 (30.1)	96.3 (7.4)	86.8 (22.8)	84.7 (24.4)
Symptom scales/items						
Fatigue	51.8 (27.6)	47.8 (23.7)	50.4 (29.6)	19.8 (12.1)	30.0 (27.2)	29.9 (26.2)
Nausea/vomiting	10.3 (17.7)	8.9 (17.1)	9.2 (18.0)	0.0 (0.0)	3.9 (11.4)	3.8 (11.8)
Pain	35.3 (34.6)	31.8 (29.6)	35.3 (32.4)	5.6 (11.8)	12.4 (22.3)	17.5 (26.0)
Dyspnea	32.3 (31.0)	30.6 (30.3)	32.8 (31.1)	3.7 (11.1)	14.2 (23.8)	21.1 (28.6)
Insomnia	50.7 (36.5)	51.7 (37.5)	46.5 (36.1)	18.5 (17.6)	22.7 (31.0)	28.3 (32.8)
Appetite loss	35.3 (33.4)	25.0 (31.0)	27.6 (34.1)	0.0 (0.0)	6.7 (17.6)	7.0 (18.4)
Constipation	11.0 (21.2)	14.1 (25.4)	19.9 (29.4)	18.5 (24.2)	10.4 (23.2)	11.0 (22.3)
Diarrhea	9.3 (19.6)	9.2 (19.7)	9.1 (20.6)	7.4 (14.7)	6.1 (17.1)	6.9 (17.8)
Financial difficulties	22.0 (33.3)	24.4 (35.8)	22.3 (32.3)	0.0 (0.0)	6.1 (17.1)	6.9 (17.8)
Global health/quality of life	55.6 (23.2)	55.9 (23.4)	53.4 (22.9)	86.1 (11.8)	75.8 (19.7)	71.3 (20.9)

TABLE 5 Mean HRQoL scores (QLQ-C30) per domain for HL patients and HL survivors stratified by gender

	HL patients		HL survivors	
	Female (n = 84)	Male (n = 259)	Female (n = 846)	Male (n = 819)
Domain	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Function scales				
Physical function	74.7 (23.8)	78.1 (21.0)	85.0 (17.9)	89.7 (15.2)
Role function	58.5 (36.2)	56.3 (33.6)	82.7 (26.0)	88.3 (22.2)
Emotional function	62.2 (26.2)	67.9 (22.7)	72.8 (25.1)	79.4 (22.6)
Cognitive function	80.2 (23.1)	85.9 (19.7)	81.8 (22.9)	84.6 (20.8)
Social function	65.4 (33.9)	72.5 (28.8)	83.3 (25.4)	88.0 (21.7)
Symptom scales/items				
Fatigue	55.2 (28.7)	48.3 (26.6)	33.6 (26.9)	26.1 (25.9)
Nausea/vomiting	11.7 (20.8)	8.7 (16.4)	5.0 (13.1)	2.6 (9.7)
Pain	33.5 (31.7)	34.4 (32.4)	18.1 (26.4)	12.7 (22.5)
Dyspnea	31.7 (33.5)	32.0 (29.9)	20.2 (27.9)	16.3 (25.9)
Insomnia	47.6 (37.1)	49.9 (36.6)	30.3 (33.5)	21.6 (30.1)
Appetite loss	35.7 (35.4)	26.9 (32.1)	8.1 (19.2)	5.5 (16.7)
Constipation	14.7 (23.9)	15.7 (26.8)	15.6 (26.3)	6.0 (16.9)
Diarrhea	7.9 (19.8)	9.6 (20.1)	7.1 (18.3)	6.1 (16.6)
Financial difficulties	20.3 (32.7)	23.7 (34.0)	10.8 (24.8)	11.1 (25.1)
Global health/quality of life	50.6 (25.1)	56.3 (22.3)	71.2 (21.1)	75.2 (19.8)

Second, the comparison between survivors' HRQoL scores and the general population, informing the potential long-term effects on HRQoL of having experienced HL and the associated therapies, did not demonstrate consistent differences. Indeed, survivors reported similar scores across most HRQoL domains and worse pain levels but a better GHQ compared with the general population (Appendix C).

Finally, our results indicate consistent differences in HL patients' HRQoL as a function of gender but not age. Survivors' HRQoL differed by both covariates. The absence of difference in patients' HRQoL scores as a function of age is a result worth noting. Indeed, previous research reported reduced HRQoL levels as a function of age in hematological cancer patients.[37] However, this study[37] targeted the entire spectrum of hematological cancers and not only HL, which may underlie this discrepancy. On the contrary, older survivors systematically reported worse scores for most HRQoL functional domains and symptoms in the current study. Male patients reported a better GHQ than female patients, as expressed by reports of better functioning and less experience of fatigue and appetite loss. Male survivors also reported less severe fatigue, insomnia, and constipation than female survivors. These findings are in accordance with most studies investigating the potential effect of gender on HRQoL levels in HL patients,[20,38-40] demonstrating a larger deterioration of female patients' quality of life as compared to male patients.

4.3 | Limitations

This study was not without limitations. First, the high incidence of HL in young adults[21] and the very nature of survivors' samples induced an age imbalance between the two clinical groups being compared. Second, the patient group was exclusively composed by patients diagnosed with an advanced stage of HL, which might not be representative of patients with early-stage HL. Third, most survivors in the current study were diagnosed with an early-stage HL, which may overestimate HRQoL scores in survivors with more advanced HL forms. Fourth, a positive bias cannot be excluded in the survivors' group as individuals willing and able to participate to such follow-ups could be more likely biased toward a healthier quality of life.[41] Finally, the European general population normative data[10] are based on a sample that is not matched in age or gender with the sample of patients analyzed in the current study, which may have, to some extent, influence on the magnitude of the differences in HRQoL scores observed when comparing both samples.

5 | CONCLUSION

This study provides reference values for the EORTC QLQ-C30 for both patients with HL and survivors. The reference values reported here can enable valid comparisons for advanced-stage HL patients' and HL survivors' data, can guide HRQoL assessments, and support clinical decisions in this population. Our findings suggest that although HL patients' HRQoL scores are worse than the general population, HRQoL scores may normalize over long-term survival.

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DISCLOSURES

None.

AUTHOR CONTRIBUTION

Hugo Vachon and Justyna Mierzynska wrote the original draft, wrote, reviewed, and edited the manuscript, and performed visualization. Mekdes Taye, Corneel Coens, and Catherine Fortpied performed formal analysis and data curation, and wrote, reviewed, and edited the manuscript. Madeline Pe and Francesca Martinelli contributed to methodology, and wrote, reviewed, and edited the manuscript. Henning-Hans Flechtner, Maja Vestmoe Maraldo, Martin Hutchings, Paul Meijnders, Berthe Aleman, Pieternella Lugtenburg, Michele Spina, Marc André, Mark Hertzberg, and Javier Briones contributed to investigation and resources, and wrote, reviewed, and edited the manuscript. Andrew Bottomley contributed to conceptualization, methodology, writing, reviewing, and editing of the manuscript, supervision, and funding acquisition.

DATA AVAILABILITY STATEMENT

EORTC complies with the OECD Principles and Guidelines for Access to Research Data from Public Funding and with the National Institutes of Health Final Statement on Sharing Research Data released on February 26, 2003; it is committed to do so within the limits needed to guarantee the protection of personal data in accordance with the EU data protection rules and other applicable European legislation.

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ENDNOTES

[1] Further details are reported elsewhere (Nolte et al, 2019).

[2] This cutoff sample size was selected to prevent the potential biases related to the inclusion of datasets from prematurely closed trials.

[3] Such thresholds have not been defined for the Emotional Functioning scale in Cocks et al (2011). Following common practice, a 10-point difference was considered clinically meaningful for this subdomain.

[4] Not all clinical characteristics of HL survivors were assessed at the time of the follow-up. Data for GP were only provided when deemed comparable with the current study dataset.

[5] For more details, see Appendices C to E.

[6] Reference values stratified by age and gender are provided in Appendix B.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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