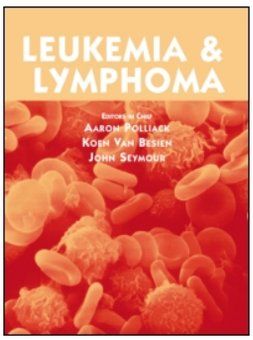

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ORIGINAL ARTICLE

Quality of life in adults with acute lymphoblastic leukemia in France: results from a French cross-sectional study

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ABSTRACT

In recent years, treatment of acute lymphoblastic leukemia (ALL) has improved substantially, leading to longer survival. This has necessitated a greater focus on health-related quality of life (HRQoL), but data are lacking. In a part-prospective, part-retrospective study, we enrolled 219 adults with ALL in France to assess the impact of key disease and treatment characteristics on HRQoL. Overall HRQoL and most specific QoL domain scores were consistently better among patients receiving front-line therapy, those currently in complete remission, and those who had previously received hematopoietic stem-cell transplantation. Furthermore, HRQoL was consistently impaired in patients with minimal residual disease present (MRD+). In multivariate analyses, multiple lines of therapy, MRD+, leukopenia, comorbidities, and anemia were significantly associated with impaired HRQoL. This study provides real-world data on HRQoL in adults with ALL in France and shows the positive impact of MRD-negative status on HRQoL.

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Acute lymphoblastic leukemia; health-related quality of life; minimal residual disease; real-world data

Introduction

Acute lymphoblastic leukemia (ALL) is a malignant clonal disorder of the bone marrow lymphopoietic precursor cells that is associated with varied hematologic disorders ranging from pancytopenia to hyperleukocytosis [1,2]. The diagnosis and classification of ALL are based on various techniques, including morphology, cytochemistry, cytogenetics, and molecular biology. In addition, immunophenotyping is essential for characterization of tumor and leukemic cells (also known as blast cells), allowing the cell lineage, maturation, and phenotypic aberrations to be identified [3]. Based on the lineage of the blasts, ALL can be classified into B-cell ALL (accounting for 75–85% of cases) and T-cell ALL [4,5]. Furthermore, ALL can be classified based on the presence of a Philadelphia chromosome (Ph+) (including patients with a *BCR-ABL* fusion transcript), which is associated with poor prognosis compared with absence of a Philadelphia chromosome (Ph–) [6] and so provides a guide to early treatment decisions. Around 15–36% of patients with ALL overall are Ph+, the percentage increasing with age from ~2% in young children to 18–50% in elderly individuals [5,7].

The annual incidence of ALL in France, is estimated at 1.6 per 100,000 men and 1.1 per 100,000 women [8]. In recent years, this incidence has remained stable overall, and has even slightly decreased in women. Around 60% of new cases of ALL are adults, although the incidence rate is highest in children <5 years of age. Beyond this age, incidence declines slowly until the mid-20s and then increases again in people >50 years of age.

Over the past 15 years, treatment of adults with ALL has greatly improved, with resultant increases observed both in rates of complete remission (CR) and CR with partial hematological recovery (CRh), and overall survival (OS) [4,9–12]. In particular, the use of allogenic hematopoietic stem-cell transplantation (HSCT) in front-line therapy has improved outcomes, independent of Ph status [4], while access to tyrosine kinase inhibitors, particularly imatinib, has dramatically

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Supplemental data for this article can be accessed here.

improved the prognosis of patients with Ph + ALL [12]. An important prognostic factor in ALL is the presence of minimal residual disease (MRD), defined as the presence of blasts >0.01% using polymerase chain reaction or flow cytometry in patients with CR/CRh [13]. The presence of MRD indicates resistance to standard chemotherapy and is the most important risk factor for hematologic relapse in adults and children with ALL [14,15]. For example, an analysis of ALL study groups across Europe ($n = 287$) found that both relapse-free and overall survival were significantly prolonged in patients negative for MRD compared with those in whom MRD was present [15], and this result was confirmed in a meta-analysis of 23 studies in patients with precursor B-cell acute lymphoblastic leukemia [16]. Assessment of MRD at diagnosis (for prognostic classification), and after induction and consolidation therapy (for treatment monitoring and detection of resistance) is therefore recommended in European guidelines for management of ALL [13].

The shift from palliative care to prolongation of response and, in some cases, even cure in adults with ALL [17] has meant that health-related quality of life (HRQoL) has become increasingly important. Data on HRQoL adults with ALL are, however, scarce. The primary objective of this study was to assess the HRQoL of adults with B-cell ALL, stratified by Ph status (Ph– vs. Ph+), treatment setting (front-line vs. salvage therapy), current treatment response (in CR or CRh vs. not in CR or CRh), and allogenic HSCT status (with prior HSCT vs. without prior HSCT). Secondary objectives included describing the demographic and clinical characteristics of patients with B-cell ALL by Ph status, treatment setting, current treatment response and allogeneic HSCT status. Exploratory objectives included the identification of factors affecting HRQoL in adults with ALL, and the assessment of HRQoL by MRD status (MRD + vs. MRD–) in patients with CR/CRh after front-line and/or salvage therapy.

Methods

Study design, patients and data collection

This was a non-interventional, multicenter cross-sectional study with retrospective chart data extraction and prospective collection of patient-reported outcomes, conducted in France between 30 March 2018 and 18 January 2019.

In total, 25 hemato-oncologists were selected based on an analysis of the French national hospital discharge database ('Programme de Médicalisation des Systèmes d'Information' [PMSI]) [18], taking into consideration center size and type, and regional quotas, to maximize the representativity of the study sample. Each participating investigator enrolled consecutive patients who met the eligibility criteria within the five pre-defined patient groups (see Analyses section below), based on individual center size. Eligible patients were adults (aged ≥18 years) with B-cell ALL, regardless of Ph status, treatment setting, current treatment response, and allogeneic HSCT status. Patients currently participating in a clinical trial were excluded. All patients provided written informed consent.

Demographic and clinical data were obtained retrospectively from patients' medical records. Prospectively, each patient completed a questionnaire that combined three HRQoL scales: the cancer-specific European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (QLQ-C30), the leukemia-specific Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu), and the generic EuroQoL 5-Dimension questionnaire 3-level version (EQ-5D-3L).

The QLQ-C30 questionnaire comprises both multi-item scales and single-item measures. These include five functional scales (Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, and Social Functioning), three symptom scales (Fatigue, Nausea/Vomiting, and Pain), a global health status (GHS)/QoL scale, and six single items (Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea, and Financial Difficulties) [19]. All the scales and single-item measures range in score from 0 to 100. High scores for the GHS/QoL scale and the functional scales represent a healthy level of QoL/functioning, whereas a high score for a symptom scale or single item represents a high level of symptomatology or other problems.

The FACT-Leu questionnaire uses a modular approach to assess HRQoL and leukemia-specific concerns, using a core set of questions suitable for any patient with cancer (FACT-General [FACT-G]) and a leukemia-specific subscale. For all FACT-Leu scales and subscales, higher scores indicate better HRQoL [20]. The FACT-G is a 27-item questionnaire scored on a five-point scale ranging from 0 (not at all) to 4 (very much) (overall range, 0–108). The items are divided into four primary HRQoL domains: Physical Wellbeing (seven items; range, 0–28), Social/Family Wellbeing (seven items; 0–28), Emotional Wellbeing (six items; 0–24), and Functional Wellbeing (seven items; 0–28). The Leukemia subscale is a 17-item scale (overall range, 0–68) designed to assess patient concerns

relating to leukemia. Combination of the FACT-G and leukemia subscale produces the FACT-Leu total score (overall range, 0–176). The FACT-Leukemia Trial Outcome Index (overall range, 0–124) is a summary scale composed of the Physical Wellbeing and Functional Wellbeing domains of the FACT-G, and the Leukemia subscale.

The EQ-5D-3L questionnaire can be used to calculate health state utility value using responses on a three-point scale covering five different dimensions of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [21]. Health state utility values range from 0 (death) to 1 (perfect health). The EQ-5D-3L also includes a 100-mm visual analog scale that reflects how patients position their health state compared with the best (100) and worst (0) health states they can imagine.

This study did not alter the clinical management of the patients, no clinic visits other than those routinely scheduled were required, and no procedures other than those connected with routine standard of care were performed. The study was approved by appropriate ethics committees according to French regulations.

Analyses

The planned sample size was 280 patients with B-cell ALL, comprising 70 patients in each of three predefined groups of patients with Ph- ALL (those in CR/CRh with prior HSCT, those in CR/CRh without prior HSCT, and those not in CR/CRh), and 35 patients in each of two predefined groups of patients with Ph + ALL (those in CR/CRh during their current or most recent treatment, and those not in CR/CRh). Precision estimates and associated sample sizes were calculated based on both the primary objective and the target patient population. Sample sizes of approximately 70 and 35 patients provide a half-width for the 95% confidence intervals around the mean FACT-Leu score estimate of $\leq$5.06 and $\leq$7.16, respectively.

Scoring guidelines for handling missing data were applied for the HRQoL scales [22,23]. Data were analyzed using descriptive statistics with Dasie software (version 2.4) for descriptive and bivariate analyses. Between-subgroup analyses were performed using the χ^2 test, Z-test, T-test, or analysis of variance, as appropriate. Multiple linear regressions were performed to determine the independent effect of factors associated with HRQoL, with backward-elimination selection used to identify the factors most predictive of overall HRQoL. The best models were identified as those that minimized the residual mean square, thereby maximizing the multiple correlation value, R^2. The variables eliminated first were those that contributed the least to the model. The threshold for statistical significance was 0.05 in all analyses.

An exploratory analysis of the impact of MRD status on QoL was conducted in patients who had data on MRD status at their most recent MRD test. An exploratory analysis of QoL in patients who had HSCT in the previous 12 months compared with those who had undergone HSCT less recently was also conducted.

Results

Patient characteristics

Of 234 patients approached to participate in the study, 219 were enrolled by 25 hemato-oncologists and included in the analysis, which comprised 59 Ph– patients in CR/CRh with prior HSCT, 67 Ph– patients in CR/CRh without prior HSCT, 42 Ph– patients not in CR/CRh, 38 Ph + patients in CR/CRh, and 13 Ph + patients not in CR/CRh. Overall, mean (standard deviation [SD]) age at inclusion was 55 (16.4) years, 61% of patients were men and 37% had previously received HSCT (Table 1). Almost half of patients had at least one comorbidity (46%), the most frequent being hypertension (27% of patients) and diabetes (16%). At least one MRD test was performed in 189 of the 219 patients (86%), comprising 126 of 140 patients currently receiving front-line therapy (90%) and 63 of 79 patients currently in salvage therapy (80%). The median time from the most recent MRD test to completing the study questionnaires ($n = 180$ patients with available data) was 1.7 months (range, 0–341 months), although 63 patients (35%) had a duration of $>$1 year between their most recent test and completion of the study questionnaires. Of these 189 patients, 151 of them (80%) had data on MRD status at their most recent MRD test and were included in the exploratory MRD analysis. Overall, patients had received a mean of four prior MRD tests. In patients who had previously received HSCT, the mean (SD) time since transplantation was 4.7 (7.4) years.

Baseline characteristics were generally well balanced between subgroups, although there were some exceptions (Table 1). For example, patients in CR/CRh were younger than those not in CR/CRh, and patients who had previously received HSCT were younger, with a longer time since diagnosis, than those who had not previously received HSCT ($p < .05$ for all comparisons). Patients with Ph + status had a shorter time since diagnosis than Ph– patients. Patients were more likely to have an Eastern Cooperative Oncology Group

Table 1. Current baseline characteristics in the pre-specified subgroups and the exploratory analysis based on MRD status.

		Pre-specified subgroups								Exploratory analysis	
		Ph status		Treatment line		Current response		Prior HSCT		Last MRD status	
	Total ($N = 219$)	Ph– ($n = 168$)	Ph+ ($n = 51$)	Front-line ($n = 140$)	Salvage ($n = 79$)	CR/CRh ($n = 164$)	Non-CR/CRh ($n = 55$)	Yes ($n = 80$)	No ($n = 139$)	MRD+ ($n = 28$)	MRD– ($n = 123$)
Age (years), mean (SD)											
At inclusion	55.0 (16.4)	55.7 (16.6)	52.5 (15.5)	53.5 (16.5)	57.7 (15.8)	51.8 (16.0)	64.6 (13.4)*	48.0 (13.0)	59.0 (16.8)†	55.1 (16.4)	51.5 (16.0)
At diagnosis	50.8 (18.1)	51.1 (18.6)	50.0 (16.2)	49.3 (17.8)	53.6 (18.4)	46.5 (17.3)	63.7 (13.8)*	42.1 (14.8)	55.9 (17.9)†	52.3 (19.7)	47.6 (17.3)
Sex, n (%)											
Male	133 (60.7)	102 (60.7)	31 (60.8)	84 (60.0)	49 (62.0)	99 (60.4)	34 (61.8)	48 (60.0)	85 (61.2)	17 (60.7)	76 (61.8)
Female	86 (39.3)	66 (39.3)	20 (39.2)	56 (40.0)	30 (38.0)	65 (39.6)	21 (38.2)	32 (40.0)	54 (38.8)	11 (39.3)	47 (38.2)
Time since diagnosis (years), mean (SD)	4.2 (6.4)	4.7 (7.0)	2.3 (3.2)‡	4.3 (6.7)	3.9 (5.9)	5.2 (7.1)	1.1 (1.3)*	6.0 (7.4)	3.1 (5.5)†	3.0 (5.3)	3.8 (4.1)
ECOG PS at inclusion											
0–1	176 (80.4)	137 (81.5)	39 (76.5)	128 (91.4)	48 (60.8)¶	151 (92.1)	25 (45.5)*	72 (90.0)	104 (74.8)†	20 (71.4)	113 (91.9)§
2	34 (15.5)	24 (14.3)	10 (19.6)	10 (7.1)	24 (30.4)¶	10 (6.1)	24 (43.6)*	5 (6.3)	29 (20.9)†	7 (25.0)	8 (6.5)§
3–4	9 (4.1)	7 (4.2)	2 (3.9)	2 (1.4)	7 (8.9)¶	3 (1.8)	6 (10.9)*	3 (3.8)	6 (4.3)	1 (3.6)	2 (1.6)
Comorbidities											
Yes	101 (46.1)	70 (41.7)	31 (60.8)‡	60 (42.9)	41 (51.9)	71 (43.3)	30 (54.5)	29 (36.3)	72 (51.8)†	14 (50.0)	55 (44.7)
No	116 (53.0)	96 (57.1)	20 (39.2)‡	79 (56.4)	37 (46.8)	92 (56.1)	24 (43.6)	51 (63.8)	65 (46.8)†	14 (50.0)	67 (54.5)
Unknown	2 (0.9)	2 (1.2)	0	1 (0.7)	1 (1.3)	1 (0.6)	1 (1.8)	0	2 (1.4)	0	1 (0.8)
Time since stopping treatment, n (%)											
Currently receiving treatment	112 (51.1)	73 (43.5)	39 (76.5)‡	63 (45.0)	49 (62.0)¶	62 (37.8)	50 (90.9)*	21 (26.3)	91 (65.5)†	19 (67.9)	52 (42.3)§
<6 months	5 (2.3)	5 (3.0)	0 (0)	2 (1.4)	3 (3.8)	2 (1.2)	3 (5.5)	2 (2.5)	3 (2.2)	(7.1)	2 (1.6)
6–12 months	16 (7.3)	14 (8.3)	2 (3.9)	12 (8.6)	4 (5.0)	16 (9.8)	0 (0)	9 (11.3)	7 (5.0)	1 (3.6)	13 (10.6)
12–24 months	26 (11.9)	25 (14.9)	1 (2.0)‡	15 (10.7)	11 (13.9)	26 (9.8)	0 (0)	18 (22.5)	8 (5.8)†	2 (7.1)	17 (13.8)
>24 months	55 (25.1)	49 (29.2)	6 (11.8)‡	44 (31.4)	11 (13.9)¶	55 (33.5)	0 (0)	29 (36.3)	26 (18.7)†	4 (14.3)	37 (30.0)
No data	5 (2.3)	2 (1.2)	3 (5.9)	4 (2.9)	1 (1.3)	3 (1.8)	2 (3.6)	1 (1.3)	4 (2.9)	0	2 (1.6)
Therapy line											
Front-line	140 (63.9)	101 (60.1)	39 (76.5)‡	140 (100)	0 (0)	127 (77.4)	13 (23.6)*	49 (61.3)	91 (65.5)	17 (60.7)	101 (82.1)§
1st salvage therapy	63 (28.8)	54 (32.1)	9 (17.6)‡	0 (0)	63 (79.7)	29 (17.7)	34 (61.8)*	22 (27.5)	41 (29.5)	7 (25.0)	17 (13.8)
2nd salvage therapy	16 (7.3)	13 (7.7)	3 (5.9)	0 (0)	16 (20.3)	8 (4.9)	8 (14.5)	9 (11.3)	7 (5.0)	4 (14.3)	5 (4.1)§
Response status											
CR/CRh	164 (74.9)	126 (75.0)	38 (74.5)	127 (90.7)	37 (46.8)¶	164 (100)	0 (0)	75 (93.8)	89 (64.0)†	14 (50.0)	121 (98.4)§
Non-CR/CRh	55 (25.1)	42 (25.0)	13 (25.5)	13 (9.3)	42 (53.2)¶	0 (0)	55 (100)	5 (6.3)	50 (36.0)†	14 (50.0)	2 (1.6)§
Prior HSCT											
Yes	80 (36.5)	59 (35.1)	21 (41.2)	49 (35.0)	31 (39.2)	75 (45.7)	5 (9.1)*	80 (100)	–	13 (46.4)	47 (38.2)
No	139 (63.5)	109 (64.9)	30 (58.8)	91 (65.0)	48 (60.8)	89 (54.3)	50 (90.9)*	–	139 (100)	15 (53.6)	76 (61.8)
Ph status											
Ph+	51 (23.3)	0 (0)	51 (100)	39 (27.9)	12 (15.2)¶	38 (23.2)	13 (23.6)	21 (26.3)	30 (21.6)	9 (32.1)	31 (25.2)
Ph–	168 (76.7)	168 (100)	0 (0)	101 (72.1)	67 (84.8)¶	126 (76.8)	42 (76.4)	59 (73.7)	109 (78.4)	19 (67.9)	92 (74.8)
Result of last MRD test during front-line therapy											
MRD+	57 (30.2)	40 (28.6)	17 (34.7)	17 (13.5)	40 (63.5)¶	19 (13.3)	38 (82.6)*	18 (26.1)	39 (32.5)	24 (85.7)	4 (3.4)§
MRD–	119 (63.0)	89 (63.6)	30 (61.2)	101 (80.2)	18 (28.6)¶	115 (80.4)	4 (8.7)*	46 (66.7)	73 (60.8)	3 (10.7)	112 (96.6)§
No answer	13 (6.9)	11 (7.9)	2 (4.1)	8 (6.3)	5 (7.9)	9 (6.3)	4 (8.7)	5 (7.2)	8 (6.7)	1 (3.6)	0 (0)

*$p < .05$ vs. CR/CRh; †$p < .05$ vs. prior HCST; ‡$p < .05$ vs. Ph + patients; ¶$p < .05$ vs. front-line therapy; §$p < .05$ vs. positive MRD status.

CR: complete remission; CRh: complete remission with partial hematological recovery; ECOG PS: Eastern Cooperative Oncology Group performance status; HSCT: hematopoietic stem cell transplant; MRD: minimal residual disease; Ph: Philadelphia chromosome; SD: standard deviation.

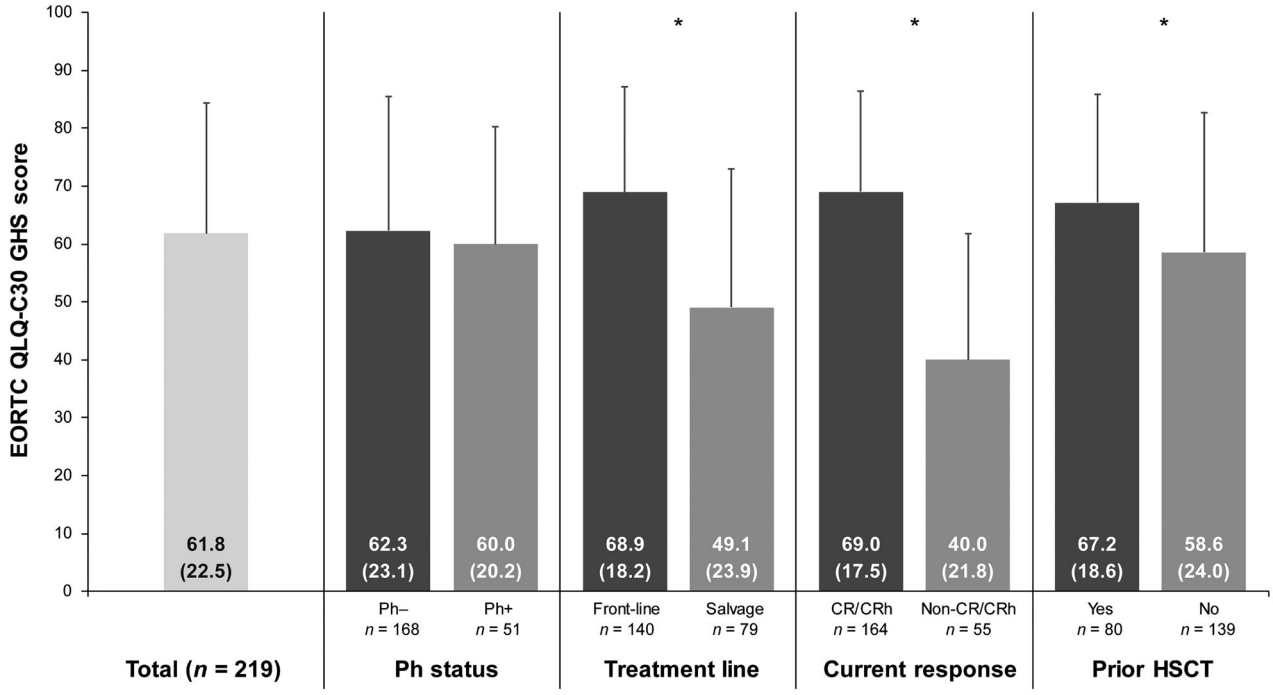

Figure 1. EORTC QLQ-C30 GHS score overall and in the pre-specified subgroups. Data are presented as mean (SD). $^{*}p < .05$ for difference between subgroups. CR: complete remission; CRh: complete remission with partial hematological recovery; EORTC-QLQ-C30; European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; GHS: global health status; Ph: Philadelphia Chromosome.

(ECOG) performance status 0 or 1 if they were receiving front-line therapy, were in CR/CRh, or had previously received HSCT.

QoL scores

On the QLQ-C30, the lowest overall GHS scores (i.e. worst HRQoL) were observed in patients who were not in CR/CRh at baseline (mean ± SD score, 40.0 ± 21.8) and in those receiving salvage therapy (49.1 ± 23.9) (Figure 1). Mean GHS score increased with time since stopping therapy, from 54.9 in patients who were still receiving therapy or who had stopped <6 months before inclusion, to 66.2 in patients who had stopped treatment 6–12 months previously, 68.9 in those who had stopped treatment 12–24 months previously, and 73.5 in those who had stopped treatment >24 months before inclusion.

Overall, the QLQ-C30 GHS score and the five functional scores were higher (better HRQoL) in patients who were receiving front-line therapy at baseline than in patients who were receiving salvage therapy (Figure 1; Table 2). GHS scores were also higher in patients who achieved CR/CRh than in those who did not and in patients who had previously received HSCT compared with those who had not (Figure 1). No difference in GHS score was noted between Ph– and Ph + patients. In the exploratory analysis in patients who had undergone HSCT ≤12 months previously ($n = 30$), mean (SD) QLQ-C30 GHS was lower compared with 80 patients who underwent HSCT >12 months previously (62.2 [16.6] vs. 70.2 [19.0]).

Almost all symptom and single-item scores on the QLQ-C30 were more impaired in patients who received salvage therapy (vs. those receiving front-line therapy), in patients who did not achieve CR/CRh (vs. those in CR/CRh) and in patients who did not receive HSCT (vs. those who did) (Table 2). The exceptions were Pain, Dyspnea, Insomnia, and Diarrhea, for which HRQoL did not differ according to HSCT status. The Financial Difficulties item was more impaired in patients who received salvage therapy compared with front-line therapy, and in patients who were not in CR/CRh compared with those who were.

Results for the FACT-Leu total score, FACT-G and leukemia subscale scores (Table 3) and the EQ-5D-3L (Supplementary Table 1) were consistent with those of the QLQ-C30 (Table 3).

Factors associated with HRQoL

In the multiple regression analysis, anemia, leukopenia, presence of MRD, comorbidities and multiple lines of therapy were associated with worse HRQoL on the

Table 2. HRQoL functional and symptom domain scores measured using the EORTC-QLQ-C30 questionnaire.

		Ph status		Treatment line		Current response		Prior HSCT	
	Total	Ph–	Ph+	Front-line	Salvage	CR/CRh	Non-CR/CRh	Yes	No
Physical functioning	$N = 211$	$n = 163$	$n = 48$	$n = 134$	$n = 77$	$n = 158$	$n = 53$	$n = 77$	$n = 134$
	70.0 (26.5)	70.0 (27.3)	69.9 (23.5)	78.8 (19.4)	54.5 (29.9)†	78.3 (21.1)	45.0 (25.3)‡	77.7 (21.8)	65.5 (27.9)¶
Role functioning	$N = 217$	$n = 166$	$n = 51$	$n = 140$	$n = 77$	$n = 163$	$n = 54$	$n = 79$	$n = 138$
	62.4 (30.1)	62.9 (30.9)	60.8 (27.2)	70.2 (24.4)	48.1 (34.0)†	71.3 (25.1)	35.5 (27.8)‡	69.0 (24.6)	58.6 (32.2)¶
Emotional functioning	$N = 212$	$n = 163$	$n = 49$	$n = 136$	$n = 76$	$n = 159$	$n = 53$	$n = 77$	$n = 135$
	66.1 (27.9)	65.3 (29.0)	68.7 (23.7)	71.7 (24.3)	56.1 (31.1)†	73.2 (24.1)	45.0 (28.1)‡	73.4 (22.5)	62.0 (29.8)¶
Cognitive functioning	$N = 216$	$n = 165$	$n = 51$	$n = 139$	$n = 77$	$n = 162$	$n = 54$	$n = 79$	$n = 137$
	69.5 (27.4)	69.9 (28.8)	68.3 (22.2)	75.7 (24.6)	58.4 (28.8)†	75.6 (24.6)	51.2 (27.4)‡	74.3 (23.5)	66.8 (29.1)¶
Social functioning	$N = 215$	$n = 166$	$n = 49$	$n = 138$	$n = 77$	$n = 162$	$n = 53$	$n = 80$	$n = 135$
	63.3 (30.2)	65.1 (30.4)	57.5 (28.6)	69.1 (28.6)	53.0 (30.1)†	69.9 (28.0)	43.4 (27.7)‡	69.0 (26.2)	60.0 (31.8)¶
Fatigue	$N = 214$	$n = 163$	$n = 51$	$n = 138$	$n = 76$	$n = 161$	$n = 53$	$n = 78$	$n = 136$
	43.6 (27.7)	43.2 (28.2)	44.7 (25.9)	37.4 (26.5)	54.7 (26.4)†	35.9 (24.8)	66.9 (22.4)‡	38.0 (25.1)	46.7 (28.6)¶
Nausea/vomiting	$N = 217$	$n = 166$	$n = 51$	$n = 139$	$n = 78$	$n = 163$	$n = 54$	$n = 80$	$n = 137$
	11.8 (18.9)	12.3 (19.8)	10.1 (15.5)	5.6 (10.7)	22.9 (24.5)†	6.6 (12.6)	27.5 (25.1)‡	8.3 (14.9)	13.9 (20.6)¶
Pain	$N = 216$	$n = 165$	$n = 51$	$n = 138$	$n = 78$	$n = 162$	$n = 54$	$n = 79$	$n = 137$
	25.5 (27.0)	24.9 (27.0)	27.5 (26.8)	17.8 (22.4)	39.3 (28.9)†	19.8 (23.1)	42.9 (30.0)‡	23.4 (24.8)	26.8 (28.1)
Dyspnea	$N = 218$	$n = 167$	$n = 51$	$n = 140$	$n = 78$	$n = 164$	$n = 54$	$n = 80$	$n = 138$
	33.6 (28.6)	31.7 (27.5)	39.9 (31.0)	28.8 (25.9)	42.3 (31.0)†	27.2 (25.3)	53.1 (29.1)‡	32.1 (27.6)	34.5 (29.1)
Insomnia	$N = 217$	$n = 166$	$n = 51$	$n = 139$	$n = 78$	$n = 163$	$n = 54$	$n = 80$	$n = 137$
	33.5 (27.6)	32.5 (28.1)	36.6 (25.8)	29.0 (27.9)	41.5 (25.1)†	28.0 (25.3)	50.0 (27.8)‡	33.3 (25.3)	33.6 (28.9)
Appetite loss	$N = 217$	$n = 166$	$n = 51$	$n = 139$	$n = 78$	$n = 163$	$n = 54$	$n = 80$	$n = 137$
	26.0 (27.8)	26.7 (27.4)	23.5 (29.0)	19.4 (24.3)	37.6 (29.9)†	17.4 (21.3)	51.9 (29.2)‡	18.8 (22.9)	30.2 (29.6)¶
Constipation	$N = 217$	$n = 166$	$n = 51$	$n = 139$	$n = 78$	$n = 163$	$n = 54$	$n = 80$	$n = 137$
	17.4 (26.0)	17.3 (25.0)	17.6 (29.0)	12.9 (23.1)	25.2 (28.8)†	11.2 (21.0)	35.8 (30.7)‡	10.0 (17.8)	21.7 (28.9)¶
Diarrhea	$N = 217$	$n = 166$	$n = 51$	$n = 139$	$n = 78$	$n = 163$	$n = 54$	$n = 80$	$n = 137$
	10.9 (20.7)	10.0 (20.2)	13.7 (22.1)	7.2 (16.4)	17.5 (25.4)†	8.0 (17.6)	19.8 (26.1)‡	10.0 (19.3)	11.4 (21.5)
Financial difficulties	$N = 217$	$n = 166$	$n = 51$	$n = 139$	$n = 78$	$n = 163$	$n = 54$	$n = 80$	$n = 137$
	25.2 (31.4)	24.5 (31.1)	27.5 (32.1)	19.4 (28.5)	35.5 (33.5)†	21.7 (29.9)	35.8 (33.2)‡	23.3 (31.4)	26.3 (31.3)

*One patient did not answer; †$p < .05$ vs. front-line therapy; ‡$p < .05$ vs. CR/CRh; ¶$p < .05$ vs. prior HSCT. Data are expressed as mean (standard deviation).
CR: complete remission; CRh: complete remission with partial hematological recovery; EORTC-QLQ-C30; European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; HRQoL: health-related quality of life; HSCT: hematopoietic stem cell transplant; MRD: minimal residual disease; Ph: Philadelphia chromosome.

Table 3. HRQoL results measured using the FACT-Leu questionnaire.

		Ph status		Treatment line		Current response		Prior HSCT	
	Total ($N = 219$)	Ph– ($n = 168$)	Ph+ ($n = 51$)	Front-line ($n = 140$)	Salvage ($n = 79$)	CR/CRh ($n = 164$)	Non-CR/CRh ($n = 55$)	Yes ($n = 80$)	No ($n = 139$)
FACT-Leu total score	112.2 (32.1)	112.3 (33.6)	111.9 (26.1)	121.0 (26.9)	96.6 (34.4)*	123.3 (24.7)	79.1 (28.5)†	122.8 (25.4)	106.1 (33.8)‡
FACT-General total score	66.4 (19.9)	66.5 (21.0)	66.1 (15.9)	71.7 (17.4)	56.9 (20.7)*	73.0 (16.2)	46.7 (16.8)†	72.5 (16.5)	62.9 (20.9)‡
Physical Wellbeing	20.0 (6.5)	20.3 (6.7)	19.3 (5.8)	22.2 (5.1)	16.3 (7.2)*	22.1 (5.1)	13.8 (6.4)†	21.7 (5.5)	19.1 (6.9)‡
Social/ Family Wellbeing	19.0 (5.3)	19.1 (5.6)	18.8 (4.1)	19.1 (5.4)	18.7 (5.1)	19.6 (5.2)	17.2 (5.3)†	20.0 (4.9)	18.4 (5.5)‡
Emotional Wellbeing	14.6 (5.3)	14.4 (5.6)	15.1 (4.1)	15.8 (4.7)	12.3 (5.7)*	16.3 (4.1)	9.3 (5.1)†	16.1 (4.1)	13.6 (5.7)‡
Functional Wellbeing	12.8 (7.5)	12.8 (7.8)	12.9 (6.2)	14.7 (6.7)	9.5 (7.5)*	15.0 (6.6)	6.4 (6.1)†	14.8 (6.6)	11.7 (7.7)‡
Leukemia subscale	45.8 (13.1)	45.8 (13.7)	45.8 (11.1)	49.2 (10.4)	39.7 (15.1)*	50.3 (9.5)	32.5 (13.3)†	50.3 (9.7)	43.2 (14.1)‡
FACT-Leu Trial Outcome Index	78.6 (25.4)	78.8 (26.5)	78.0 (21.3)	86.0 (20.3)	65.5 (28.0)*	87.3 (19.1)	52.6 (23.8)†	86.7 (19.7)	74.0 (27.0)‡

*$p < 0.05$ vs. front-line therapy; †$p < 0.05$ vs. CR/CRh; ‡$p < 0.05$ vs. prior HSCT. Data are expressed as mean (standard deviation).
CR: complete remission; CRh: complete remission with partial hematological recovery; FACT: Functional Assessment of Cancer Therapy; HRQoL: health-related quality of life; HSCT: hematopoietic stem cell transplant; Leu: leukemia; MRD: minimal residual disease; Ph: Philadelphia chromosome.

QLQ-C30 questionnaire, while consolidation/maintenance treatment and stopping treatment >12 months previously were significant predictors of better HRQoL (Table 4). Results with the FACT-Leu were consistent with those of the QLQ-C30, although there was also a trend toward worse HRQoL in women (Table 4).

HRQoL in patients by MRD status

In the exploratory analysis, baseline characteristics were well balanced between MRD + and MRD– patients, although MRD– patients were more likely to have an ECOG performance status 0 or 1 (Table 1).

Table 4. Multiple regression analysis for EORTC-QLQ-C30 and FACT-Leu.

	EORTC QLQ-C30 ($n = 212$)			FACT-Leu ($n = 212$)		
Parameter	Estimate (mean ± SD)	*p*-value	Multiple R^2	Estimate (mean ± SD)	*p*-value	Multiple R^2
Female sex	−3.404 ± 2.570	.1870	0.404	−1.339 ± 0.730	.0682	0.443
Anemia	**−17.74 ± 3.649**	**<.0001**		**−5.166 ± 1.036**	**<.0001**	
Time since stopping treatment						
<6 months*	7.226 ± 8.542	.3986		2.343 ± 2.425	.3353	
6–12 months	3.752 ± 4.884	.4433		1.119 ± 1.387	.4208	
12–24 months	**8.214 ± 3.969**	**.0398**		**2.383 ± 1.127**	**.0357**	
>24 months	**8.207 ± 3.198**	**.0110**		**3.566 ± 0.908**	**.0001**	
Leukopenia	**−0.001 ± 0.000**	**.0071**		**0.000 ± 0.000**	**.0016**	
Presence of comorbidities	**−2.514 ± 1.098**	**.0231**		**−0.828 ± 0.312**	**.0085**	
MRD + status	**−8.699 ± 3.733**	**.0208**		**−2.310 ± 1.060**	**.0305**	
Consolidation/maintenance therapy	**6.647 ± 2.612**	**.0117**		**2.404 ± 0.742**	**.0014**	
Multiple lines of treatment	**−9.366 ± 2.127**	**<.0001**		**−2.133 ± 0.604**	**.0005**	

*Includes patients currently receiving treatment. Statistically significant parameters in **bold**.
EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; FACT-Leu: Functional Assessment of Cancer Therapy – Leukemia; MRD: minimal residual disease; SD: standard deviation.

Overall, QLQ-C30 GHS score and scores on the Physical Functioning and Role Functioning domains were higher in MRD− patients compared with MRD + patients (Figure 2(a)). In addition, scores on the Fatigue, Nausea/Vomiting, Pain, Dyspnea, Insomnia, and Appetite scales indicated less impairment in MRD− patients than in MRD + patients (Figure 2(b)). Results for the FACT-Leu total score and FACT-G and leukemia subscale scores (Supplementary Table 1) and the EQ-5D-3L (Supplementary Table 2) were consistent with those of the QLQ-C30 (Figure 2).

Discussion

To our knowledge, this is the first study to report on HRQoL in adults with B-cell ALL in France. Futhermore, the sample size ($n = 219$) represents a large population for an HRQoL study in patients with ALL. The results of this study show clear differences in HRQoL in patients with B-cell ALL receiving front-line therapy and those receiving salvage therapy, between patients in CR/CRh compared with those who do not achieve this level of response, and between MRD− patients compared with MRD + patients. Regardless of the questionnaire used, better overall scores and most specific QoL domain scores were observed among patients receiving front-line therapy, those currently in CR/CRh, and those with the absence of MRD. Interestingly, patients who had previously received HSCT generally reported better HRQoL than those who had not, although exploratory analysis showed that those who had undergone HSCT in the previous 12 months had worse QoL than those who had undergone HSCT >12 months ago. In the multivariate analysis, multiple lines of therapy, MRD+, comorbidities, anemia and leukopenia were significantly associated with impaired HRQoL. No significant associations between prior HSCT or age, however, were observed on either the QLQ-C30 or FACT-Leu.

Treatment line and response to treatment both had an impact on HRQoL. For example, a close relationship between multiple lines of therapy and HRQoL deterioration has previously been observed in real-world studies of French [24], Spanish [25], and German [26] patients with multiple myeloma. Indeed, the health of patients with relapsed/refractory disease is compromised by the highly toxic multidrug salvage chemotherapy regimens that are commonly used. In a previous study of population health state preferences in the UK, the highest preference values were shown for complete remission, followed by complete remission with partial hematological recovery [27]. In the current study, these states were associated with a higher level of HRQoL, and GHS score and the five functional domain scores were also higher in patients who had previously received HSCT compared with those who had not. This may be explained by the fact that patients who had previously received HSCT were more likely to be receiving front-line therapy and to be in CR/CRh than those who had not, and by the long time (mean, 4.7 years) since transplantation. However, no interaction analysis between prior HSCT and CR/CRh was conducted to be able to determine if this was the case. Some data are available from previous studies in patients with leukemia. For example in patients with acute myeloid leukemia, a retrospective analysis of QLQ-C30 data from ∼2800 patients showed that HRQoL reached its lowest level during the inpatient phase of transplantation, but recovered to pre-transplant levels by 1 year after transplantation [28]. Similar results have also been seen using the Short Form 36 HRQoL questionnaire [29]. Indeed, the time elapsed since the end of the last treatment seems to have an impact on HRQoL, with better

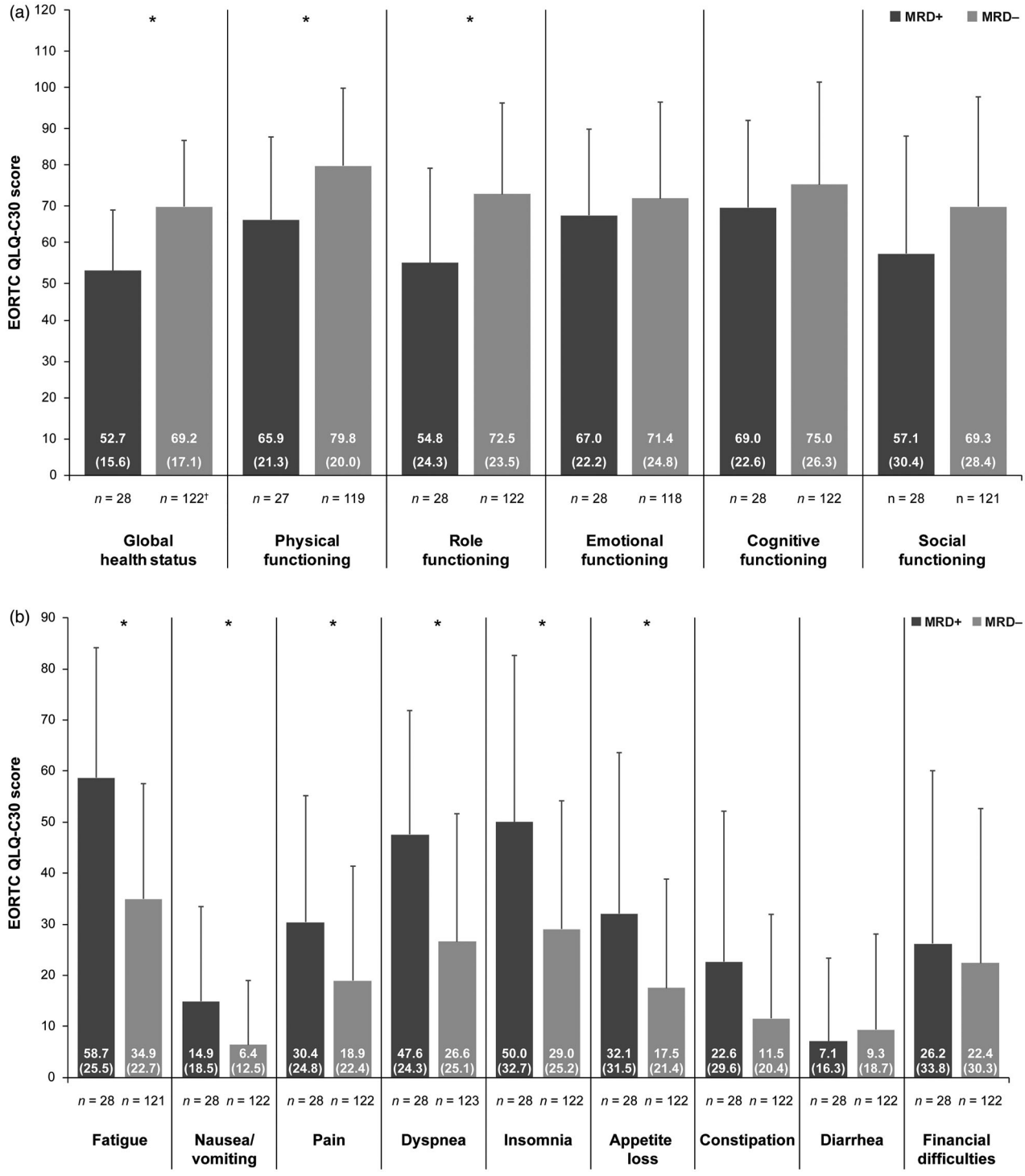

Figure 2. Exploratory analysis of (a) EORTC-QLQ-C30 GHS and functional scores and (b) EORTC-QLQ-C30 symptoms scores by MRD status. *$p < .05$ for difference between MRD + and MRD–; †One patient did not answer. Data are expressed as mean (standard deviation). EORTC-QLQ-C30; European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; GHS: global health status; MRD: minimal residual disease.

scores observed in the present study in patients who stopped treatment >24 months before inclusion. After a treatment-free interval of >24 months, disease-free patients appear to have recovered a large portion of the HRQoL lost during treatment and just after its cessation. A similar effect of treatment on HRQoL and post-treatment recovery has previously been reported in patients with acute myeloid leukemia [30] and in real-world studies of French [24] and German patients [26] with multiple myeloma.

In adults with ALL, the presence of MRD is widely recognized as the most sensitive prognostic factor for relapse and death regardless of treatment choice and risk classification [14]. ALL-specific treatment guidelines and protocols now recommend MRD testing [13,31]. Such testing is common in France, with 86% of patients in the present analysis, and 90% of those receiving front-line therapy, undergoing at least one MRD test. Data on how MRD status affects HRQoL in adults with ALL were, however, lacking. Our results consistently showed impaired HRQoL in MRD + patients compared with MRD– patients, with MRD– patients having a similar HRQoL to patients in CR/CRh, those receiving front-line treatment, and those who had previously received HSCT. Most QLQ-C30 functional and symptom scores were also significantly better in MRD– patients compared with MRD + patients. There were, however, no differences in the Emotional, Cognitive, and Social functioning domains, which may be because patients are not routinely given the results of their MRD tests. Moreover, MRD testing represents biological data on the depth of response, whereas the impact of achieving or not acheving CR is likely to be more important for determining HRQoL. The impact of MRD status on HRQoL may also be related to the time elapsed since treatment cessation, as patients who are disease free after 2 years are likely to be mostly MRD–.

The significant association of anemia and leukopenia with impaired HRQoL indicates that the worst HRQoL is observed during or just after B-cell ALL treatment. This does not, however, explain the plateau in HRQoL observed between 6 and 24 months after stopping treatment, a time at which hematological toxicities of treatment should have resolved. Overall, the model explained 39% of the variance in HRQoL as measured by the QLQ-C30, and it is not clear whether the remainder of the variance is explained by variables not included in the model, or whether HRQoL is affected by different variables depending on the line of therapy, time since stopping treatment, and other factors.

Overall, results on the QLQ-C30, FACT-Leu and EQ-5D-3L questionnaires were similar to those previously reported for patients with leukemia [19,27,32–34]. It should be noted that the inclusion criteria for this study were designed to recruit patients fitting specific B-cell ALL profiles (Ph– patients in CR/CRh with prior HSCT, in CR/CRh without prior HSCT, and not in CR/CRh, and Ph + patients in CR/CRh during their current or most recent treatment, and those not in CR/CRh), and therefore the study population cannot be considered representative of the prevalent ALL population in France. As patients were enrolled by their physicians, the potential exclusion of patients in a critical condition, or who had a poor physician–patient relationship, may have led to selection bias. The patient sample selection process was, however, designed to minimize the impact of this bias, particularly by requiring partcipating physicians to include patients who were not in CR/CRh. Another limitation was that the total enrollment was lower than the planned sample size of 280, largely as a result of difficulties recruiting patients in some stratification subgroups that are not well represented in a real-world patient population. A total of 219 patients, however, still represents a large patient sample for a study of HRQoL in ALL, and this lower enrollment than expected is not anticipated to have substantially affected the results of this descriptive study. Recruitment may have been affected by the rarity of the condition, as well as the exclusion of patients participating in clincial trials, which is common at large treatment centers. In particular, the number of patients in each subgroup was too small to assess specific criteria driving HRQoL.

In conclusion, this is the first study to report on HRQoL in adults with B-cell ALL in France. The number of lines of treatment and response to treatment significantly affected HRQoL, and in the multivariate analyses, anemia, leukopenia, multiple lines of therapy, the presence of MRD, and the presence of comorbidities all negatively affected HRQoL. Overall, the presence of MRD appeared to have a detrimental impact on HRQoL. Further studies are needed to confirm this effect.

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Lucie Kutikova was an employee and stockholder of Amgen (Europe) GmbH at the time the study was conducted.

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Data availability statement

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparencypractices/clinical-trial-data-sharing-request/.

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