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REVIEW

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Health-related quality of life of children on treatment for acute lymphoblastic leukemia: A systematic review

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Abstract

Children with acute lymphoblastic leukemia (ALL) undergo intense anticancer treatment. We systematically reviewed 22 studies evaluating 2,073 ALL patients' health-related quality of life (HRQL) and its clinical/demographic correlates during treatment. Overall HRQL was significantly reduced on treatment. Despite HRQL improvements over time, longitudinal studies reported a proportion of children continued to experience reduced HRQL after treatment completion. We found inconsistent associations between clinical/demographic factors and HRQL outcomes. Tentative evidence emerged for worse HRQL being associated with intensive phases of chemotherapy, corticosteroid therapy, experiencing greater toxicity, older age, and female sex. Longitudinal studies are needed to identify children at-risk of reduced HRQL.

KEYWORDS

acute lymphoblastic leukemia, pediatric oncology, quality of life, systematic review, treatment

1 | INTRODUCTION

Acute Lymphoblastic Leukemia (ALL) is the most common childhood cancer, and due to ongoing refinement of treatment, 5-year survival rates for children diagnosed with ALL now account for 80–90%.[1–3] However, the burden of treatment-related side effects can be significant. While on treatment children can experience life-threatening toxicities such as venous thromboembolism (5% of children),[4] severe pancreatitis (in 5–10% of children),[5] and neurological complications such as seizures and encephalopathy (1–3% of children).[6,7] More commonly, children can experience some degree of nausea, pain, fatigue, or sleep disruption, and psychological disturbance associated with their ALL treatment,[8,9] symptoms which are rated as severe and distressing by parents.[10,11] Survivors also face increased risk of late occurring and long-term side effects as a result of treatment, including cardiovascular disease, endocrine dysfunction, second cancers, neuropsychological impairment, and psychosocial difficulties.[12,13] With increasing numbers of children surviving their cancer, reducing the impact of acute and chronic treatment-related side effects and improving the quality of survival become paramount.[3,13]

Increasingly, health-related quality of life (HRQL) assessment across treatment has become an important outcome for pediatric

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HRQL, health related quality of life; HUI, Health Utility Index; PedsQL, Pediatric Quality of Life Inventory; rHuEPO, recombinant human erythropoietin

oncology.[14–16] HRQL assessment captures more than just the presence or absence of symptoms,[17] and is recommended for use in clinical trials.[18] HRQL is a multidimensional concept encompassing physical, psychological, and social domains.[17,19] HRQL characterizes the individual's perception of the impact of an illness on their health, well-being, and functioning within their cultural context.[17,19] For children, this also encompasses their family context.[20] HRQL assessment across treatment can aid clinicians' decision making,[21,22] particularly in the case where different treatment protocols have the same survival outcome, but different profiles of toxicities and impact on the child and family. Evaluating HRQL during cancer treatment therefore provides insight into the burden of treatment from the child's and/or parent's perspective.[14,22]

Assessment of HRQL in children is complex. Differences can exist between child reports and reports of their carers and physicians (proxy raters).[15,23–25] Children's perspectives of their HRQL are underrepresented.[14,15] Although children can adequately describe their HRQL by the age of 7 years,[14,15] proxy reporting remains the mainstay in ALL. Most ALL diagnoses occur between the ages of 2 and 4 years and therefore children may not be able to report their HRQL while on treatment.[3,26] HRQL measures are frequently adapted from adult measures,[14] and may not take into account the developmental changes that pediatric ALL patients experience during treatment, which can span several years in some instances, or do not have age-appropriate reference data.[27] For example, while models of HRQL encompass well-being across physical, psychological, and social domains, how the relative importance of these domains varies over the lifespan and contributes to a child's HRQL is unclear.[28] This is a clear limitation; what constitutes good HRQL in a 2-year old is clearly different to what constitutes good HRQL in a 5-year old.

Several previous reviews have reported on the methodology employed to evaluate the impact of ALL on HRQL.[14,15,29] These reviews found most studies consisted of small cross sectional samples, and did not consistently use the same HRQL measure in children with ALL.[14,15] While these reviews are informative for researchers considering study design and measure selection, they do not provide an account of HRQL over the course of treatment and factors that are associated with better or worse HRQL in children receiving treatment for ALL. Therefore, this review aims to (i) evaluate HRQL in comparison to other groups (e.g., healthy controls, other diagnoses), (ii) synthesize the literature describing HRQL over the course of ALL treatment, and (iii) identify correlates of HRQL in children on treatment for ALL.

2 | METHODS

We conducted a systematic literature review on HRQL of ALL patients on treatment according to PRISMA guidelines.[30] We searched PubMed (including Medline), PsycInfo, Embase, and the Cochrane database without language restrictions and include all years up to March 2, 2016. The following search terms were used in each database: (i) (child* OR infan* OR "young adults" OR pediatric OR pediatric OR adolescent* OR sibling* OR parent* OR family OR families) AND (ii) ("acute lymphoblastic" OR leukemia OR leukemia OR "mixed phenotype acute leukemia") AND (iii) ("quality of life" OR QoL OR "health related quality of life" OR HRQL OR HRQOL). We checked reference lists and examined citations of recent relevant papers to find papers not identified by our database searches. We screened titles and abstracts of all papers and included them for full text review if they contained information on HRQL in ALL patients on treatment. In the full text review, we focused on HRQL scores, quality of life tools used, and correlates of HRQL.

2.1 | Inclusion and exclusion criteria

Publications were included if they fulfilled all of the following criteria: (i) the child was diagnosed with ALL <18 years, (ii) the paper assessed HRQL on treatment, and (iii) the paper was published in German, English, French, or Italian. We excluded publications if they did not report HRQL in ALL patients on treatment, included only survivors of ALL posttreatment, or were based on qualitative data.

2.2 | Screening and data extraction

Independent reviewers (J.F., J.V., and L.T.) screened titles and abstracts of all citations returned by the search strategy and obtained full text of potentially eligible papers. Each full-text article was read and examined by two reviewers (J.F. and J.V.). Differences were discussed until consensus was reached. Studies were excluded at this stage if it was apparent that they did not meet inclusion criteria or provided insufficient information. Data from each article were then independently extracted by one reviewer (J.F., J.V., or A.C.).

2.2.1 | Quality assessment

We used Kmet et al.'s quality assessment tool to rate the quality of the papers.[31] Study design, methods, measurements used, and description of outcomes are assessed on 14 items scored on the degree to which the specific criteria were met ("yes" = 2, "partial" = 1, "no" = 0, n/a for items not applicable is scored 2). A total score is then calculated with a maximum score of 28 indicating high quality. Two reviewers (J.V. or A.C.) assessed the quality of the studies, after assessing the first 20% of studies quality ratings together. Interrater reliability was over 90%, disagreements were resolved by discussion with a third reviewer (J.F.).

3 | RESULTS

Our search returned 1,054 articles after duplicate removal (Fig. 1). We excluded 905 articles after screening titles and abstracts, and excluded an additional 129 articles after screening the full texts. Two articles were found through hand search. This led to 22 eligible articles for which data were extracted. Details of included studies can be found in Supplementary Table S1; a summary is provided in Table 1. The average quality rating was 25.9 (out of 28) and the range was 21–28 (Supplementary Table S1). Lower quality ratings were common due to

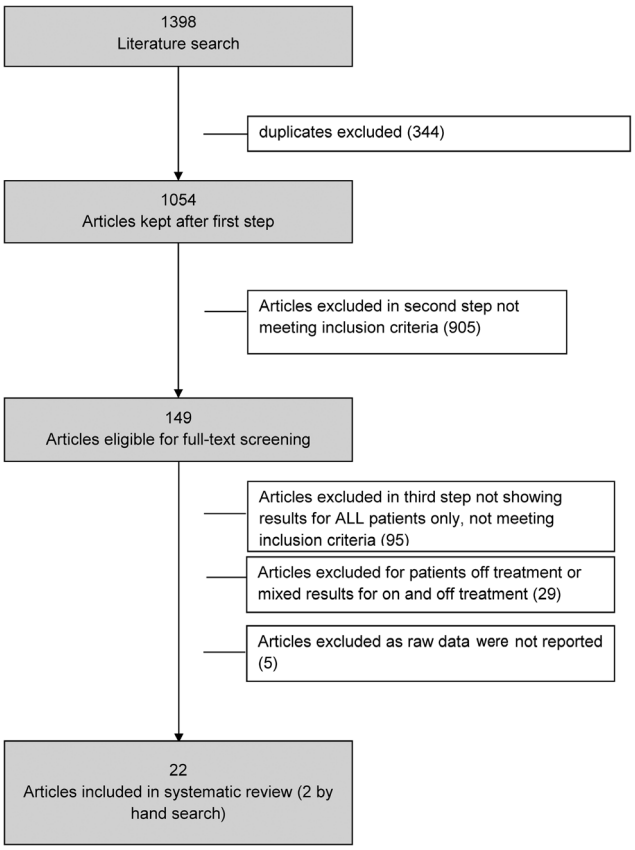

FIGURE 1 Flow diagram of study selection and review

small sample sizes (13 studies, with three studies describing samples under 30), and failure to control for possible confounders in interpreting results (16 studies). Sample sizes ranged from N = 18 to 375, with a median sample size of 68 and a total of 2,073 ALL patients included across the 22 studies. Response rate was reported in 13 studies and was on average 74.3%.

In 21 of 22 studies, proxy measurement was used: 16 studies used a parent-proxy only, one used a nurse-proxy,[32] and two studies used different proxies: parent-proxy, nurse-proxy, and/or physician-proxy.[33,34] Six studies additionally included a child self-report questionnaire. One study described child self-reported HRQL in the absence of proxy data.[35] Treatment regimens and protocols were mentioned in 15 of 22 studies and varied across studies and countries (Supplementary Table S1). Eleven of the studies were cross-sectional, nine longitudinal, one a 12-week case–control study, and one was a quasi-experimental intervention. Of the nine longitudinal studies, two evaluated HRQL after treatment completion.[34,36] The time points in the longitudinal studies varied, with assessments ranging from 2 weeks after diagnosis till 4 years posttreatment. Four studies were conducted in the context of a randomized control trial.[34,36–38]

The construct HRQL was formally defined by eight of the 22 studies included in this review. It was described as patients' perception of health and functioning influenced by the disease and its treatment. The different dimensions of HRQL which were assessed included physical, functional, perceptual, emotional, psychological, and social health.[32,33,35,39–43]

There was considerable diversity in the measures used to assess HRQL in ALL patients. Both generic and disease-specific measures were employed. The measurement tool most often used was the Measurement Model for the Pediatric Quality of Life inventory (PedsQL).[44] Used in 13 studies, the PedsQL has a modular approach to measuring HRQL, and encompasses both generic core scale and disease-specific acute cancer module. The next most commonly used measurement tool was the Child Health Questionnaire Parent-Form 50,[45] which is used in four studies. However, a large variety of other tools such as the Health Utility Index marks 2 and 3 (HUI2/ HUI3),[46] KINDL,[47] pediatric cancer quality of life inventory-32,[48] and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire[49] were also used (Table 1).

3.1 | HRQL outcomes

All studies reported lower HRQL outcomes for ALL patients when compared with healthy norms or siblings.[26,34,35,38,39,41,43,50–55] For example, Furlong et al. reported that patients lost approximately 0.2 quality adjusted life years during active treatment, equivalent to losing approximately 2 months of life in perfect health.[34] When compared with other diagnoses, children receiving treatment for ALL experienced HRQL that was better than brain tumor patients,[26] but lower than children receiving treatment for other leukemias (e.g., acute myeloid leukemia [AML]),[54] or solid tumors.[43] Zareifar et al. reported higher HRQL in ALL and AML patients compared with Iranian patient norm scores.[54]

Most studies reported that all domains of HRQL were affected by ALL treatment. The physical, psychosocial, social, emotional, and school domains were most commonly measured, and all were reported to be lower in ALL patients than in healthy children and siblings.[35,39] More pain and hurt, and procedural anxiety were reported when children were on steroids compared with off steroids.[56] When compared to AML patients, ALL patients had worse scores in physical, role, emotional, and cognitive functioning, and better scores for fatigue, nausea and vomiting, pain, insomnia, appetite loss, and constipation.

Few studies evaluated the impact of treatment phase. Sung et al. found no difference between those pre- and postmaintenance therapy,[55] while two studies found HRQL steadily improved across treatment phases to treatment completion.[34,36] Furlong et al. reported reductions in HRQL most commonly occurred during intensification and continuation phases of treatment.[34] There was evidence from three studies that HRQL was significantly compromised while on corticosteroids,[33,50,56] although one study found no difference in HRQL when children were on and off dexamethasone.[51] There was conflicting evidence that HRQL differed according to different types of corticosteroids, with one study reporting dexamethasone treatment resulted in more cognitive difficulties in toddlers compared to prednisone,[56] and two studies finding no difference between dexamethasone and prednisone.[8,38] Children's HRQL was higher when treated with recombinant human erythropoietin (rHuEPO) when compared to a control group not receiving rHuEPO.[37]

TABLE 1 HRQL outcomes by study

Reference/ country	ALL sample size	Age at study participation	Comparison control group and sample size	HRQL tool	Results
Abdelrazik et al.[37]/Egypt	30 receiving epoeitin alfa (17 males, 13 females); case control open study of EPO for anemia	Median 7 years, (range 3–1) rHuEPO group: 6.8 years ±2.33, control group: 6.76 years ±2.28	Control group no epoetin alfa 30 cases, (16 males, 14 females)	Cancer linear analogue scale Parent proxy	• HRQL was low at baseline (while on maintenance therapy) but significantly improved over time • Overall HRQL, energy level and ability to perform daily activities were lower in the control group that did not receive rHuEPO compared to those receiving rHuEPO
Bansal et al.[39]/India	40 ALL patients, male/female not known	5–18 years	40 sibling and parents and 40 healthy control group, age matched (5–18 years), male/female not known	PedsQL 4.0 generic core hindi Child-self report, parent proxy	• Children with ALL had lower HRQL overall and across multiple domains compared to siblings and healthy controls • Parents significantly overrated the HRQL of ALL patients, their siblings, and healthy children in comparison with child self-report in all domains of health • Siblings and healthy children did not differ
Bansal et al.[35]/India	40 ALL patients, male/female not known	5-18 years	40 sibling and parents and 40 healthy control group, age matched (5–18 years), male/female not known	PedsQL 4.0 generic core hindi Self-report	• Overall HRQL and domains including physical, emotional, social, and school health were significantly lower for children with ALL compared to siblings and healthy controls children
Barr et al.[33]/Canada	18 (12 male, six female) standard and high risk (n = 9)	11 months–14 years	No comparison group	HUI2 HUI3 Parent proxy, physician proxy, nurse proxy	• No difference between assessor (parent, physician, nurse) in rating child's HRQL • Difference between the three assessment time points with highest burden in middle of cycle after corticosteroid administration • Most affected domains included pain, emotion, and mobility/ ambulation
Barrera et al.[43]/Canada	111 parents and their children (41 females and 70 males)	Total sample: mean 10.43 years (SD = 5.11), range 3–17	Population normative data, healthy children norms (5–18 years) were used	CHQ-PF50, POQOL Parent proxy	• ALL patients have lower scores in total and physical and psychosocial domain than cancer norms and healthy children
Cox et al.[32]/United States	25 male/female not known	Median 10 years (range 6–18)	No comparison group	HUI3 Nurse proxy	• No difference of scores over time • Assessable scores decreased with patients health state • Nurses found it difficult to score their patients

(continues)

TABLE 1 *(Continued)*

Reference/ country	ALL sample size	Age at study participation	Comparison control group and sample size	HRQL tool	Results
Daniel et al.[8]/United States	81 parents (female 35, 46 male) (n = 55 dexamethasone, 22 female, 33 male; n = 26 prednisone, 11 female, 15 male)	Mean 6.21 years, SD = 2.22, range 3–12	No comparison group	PedsQL Parent proxy	• HRQL similar between steroid groups, but worse sleep outcomes were reported in children receiving dexamethasone compared to prednisone
de Vries et al.[50]/the Netherlands	41 (23 males, 18 females), Different risk groups, dexamethasone	5.6 years (SD = 3.3)	Population normative data	PedsQL 3.0 acute cancer version Dutch CHQ-PF50 Self-report and parent proxy	• HRQL scores lower on dexamethasone as reported by parents. • HRQL was significantly more impaired during periods on dexamethasone for both physical summary score and psychosocial summary score and were significantly lower than Dutch population norms • No difference for HRQL as reported by the child on or off dexamethasone at the end of treatment • Over time, HRQL became more impaired for specific domains (pain, cognitive functioning, emotion/behavior and physical functioning)
Eiser et al.[38]/UK	45 mothers (32 male, 13 female) prednisone (28), dexamethasone (17)	T1: 7 years 3 months T2: 8 years 3 months	Population normative data	PedsQL 4.0 generic measure Parent proxy	• HRQL below population norm, but improved over time • No difference in HRQL between prednisone and dexamethasone • ALL patients had lower scores in physical, social, and emotional domain than norms, but emotional and physical score increased significantly from diagnosis to 1 year later • No significant change over time for the social functioning subscale
Eiser et al.[57]/UK	46 children (17 females, 29 males)	Overall 7 years, Girls: mean = 7.5 years, range 2.9-16 Boys: mean = 6.6 years, range 2.4–14.9	No comparison group	PedsQL 4.0 generic measure Parent proxy	• Overall HRQL improved over time
Furlong et al.[34]/Canada	375 (168 female, 207 males)	Mean 6.11 (SD = 4.25)	Population normative data	HUI2 HUI3 Parent proxy, self-report, clinician proxy	• HRQL increased from induction to posttreatment phase • On treatment HRQL was significantly below controls but posttreatment HRQL was similar to controls • HUI3 scores lower than HUI2 scores

(continues)

TABLE 1 *(Continued)*

Reference/ country	ALL sample size	Age at study participation	Comparison control group and sample size	HRQL tool	Results
Hashemi et al.[58]/Iran	60 parents (30 control not receiving education, 18 males, 12 female; 30 intervention, 20 males, 10 females)	8.45 years in experimental group 8.13 years in control group (range 7–10)	No comparison group	TNO-AZL parent form quality of life in seven dimensions Parent proxy	• Parents education increases ratings of HRQL of children after intervention compared to control group
Meeske et al.[26]/United States	256 families, brain tumor (n = 86), ALL (n = 170), 151 female, 19 male	ALL 7.8 years (SD 4.1) BT 9.7 years (SD 4.4)	Brain tumor (BT), normative data of healthy children	PedsQL 4.0 generic core scales; PedsQL 3.0 acute cancer module; PedsQL multidimensional fatigue scales and PedsQL family information form Parent proxy	• HRQL lower in children with BT compared to children with ALL. But, HRQL for children with ALL was >1 SD below norms • Core Physical Health and Fatigue Total scores for patients with ALL were highest for those who had not received treatment for more than 12 months • Fatigue scale normal for children with ALL compared to healthy controls
Mitchell et al.[36]/United States	Parents of 160 standard risk ALL patients (77 female, 83 male)	Mean age 4.9 years (SD 2.9)	No comparison group	PedsQL 4.0 generic core scales Proxy-parent	• Physical, emotional, and social functioning impaired at 1 month after diagnosis, and improved over time
Peeters et al.[41]/Germany	74; 38 male, 36 female	Mean age T1 = 7.1 years (SD 3.7) T2 = 7.7 years (SD 3.7) T3 = 8.2 years (SD 3.4)	Sample of 397 German children (values used for the general po- pulation sample were formed by calculating the arithmetic mean of the published results of a survey of the same population sample at two diff erent points in time)	Parent-questionnaire (POQOLS) and a patient-questionnaire (KINDL) Proxy-parent and self-report	• Lower values for ALL than norm population, scores, improved over time as reported by parents and child but was still lower than the values from the general population at the end of maintenance therapy • Physical, mental components improved over time, functional and social domain did not improve over time and remained below norm
Pound et al.[56]/Canada	60 families were approached. A sample of 43 patients were included (21 male and 22 female), thirty-three (76.7%) children received dexamethasone, whereas 10 (23.2%) received prednisone	7.0 years (SD 4.1), range 3–18	No comparison group	PedsQL 3.0, cancer module Proxy-parent and self-report	• HRQL was higher when children were off steroids compared to on steroids • No significant difference between parent and child reports • Parent reported: more pain and hurt, procedural anxiety and nausea when children were on steroids as compared with off steroids • More cognitive problems and communication problems in toddlers • In young children (5–7 year old) more pain and hurt • Children 5 years and above reported more pain and hurt and teens 13–17 years reported more cognitive problems when receiving steroid therapy

(continues)

TABLE 1 *(Continued)*

Reference/ country	ALL sample size	Age at study participation	Comparison control group and sample size	HRQL tool	Results
Sitaresmi et al.[40]/Indonesia	98 guardians (74 mothers; 54 male children), 55 patients (27 male, 28 female)	6.6 years (SD = 3.7) range 2–16 years	No comparison group	PedsQL 4.0 generic core scale, PedsQL 3.0 acute cancer module Proxy-parent and self-report	• Guardians tended to report worse HRQL than patients in cancer scale • Psychosocial health subscale was better than physical health subscale for both self-report and proxy report • No difference between parent report and proxy report
Sung et al.[55]/Canada	A total of 513 parents of children with any type of cancer were asked to participate and 501 agreed. No. of ALL 206 (57.8%), 119 male, 87 female	5.6 years, range 2.3–18.1	Population normative data	PedsQL 4.0 generic core scales PedsQL 3.0 acute cancer module. Proxy-parent	• HRQL scores were >1 SD below normative scores • Lower HRQL in high-risk ALL compared to standard risk • High-risk ALL had worse HRQL with respect to overall, physical, psychosocial, emotional, and social scores • HRQL scores were generally constant across phases of ALL therapy
van Litsenburg et al.[51]/ The Netherlands	21 children and their parents were eligible and were invited (17 out of 21 could be analyzed, seven male, 10 female)	2–18 years	Dutch population normative data	CHQ-PF50 pediatric quality of life inventory 3.0 Proxy-parent	• HRQL was lower in children with ALL compared to norm • No difference in HRQL on and off dexamethasone • Lower scores for ALL in all domains
van Litsenburg et al.[52]/ The Netherlands	164 were invited to participate; informed consent 159; (from 131 children with ALL, 62 female, 69 male)	Mean age 5.7 years (IQR 6.1); range 2–18	Dutch population normative data	CHQ-PF50 PedsQL acute cancer version Proxy-parent	• HRQL scores for ALL were lower than norms, with large effect sizes ranging between 1.0 and 2.5 • ALL HRQL domains worse in ALL than norms, particularly in physical HRQL than psychosocial HRQL
Waters et al.[53]/Australia	Parents of 31 children with ALL participated (16 male, 15 female)	Mean age 11.6 years (SD 3.5) range 5–18	Australian population normative data	CHQ PF-50 PCQL-32 Proxy-parent	• Lower scores for ALL patients in all domains than healthy norms.
Zareifar et al.[54]/Iran	100 (54 male, 46 females) 76 patients ALL, 24 patients AML	Mean = 10.8 years (SD = 3.2) range 6–18	AML patients and reference values (Iranian patients)	EORTC QLQ-C30 Persian translated Mother-proxy reported	• ALL have lower overall scores and lower scores in physical functioning, role functioning, emotional functioning, cognitive functioning, and higher scores for fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation than AML patients • ALL/AML compared to Iranian patients achieved higher scores • ALL/AML sample had lower scores than reference values in fatigue, pain, dyspnea, insomnia, and constipation

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BT, brain tumor; CHQ, child health questionnaire; CHQ-PF50, child health questionnaire parent-form 50; EORTC QLQ-30, European Organization for Research and Treatment of Cancer quality of life questionnaire; HRQL, health-related quality of life; HUI, health utilities index; n/a, not available; PCQL-32, pediatric cancer quality of life inventory-32; PedsQL, pediatric quality of life inventory; QALY, quality adjusted life years; rHuEPO, recombinant human erythropoietin.

Nine studies assessed HRQL longitudinally with HRQL assessment spanning different time points throughout treatment. These generally reported an improvement in overall HRQL over time.[34,36–38,41,57] Peeters et al. reported that even though scores improved over time, they were still lower than the general population at the end of maintenance therapy,[41] and a significant proportion of children completing therapy had persistent decrements in HRQL.[36] There was also evidence that social and emotional domains of HRQL were particularly vulnerable and did not improve over time.[36,38,41,55] One study reported that HRQL did not change over time and remained low at treatment completion.[50] Two studies described HRQL outcomes during and after treatment. At 3 months after treatment, 28% of children experienced ongoing poor physical HRQL, and 26% experienced poor emotional HRQL.[36] At 2–4 years posttreatment, mean HRQL was similar to healthy controls.[34] When parents were educated about leukemia and how to communicate with their child, parents' proxy reports of their child's HRQL were higher than parents not receiving leukemia education.[58]

Six studies included child self-reports of HRQL. There were no consistent differences between children (>5 years old) self-reporting and parents proxy reports of their child's HRQL while on treatment. One study found that parents reported higher HRQL than children's self-reports,[39] two reported no difference,[50,56] and one found lower scores for parents report.[40] One study found no difference in HRQL outcomes between different proxy raters: parents, physician, and nurse reports.[33]

3.2 | Correlates of HRQL

Twelve of 22 studies assessed predictors of HRQL outcomes, a summary of results is provided in Table 2.

3.2.1 | Child clinical characteristics

Clinical characteristics associated with poor HRQL outcomes were being on treatment,[26,55,56] being in the induction phase of treatment,[36] getting intensive continuation of chemotherapy,[55] receiving *Escherichia coli* asparaginase,[34] and being treated on a high-risk ALL protocol.[50,55] However, another study found no association for diagnostic risk groups or treatment modalities.[34] Shorter time since diagnosis was associated with worse bodily symptoms,[52] but longer time since diagnosis was associated with worse HRQL in another study.[55] More days in hospital were associated with lower overall HRQL scores.[8,51,52] A greater number of parent reported sleep problems in the child were associated with reduced HRQL.[8] Two studies reported on treatment-related toxicities.[36,52] More treatment-related toxicities were associated with worse HRQL as measured by the PedsQL treatment anxiety subscale, and bodily pain subscale on the CHQ.[52] When adverse neurological events including seizures, loss of limb function, and altered mental status/loss of consciousness were measured by parent report during treatment, this was associated with reduced physical and social functioning at 3 months posttreatment, but the on-treatment HRQL impact of such toxicities was not evaluated.[36]

3.2.2 | Child sociodemographic characteristics

Equivocal evidence emerged regarding child demographics. Six studies reported that increasing age of the child was associated with worse overall HRQL and/or specific HRQL domains (Table 2).[26,36,43,52,54,55] For example, Mitchell et al. reported that children aged 5–12 years at diagnosis had worse physical HRQL compared to children aged 2–4 years.[36] This result is consistent with others,[26,43] suggesting school age children (i.e., those >5 years) experience greater reductions in HRQL compared to younger preschool age children, though such a group difference according age was not explicitly tested and should be considered with caution. However, three studies found no association of age and HRQL.[34,41,43] General anxiety, treatment anxiety, communication and pain, and hurt scale scores were worse in younger children.[40,52,56] HRQL outcomes were worse for girls than boys in three studies,[26,52,55] but two studies found no such difference.[34,56] One study reported that boys self-report more cognitive problems when treated with steroids.[56]

3.2.3 | Parent and family characteristics

Parents' demographic factors were rarely associated with their child's HRQL. No association was found for ethnic background,[26] socioeconomic status, education, and marital status.[26,55] Mothers were more likely to report better HRQL in their child than fathers.[52] High levels of household income were associated with better HRQL in one study.[55] Mitchell et al. found problematic family functioning and larger household size were associated with impaired emotional and social functioning.[36]

4 | DISCUSSION

Assessing HRQL across ALL treatment is important to understand the natural course of HRQL and determinants of HRQL to be able to devise methods of reducing the short- and long-term impacts of successful therapy. Our review of 22 studies representing 2,073 children found overall HRQL is reduced among children with ALL on treatment when compared to healthy control or sibling control groups. While HRQL was reported to improve over time, a significant proportion of children appear to experience ongoing reductions in HRQL. Just over half of the included studies (12/22) documented clinical and sociodemographic factors associated with, and potentially causal for, poor HRQL outcomes, despite the importance of identifying children at increased risk of worse HRQL while on treatment. There was low consistency across studies with regard to possible correlates of poor HRQL. Therefore, only tentative evidence exists for clinical factors associated with poor HRQL including being on more intensive phases of chemotherapy,[36,40,55] currently receiving corticosteroid therapy,[33,50,56] and experiencing a greater number of different toxicities.[36,52] Child demographic factors frequently associated with reduced HRQL included older age [26,36,43,52,54,55] and female sex.[26,52,55] Parent and family factors associated with HRQL included household income,[55] household size,[36] and problematic family functioning.[36] Although studies were of reasonable quality and generally

TABLE 2 Clinical and sociodemographic correlates of HRQL[a]

Factor	Associated with worse HRQL	No association with HRQL	Associated with better HRQL
Clinical			
On treatment	Overall HRQL[26]	Overall HRQL[54] Psychosocial domain[26,54] Physical, social, emotional, domains, and school subscale[54]	
Intensive continuation of chemo	Physical, social, emotional domains[54] Overall HRQL[39]		
Continuation phase	Overall HRQL (*E. coli* asparaginase worse than *E. coli* minus Erwinia)[34]		
Induction phase	Overall HRQL[56]		
On steroids	Overall HRQL (Dexamethasone)[49] Procedural anxiety, nausea, pain and hurt subscales (dexamethasone or prednisone)[55]	Overall HRQL[51]	
Time since diagnosis	Social[54]		Bodily subscale[51]
ALL diagnosis	Emotional distress[42]	Overall HRQL, and physical and psychosocial domains[42]	
High risk	Overall HRQL, psychosocial, physical, emotional domains[54] Cognitive subscale[49]	Overall HRQL[34]	
Toxicity	Overall HRQL[51] Physical and social domains[56]		
Days in hospital	Overall HRQL[51]		
Sleep	Overall HRQL[8,50]		
Child characteristics			
Age	Overall HRQL[26,42,51,54] Psychosocial domain[54] Physical domain[26,51,56] Fatigue subscale[26] Self-esteem subscale[42] School subscale[54] Cognitive function subscale[51,53] Worry subscale[51]	Overall HRQL[34,40,42] Psychosocial and physical domains[42]	Anxiety subscale[39,51] Treatment anxiety, communication subscales[39]
Sex Female	Overall HRQL[26,51,54] Psychosocial, social, emotional domains[54] Physical domain[26,54] School subscale[54] Appetite subscale[53] Cognitive functioning subscale[55]	Overall HRQL[34,55]	
Parent characteristics			
Ethnicity		Overall HRQL and fatigue subscale[26]	
SES		Overall HRQL and fatigue subscale[26]	
Education		Overall HRQL and fatigue subscale[26]	
Household income			Overall HRQL and physical, psychosocial, and social domains[54]
Marital status		Psychosocial and emotional domains[54]	
Household size	Emotional, social domains[56]		
Parents' sex (Mother)			Overall HRQL[51]
Poor family functioning	Emotional, social domains[56]		

[a]Associations are presented where tested. Associations with overall HRQL are presented first followed by domains and then subscales.

representative of the population of children with ALL receiving treatment, these results require further validation; as in many cases, the finding was not consistent across all studies that examined these correlates.

Children undergoing treatment for ALL move through different phases of treatment including induction, consolidation, and maintenance therapy, which can span between 2 and 3 years.[1] HRQL generally improved over time, yet remained lower than the general population after treatment, with social and emotional domains of HRQL particularly vulnerable to lasting decrements. Few studies specifically investigated changes in HRQL according to treatment phase or type, and these results were not consistent. Overall, children currently on active treatment for ALL experienced worse HRQL than those not receiving active treatment. Children currently receiving corticosteroid treatment experienced declines in HRQL, consistent with qualitative studies where parents report all aspects of their child's HRQL are significantly compromised while on corticosteroids.[59,60] For example, children experience distressing emotional side effects (depression, increased aggression, and agitation) as well as physical side effects (nausea, vomiting, lethargy, weight gain, and disrupted sleep).[59] Despite having a potentially profound impact on HRQL, treatment-related toxicities were rarely investigated. Side effects of treatment worry and distress parents.[10,11,61] Landolt et al. suggested that experiencing a greater number of toxicities during initial treatment may account for the relationship between high treatment intensity and worse HRQL.[62] Understanding what impact treatment-related side effects have on HRQL may be important for determining whether changes in the patient's management are required.[63,64] Longitudinal studies which document a child's HRQL during treatment and beyond are needed to identify ways to best manage the impact of treatment-related side effects in the acute setting and maximize longer term functional and survival outcomes.

Conceptualizations of HRQL emphasize the importance of social–cultural context,[19] and for children, this encompasses family context as a key determinant of their HRQL.[28] The treatment for ALL causes significant disruption to normal family life. Usual routines for parents, healthy siblings, and the ill child become interrupted due to the ongoing requirements of treatment. For example, parents report missing significant amounts of work as they care for their child,[65] and both the unwell child and healthy sibling may miss significant amounts of school due to treatment.[66,67] This separation from home, family, siblings, and classmates may potentially have the greatest impact on the child's HRQL during ALL treatment, as indicated by persistent reductions in social and emotional HRQL when compared to other domains. However, standardized measures of HRQL in children often lack reference to the family and community context in which children live.[68] The only study to investigate family function included in our review found children from families with poor functioning had compromised HRQL particularly in the domains of social and emotional well-being.[36] Further research is needed to understand how families and children cope and function in the face of ALL treatment and how this ultimately impacts on a child's HRQL.

Measuring HRQL throughout treatment should remain a priority to improve the quality of care patients receive.[63] Although implementing routine HRQL assessment in clinical practice may be challenging,[69] psychosocial standards of care recommend assessment taking into account HRQL changes throughout treatment to enhance the care families and patients receive.[70] Within adult oncology, routine use of patient reported outcomes in clinical practice has been associated with improved service delivery, doctor–patient communication and greater patient satisfaction, and in some cases better outcomes such as improved symptom control and increased supportive care.[71,72] Qualitative research with children with other chronic diseases (such as type 1 diabetes) suggests returning results of HRQL assessment back to children and their families provides insight into their health condition and motivation to engage in healthy lifestyle behaviors.[73] Providing patient- and family-reported HRQL scores to pediatric oncologists increases discussion of emotional and psychosocial functioning without increasing consultation length.[74–76] Hashemi et al. found that parents randomized to receive education about ALL, the impact ALL treatment has on their child, and ways to improve HRQL led to improvements in parent-proxy reported HRQL compared to the control group.[58] Future research into how early signs of poor HRQL functioning could be addressed acutely, for example, by active parent education or active parent participation in research about the underlying diagnosis and toxicities experienced by their child, or targeted psychosocial support for children and families identified at risk, will be important for enhancing HRQL through treatment and beyond.

4.1 | Limitations

Studies did not consistently investigate risk factors for poor HRQL during treatment, and results were not reliable across studies. As such, the conclusions of our review are tentative and should be considered a starting point for further investigation. Alternatively, the lack of consistent predictors of HRQL outcomes while on treatment may reflect the intensity of treatment. Clinical and sociodemographic factors may become more important for determining HRQL in survivorship where only a proportion of children may continue to experience reduced HRQL. Although measuring HRQL is increasingly considered an important outcome for inclusion in clinical trials,[14–16,18] few studies included in this review were part of clinical trials, suggesting the use of HRQL assessment continues to be underutilized in pediatric clinical trials.[77,78] Given the variability in measures employed, different time points assessed, and lack of comparison across treatment protocols, the current data did not allow us to undertake a formal meta-analysis. Children's perspectives were underrepresented with only seven studies reviewed including child self-report of HRQL. In addition, most studies employed generic measures of HRQL (e.g., PedsQL Generic Core Scale, HUI 2/3). However, these measures may lack sensitivity to changes in HRQL for children on treatment when compared to cancer specific measures (e.g., PedsQL Acute Cancer Module).[28] The results in this review may therefore underestimate the impact of ALL treatment on a child's HRQL. Future research with routine collection of HRQL outcomes using sensitive measures during treatment will be crucial for informing clinician's treatment decisions where survival outcomes are similar but HRQL outcomes may differ.

5 | CONCLUSIONS

In our review of 22 studies, we found the HRQL of children with ALL was significantly compromised while currently receiving treatment. Although HRQL generally improved over time, there was some evidence to suggest a proportion of children may experience ongoing reductions in HRQL during survivorship. We identified few consistent clinical and sociodemographic factors that were associated with HRQL while on treatment. Poor HRQL appeared to be associated with intensive phases of chemotherapy, corticosteroid therapy, experiencing greater toxicity, older age, and female sex. Understanding HRQL across ALL treatment allows at risk patients to be identified early and offered intervention or support with the potential to alter HRQL while on treatment and beyond.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Additional Supporting Information may be found online in the supporting information tab for this article.

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