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ORIGINAL ARTICLE

Health-related quality of life in paediatric patients up to five years post-treatment completion for acute lymphoblastic leukaemia: a systematic review

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Abstract

Purpose Despite survival rates greater than 90%, treatment for paediatric acute lymphoblastic leukaemia (ALL) remains challenging for families. The early post-treatment phase is an especially unique time of adjustment. The primary aim of this review was to identify and synthesise research on health-related quality of life (HRQoL) for patients up to five years post-treatment. The secondary aim was to identify if theorised risk/resistance model factors could explain any variance in reported HRQoL.

Methods We conducted a systematic review using the PRISMA guidelines across five databases: Embase, Medline, Psychinfo, Pubmed, and Cochrane. Only studies examining HRQoL up to five years post-treatment were included. Studies were excluded if they covered periods greater than five years post-treatment or did not differentiate between patients with ALL and other cancers. After assessing the quality of each study sample size, patient characteristics, HRQoL outcomes and HRQoL correlates were extracted and summarised.

Results A total of 14 studies representing 1254 paediatric patients, aged 2–18 years, were found. HRQoL findings were mixed, dependent on time since completion and comparison group. Patient HRQoL was mostly lower compared to normative data, whilst higher compared to healthy control groups, patients on treatment, and patients with other types of cancers. Lower HRQoL was also found to be associated with demographic (age and sex), family dysfunction, and treatment-related factors.

Conclusions Completing treatment signalled a significant improvement in HRQoL for patients compared to being on treatment. Overall, however, HRQoL was still significantly lower than the population during the early post-treatment period.

Keywords Health-related quality of life · Acute lymphoblastic leukaemia · Systematic review · Post-treatment completion · Paediatric cancer

Abbreviations

ALL	Acute lymphoblastic leukaemia
HRQoL	Health-related quality of life
QoL	Quality of life
PedsQL	Paediatric quality of life inventory
CHQ	Child health questionnaire

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Introduction

Acute lymphoblastic leukaemia (ALL) is the most commonly diagnosed cancer in children, with survival rates now exceeding 90% [1, 2]. Paediatric cancer differs from many other paediatric health conditions in that ongoing monitoring is recommended following curative treatment [3, 4]. From a psychosocial perspective, diagnosis and treatment of ALL have been shown to lead to adjustment difficulties for not only the patients but also their families [5–7]. Upon completing treatment, patients and their families attempt to re-adjust and return to pre-diagnosis life. Adjustment, according to the World Health Organisation (WHO) definition, is more than just the absence

of disease and should encompass physical, mental, and social well-being [8]. Numerous instruments for measuring adjustment exist based on differing interpretations of this definition; however, most research that covers paediatric populations operationalises adjustment as health-related quality of life (HRQoL) incorporating the influence of illness and treatment across multiple domains including the following: physical health, psychological state, levels of independence, social relationships, and environmental features [9]. In addition, patient self-reported HRQoL is often considered the standard in paediatric cancer populations; however, parent proxy reports of HRQoL have been validated and used where patients are too ill and physically unable to complete instruments [9]. Previous reviews of patients on treatment for ALL, as well as long-term survivors of ALL, have found that a large percentage report lower HRQoL during treatment and a subset continue to report lower HRQoL many years following treatment completion [10–13]. Despite recent improvement in survival rates, there has generally been little focus on HRQoL during the immediate period following treatment completion or on identifying non treatment-related potential predictors of long-term HRQoL.

Following the completion of treatment for ALL, regular surveillance is usually recommended for approximately five years, a period when interactions with health services can be markedly reduced when compared to interactions during treatment. Previous reviews on the adjustment of patients following treatment for ALL typically include studies of long-term outcomes, i.e. five or more years, and up to 30 years, post-treatment completion [11, 13]. Findings have been mixed, with some studies in these reviews reporting lower HRQoL whilst others have reported no difference between patients and controls suggesting possible changes in adjustment over time [11, 13]. In addition, studies that consider HRQoL during treatment are mostly cross-sectional and tend to rely on parent proxy reports given the age and capacity of the patients, whilst studies that focus on long-term outcomes often shift to patient self-reports of HRQoL [10–13]. Previous reviews have also lacked a theoretical framework to guide interpretation of the variance in HRQoL reported post-treatment. As a result, relatively little is known about the general adjustment of patients during the period between treatment completion and the initial years of surveillance. It is also difficult to extrapolate the findings of the current literature for patients who have completed treatment for ALL using modern regimens with reduced toxicity and improved survival rates [14].

Patient and family experiences in the first few years of surveillance after treatment completion may be markedly different from the active treatment phase and the longer-term survivorship period. During post-treatment surveillance, the available literature shows that parents of patients can have mixed feelings of gratefulness and uncertainty, along with the pervasive fear of their child relapsing, whilst patients themselves report relief as they no longer face the physical and psychological demands of treatment [15–17]. In order to understand these differing experiences of patients and their parents across this period, the risk/resistance model provides a theoretical framework for investigating and understanding how the adjustment of one significantly ill family member can affect the individual as well as other members of the family [18]. The underlying assumptions of the risk/resistance model are that risk factors (e.g. physical illness and associated parental stress), intrapersonal factors (e.g. optimism), social-ecological factors (e.g. family functioning), and stress processing factors (e.g. coping styles) interrelate to influence individual adjustment when a family member is suffering from a health condition [18]. As such, this review aims to (i) identify and synthesise cross-sectional and longitudinal research on parent proxy and self-reported adjustment, operationalised as HRQoL, following treatment for ALL solely within the first five-year surveillance period, (ii) compare the reported HRQoL of this cohort with normative data or controls if included, and (iii) identify if the theorised risk or resistance factors are associated with HRQoL in order to guide future interventions.

Methods

We conducted a systematic literature review targeting studies that examined the HRQoL of survivors of paediatric ALL using the PRISMA guidelines across five databases: Embase, Medline, Psychinfo, Pubmed, and Cochrane [19]. The initial search was completed on 20 October 2017 and a repeat search completed on 10 February 2019. We used the following search terms with limits to only include studies published after 2000: ((acute or (precursor adj cell)) adj1 (lymphoblastic or lymphocyt* or lymphoid or lymphatic) adj1 (leuk?emia or lymphoma)) AND ((quality adj2 life) or qol or hrqol) AND (newborn* or baby or babies or neonat* or infan* or toddler* or pre-schooler* or preschooler* or kindergarten or boy or boys or girl or girls or child or children or childhood or adolescen* or pediatric* or paediatric* or youth* or teen or teens or teenage*). A follow-up search of the reference lists of the included studies was also completed. Non-peer reviewed grey literature was not included in this review. Studies published prior to 2000, a period when radiation therapy was also regularly used during treatment, were not included in this review to ensure that we primarily covered patients treated using modern regimens likely to only involve chemotherapy [20, 21].

Inclusion and exclusion criteria

We used the following inclusion criteria to screen studies: (i) patients diagnosed with ALL aged up to 18 years at the time of diagnosis; (ii) studies examining HRQoL using a validated instrument with adequate reliability and validity, primarily

based on the list of instruments thoroughly reviewed by Palermo et al. [9]; (iii) studies solely covering the period up to five years post-treatment completion for ALL; and (iv) studies published in English. The exclusion criteria were as follows: (i) studies combining the HRQoL data of patients with ALL with the HRQoL data of patients with other types of paediatric cancer and (ii) studies combining the HRQoL data of patients with ALL for both periods less than five years post-treatment completion and periods greater than five years post-treatment completion.

Screen and data extraction

Independent reviewers (AG and BD) screened the titles and abstracts of the search results. Reviewers obtained full texts of studies that potentially met the inclusion criteria. These were then assessed by the reviewers to determine inclusion, with a third independent reviewer (MM) consulted if consensus could not be reached. Data extraction of the final studies, which included study type, sample size, patient characteristics, HRQoL outcomes, and HRQoL correlates was completed by the reviewers (AG and BD) with results compared for the first 25% of studies to verify the data extraction procedure.

Quality assessment

We completed quality assessments for each study using the instrument developed by Kmet et al. [22]. This instrument has been previously used in similar reviews [10, 11] and adequately covers fundamental aspects of study designs, methods, measurements, outcomes, and bias using 14 items, rated on the degree to which they meet the criteria (2 = "Yes", 1 = "Partial", 0 = "No" or N/A) [22]. A total score is then calculated and adjusted for the number of "N/A" responses. Higher scores equate to higher quality studies. Two independent reviewers (AG and BD) assessed the quality of the first 25% of studies together, after which the remaining studies were assessed separately with an inter-rater reliability of > 90% (see Online Resource 1).

Results

Both the initial and updated searches returned a combination of 994 studies after the removal of duplicates. Titles and abstracts were screened leading to the exclusion of a further 882 studies. The full texts of the remaining 112 studies were reviewed, and studies that did not meet the inclusion criteria were excluded (see Fig. 1). An additional five identified studies were included after a hand search, resulting in a final 14 studies, representing 1254 patients being identified as eligible for data extraction. No qualitative studies were included due to the requirement that HRQoL be measured using a validated instrument. No studies were excluded due to the instrument used, as all included studies utilised reliable and valid instruments. A summary of the data extracted from these studies is presented in Table 1.

The majority of studies rated well in terms of the quality assessment ($M = .85$, $SD = .10$, range = 0.68–0.95). All studies appeared to report their results adequately with no missing data. Lower quality ratings were primarily due to relatively small sample sizes [23, 27–29, 31, 32, 34]. This was expected given the overall incidence rates of ALL in the population. Kobayashi et al., for example, had a total sample of 35 participants; however, only data from a subset of six participants was used in this review as this was the total number of participants in the post-treatment phase [28]. Studies were also rated lower for not considering or controlling for potentially confounding variables, such as type or duration of treatment (see Supplementary Table S1). The four lowest rated studies were due to a combination of the abovementioned factors [25, 27, 28, 34]. The data reported in studies with lower quality ratings were not excluded given the overall small number of identified studies that met the selection criteria. The findings of these lower quality studies, however, were interpreted cautiously.

With regard to measurement instruments, six studies defined and measured HRQoL as outlined in the Paediatric Quality of Life Inventory using self-report or parent proxy forms [24, 28–30, 32, 35]. The remaining studies used a range of different instruments that broadly covered adjustment, operationalised as quality of life, including the Health Utilities Index and the Child Health Questionnaire, amongst others [16, 23, 25–27, 31, 33, 34]. Nine studies compared self-report and parent proxy responses with normative data [16, 23, 24, 26, 27, 29–31, 34]. Five studies relied solely on parent proxy reports of their child's HRQoL post-treatment completion [24, 29, 30, 34, 35]. Countries of origin were diverse, with seven studies using instruments in a language other than English [23, 25, 27, 28, 31, 32, 34]. Four studies examined HRQoL immediately following treatment completion [23, 24, 31, 35], with the remaining studies covering reported HRQoL between two months and five years post-treatment completion [16, 25–30, 32–34]. Six of the included 14 studies tracked the HRQoL of patients longitudinally [23, 24, 26, 30, 31, 35] either from diagnosis onwards or treatment completion onwards. Given these reasons, the extracted data was not deemed suitable for quantitative analysis given the heterogeneity of methodology, and differing reports (parent proxy versus self-report) and measurement instruments.

HRQoL post-treatment completion

The findings of this review, both within and between studies, were mixed. The same study could report both higher and lower HRQoL depending on whether comparing to normative data, controls, patients on treatment for ALL, or patients with

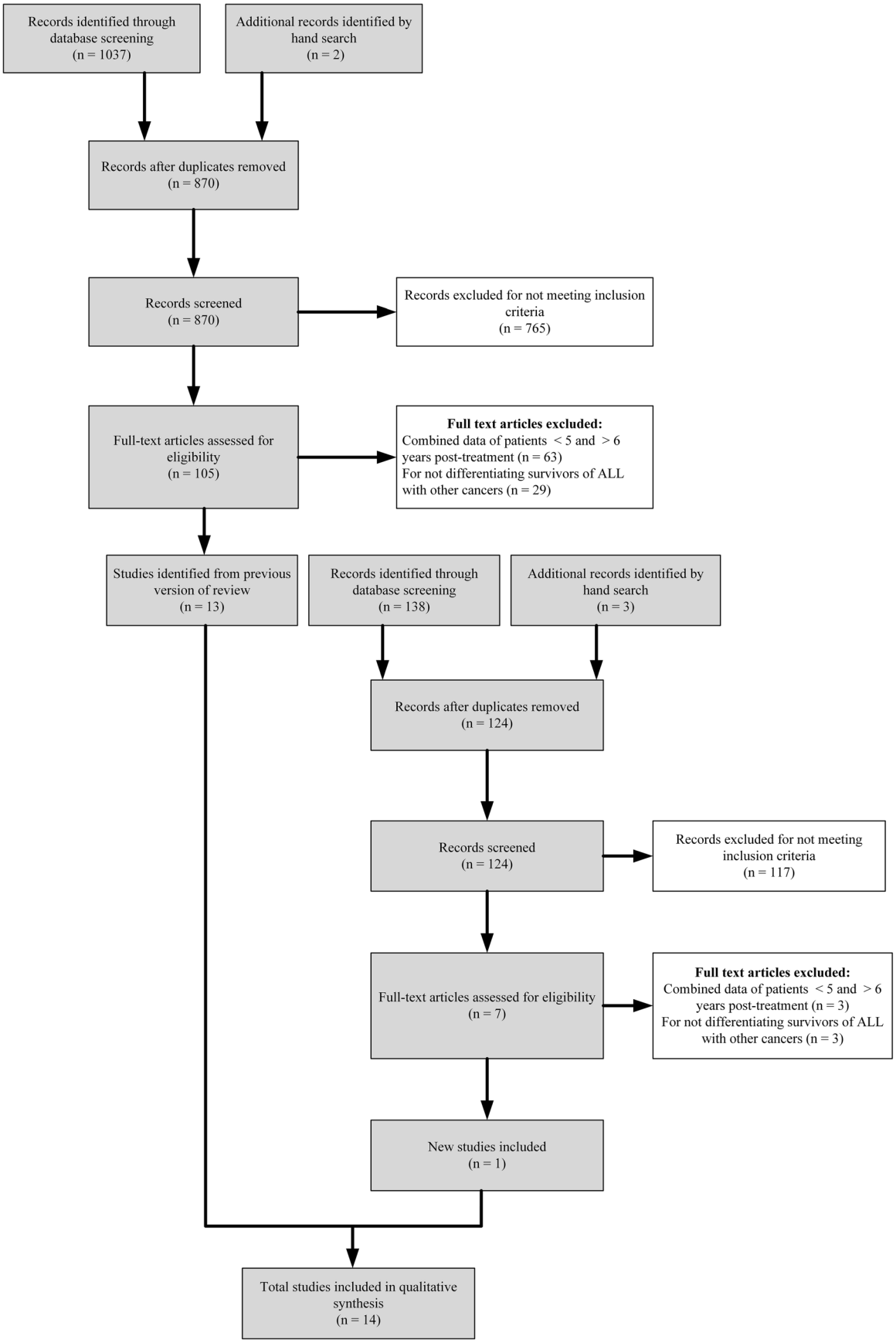

Fig. 1 Flow diagram of study selection and review

Table 1 Post ALL treatment completion HRQoL outcomes by study

Study/ country	ALL sample/overall study characteristics	Age at study	Control group	Post-treatment period	Instrument	Results
de Vries et al., 2008 [23]. Netherlands	37 parents and 12 patients with ALL. Longitudinal study tracking patients from midpoint of ALL treatment (time-point 1) to treatment completion (time-point 2).	*M* = 5.6 *SD* = 3.3	Population normative comparison data.	At treatment completion	Paediatric cancer quality of life inventory—self-report and parent proxy (Dutch). Child Health Questionnaire (CHQ)—parent proxy (Dutch).	▪ Self-reported quality of life (QoL) was significantly lower than population norms both during treatment and post-treatment completion. ▪ Self-reported QoL post-treatment completion was significantly higher than during treatment. ▪ Parent proxy reports were significantly lower than norms both during and post-treatment completion. ▪ Parent proxy reports were significantly higher post-treatment completion than during treatment.
Eiser et al., 2017 [24]. UK.	Parents of 139 patients with ALL. Longitudinal study tracking patients from ALL diagnosis (time-point 1) through to treatment completion (time-point 5).	Median = 8 Range = 4–18	Population normative comparison data.	At treatment completion.	Paediatric quality of life inventory (PedsQL) 4.0—parent proxy.	▪ Parent proxy reports were significantly lower than normative data at all time-points including treatment completion.
Fluchel et al., 2008 [25]. Uruguay.	49 patients with ALL and their parents. Cross-sectional study of the HRQoL of paediatric patients diagnosed with ALL and patients diagnosed with brain tumours, post-treatment completion.	*M* = 13.6 *SD* = 4.26	96 healthy controls.	2 years post-treatment completion.	Health utilities index—self-report and parent proxy (Spanish).	▪ Patients with ALL self-reported lower overall HRQoL post-treatment completion when compared to controls. ▪ Patients with ALL self-reported higher overall HRQoL post-treatment completion when compared to patients with brain tumours.
Furlong et al., 2012 [26]. Canada.	171 patients with ALL and their parents. Longitudinal study tracking patients with ALL from initial induction (time-point 1) through to 2 years post-treatment completion (time-point 5).	*M* = 9.8	Population normative comparison data.	2 years post-treatment completion.	Health utilities index—self-report and parent proxy.	▪ Patients with ALL self-reported significantly lower overall HRQoL when compared to normative data when on active treatment. ▪ No significant differences found between self-reported overall HRQoL of patients with ALL and normative data 2 years post-treatment completion.
Gordijn et al., 2013 [27]. Netherlands.	35 patients with ALL and 61 parents. Cross-sectional study of QoL in patients with ALL post-treatment completion.	*M* = 9.7 *SD* = 3.2	Population normative comparison data.	22–62 months post-treatment completion.	CHQ—self-report and parent proxy (Dutch).	▪ Patients with ALL had significantly higher self-reported QoL across several domains following treatment completion when compared to normative data. ▪ Parent proxy reports of QoL were significantly lower than normative data following treatment completion for ALL.
Kobayashi et al., 2017 [28]. Japan.	6 patients with ALL and their parents in the off-treatment group. Cross-sectional study of different groups of patients with ALL at multiple treatment phases: consolidation, maintenance and 2-month off--treatment.	*M* = 7.8 *SD* = 1.9	Two control groups: sibling group and age-/gender--matched group.	2 months post-treatment completion.	PedsQL 4.0—self-report and parent proxy (Japanese).	▪ In the consolidation and maintenance phase groups, patients with ALL self-reported significantly lower HRQoL when compared to the control groups. ▪ No significant differences found between self-reported overall HRQoL and control groups 2 months post-treatment completion. ▪ At 2 months post-treatment completion, patients with ALL self-reported higher HRQoL—social functioning when compared to the control groups.
Meeske et al., 2004 [29].	26 parents of patients with ALL. Cross-sectional study comparing parent reports of patients with ALL and parent reports of patients with brain tumours on active treatment and	*M* = 7.8 *SD* = 4.1	Population normative comparison data.	< 12 months post-treatment completion.	PedsQL 4.0—parent proxy.	▪ A significant improvement was found between parent proxy reports for patients ≥ 12 months post ALL treatment completion and patients

Table 1 (continued)

Study/ country	ALL sample/overall study characteristics	Age at study	Control group	Post-treatment period	Instrument	Results
USA.	post-treatment completion (two separate groups: ≥ 12 months post-treatment completion and < 12 months post-treatment completion).					< 12 months post ALL treatment completion when compared to normative data. ▪ No significant differences were found between parent proxy reports for patients on active treatment for ALL when compared to patients < 12 months post ALL treatment completion and patients ≥ 12 months post ALL treatment completion.
Mitchel et al., 2016 [30]. USA & Australia.	100 parents of patients with ALL. Longitudinal study tracking patients with ALL at initial induction (time-point 1) throughout treatment (time-points 2–3) and 3 months post-treatment completion (time-point 4).	*M* = 4.9 *SD* = 2.9	Population normative comparison data.	3 months post-treatment completion.	PedsQL 4.0—parent proxy.	▪ Parent proxy reports were significantly lower on overall HRQoL when compared to normative data at the start of treatment. Parent proxy reported HRQoL at start of treatment was also lower when compared to HRQoL during treatment and lower again when compared to HRQoL 3 months post-treatment completion. ▪ Parent proxy reports showed significantly higher HRQoL at 3 months post-treatment completion when compared to normative data.
Peeters et al., 2009 [31]. Germany.	20 patients with ALL and 39 parents. Longitudinal study tracking patients with ALL at diagnosis (time-point 1) through active treatment and treatment completion (time-point 3).	*M* = 8.2 *SD* = 3.4	Population normative comparison data.	At treatment completion.	KINDL—self-report (German). Paediatric oncology quality of life scale—parent proxy (German).	▪ Self-report of overall QoL for patients with ALL and parent proxy reports were significantly lower than normative data at all time-points. ▪ In regards to specific time-points, patients with ALL self-reported significantly higher overall QoL at treatment completion when compared to diagnosis or active treatment, despite still being lower than normative data. ▪ Parent proxy reports of overall QoL significantly improved at treatment completion when compared to diagnosis and active treatment, despite still being lower than normative data.
Pogorzala et al., 2009 [32]. Poland.	18 patients with ALL. Cross-sectional study of patients in remission from ALL and patients in remission from brain tumours.	Median = 11.9 Range = 8.2–18.6	60 healthy controls.	≤ 3 years post-treatment completion.	PedsQL 4.0—self-report (Polish).	▪ Both brain tumour patients and patients with ALL self-reported significantly lower HRQoL ≤ 3 years post-treatment completion when compared to controls.
Shankar et al., 2005 [33]. USA.	44 patients with ALL. Cross-sectional study comparing patients on active treatment for several types of cancers including ALL, and patients post-treatment completion.	Median = 10.6 Range = 8–13	481 age-matched healthy controls.	< 5 years post-treatment completion.	Minneapolis-Manchester quality of life youth form—self-report.	▪ Patients with ALL who were between 1 and 5 years post-treatment completion self-reported significantly higher overall QoL when compared to case matched controls.
Stam et al., 2006 [16]. Denmark.	64 patients with ALL and their parents. Cross-sectional study of patients post-treatment completion for several types of cancers including ALL.	*M* = 8.3 *SD* = 4.6	Population normative comparison data.	< 6 months post-treatment completion.	TAPQOL, TACQOL—self-report and parent proxy.	▪ Parent proxy reports of overall QoL was significantly lower than normative data < 6 months post-treatment completion for children under 8 years of age. ▪ No significant differences were found between self-reported overall QoL of patients with ALL aged 8–11 < 6 months post-treatment completion.

Table 1 (continued)

Study/country	ALL sample/overall study characteristics	Age at study	Control group	Post-treatment period	Instrument	Results
						▪ Patients with ALL aged > 11 self-reported significantly lower overall QoL when compared to normative data < 6 months post-treatment completion.
van Litsenburg et al., 2013 [34]. Netherlands.	33 patients with ALL. Cross-sectional study of patients with ALL up to 4 years post-treatment completion.	*M* = 9.3 *SD* = 3.3	Population normative comparison data.	< 4 years post-treatment completion.	Health utilities index—parent proxy (Dutch).	▪ No significant differences found between parent proxy reports of overall QoL and normative data < 4 years post-treatment completion.
Zheng et al., 2018 [35]. USA	162 female patients with ALL and 133 male patients with ALL. Longitudinal study of patients with ALL 2 months post-diagnosis up to treatment completion.	*M* = 6 *SD* = 1.6 (at diagnosis, not reported for completion of treatment).	Population normative comparison data.	At treatment completion (26 months post-diagnosis for females and 38 months for males.)	PedsQL 4.0—parent proxy.	▪ Despite improving over time, significant impairments were still found across physical, emotional, and social functioning domains of HRQoL at treatment completion (26 months for females and 38 months for males post-diagnosis) when compared to population comparative data.

other types of cancers, and also depending on age, time following treatment completion and parent proxy or self-report. Where higher HRQoL scores were reported, this indicated better or improved HRQoL, whilst lower HRQoL scores suggested difficulties or challenges with HRQoL, but not necessarily clinical impairments.

Seven of the 14 studies reported higher overall HRQoL for patients post ALL treatment completion when patients were compared to normative data, controls, patients on treatment for ALL, and patients with other types of cancers [25, 27–31, 33]. Four of the 14 studies reported no difference in overall HRQoL dependent upon which group patients were being compared to [26, 28, 29, 34]. For example, patients completing treatment for ALL in one study showed no difference in HRQoL when compared to normative data [26]. Significantly lower overall HRQoL was reported by six of the 14 studies, again depending on which group that the patients completing treatment for ALL were being compared to; normative data, controls, patients on treatment for ALL, and patients with other types of cancers [16, 23–25, 27, 31, 32]. One study did not include an overall measure of HRQoL, reporting on only three of the subscales (physical, emotional, and social functioning) and finding all three to be lower than normative data at treatment completion [35].

Regarding correlates of HRQoL, three of the 14 studies found that patients who were younger or female were more likely to report lower overall HRQoL [29, 30, 34]. Furthermore, Stam et al. found that parents of patients who were less than 8 years old reported that their children had more problems with sleep, behaviour, and appetite, as well as lower HRQoL when compared to normative data [16].

In terms of the specific domains that comprise HRQoL, studies included in this review reported on overall HRQoL as well as at least two of the three domains of adjustment used in the WHO definition (physical, emotional, or social) dependent upon the instrument used [8]. With regard to statistically significant differences reported on individual HRQoL domains, nine of the 14 studies specifically reported lower physical functioning at some point in the post-treatment completion period, mostly nearer to treatment completion [16, 23, 24, 27, 29–32, 35]. This appeared to improve over time, with Meeske et al. reporting significantly higher physical functioning in a small sample of patients that were more than 12 months off treatment when compared to patients less than 12 months off treatment [29]. In addition, seven studies examining either emotional, social, or school/environmental functioning reported these domains as significantly lower depending on the instrument used and comparison group [16, 23–25, 31, 32, 35], whilst three found no difference in these domains, also depending on comparison groups [26, 28, 29, 34]. Only four of the 14 studies reported significantly higher emotional, social, or school/environmental functioning post-treatment completion when compared to controls, normative data, and patients with different types of cancers [23, 24, 30, 32].

Seven of the 14 studies included both parent proxy and self-reports [16, 23, 25–28, 31], with two of these studies finding that parents reported their child's overall HRQoL to be significantly lower than parents of controls [27, 31], whilst another study found no difference [23]. However, in these same studies, self-reported overall HRQoL was higher than the corresponding parent proxy reports across the separate domains of HRQoL [27, 31]. Of the four studies that only included parent proxy reports of their child's HRQoL post-treatment completion, results were mixed, with two showing no difference in overall HRQoL [29, 34], and two showing significantly lower overall HRQoL, and specific domains of HRQoL, when compared to normative data [24, 35].

HRQoL over time

Across the four studies examining overall HRQoL or domains of HRQoL at treatment completion, patients who had completed treatment appeared more likely to self-report higher HRQoL than those patients still on treatment [23, 24, 31, 35]. The patients in these four studies, however, still displayed significantly lower HRQoL when compared to normative data, as reported via parent proxy (see Fig. 2) [23, 24, 31, 35]. For the three studies that covered six months or less post-treatment, patients were found to be either no different to control groups or more likely to self-report higher HRQoL than normative data [16, 28, 30]. For the same period, parent proxy reports continued to be significantly lower than normative data or patients on treatment [16, 28, 30]. The remaining seven out of 14 studies covering the period 12 to 60 months post-treatment showed that both self-reports and parent proxies were mostly higher in terms of HRQoL when compared to normative data, control groups, or patients on treatment [25–27, 29, 32–34].

Risk/resistance factors

With regard to patient-related risk factors, Mitchell et al. found adverse events such as seizures or impaired limb functioning during treatment, predicted lower overall HRQoL in patients three months post ALL treatment completion [30]. Gordijn et al. reported that parent ratings of their child's impaired sleep and increased fatigue correlated with lower physical functioning during the post-treatment period [27]. Inversely, the patients themselves reported less sleep problems as well as improved social functioning in the same study [27]. Two studies reported correlations between the type of treatment (e.g. radiotherapy) and lower physical functioning during the post-treatment period [23, 32]. One study examined the social-ecological resistance factor of family functioning, finding that after controlling for age and sex, family dysfunction predicted poor emotional functioning at treatment completion [35]. Intrapersonal and stress processing resistance factors were not examined in any of the 14 studies included in this review.

Discussion

The overall aims of this review were to summarise the literature available on the adjustment, operationalised as HRQoL, of paediatric patients in the first five years post-treatment completion for ALL, as well as examining if theorised risk or resistance factors were associated with adjustment. This review identified

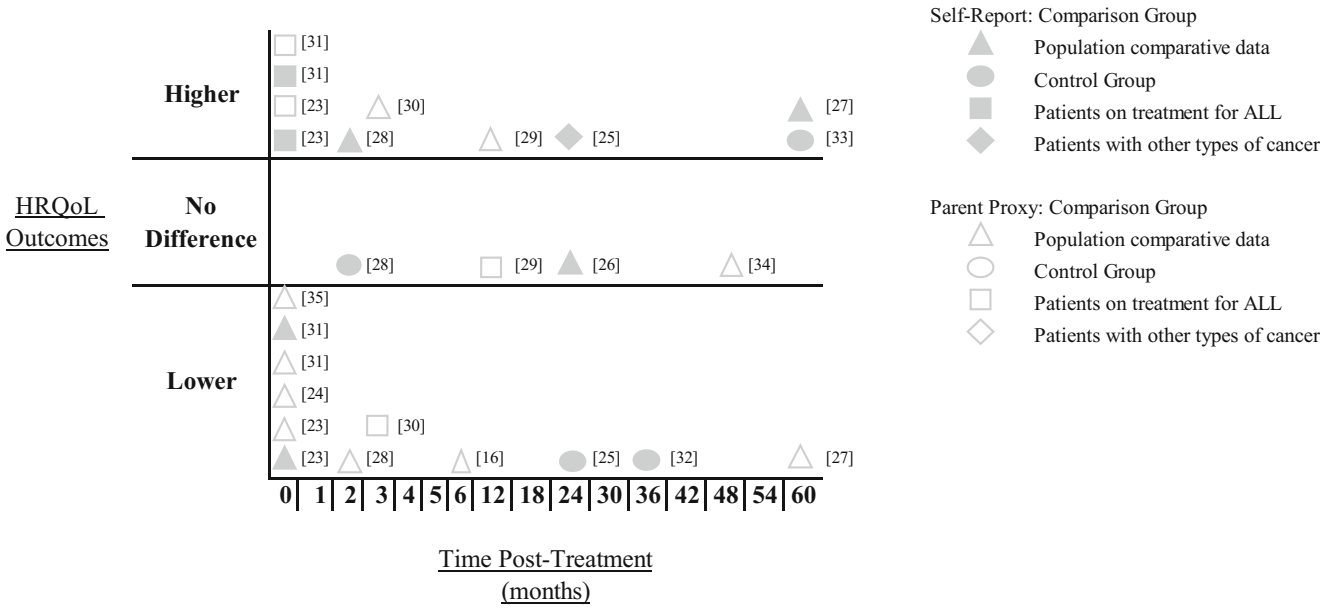

Fig. 2 HRQoL reported by study over time

and synthesised 14 studies covering this period, finding that patients who had completed ALL treatment reported higher HRQoL or no difference when compared to patients on treatment [23, 26, 29, 31], control groups [28], normative data [26–30, 34], and patients with other types of cancers [33]. A subset of patients were found to have lower HRQoL when compared to normative data shortly after treatment, primarily reported by parent proxy [16, 23, 24, 28, 31, 35]. As theorised by the risk/resistance model, this review also identified that the presence of risk factors, such as treatment-related side effects or child characteristics including poor sleep patterns, were more likely to be associated with poorer quality of life post-treatment completion [16, 30]. Social-ecological resistance factors, such as family dysfunction, were also found to predict domains of HRQoL highlighting the influence of the family environment on the patient [35].

Previous reviews have found that long-term survivors of ALL often report lower HRQoL experienced many years after treatment completion that is usually attributable to adverse late effects, such as secondary cancers, cognitive late effects, fertility issues, psychosocial issues, and higher incidence of psychopathology [10–12]. In this review, the improvements across HRQoL domains were found shortly after treatment completion and mainly when patients were compared to those still on treatment [23, 30, 31]. This may simply be attributable to the immediate relief of being "cured" of ALL, marking an important milestone for the patient and their parents as they are no longer undergoing intensive treatment regimens with potential adverse side effects. Despite this, however, most patients still reported lower HRQoL when compared to healthy children shortly after treatment [16, 23, 24, 28, 31, 35]. These patients, despite being free of disease and no longer undergoing treatment, continued to exhibit lower HRQoL similar to the findings of previous reviews that focused on long-term survivorship [10, 11]. HRQoL did, however, appear to improve slightly as time progressed [25, 27, 29, 33], possibly due to improved physical recovering over time, as well as, the fear of relapse subsiding as patients transition to long-term survivorship. HRQoL, therefore, may be influenced by factors relating to the patients and family and not just improved treatment regimens.

Multiple studies found that lower HRQoL was reported via parent proxy and not the patients themselves, suggesting that parents were perceiving treatment completion as a negative experience on behalf of their child [16, 23, 24, 27, 28, 30, 31, 35]. This could be as a result of the significant distress, fatigue, loneliness, and fear of relapse that parents themselves often report following their child's treatment [17]. The post-treatment period is also characterised by reduced interactions with health services, leaving patients and their parents with diminishing support as they attempt to recover from their cancer experience. Additionally, for patients who have ongoing complications from treatment-related side effects, the period immediately following treatment completion is likely to continue to cause significant distress leading to lower HRQoL.

When considered with respect to the theoretical framework of the risk/resistance model, as expected, the presence of ongoing risk factors, such as treatment-related physical effects or child characteristics including poor sleep patterns and family dysfunction, was more likely to be associated with lower HRQoL post-treatment completion [16, 30, 35]. For families where parents reported child lower HRQoL and the patient themselves did not, one possible explanation could be the presence of intrapersonal resistance factors (e.g. optimism) that mitigate the impact of risk factors (e.g. parental distress or family dysfunction). For example, patients may be more likely to better adjust post-treatment completion if they are optimistic of returning to pre-diagnosis life and have adequate social support, despite ongoing risk factors, such as parental distress or persistent complications of treatment. As the studies included in this review appeared to focus primarily on examining correlating risk factors, future research would benefit from considering intrapersonal and socioecological resistance factors. By identifying resistance factors amenable to intervention, health services will be able to better allocate their limited post-treatment resources to target this group. The early post-treatment period presents the most opportune time to engage patients and their families in useful education programs and targeted interventions. Due to reduced medical requirements but ongoing links with health services, patients and their families could, therefore, be engaged in proactive programs to avert negative long-term outcomes.

Limitations

The sample sizes of studies included in this review were relatively small, attributable to the low incidence rates of ALL and study participation rates. Several studies cited this factor as an important consideration when interpreting results and a potential risk of bias. The inconsistent use of HRQoL instruments, sometimes in multiple languages, also leads to difficulty comparing and generalising results. Studies conducted in different languages may mask important social and cultural differences that influence HRQoL for those patients and their parents. It is also important to note that the majority of studies reporting significantly lower HRQoL tended to be those with lower quality ratings due to smaller sample sizes and inability to control for confounds, such as type and duration of treatment [23, 25 27, 28–29, 31–32, 34]. Different stages of disease risk and different modes of treatments that cause side effects of varying severity may have potentially significant influences on HRQoL post-treatment completion [12]. Where possible, future studies should endeavour to utilise homogenous patient samples whom have undergone similar types of ALL treatment, whilst managing confounds such as incidence of relapse, pre-existing health conditions, and cultural and socio-demographic factors.

Conclusions

This systematic review of 14 studies found that overall HRQoL for patients within the first five years post-treatment completion for ALL was similar to, or higher than, patients on active ALL treatment, normative data, control groups, and patients with other types of cancers [23, 25, 27–31, 33]. A subset of patients were found to have lower HRQoL post-treatment completion when compared to normative data, controls, patients on treatment for ALL, and patients with other types of cancers [16, 23–25, 27, 28, 31, 32]. Despite reporting improved overall HRQoL, many patients continued to report lower physical functioning post-treatment completion [16, 23, 24, 27, 29–32, 35]. Risk factors found to contribute to lower HRQoL (overall and physical functioning) included: age at completion, sex, family dysfunction, type of treatment, and the experience of adverse events during treatment, as theorised by the risk/resistance model [29, 30, 34]. Protective resistance factors, however, were not identified as studies focused more on reporting on HRQoL outcomes, rather than explaining the variance. More research is required to understand this variability in adjustment for the initial period post-treatment completion and to identify potential resistance factors, suggested by the risk/resistance model, that are amenable to intervention in order to better support those patients susceptible to negative long-term outcomes.

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Compliance with ethical standards

Conflict of interest statement The authors declare that they have no conflict of interest.

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