Comparison of child and family reports of health-related quality of life in pediatric acute lymphoblastic leukemia patients after induction therapy

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Abstract

Purposes: To determine the health-related quality of life (HRQOL) of children with acute lymphoblastic leukemia (ALL) during induction therapy, clarify the agreement between child self-reported and family proxy-reported HRQOL, and examine the related factors of HRQOL, especially child age, family attendance, and children's social relationships outside of the family. Methods: We analyzed questionnaire data (2012–2017) from the Japanese Pediatric Leukemia/Lymphoma Study Group's ALL-B12. Participants were children with B-cell Precursor ALL aged 5–18 and their families. Participants answered the Pediatric Quality of Life Inventory TM (PedsQL TM) Generic Core Scales (PedsQL-G) and Cancer Module (PedsQL-C) to measure pediatric HRQOL. We calculated the differences between child self-reported and family proxy-reported subscale scores along with intraclass correlation coefficients (ICC). We conducted multiple regression analyses according to all participant pairs and age groups (young child, school age and adolescent), with ICCs for all PedsQL-G subscales (ICC-G) and all PedsQL-C subscales (ICC-C) as the outcome variables. Results: Five hundred twenty-two pairs of children and their families were analyzed. We observed a moderate level of agreement on most PedsQL subscales between the child self-reports and family proxy-reports; however, worry had the weakest agreement for all PedsQL subscales (ICC = .32). The agreement of ICC-C was positively related to family attendance for the young child group (B = .185, p = .003). Conclusion: We observed some differences between child self-reports and family proxy-reports of HRQOL of children with ALL, suggesting that both parties should be administered HRQOL measurements during treatment.

Background

Acute lymphoblastic leukemia (ALL) is the most common type of childhood cancer, accounting for about 25% of pediatric cases (Ishii 2009). Treatment for ALL, divided into the stages of induction therapy, intensive therapy, and maintenance therapy is recommended to be given within at least 3 years of diagnosis (Matloub et al. 2011). Early treatment of high-risk groups and advancements in the use of multiagent and intrathecal chemotherapy, etc., has led to a dramatic increase in the five-year survival rate; it now stands at approximately 80% (Inaba et al. 2013; Pui et al. 2008). With the rise of survival rate, researchers conducting clinical trials have increasingly valued determining time-to-event outcomes such as overall and disease-free survival rate, as well as patients' subjective outcomes, which are more easily assessed, such as quality of life (Eiser and Morse 2001). One particularly important factor is health-related quality of life (HRQOL), a multidimensional construct broadly conceptualized as the effect of a disease and its treatment on individuals' physical, emotional and social well-being functioning (Upton et al. 2008; Varni et al. 1999). Scales for assessing HRQOL are generally divided into two types. First are "generic scales," focused on children's general health condition regardless of the presence of a specific disease or disorder. Generic scales can be used to compare the HRQOL of children with a variety of diseases or none at all (Varni et al. 2002). The second type can be referred to as "disease-specific scales," which are focused on the domains of health affected by a specific illness and its treatment. Disease-specific scales are able to precisely pinpoint the impacts of a given disease on children's health and functioning (Matsuda et al. 2006; Varni et al. 2002).

A recommended form of investigating HRQOL is through subjective assessment. However, it is important to understand the degree of agreement or mismatch between HRQOL as assessed by children (i.e., child self-report) in contrast to those of family members (family proxy-report), especially when considering the age, developmental stage, disease condition, cognitive ability, and linguistic skill of children (Hinds et al. 2007; Ishida et al. 2003; Warschburger et al. 2003). The degrees of agreement or mismatch between child self-reports and family proxy-reports have been found to vary according to family, child characteristics and physical and psychosocial domains (Eiser and Varni 2013), suggesting the importance of clarifying agreement between these reports of HRQOL among children with ALL.

One previous study examined the level of agreement between child self-reported and family proxy-reported HRQOL among pediatric patients with ALL, and determined that children's age, sex, treatment intensity, and steps were related to this agreement (Parsons et al. 2012). Given the influencing effect of child age, it is possible that the agreement between reports depends on the time families spend with children, supposedly since the more time spent, the better are the chances of understanding the child's HRQOL (Eiser and Varni 2013). This is indirectly supported by research targeting older adults with dementia, where nursing time per week has been found to be associated with degree of agreement in reports of HRQOL (Tamim et al. 2002). Therefore, we can suppose that the amount of time children spend with their family members will improve agreement. Additionally, we suspect that the amount of time that children spend in social relationships outside the family, such as in nursery or elementary schools, affects the agreement between reports—that is, the less time children spend with their family and the more children interaction is focused on friends rather than family, the weaker the degree of agreement between reports (Eiser and Varni 2013).

To investigate issues related to agreement between reports, we drew on the clinical trial data of the Japanese Pediatric Leukemia/Lymphoma Study Group's (JPLSG) "JPLSG ALL-B12: A Multi-Center Phase II/III Study in Children with Newly Diagnosed B-cell Precursor ALL" (hereinafter, ALL-B12). In this trial, HRQOL was set as the secondary outcome, which is the first time this has been done in a large clinical trial in Japan. The ALL-B12 is expected to elucidate the randomized treatments effect of HRQOL. However, to clarify agreement between child self-reports and family proxy-reports of HRQOL, and factors related to this agreement, we thought it suitable to use the ALL-B12 at baseline before randomization of therapies (post-induction therapy).

Induction therapy comprises multidrug chemotherapy and invasive interventions such as repeated lumbar puncture and bone-marrow puncture (Oka and Tsurusawa 2005a). These are known for potential serious side effects such as pyrexia, nausea, and diarrhea (Viele 2003). Furthermore, patients undergoing induction therapies spend long periods in the hospital and have notable limitations in daily life (McCubbin et al. 2002). Given these conditions, we hypothesized that HRQOL would reach its lowest during induction therapy in comparison to other points of treatment. Accordingly, longitudinal HRQOL surveys of children with ALL have shown that, at one-month post-diagnosis (Children's Oncology Group, COG) (Mitchell et al. 2016) or 35 days post-diagnosis (Japan Association of Childhood Leukemia Study, JACLS) (Ishida et al. 2011), HRQOL was worst during induction therapy when compared with consolidation therapy,

maintenance therapy, or after therapy. Most studies on the HRQOL of children with ALL have almost exclusively focused on the post-chemotherapy period (Sung et al. 2011); however, focus on induction therapy has steadily increased within the last decade (Mitchell et al. 2016; van Litsenburg et al. 2014). Thus, we sought to clarify factors involving agreement of child-report and family proxy-report of HRQOL at induction therapy.

Therefore, the purpose of this study is (1) to clarify the degree of agreement between child self-reports and family proxy-reports of HRQOL among children with ALL, and (2) to determine the factors related to this agreement. Given prior findings, we were particularly interested in the influence of child age, family attendance, and social relationships outside of the family.

Methods

1. Data

We obtained and analyzed the data from questionnaires answered by children and their families in the ALL-B12. The following inclusion criteria were used to select relevant child–family pairs: (1) children with B-cell Precursor ALL and their family had entered ALL-B12 from December 2012 to November 2017; (2) children with B-cell Precursor ALL were aged 5–18 years; and (3) both children and their family returned completed and returned all questionnaires to the Center for Quality of Life Research after induction therapy (about 6 weeks from start of therapy).

2. Data collection

Children and their families were given questionnaires and a self-addressed stamped envelope by their attending physician before and after 2 weeks of the scheduled date of the end of induction therapy. Children and their families answered the questionnaires within four weeks of receiving them, and then sent them to the Research Center using the self-addressed stamped envelope.]

3. Measurements

1) HRQOL

We used the Pediatric Quality of Life Inventory Japanese Version (PedsQL) (Kobayashi and Kamibeppu 2010; Tsuji et al. 2011) to measure pediatric HRQOL. PedsQL was developed using surveys of various children, including healthy children and children with various types of disease (e.g., cancer), their families, and healthcare professionals. It is designed to measure pediatric HRQOL in the past month (Varni et al. 1999, 2001, 2002). PedsQL Generic Core Scales (PedsQL-G) (Kobayashi and Kamibeppu 2010) measure general HRQOL using the World Health Organization's (WHO) definition of health—"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"—with the added dimensions of role/school functioning (The WHO Group 1998). It comprises 21 items for children 5 to 7 years old and 23 items for those 8 to 18 years old in four functioning subscales (*physical, emotional, social* and *school functioning*). We also used the PedsQL Cancer Module (PedsQL-C) (Tsuji et

al. 2011), which focuses on dimensions of health affected by pediatric cancer and its treatment. It comprises 26 items for those aged 5 to 12 and 27 items for those 13 to 18 years old in eight subscales (level of *pain, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance,* and *communication*). Children and families answered each item on a 5-point Likert scale, where *0 = no problem, 1 = almost never, 2 = sometimes, 3 = often, and 4 = almost always*. However, children aged 5 to 7 years answer each item on a 3-point Likert scale adopting faces corresponding to frequencies: *a smiley face* representing "*0 = no problem*," *a neutral face* representing "*2 = sometimes*," and *a frowning face* representing "*4 = almost always*." Children answered the questionnaires with the help of their family or medical staff, if necessary. In such cases, we requested family members to first answer their questionnaires before helping children. Based on the PedsQL scoring algorithm (Varni 2017), we calculated the average score of each item in the subscales of both the child self-report and family proxy-report, and then transformed them to a 0–100 scale, where high scores indicated high HRQOL. If participants answered fewer than 50% of items in a subscale, the subscale was considered to have missing scores. For all domains, Cronbach's alphas exceeded .80 for both children and family members. These scales were, therefore, adequately valid in target participants.

2) Family attendance

Family members answered the number of days of hospitalization and their own attendance of their children during that hospitalization in the previous month. From these, we calculated the family attendance ratio by dividing the number of days of family attendance in the previous month by the number of days of hospitalization in that month.

3) Social relationships and nursery/school characteristics

Children reported the number of friends they perceived themselves to have (*1 = none, 2 = one friend, 3 = 2–3 friends, 4 = over 4 friends*), while their family answered whether children were attending a nursery or school and how present they were *(1 = almost always absent, 2 = present one-third of the time, 3 = present two-thirds of the time, 4 = almost always present*).

4) Demographic variables

Children reported their age and sex, while family members answered their age and relationship to the child.

4. Statistical analyses

We used R ver. 3.5.0 (R Core Team 2018) and set the significance level to 5% (two-tailed test). As a first step in the analysis, we calculated descriptive statistics classifying all children by their age group, as follows: young child (aged 5–7 years old), school-age (aged 8–12 years old), and adolescent (aged 13–18 years old).

To verify agreement between the child self-reports and family proxy-reports, we calculated differences in each PedsQL subscale between the types of reports using *t*-statistics and their 95% confidence intervals (95% CI). We also calculated intraclass correlation coefficients (ICCs) between child self-reports and parent proxy-reports, and their 95% CIs based on a two-way random effects model (Shrout and Fleiss 1979). Using Landis *et al.*'s criteria, ICCs were categorized as weak (≤ .40), moderate (.41–.60), substantial (.61–.80), and almost perfect (≥ .81) (Landis and Koch 1977).

To explore the factors influencing agreement between child self-reports and family proxy-reports for each family, we conducted multiple regression analyses for all participant pairs and age groups. The explanatory variables were the seven items previously mentioned, including (1) child's age, (2) child's sex, (3) family member's age, (4) family member's relationship to the child, (5) number of friends, (6) attendance at nursery/school, and (7) family attendance ratio; all were simultaneously entered into the regression analyses.

For outcome variables, we used several indicators of agreement, according to previous studies, including the absolute difference between PedsQL scores and the ICCs for all subscales between child self-reports and family proxy-reports. Previous studies have used both the difference (Parsons et al. 2012), and absolute difference (Juniper et al. 1996) in scores as indicators of agreement. In this study, the raw difference between reports was deemed inappropriate for multiple regression because larger numerical values would indicate less agreement when the difference was positive, but greater agreement when the difference was negative. Thus, we instead used the absolute values of the difference for subscale of the PedsQL. Finally, we calculated the ICCs for child self-reports and family proxy-reports of all 4 PedsQL-G subscales (ICC-G), which was defined as the agreement for overall pediatric HRQOL. Similarly, we calculated the ICCs of child self-reports and family proxy-reports of all 8 PedsQL-C subscales (ICC-C), which we defined as the agreement of pediatric HRQOL specific to cancer and its treatment.

5. Ethical considerations

The ALL-B12 was approved by the institutional review board of the Japanese Society of Pediatric Hematology/Oncology and the Graduate School of Medicine, The University of Tokyo. It also received approval from each participating medical center and hospital. We obtained permission to use the anonymized data of participants from the Japanese Society of Pediatric Hematology/Oncology ALL committee. We made sure to protect participants' personal information by conducting all de-identified data handling and analyses in the Research Center.

Results

1. Participants (Table 1)

A total of 961 children aged 5–18 years old registered in the ALL-B12 during the study period and received induction therapy, including 520 boys (54.1%) and 441 girls (45.9%). A total of 545 pairs of children and family members returned questionnaires (response rate: 56.7%). Twenty-three pairs were excluded for not

fully completing the PedsQL items, either for the child self-report (n = 17) or for the family proxy-report (n = 6). Thus, a total of 522 pairs (valid response rate: 54.3%) were used in the analysis.

Children's mean age was 9.2 years while that of family members was 40.1 years [range: 16–68]. Two hundred sixty-six children were male (51.0%). Regarding family relationship, the vast majority were mothers (481; 92.1%), 35 were fathers (9.7%), and the rest were grandparent or siblings. By age group, 205 were young children (39.3%), 215 were school age (41.2%), and 102 were adolescents (19.5%).

Children who had received six weeks of induction therapy tended to be hospitalized for most of the days in the past month. The mean number of days of family attendance in the past month was 18.7 days, and 289 family members (55.4%) spent every day with children while they were in the hospital (i.e., had a 100% family attendance ratio). By age group, the family attendance ratio was smaller for adolescents than for school-aged children and young children.

2. Agreement between child self-reports and family proxy-reports

To obtain the differences, we subtracted the family proxy-report scores from the child self-report scores for all PedsQL subscales. We observed significant differences in physical functioning (differences = 9.30; 95% CI: 7.4–11.2), emotional functioning (differences = 5.40; 95% CI: 3.2–7.6), social functioning (differences = 2.69; 95% CI: 0.8–4.6), pain and hurt (differences = 3.48; 95% CI: 1.1–5.9), nausea (differences = -3.65; 95% CI: -5.5–-1.8), procedural anxiety (differences = -5.58; 95% CI: -7.8–-3.4), and cognitive problems (differences = -1.27; 95% CI: -5.8–-1.9) among all children (Table 2).

According to the ICCs, however, worry had the weakest agreement for all PedsQL subscales (ICC = .32). For the other subscales, the degree of agreement was moderate to substantial (ICC = .41–.70). By age group, social functioning among adolescents (ICC = .32) and worry among young children (ICC = .24) and school age (ICC = .34) indicated weak agreement. The other PedsQL subscales indicated moderate to strong agreement. The mean ICC-G and ICC-C between child self-report and family proxy-reports were 0.54 and 0.48, respectively.

3. Factors related to agreement

When we set the absolute difference between child self-report and family proxy-reports as the outcome variable in the regression analysis, we observed no significant relationships and the coefficients of determination were nearly zero. The same finding was obtained when the ICC-G was used as the outcome variable (Table 3). However, when the ICC-C was set as the outcome, we found that family attendance ratio (*B* = .185, *P*-value = .003) were significantly related to agreement in the young child group (Table 4); there were no significant relations in the school-aged and adolescent groups.

Discussion

We investigated the agreement in child self-reports and family proxy-reports of HRQOL among children with ALL (especially young children) receiving induction therapy and its related factors.

1. Participant demographics

We selected children and adolescents from 5 to 18 years in this study, as the incidence of ALL has been found to be highest among 5 year-olds and decreasing with age (Ishii 2009). Furthermore, the gender ratio in terms of incidence has been reported as 1:1.3 (girl: boy) (Inaba et al. 2013). In line with these past findings, the largest group of participants was composed of young children, followed by school-aged and adolescents, and the number of boys was larger than that of girls. The ALL-B12 was conducted in almost all hospitals and centers treating childhood cancer in Japan. Therefore, we might safely conclude that there is no selection bias among participants—they may be considered suitably representative of children and adolescents aged 5 to 18 years old, having B-precursor ALL, and receiving induction therapy.

2. Agreement and discrepancy between child self-report and family proxy-report

Physical functioning had the lowest score of all PedsQL subscales, which corresponds to the findings of a previous Japanese study (Ishida et al. 2003). This is likely due to the effects of induction therapy. Furthermore, the family proxy-reports of physical functioning were significantly lower than were child self-reports; this result shows that family members who attended their children assessed their child's physical functioning lower than did the children themselves [31]. However, interestingly, the ICC of physical functioning was stronger than that of the other PedsQL-G subscales. The greater degree of concordance is perhaps because physical functioning is more observable than are the more subjective dimensions of functioning such as emotional and social functioning (Eiser and Morse 2001). More specifically, when children's health status was poor, their family members tended to observe them more carefully (Eiser and Morse 2001). Thus, although there were some differences between child self-reports and family proxy-reports, these differences were rather small, and the agreement was overall quite strong. Based on the results, we might say that family proxy-reports of children's HRQOL are somewhat worse than child self-reports in terms of physical functioning, although this deserves more thorough investigation.

Child self-reported role/school functioning scores were lower than were family proxy-reported scores on all PedsQL-G subscales within the young child group. This may be because family members did not consider it as much of a problem that children were absent from their nursery or school, as they were primarily concerned with their children's disease and treatment. In contrast, children felt worse about being absent from their nursery or school compared to staying at the hospital for treatment.

We found that the child self-reported procedural anxiety score was significantly lower than that of the family proxy-report—this difference was the largest of all PedsQL subscales. This subscale concerned children's feelings of fear and pain in having their blood sampled or having needles inserted in them. A previous Canadian study conducted among 260 children with ALL receiving treatment (Sung et al. 2011) similarly found that child self-reported procedural anxiety had lower scores than all other PedsQL-C subscales. The developmental literature of the Japanese version of the PedsQL-C (Tsuji et al. 2011) also found that the child self-reported procedural anxiety was the lowest scoring domain of HRQOL among young children. It seems clear that the fact that participants were involved in induction therapy is a justifiable reason for the finding lower scores, given that induction therapy includes highly invasive

examinations and combination treatments, such as repeated blood sampling, intrathecal chemotherapy (Pui et al. 2008), and bone-marrow aspiration (Oka and Tsurusawa 2005b).

Our present data showed that agreement between child self-reports and family proxy-reports ranged from moderate to strong for almost all of the subscales. However, worry showed the weakest level of agreement at all age groups, especially within young children. The child self-reported worry score was lower than was the family-proxy-reported score. A possible reason is that family members might have felt that children would find it difficult to predict the side effects of induction therapy or the likelihood of relapse; in contrast, children may have found it difficult to understand the future effects of induction therapy, thus leading to lower agreement.

A previous study including 51 families has suggested that both discrepancy and agreement are important indices to consider when examining the consensus between child self-reports and parent proxy-reports (Schulte et al. 2016). Indeed, we found differences between child self-reports and family proxy-reports in some domains of HRQOL among young children with ALL. This suggests that both reports are important for interpreting children's HRQOL, as they allow us to draw an accurate portrait of HRQOL.

3. Exploring the related factors of agreement between child self-reports and family proxy-reports

The standard deviations of ICC-G and ICC-C between child self-reports and family proxy-reports were variable. Additionally, we found that, in the young children group, agreement according to the ICC-C was stronger when family attendance ratio was higher. We confirmed Eiser *et al.*'s proposal (Eiser and Varni 2013) that parents spend more time with younger children and therefore might be expected to have a more comprehensive overview of their children's physical, emotional, and social functioning, thus leading to greater agreement between parents and younger children. An alternative explanation for influencing effect of family attendance ratio on agreement in the young children group is that family members might have asked medical staffs (e.g., doctors, nurses) about their children's symptoms while family members left their children's side. However, doctor–child agreement has been found to be weaker than parent–child agreement (Morrow et al. 2012), indicating that family members might have difficulty inferring their children's HRQOL from objective symptoms that medical staffs reported. Therefore, the longer family members spend with their child in the hospital, the stronger the agreement of their ratings with the child would seem because family members can observe children's symptoms directly.

Notably, no factors were related to agreement among all children or among school-aged children and adolescents. This is probably because school-aged children and adolescents do not spend as much time with their family, and their social interactions are predominantly outside of the family. Furthermore, in line with their growth, children are likely to become increasingly separated from their family as they age. However, family members would ask school-aged children and adolescents about their symptoms, which is perhaps why the time they spend with children (e.g., family attendance) and social relationships outside family are not related with agreement.

Several limitations to this study warrant mention. First, family attendance might not reflect actual family attendance because the questionnaire only assessed the number of “days” of family attendance. It would be necessary to add “hours and/or weekdays/weekends” to the family attendance ratio in a future study in order to improve our understanding of the relation of agreement with family attendance. Second, approximately 40% of children and their family members showed attrition in this study. A reason for this is likely children’s medical condition or higher psychological distress caused difficulty in answering the questionnaire. Further research should consider how to better retain these cases.

This study was a national survey conducted in numerous centers and hospitals treating pediatric cancer patients in Japan, and this study was the first to clarify the level of agreement between child self- and family-reported HRQOL, and how this is influenced by family attendance ratio during induction therapy. In the future, it is important to discuss the HRQOL of children with ALL who are receiving induction therapy while considering the results of this study.

Conclusion

This study showed the agreement between child self-reported and family proxy-reported HRQOL of children with ALL at induction therapy. Overall, we found a moderate level of agreement for most HRQOL subscales, despite some notable absolute differences. Furthermore, we found that a higher family attendance ratio was positively related to the agreement of cancer-specific HRQOL among young children. Therefore, we suggest that HRQOL measurements consider both children’s and family members’ perspectives.

Abbreviations

ALL: acute lymphoblastic leukemia

CI: confidence intervals

ICC: intraclass correlation coefficient

HRQOL: health-related quality of life

PedsQL: Pediatric Quality of Life Inventory^{TM}

Declarations

Ethics approval and consent to participate

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The ALL-B12 was approved by the institutional review board of the Japanese Society of Pediatric Hematology/Oncology

and the Graduate School of Medicine, The University of Tokyo (No. 3871). It also received approval from each participating medical center and hospital. We obtained permission to use the anonymized data of participants from the JPLSG ALL committee.

Informed Consent: We obtained written informed assent from all participants, especially under the age of 16, we obtained informed consent from all their guardians.

Consent for publication

Not applicable.

Availability of data and materials

The dataset in this study is accessible at the corresponding author upon a reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SN, IS, TS and KK designed this secondary study, and analyzed the data; and SN, IS, TS, KK wrote the paper. KK, MK, YO, TI, YI helped supervise this study. All authors have reviewed and approved the manuscript.

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Tables

Table 1: Demographic of children and their family members ($N = 522$)

		All Children ($N = 522$) n (%) or $mean \pm SD$		Young child ($n = 205$) n (%) or $mean \pm SD$		School age ($n = 215$) n (%) or $mean \pm SD$		Adolescent ($n = 102$) n (%) or $mean \pm SD$	
Child's age (years)		9.2	± 3.5	5.9	± 0.9	9.7	± 1.5	14.8	± 1.4
Child's sex	Male	266	(51.0)	109	(53.2)	107	(49.8)	50	(49.0)
	Female	256	(49.0)	96	(46.8)	108	(50.2)	52	(51.2)
Family member's age		40.1	± 6.4	37.3	± 4.9	40.5	± 6.3	44.9	± 6.3
Family member's relationship to the child	Mother	481	(92.1)	190	(92.7)	197	(91.6)	94	(92.1)
	Father	35	(6.7)	13	(6.3)	15	(7.0)	7	(6.9)
	Other	6	(1.2)	2	(1.0)	3	(1.4)	1	(1.0)
Number of friends (child perspective)	None	31	(6.3)	10	(5.1)	15	(7.4)	6	(6.2)
	One friend	23	(4.6)	10	(5.1)	10	(5.0)	3	(3.1)
	2—3 friends	134	(27.1)	72	(36.5)	45	(22.4)	17	(17.5)
	over 4 friends	307	(62.0)	105	(53.3)	131	(60.2)	71	(73.2)
Attending a nursery or school	Yes	426	(85.5)	143	(70.1)	200	(98.0)	83	(92.2)
	No	72	(14.5)	61	(29.9)	4	(2.0)	7	(7.8)
Presence at nursery or school	Almost always presence	132	(31.3)	43	(29.5)	73	(37.8)	16	(19.3)
	Presence two-thirds of the time	87	(20.6)	21	(14.4)	48	(24.9)	18	(21.7)
	Presence one-third of the time	50	(11.8)	12	(8.2)	33	(17.1)	5	(6.0)
	Almost always absence	153	(36.3)	70	(47.9)	39	(20.2)	44	(53.0)
Number of days of hospitalization in the previous month (days)		29.4	± 3.9	29.4	± 3.5	29.1	± 4.7	29.8	± 2.8
Number of days of family attendance in the previous month (days)		18.7	± 13.8	23.0	± 12.1	18.8	± 13.9	10.0	± 12.8
Family attendance rate		0.64	± 0.45	0.78	± 0.39	0.65	± 0.45	0.34	± 0.43

Notes: Excluding missing values.
Abbreviations: SD = Standard deviation.

Table 2: Agreement of child self-reports and family proxy-reports of pediatric health-related quality of life ($N = 522$)

		n	Child self-reports		Family proxy-reports		Diffences[a)]	*t*-value[b)]	95% CI for Differences (*lower*) (*upper*)		ICC[C)]	95% CI for ICC (*lower*) (*upper*)	
PedsQL-G (Generic Core Scales)													
Physical functioning	**All Children**	**518**	**54.4**	**± 25.5**	**45.0**	**± 26.2**	**9.3**	**9.64**	**7.4**	**11.2**	**.60**	**.47**	**.70**
	Young Child	204	56.9	± 24.5	47.4	± 27.3	9.3	6.08	6.3	12.3	.61	.45	.72
	School age	212	53.0	± 26.9	44.7	± 26.4	8.2	5.18	5.1	11.3	.60	.47	.70
	Adolescent	102	52.7	± 24.1	41.1	± 23.1	11.6	5.88	7.7	15.6	.58	.30	.73
Emotional functioning	**All Children**	**518**	**68.6**	**± 26.1**	**63.2**	**± 24.9**	**5.4**	**4.84**	**3.2**	**7.6**	**.49**	**.42**	**.56**
	Young Child	204	64.3	± 27.2	65.8	± 25.4	-1.3	-0.71	-5.1	2.4	.48	.36	.58
	School age	212	72.2	± 24.9	62.1	± 25.7	10.0	5.98	6.7	13.3	.50	.35	.62
	Adolescent	102	69.9	± 25.1	60.5	± 21.6	9.4	4.39	5.1	13.6	.54	.34	.68
Social functioning	**All Children**	**494**	**84.5**	**± 18.3**	**82.0**	**± 21.4**	**2.7**	**2.76**	**0.8**	**4.6**	**.41**	**.33**	**.48**
	Young Child	193	81.8	± 18.2	82.7	± 21.0	-0.8	-0.51	-3.9	2.3	.40	.28	.51
	School age	209	86.8	± 17.9	80.6	± 22.4	6.3	4.37	3.4	9.1	.46	.34	.57
	Adolescent	92	85.4	± 18.5	83.8	± 20.2	1.9	0.80	-2.8	6.6	.32	.12	.49
School functioning	**All Children**	**391**	**75.1**	**± 27.2**	**74.5**	**± 26.0**	**1.3**	**1.02**	**-1.2**	**3.7**	**.55**	**.48**	**.61**
	Young Child	119	63.8	± 31.0	78.1	± 25.4	-12.2	-5.45	-16.7	-7.8	.56	.35	.71
	School age	196	82.7	± 21.9	75.0	± 25.7	7.2	4.61	4.1	10.3	.54	.41	.65
	Adolescent	76	74.4	± 26.6	66.6	± 21.6	7.2	2.60	1.7	12.7	.57	.40	.71
PedsQL-C (Cancer Module)													
Pain and hurt	**All Children**	**521**	**74.6**	**± 31.3**	**71.1**	**± 29.9**	**3.5**	**2.87**	**1.1**	**5.9**	**.59**	**.53**	**.64**
	Young Child	204	72.8	± 32.8	74.7	± 28.5	-1.9	-0.97	-5.8	2.0	.59	.49	.67
	School age	215	77.7	± 30.2	70.4	± 31.2	7.3	3.79	3.5	11.1	.56	.45	.65
	Adolescent	102	71.5	± 30.0	65.3	± 28.8	6.1	2.62	1.5	10.8	.67	.54	.76
Nausea	**All Children**	**520**	**65.6**	**± 28.3**	**69.4**	**± 28.3**	**-3.7**	**-3.80**	**-5.5**	**-1.8**	**.70**	**.65**	**.74**
	Young Child	203	61.8	± 26.9	76.0	± 24.7	-14.0	-10.04	-16.8	-11.3	.61	.28	.78
	School age	215	71.0	± 28.6	67.3	± 30.4	3.6	2.68	1.0	6.3	.77	.71	.82
	Adolescent	102	62.0	± 29.1	60.4	± 27.8	1.6	0.73	-2.7	5.9	.70	.59	.79
Procedural	**All Children**	**520**	**63.9**	**±**	**69.5**	**±**	**-5.6**	**-4.99**	**-7.8**	**-3.4**	**.65**	**.59**	**.71**

anxiety				**32.2**		**30.0**						
	Young Child	205	50.9	± 30.7	64.1	± 30.9	-13.2	-7.45	-16.7	-9.7	.61	.40	.73
	School age	214	69.5	± 32.3	70.2	± 30.4	-0.6	-0.37	-4.0	2.7	.69	.61	.76
	Adolescent	101	78.4	± 24.4	78.9	± 24.3	-0.6	-0.25	-5.2	4.1	.53	.38	.66
Treatment anxiety	**All Children**	**509**	**86.3**	**± 22.5**	**85.6**	**± 21.3**	**0.6**	**0.65**	**-1.2**	**2.3**	**.58**	**.52**	**.64**
	Young Child	199	82.6	± 25.7	84.3	± 22.4	-2.1	-1.39	-5.0	0.9	.62	.53	.70
	School age	212	87.6	± 21.3	86.3	± 20.6	1.3	0.98	-1.3	3.9	.58	.48	.66
	Adolescent	98	91.0	± 16.4	86.8	± 20.5	4.3	2.26	0.5	8.1	.48	.31	.61
Worry	**All Children**	**515**	**65.6**	**± 30.4**	**66.3**	**± 31.7**	**-0.5**	**-0.33**	**-3.7**	**2.6**	**.32**	**.24**	**.40**
	Young Child	200	64.8	± 32.6	75.7	± 29.7	-11.1	-4.12	-16.4	-5.8	.24	.10	.36
	School age	214	69.4	± 28.0	64.6	± 31.3	5.0	2.14	0.4	9.5	.34	.22	.45
	Adolescent	101	59.2	± 30.0	51.0	± 30.3	8.7	2.80	2.5	15.0	.44	.27	.58
Cognitive problems	**All Children**	**508**	**75.6**	**± 23.7**	**79.4**	**±22.5**	**-3.9**	**-3.92**	**-5.8**	**-1.9**	**.53**	**.46**	**.59**
	Young Child	199	74.1	± 28.0	83.6	± 19.7	-9.6	-6.04	-12.7	-6.5	.43	.26	.56
	School age	212	78.1	± 26.3	78.5	± 22.2	-0.5	-0.34	-3.1	2.2	.64	.55	.71
	Adolescent	96	73.3	± 30.9	72.4	± 24.7	0.5	0.20	-4.5	5.5	.50	.33	.63
Perceived physical appearance	**All Children**	**488**	**73.1**	**± 27.9**	**74.2**	**± 27.6**	**-1.3**	**-0.98**	**-3.8**	**1.3**	**.48**	**.40**	**.54**
	Young Child	203	71.1	± 28.0	81.7	± 23.1	-10.6	-5.70	-14.3	-7.0	.43	.28	.55
	School age	197	75.8	± 26.3	70.1	± 29.6	6.0	3.28	2.4	9.7	.57	.46	.66
	Adolescent	88	71.6	± 30.9	66.6	± 28.4	4.0	1.13	-3.0	10.9	.41	.22	.57
Communication	**All Children**	**483**	**63.4**	**± 30.7**	**63.6**	**± 29.0**	**-1.0**	**-0.78**	**-3.4**	**1.5**	**.58**	**.52**	**.64**
	Young Child	197	55.8	± 31.1	63.9	± 29.2	-7.8	-4.08	-11.5	-4.0	.58	.48	.68
	School age	198	65.8	± 29.2	60.7	± 30.3	4.6	2.49	1.0	8.3	.61	.51	.69
	Adolescent	88	73.8	± 29.6	69.7	± 24.5	1.7	0.55	-4.3	7.7	.48	.30	.62

Notes: Excluding missing values.

a) Mean of the differences subtracting family proxy-reports from child self-reports, b) Comparing child self-reports and family proxy-reports using paired *t*-test

Abbreviations: CI = confidence interval, ICC = intraclass correlation coefficient, PedsQL = Pediatric Quality of Life Inventory™, *SD* = standard deviation.

Table 3: Multiple regression analysis of predicting ICC-G (intraclass correlation coefficient of all 4 PedsQL Generic Core Scales subscales)

	All Children (N = 522)			Young child (n = 205)			School age (n = 215)			Adolescent (n = 102)		
	B	*p*	*VIF*	*B*	*p*	*VIF*	*B*	*p*	*VIF*	*B*	*p*	*VIF*
Child's age	.006	.311	1.384	-.044	.285	1.449	.006	.732	1.132	-.022	.511	1.255
Child's sex	.016	.645	1.034	.021	.730	1.090	-.006	.899	1.048	.100	.249	1.125
Family member's age	-.002	.639	1.267	.002	.773	1.013	-.005	.193	1.095	.004	.661	1.179
Family member's relationship to the child	-.068	.328	1.031	-.022	.870	1.076	-.011	.904	1.042	-.290	.136	1.146
Number of friends	-.008	.680	1.022	-.010	.802	1.042	-.025	.340	1.032	.027	.569	1.075
Attendance at nursery/school	-.017	.202	1.037	-.006	.829	1.466	-.028	.186	1.093	-.035	.333	1.208
Family attendance ratio	-.069	.080	1.144	-.046	.537	1.064	-.111	.043	1.069	-.019	.845	1.066
R^2	.022	.319		.018	.948		.046	.356		.068	.665	
Adjust R^2	.003			-.039			.005			-.028		

Notes: Excluding missing values.
Child's sex: dummy code as 1 = Male, 0 = Female; Family member's relationship to the child: dummy code as 1 = Mothers, 0 = Others; Number of friends: 1 = none, 2 = one friend, 3 = 2–3 friends, 4 = over 4 friends; Attendance at nursery/school: dummy code as 1 = Yes, 0 = No; Family attendance ratio was calculated that number of days of child hospitalization divided by number of days of family attendance in the previous a month.
Abbreviations: *B* = non-standardized partial regression coefficient, PedsQL = Pediatric Quality of Life Inventory™, R^2 = coefficient of determination, *VIF* = variance inflation factor.

Table 4: Multiple regression analysis of predicting ICC-C (intraclass correlation coefficient of all 8 PedsQL Cancer Module subscales)

	All Children (N = 522)			Young child (n = 205)			School age (n = 215)			Adolescent (n = 102)		
	B	*p*	*VIF*	*B*	*p*	*VIF*	*B*	*p*	*VIF*	*B*	*p*	*VIF*
Child's age	.002	.740	1.385	-.041	.221	1.449	-.017	.329	1.133	-.023	.418	1.255
Child's sex	.010	.753	1.035	.013	.795	1.090	.024	.623	1.052	-.019	.797	1.125
Family member's age	.004	.200	1.268	.009	.100	1.013	.001	.842	1.097	.010	.190	1.179
Family member's relationship to the child	.041	.524	1.032	-.119	.286	1.076	.125	.176	1.042	.075	.656	1.146
Number of friends	-.021	.253	1.022	-.055	.081	1.042	.013	.625	1.032	-.059	.145	1.075
Attendance at nursery/school	-.018	.157	1.038	-.019	.384	1.466	-.018	.399	1.095	-.014	.656	1.208
Family attendance ratio	.020	.593	1.145	.185	.003	1.064	-.050	.359	1.072	-.091	.282	1.066
R^2	.019	.438		.158	.003		.022	.818		.085	.506	
Adjust R^2	.000			.109			-.020			-.009		

Notes: Excluding missing values.
Child's sex: dummy code as 1 = Male, 0 = Female; Family member's relationship to the child: dummy code as 1 = Mothers, 0 = Others; Number of friends: 1 = none, 2 = one friend, 3 = 2–3 friends, 4 = over 4 friends; Attendance at nursery/school: dummy code as 1 = Yes, 0 = No; Family attendance ratio was calculated that number of days of child hospitalization divided by number of days of family attendance in the previous a month.
Abbreviations: *B* = non-standardized partial regression coefficient, PedsQL = Pediatric Quality of Life Inventory™, R^2 = coefficient of determination, *VIF* = variance inflation factor.