Original Article

Quality of Life in Children With Advanced Cancer: A Report From the PediQUEST Study

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Abstract

Context. Modifiable factors of health-related quality of life (HRQOL) are poorly described among children with advanced cancer. Symptom distress may be an important factor for intervention.

Objectives. We aimed to describe patient-reported HRQOL and its relationship to symptom distress.

Methods. Prospective, longitudinal data from the multicenter Pediatric Quality of Life and Symptoms Technology study included primarily patient-reported symptom distress and HRQOL, measured at most weekly with the Memorial Symptoms Assessment Scale and Pediatric Quality of Life inventory, respectively. Associations were evaluated using linear mixed-effects models adjusting for sex, age, cancer type, intervention arm, treatment intensity, and time since disease progression.

Results. Of 104 enrolled patients, 49% were female, 89% were white, and median age was 12.6 years. Nine hundred and twenty surveys were completed over nine months of follow-up (84% by patients). The median total Pediatric Quality of Life score was 74 (interquartile range 63−87) and was "poor/fair" (e.g., <70) 38% of the time. "Poor/fair" categories were highest in physical (53%) and school (48%) compared to emotional (24%) and social (16%) subscores. Thirteen of 24 symptoms were independently associated with reductions in overall or domain-specific HRQOL. Patients commonly reported distress from two or more symptoms, corresponding to larger HRQOL score reductions. Neither cancer type, time since progression, treatment intensity, sex, nor age was associated with HRQOL scores in multivariable models. Among 25 children completing surveys during the last 12 weeks of life, 11 distressing symptoms were associated with reductions in HRQOL.

Conclusion. Symptom distress is strongly associated with HRQOL. Future research should determine whether alleviating distressing symptoms improves HRQOL in children with advanced cancer. J Pain Symptom Manage 2016;■:■−■. © 2016 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.

Key Words

Quality of life, pediatric cancer, palliative care, end of life, patient-reported outcomes, symptom distress

Introduction

Promoting patient-centered outcomes such as health-related quality of life (HRQOL) has become a priority in pediatric research and clinical care.[1−9] This is particularly true for children with advanced cancer, where prior studies suggest a high degree of

symptom distress.[10,11] This distress, in turn, is associated with poor patient[12–14] and family[15,16] outcomes. Furthermore, patient HRQOL is a key determinant of parent decision making at the end of life, impacting participation in Phase I clinical trials,[17] use of artificial nutrition and hydration,[18] and advance care planning.[19,20]

The construct of HRQOL reflects individual perceptions of the impact of illness on overall, physical, functional, emotional, social, and spiritual well-being.[21,22] In pediatric oncology, much of the literature to date has involved parent-proxy report.[10,23–29] Fewer studies have included the voice of the child.[30–35] Likewise, prior studies have focused on survivors[26,36] or patients receiving therapy for cancers which are expected to be cured[23,25,33]; HRQOL in children with advanced cancer has seldom been described.[37–39] Deeper knowledge about patient-reported HRQOL in this group is needed to alleviate suffering and promote patient (and family) well-being.

Three recent systematic reviews identified a wide array of variables associated with HRQOL in children with cancer.[26,36,40] Factors consistently associated with poor HRQOL include concurrent cancer therapy,[41–45] higher treatment intensity,[23,46,47] poor prognosis or history of relapse,[23,26] older age,[25,36,40] cancer type (where patients with sarcomas or brain tumors have poorer HRQOL),[36,40,45,46] and female sex.[23,25,40,44] Although existing results may help identify patients at risk for poor HRQOL,[23] immediately modifiable factors of HRQOL, such as symptoms, have been insufficiently described.[26,36]

Using data from the Pediatric Quality of Life and Evaluation of Symptoms Technology (PediQUEST) study,[32] we aimed to describe 1) prospectively collected patient-reported HRQOL among pediatric patients with advanced cancer and 2) relationships between HRQOL, symptom distress, and demographic and medical factors. Based on the Wilson and Cleary HRQOL model,[48] we hypothesized that greater symptom distress would be associated with poorer HRQOL. If true, future interventions directed at recognizing and alleviating distressing symptoms could optimize clinical care and other patient-centered outcomes.

Methods

The present analyses use cohort data embedded in the PediQUEST trial.[32] PediQUEST is a computer-based data system designed to capture patient-reported outcomes (PROs) and generate reports. Results from a pilot randomized clinical trial (RCT) testing the effect of using PediQUEST to provide PRO feedback to health care providers and families (intervention arm) compared to usual care (control arm) have been published previously.[32]

Participants were recruited from three large pediatric cancer centers (Dana-Farber Boston Children's Hospital, Children's Hospital of Philadelphia, and Seattle Children's Hospital) between December 2004 and June 2009 and were eligible if they were at least two years old and had at least a two-week history of progressive, recurrent, or nonresponsive cancer. Of 147 approached patients, 104 (70.3%) enrolled.[32] Participants prospectively reported symptoms and HRQOL via the PediQUEST survey, which was administered through tablet computers during clinic or ward visits at most once weekly. For those not attending clinic, surveys were offered by phone once monthly. Participants received small nonmonetary incentives (toys for younger children, gift cards for teenagers). Patients were followed until the time of death or the end of data collection. Institutional review boards at each site approved the study. Patients aged 18 years and older, and parents of children under 18 years, provided signed informed consent. All children under 18 years provided informed assent.

Patient-Reported Outcomes Measures

The PediQUEST survey included the Pediatric Quality of Life Inventory 4.0 (PedsQL),[42] a well-validated measure of HRQOL, and the PediQUEST–Memorial Symptom Assessment Scale (PQ-MSAS),[49] an adaptation of the child MSAS which measures symptom burden. A detailed description of the PediQUEST survey has been presented elsewhere.[32] Briefly, PedsQL is a 23-item HRQOL instrument with high internal consistency (≥0.88 for both patient and proxy report), with physical, emotional, social, and school domains.[42] We used four age-appropriate versions (2–4, 5–7, 8–12, and 13–18 years old). Children may self-report from the age of five years. PQ-MSAS measures frequency, severity, and extent of bother from 24 physical and psychological symptoms with high internal consistency (>0.8). We used three age-appropriate versions (2–6, 7–12, 13–18 years old). Children may self-report from the age of seven, although the PQ-MSAS 7–12 is shorter (eight items) and complemented with parental report for the remaining 16 items.

For all ages, a PediQUEST survey consisted of a complete set of PedsQL and PQ-MSAS items. Only one respondent per tool (PedsQL or MSAS) was allowed, except for the PQ-MSAS 7–12 as explained previously. Whenever possible, children were encouraged to self-report. If no self-report version was available (children younger than five years old), or if children declined to answer, the corresponding parent-proxy versions were used. Children older than eight years completed their surveys independently; those 5–7 years old were read the questions out loud by research staff.[32] Whenever a child answered

their age-appropriate version, we considered the whole survey a self-report. For example, a self-report of a 7 year old would have child answers for PedsQL and PQ-MSAS 7–12 and parent answers for the remaining MSAS items. Equivalence across age-adapted versions and respondents was assumed.

Outcome of Interest: HRQOL (PedsQL Scores)

For each survey, PedsQL total score was calculated as the mean of the individual item scores; subscale scores reflected the means of physical, emotional, social, or school items respectively. Individual items were rated on a five-point Likert scale and scores transformed to a 0–100 scale (100 best).[42] The minimal clinically important difference (MCID) for PedsQL is estimated to be 4.4 points for the total, and 6.6–9.0 for the subscale scores.[50,51] Mean total scores among children during and more than 12 months after therapy are 70.88 (SD 17.19) and 77.66 (SD 15.25), respectively.[42] School scores were calculated for all children regardless of their school attendance following author recommendations. However, to help interpretation, the survey also included a single question about recent school attendance. For graphical purposes, we categorized HRQOL scores a priori as poor (<40), fair (40–69.9), good (70–79.9), or very good/excellent (80–100) based on prior literature suggesting these thresholds discriminate clusters of patients with progressively impaired HRQOL.[42,50,52,53]

Main Covariate of Interest: High Symptom Distress

PQ-MSAS item response options used 0–4 categorical scales for adolescent and parent-proxy versions and 0–3 scales for the 7- to 12-year-olds version. Physical symptoms included: pain, fatigue, drowsiness, nausea, anorexia, cough, diarrhea, vomiting, itching, skin issues, constipation, dysphagia, dry mouth, numbness, sweating, dyspnea, and dysuria; psychological symptoms included irritability, sleep disturbance, nervousness, sadness, worrying, difficulty concentrating, and image issues. All symptom scores were transformed to 0–100 scales (100 worst) and then categorized as high symptom distress if the score was ≥33 for adolescent or parent-proxy versions, or ≥44 for 7- to 12-year-olds PQ-MSAS. These thresholds were defined a priori, as previously described, to represent scores that implied moderate to severe distress in at least one symptom domain.[11]

Other Covariates

Clinical and demographic data were extracted from medical records, including age, sex, cancer type, date of diagnosis, and date of death (where applicable). Disease status (e.g., progressive disease with dates) and cancer-directed treatment in the 10 days before a PediQUEST administration (including dates, types

of treatment, and corresponding procedures) also were extracted. As previously reported, cancer-directed treatment was classified according to its intensity: mild (oral or outpatient chemotherapy and/or minor procedures), moderate (inpatient intravenous chemotherapy, radiation alone or with oral chemotherapy, or major procedure), or intense (hematopoietic stem cell transplant conditioning, radiation therapy with intravenous chemotherapy, or surgery).[11]

Statistical Analyses

We report results on outcomes collected over nine months of follow-up. Variables were described according to their distribution. We assessed association between PedsQL scores and high symptom distress using linear mixed models including high symptom distress and other covariates as fixed effects, and patient as a random effect to account for repeated measures. To adjust for potential confounding, all models included sex, age (dichotomized as age ≥ 13 years), cancer type, RCT intervention arm (PediQUEST intervention vs. standard of care), time since last cancer progression (categorical variable), and intensity if treatment received in the 10 days before the survey. We forward included symptom distress by prevalence[11] and used the Akaike information criterion to define the final model. When exploring PedsQL school subscores, we ran a sensitivity analysis excluding the surveys of children who had missed school for more than two weeks; because results were unchanged, we report school subscores for all surveys where it could be calculated. In the subcohort of participants who completed surveys in the last 12 weeks of life (73 surveys from 25 children), we analyzed the relationship between HRQOL and individual symptom distress (including only those symptoms reported as distressing in at least 15 [>20% of] surveys) and adjusted only by treatment intensity and time since last progression because of sample size considerations. Given the exploratory nature of the study, we did not correct for multiple comparisons. We used a listwise approach to handle missing data because less than 2% of the surveys had incomplete information in PedsQL or PQ-MSAS scores. All analyses were performed with SAS Statistical Software, version 9.3 (SAS Institute, Cary, NC).

Results

Full Cohort

Participant Characteristics. We have described response rates and child characteristics previously.[11,32,54] Briefly, 104 of 147 approached children enrolled. Of those, 49% were female, most were non-Hispanic, white race, and the median age was

Table 1
Patient Characteristics and the Median Number of Corresponding PediQUEST Surveys Completed for Each Characteristic

Child Characteristic at the Time of Enrollment	Full Cohort (*N* = 104 Children)			Subgroup of Children With End-of-Life Surveys (*N* = 25 Children)		
	n	%[a]	Median Number of Surveys Per Patient	*n*	%	Median Number of Surveys Per Patient
Intervention arm	53	51	8.0	16	64	4.0
Control arm	51	49	7.0	9	36	1.0
Girls	51	49	8.0	12	48	3.0
Boys	53	51	7.0	13	52	2.0
White race	93	89	8.0	22	88	2.0
<13 years old	54	52	8.0	12	48	2.5
≥13 years old	50	48	8.0	13	52	2.0
Hematologic malignancy	36	35	9.0	11	44	3.0
Brain tumor	10	10	7.5	1	4	3.0
Non−central nervous system solid tumor	58	56	7.5	13	52	2.0
Months since diagnosis (median, IQR)	24 (14, 40)		—	29 (21, 35)		—
Months since last progression before enrollment (median, IQR)	3 (2, 5)		—	4 (3, 6)		—

PediQUEST = Pediatric Quality of Life and Symptoms Technology; IQR = interquartile range.
[a]Totals may not add up to 100% because of rounding. Full cohort represents all children enrolled with surveys during first nine months of follow-up; end-of-life cohort represents the subgroup of children within the full cohort that died during follow-up and completed surveys in their last 12 weeks of life.

12.6 years (interquartile range [IQR] 7.9−17.1; Table 1). Fifty-six percent had a non−central nervous system (CNS) solid tumor, 35% had a hematologic malignancy, and 10% a CNS tumor. At study entry, median times since diagnosis and most recent disease progression were 24 months (IQR 14−40) and three months (IQR 2−5), respectively. The characteristics of children who enrolled were similar to those who declined participation.[54] For each enrolled child, a median of eight surveys were completed over nine months of follow-up, for a total of 920 PediQUEST surveys in the full cohort. Self-report rates were high: 84% of all respondents including 73% among 5−7 year olds, 96% among 8−12 year olds, and 99% among teenagers. In 64% of surveys, the reporting children had active disease. In 11%, they were hospitalized, and in 26%, their disease had progressed in the 10 days before survey completion. For 45% of surveys, children had been missing school for more than two weeks.

HRQOL. The median total PedsQL score was 74 (IQR 63−87; Table 2). In 38% of surveys, the total score was below 70 and consequently categorized as "fair" or "poor" (Fig. 1a). The physical subscore ranked lowest (median 69 [IQR 50−88]); 53% of physical scores fell in the "poor/fair" categories. School subscores also were low, with 48% being "poor/fair," whereas emotional and social subscores were only "poor/fair" in 24% and 16% of surveys, respectively.

Symptom Distress. Overall, participants reported a median of three (IQR 1−6) distressing symptoms per PediQUEST administration.[11] As previously reported, symptom distress was not related to the intervention.[11] In 73% (*n* = 674) of the 920 surveys, participants simultaneously reported at least two distressing symptoms. In 35% (*n* = 326), participants reported at least five, and in 12% (*n* = 109), they reported at least nine distressing symptoms. Some symptoms were more likely to occur together. The highest correlation was observed between nausea and vomiting (Spearman correlation, *r* = 0.61); nervousness, worry, and sadness (*r* > 0.45); and fatigue and drowsiness (*r* = 0.39).

Multivariable Models. Distressing symptoms (both physical and emotional) were strongly associated with HRQOL scores (Table 3). After controlling for sex, age, cancer type, RCT arm, treatment intensity, and time since disease progression, 13 distressing symptoms were independently associated with decreases in total and/or domain-specific HRQOL scores. Ten symptoms were associated with significant reductions in the total PedsQL score including difficulty concentrating, worrying, dry mouth, pain, sadness, irritability, insomnia, fatigue, vomiting, and anorexia. Difficulty concentrating and worrying were each associated with reductions ≥MCID. Among subscales, several symptoms also were associated with reductions ≥MCID. Specifically, dry mouth and pain for PedsQL physical, and worrying, sleep disturbance, and irritability for PedsQL emotional. Joint occurrence of these distressing symptoms was common in our study population. For example, children reported 2 of the 10 distressing symptoms associated with both PedsQL total and subscores in 165 (18%) of surveys. They reported 3 symptoms in 135 (15%), 4 in 86 (9%), and ≥5 in 105 (11%). The expected corresponding reduction in total PedsQL scores ranged from 4−9 points, 7−13 points, 10−16 points, and 13−32 points when 2, 3, 4, or ≥5 distressing symptoms are concurrently reported by the child, respectively.

Table 2
Median PedsQL Scores Among Patients in Full Cohort and the Subgroup With End-of-Life Surveys

Cohort	PedsQL Scale	N	Median Score	IQR
Full cohort (N = 104 children, 920 surveys)	Total	914	74	63−87
	Physical subscale	915	69	50−88
	Emotional subscale	914	85	70−95
	Social subscale	914	85	75−100
	School subscale	863	70	55−90
End-of-life cohort (N = 25 children, 73 surveys)	Total	71	70	52−89
	Physical subscale	71	56	31−91
	Emotional subscale	71	80	60−95
	Social subscale	71	90	80−100
	School subscale	68	75	50−93

PedsQL = Pediatric Quality of Life Inventory; IQR = interquartile range.
Full cohort represents all children enrolled with surveys during first nine months of follow-up; end-of-life cohort represents the subgroup of children within the full cohort that died during follow-up and completed surveys in their last 12 weeks of life.

For example, a patient reporting distress from both difficulty concentrating and worrying would be expected to have a total PedsQL score nine points lower than a patient not experiencing either distressing symptom. When ≥5 concurrent distressing symptoms were reported, the expected total PedsQL score would be between 13 and 32 points lower than for a patient not experiencing these symptoms.

Neither cancer type, time since last progression, treatment intensity, sex, age, nor RCT arm were associated with HRQOL scores after the introduction of symptom distress in any multivariable models.

Subgroup of Children With End-of-Life PediQUEST Surveys
Participant Characteristics. Among children who died during the nine-month follow-up, PediQUEST surveys were completed for 25 children during the last 12 weeks of life. The distribution of age and sex in these children was similar to the full cohort; however, only one had a brain tumor (Table 1). A median of three surveys were completed per child. Again, the rate of self-report was high: 79% of surveys were completed by the child, including 43% among 5−7 year olds, 92% among 8−12 year olds, and 98% among teens. Children had active disease for 81% of survey completions and had disease progression in the 10 days before survey completion 48% of the time. For 55% of surveys, children had been missing school for more than two weeks.

HRQOL and Symptom Distress. In surveys completed during the last 12 weeks of life, the median PedsQL score was 70 (IQR 52−89; Table 2). Forty-seven percent of total HRQOL scores were categorized as "poor/fair" (Fig. 1b). Physical and school subscores were worse, with 58% and 47% being "poor/fair," respectively. Eleven symptoms (pain, fatigue, drowsiness, anorexia, nausea, diarrhea, irritability, vomiting, sadness, dry mouth, and worry) were reported as distressing in at least 15 surveys. All 11 were associated with significant decreases in one or more HRQOL scores (Table 4) in a mixed model including the symptom, time since last progression, and treatment intensity. Almost all significant score reductions were larger than the respective MCIDs.

Discussion
The PediQUEST study is thus far the largest prospective cohort study of PROs among children with advanced cancer and includes a rare component of pediatric quality of life research: a high degree of patient report. Our findings address important gaps in pediatric oncology research and clinical care. We found that overall HRQOL in children with advanced cancer was similar to prior studies,[51] even among children responding in the last 12 weeks of life. Importantly, however, we found that symptom distress was strongly associated with clinically meaningful reductions in HRQOL and that these associations were unchanged after adjustments for factors previously identified as potential determinants of HRQOL. Specifically, high distress from both physical symptoms such as pain, and emotional symptoms such as worrying or difficulty concentrating, spanned multiple HRQOL domains. Distress from comparatively rare symptoms such as dry mouth[11] also was associated with significant changes in HRQOL.

The National Institutes of Health (NIH), Institute of Medicine, and Food and Drug Administration have all made understanding and improving patient-reported HRQOL a priority; knowledge of patients' experiences, symptoms, physical function, and psychosocial health enables tailored anticipatory counseling, clinical decision making, and alleviation of distress.[3,55−57] This is particularly important in the setting of pediatric advanced cancer, where there may be equipoise about treatment efficacy, and HRQOL drives patient, parent, and provider decision making.[17−20]
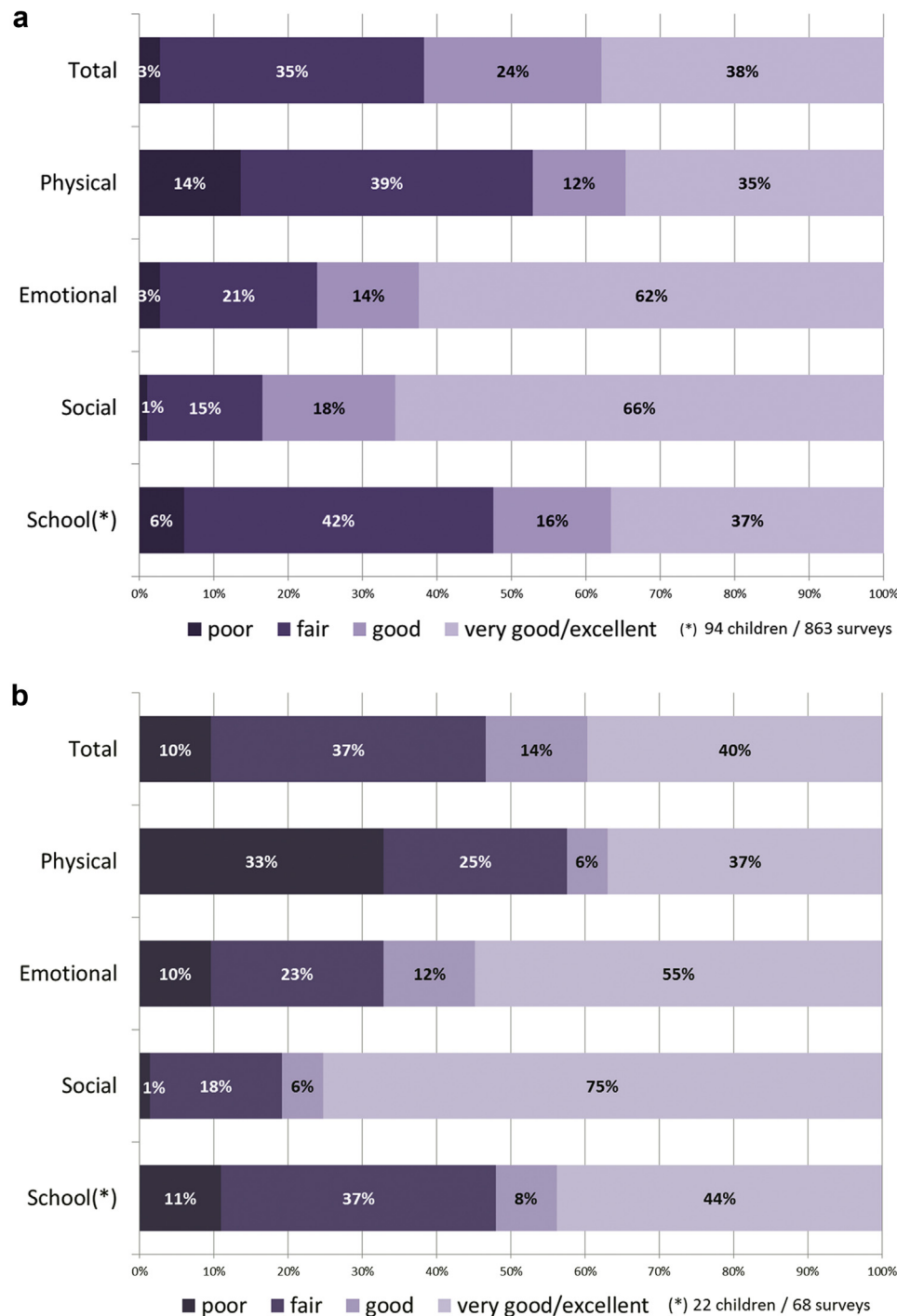
a

b

Fig. 1. Distribution of HRQOL scores among enrolled patients. a) Full cohort (all surveys [$n = 920$], all children [$n = 104$]); b) subgroup of children with end-of-life surveys (25 children, 73 surveys in the last 12 weeks of life). HRQOL = health-related quality of life.

Our findings suggest that intensive symptom management may improve HRQOL in children with advanced cancer. First, distressing physical and emotional symptoms were independently associated with reductions in patient-reported HRQOL in both the full and end-of-life cohorts. This was true regardless of symptom prevalence. Second, the presence of multiple concurrent distressing symptoms was common and had an additive effect on HRQOL scores. Third, although we are unable to determine the directionality of the association between symptom and HRQOL, the model proposed by Wilson and Cleary supports our hypothesis that symptom distress results in decreased HRQOL. Finally, none of the previously

Table 3
Multivariate Models for Full Cohort: Mean Change in HRQOL Score Associated With Moderate to Severe Distress From Given Symptom (N = 920 Surveys)

PedsQL Score	Distressing Symptom	Mean Change in QOL Score (95% CI)	P-Value
Total	Difficulty concentrating[a]	−4.75 (−7.25, −2.24)	0.0002
	Worrying[a]	−4.35 (−7.25, −2.24)	<0.0001
	Dry mouth	−3.94 (−6.98, −0.91)	0.0109
	Pain	−3.87 (−5.44, −2.30)	<0.0001
	Sadness	−3.75 (−5.96, −1.54)	0.0009
	Irritability	−3.40 (−5.96, −1.54)	0.0036
	Sleep disturbance	−3.27 (−5.36, −1.18)	0.0021
	Fatigue	−2.83 (−4.48, −1.19)	0.0007
	Vomiting	−2.03 (−3.89, −0.16)	0.0337
	Anorexia	−1.94 (−3.64, −0.24)	0.0255
Physical	Dry mouth[a]	−7.46 (−12.54, −2.38)	0.004
	Pain	−6.49 (−8.73, −4.25)	<0.0001
	Fatigue	−5.35 (−8.35, −2.36)	0.0005
	Difficulty concentrating	−4.95 (−8.63, −1.26)	0.0085
	Vomiting	−3.90 (−6.81, −0.99)	0.0085
	Worrying	−3.32 (−6.31, −0.33)	0.0294
	Irritability	−3.09 (−6.00, −0.17)	0.0382
	Anorexia	−3.07 (−5.86, −0.29)	0.0305
Emotional	Worrying[a]	−14.55 (−18.26, −10.84)	<0.0001
	Sleep disturbance[a]	−10.75 (−13.58, −7.92)	<0.0001
	Irritability	−8.56 (−11.56, −5.57)	<0.0001
	Itching	−3.43 (−6.19, −0.67)	0.015
	Pain	−2.55 (−4.34, −0.77)	0.0051
Social	Difficulty concentrating	−5.30 (−8.91, −1.68)	0.0040
	Irritability	−4.25 (−6.56, −1.93)	0.0003
	Image issues	−3.95 (−6.92, −0.98)	0.0092
	Nervousness	−3.17 (−5.67, −0.68)	0.0127
School	Difficulty concentrating	−7.53 (−11.82, −3.24)	0.0006
	Sleep disturbance	−5.18 (−8.40, −1.96)	0.0016
	Fatigue	−5.00 (−7.40, −2.60)	<0.0001
	Pain	−4.41 (−7.29, −1.53)	0.0027
	Sadness	−4.77 (−8.29, −1.26)	0.0078

HRQOL = health-related quality of life; PedsQL = Pediatric Quality of Life Inventory 4.0; QOL = quality of life.
MCID for PedsQL: total score MCID 4.4; physical subscore MCID 6.7; emotional subscore MCID 8.9; social subscore MCID 8.4; school subscore 9.1.
Estimates and P-values obtained under linear mixed models including the set of symptoms distress, cancer type, time since last progression, sex, treatment intensity, age, and intervention arm as fixed effects and child as a random effect.
[a]Indicates symptoms for which the associated score reduction reached or was larger than the corresponding minimal clinically important differences (MCIDs).

identified time-related factors of HRQOL included in our multivariable models (e.g., treatment intensity and time since progression) remained associated with patient-reported HRQOL scores after the introduction of symptom distress. Our findings also are consistent with studies of adolescents and young adults with cancer (ages 15–39), where current symptoms are independently associated with poorer HRQOL during initial cancer therapy.[45] It follows that symptom distress may play an intermediary role in the relationships between previously identified covariates and HRQOL. For these reasons, we suggest that interventions directly targeting symptom distress may help improve patient-reported HRQOL.

Limitations

There are several limitations of this study. Our analyses evaluated some known factors associated with HRQOL; however, we lacked the power or diversity to assess them all. For example, our sample included relatively few patients with CNS tumors, particularly in the end-of-life cohort. We also had relatively little racial or ethnic diversity in our sample and could not assess potential cultural differences in HRQOL. Importantly, poor child HRQOL has been associated with other unexamined factors such as socioeconomic status and parent physical and emotional health.[23,40,44,47,58,59]

Furthermore, results from the end-of-life cohort should be taken with caution. In this subgroup, the number of surveys per patient was limited and only a few were completed within the last month of life; sicker patients may be underrepresented. The sample size precluded adjustment for multiple concurrent distressing symptoms. This is important because we previously described high symptom distress in this group,[11] potentially contributing more significantly to HRQOL.

Finally, although a clear strength of our study is the high rate of child self-report, there is growing agreement that pediatric HRQOL research also should integrate the voice of parents,[30,60] and perhaps clinicians. We did not collect concurrent parent or clinician report because our overall aims were to determine if child report would influence parent and provider

Table 4
Multivariate Models for the Subgroup of Children With End-of-Life Surveys: Mean Change in HRQOL Score Associated With Moderate to Severe Distress From Given Symptom ($N = 73$ Surveys)

PedsQL Score	Distressing Symptom[a]	Mean Change in QOL Score (95% CI)[b]	P-Value
Total score	Sadness	−15.02 (−26.07, −3.97)	0.008
	Dry mouth	−12.05 (−21.03, −3.07)	0.009
	Anorexia	−11.22 (−21.65, −0.8)	0.035
	Irritability	−9.62 (−18.82, −0.42)	0.040
	Drowsiness	−9.37 (−17.42, −1.32)	0.023
	Pain	−6.63 (−13.01, −0.25)	0.042
Physical score	Dry mouth	−18.93 (−33.5, −4.36)	0.0109
	Anorexia	−18.04 (−32.74, −3.33)	0.0162
	Drowsiness	−15.33 (−23.5, −7.17)	0.0002
	Pain	−14.85 (−24.92, −4.78)	0.0039
	Diarrhea	−10.61 (−21.09, −0.13)	0.0471
	Vomiting	−9.67 (−18.22, −1.12)	0.0267
	Irritability	−7.78 (−13.64, −1.93)	0.0091
	Nausea	−7.2 (−12.64, −1.77)	0.0094
Emotional score	Sadness	−28.03 (−42.89, −13.17)	0.0002
	Worrying	−23.9 (−39.4, −8.4)	0.0025
	Irritability	−14.35 (−28.38, −0.32)	0.0449
	Drowsiness	−13.54 (−24.06, −3.03)	0.0116
Social score	Irritability	−15.17 (−29.01, −1.34)	0.0316
	Anorexia	−13.72 (−21.93, −5.51)	0.0011
	Dry mouth	−13.71 (−20.9, −6.53)	0.0002
	Fatigue	−11.76 (−22.27, −1.26)	0.0282
	Vomiting	−4.97 (−8.5, −1.45)	0.0057
School score	Dry mouth	−13.49 (−26.23, −0.74)	0.0380

HRQOL = health-related quality of life; PedsQL = Pediatric Quality of Life Inventory 4.0; QOL = quality of life.
[a]Eleven symptoms had distressful events in at least 15 surveys. Distressing symptoms listed if significantly associated with change in QOL score in a linear mixed model including the single distress symptom, treatment intensity, and time since last progression as fixed effects and child as random effect ($P < 0.05$).
[b]Minimal clinically important differences (MCIDs) for PedsQL: total score MCID 4.4; physical subscore MCID 6.7; emotional subscore MCID 8.9; social subscore MCID 8.4.

awareness of child suffering and, in turn, inform clinical care. We only included parent-proxy reports when child report was unattainable. This pragmatic approach enabled a data set of single and best respondents per family. However, although concordance between child, parent, and clinician symptom report is generally poor,[61] it is important to integrate parent and provider impressions because both impact medical decision making. How and when to use combined PRO reports in clinical and research settings remains unclear.[2,30,31,51,62]

These limitations are common in pediatric quality of life research.[22] Additional challenges include barriers to data collection and study completion,[34,35] instrument selection, and interpretation of school HRQOL among children who may be absent from school.[22,54] To mitigate this issue, we screened children for school attendance and found no differences in mean scores based on school attendance. Additionally, patient enrollment and data collection was highly successful.[54] The PedsQL instrument was chosen based on its widespread use in pediatrics,[50] as well as its proven responsiveness, and construct and predictive validity.[2,22,42,63]

Conclusion

This analysis from the PediQUEST study showed that specific, targetable symptom distress is strongly associated with HRQOL and generates hypotheses for future prospective research. For example, inquiring about specific distressing emotional symptoms and intensively treating all symptoms may improve multiple HRQOL domains. Larger cohort studies of pediatric patients at the end of life may better describe modifiable factors of HRQOL in this time period. We may not be able to alleviate all of the distress of patients and families facing life-threatening pediatric illness, but intensive symptom management presents one possibility for enhancing child and family well-being.

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