Health-Related Quality-of-Life Outcome Measures for Pediatric Palliative Care Populations: A Systematic Review

By

Kathryn Wessell

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William A. Sollecito, DrPH

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Date

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Laura C. Hanson, MD, MPH

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Date

ABSTRACT

Kathryn Wessell: Health-Related Quality-of-Life Outcome Measures for Pediatric Palliative Care Populations: A Systematic Review
(Under the direction of William Sollecito)

Background: A key goal of palliative care is to improve the quality of life for patients and families living with serious illness. However, valid, and reliable instruments are lacking to assess health-related quality of life (HRQOL) in pediatric palliative care.

The objective of this systematic literature review is to update the previous review conducted by Coombes et al[1]. and to explore recent literature and to summarize the measurement properties of identified patient- and parent-reported HRQOL outcome measures for pediatric palliative care appropriate patients.

Methods: A systematic review of the literature was conducted by searching EMBASE, Medline, and PsychInfo for recent assessment instruments that measure HRQOL in a life-limiting or life-threatening illness. The psychometric properties of identified measures were evaluated and summarized using COnsensus based Standards for the selection of health Measurement INstruments (COSMIN) guidelines.

Results: After removing duplicates, 1,401 records were screened of which 19 manuscripts of 18 studies were retained that supplied information about 12 HRQOL measures. Measurement quality varied across studies. Internal consistency and hypothesis testing for construct validity were most commonly assessed. Most instruments lacked information on measurement invariance, responsiveness, and reliability. Information on measurement error was not available for any instrument. No one instrument was identified as being appropriate for use in a non-

disease specific pediatric palliative care population. The PedsQL Epilepsy and QOLCE-55 showed promise for use in children with epilepsy and palliative care needs.

Conclusion: There was limited evidence on the psychometric properties of HRQOL instruments in a pediatric palliative care population. Future directions are identified including the need for additional research to test existing or develop new HRQOL outcome measures suitable for use in children and young people with serious and life-threatening illnesses. Patient-reported outcome and experience measures are needed to assess and provide quality care for children and young people with life-limiting illnesses. Generic measures that capture the daily burdens of living with life-limiting illness are needed to compare HRQOL across a variety of diseases and conditions.

Public health leadership skills, such as agenda setting, advocacy, and policy promotion, are needed to accelerate the development and implementation of pediatric palliative care HRQOL measures.

Keywords: pediatric palliative care, health-related quality-of-life, outcome measurement, systematic review

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LIST OF ABBREVIATIONS

BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
COSMIN	COnsensus based Standards for the selection of health Measurement INstruments
ESM	Experience Sampling
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HRQOL	Health-Related Quality of Life
mParent CFQ-R	Modified Parent Cystic Fibrosis Questionnaire—Revised
Neuro-QoL	Neurology Quality of Life Measurement System
NHANES	National Health and Nutrition Examination Survey
NPCQLQ-C	Niemann-Pick type C quality-of-life questionnaires for children
PC	Palliative Care
PedsQL GCS	Pediatric Quality of Life Inventory Generic Core Scale
PedsQL NMM	Neuromuscular Module
PedsQL SCD	Sickle Cell Disease
PRISMA	Preferred Reported Items for Systematic Reviews and Meta-Analysis
PROMIS	Patient Reported Outcomes Measurement Information System
QOLCE	Quality of Life in Childhood Epilepsy Questionnaire

Introduction

An estimated 31.6 million children are living with life-limiting or life-threatening illness across the world.[2] Over 400,000 children and young people in the United States 0-17 years of age are estimated to be living with serious illness in the United States.[3] These numbers are expected to rise as medicine continues to advance and infants and children are living longer with serious illnesses.[4] Serious illnesses throughout this paper are defined as life-limiting or life threatening conditions that adversely impact quality of life and function, and/or involve significant caregiver strain.[5] Common pediatric serious illnesses include genetic/congenital disorders (e.g., cystic fibrosis), neurologic conditions (e.g. epilepsy), neuromuscular disorders (e.g., muscular dystrophy), solid tumor cancers and hematologic malignancies (e.g. leukemia), and other complex chronic conditions associated with high morbidity or mortality.[4,6] Serious illness care often requires complicated management and intensive treatments and can place a heavy emotional, practical, and financial burden on patients, their families, and the health care system.[5]

Pediatric palliative care is a specialized model of care for children and young people living with serious illness. Palliative care is a multidisciplinary support system that functions in conjunction with primary and other specialty care and can be delivered along with disease-directed treatments.[7] The goal of palliative care is to promote quality of life and reduce suffering by providing symptom relief and psychosocial and decision support for patients and their families. Unlike hospice, which is focused on the last few months of life, palliative care is appropriate across the disease trajectory starting from time of diagnosis. The fundamental goal of palliative care is to improve quality of life while living with serious illness.

Health-Related Quality of Life

The World Health Organization defines health as a combination of physical, mental, and social well-being and quality of life as an "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns." [8] The impact that a person's health has on his or her quality of life is known as health-related quality of life (HRQOL) and has been identified as a national public health priority.[9] Measuring HRQOL can help assess the impact of social determinants of health, chronic disease, and clinical and public health interventions. For the past 30 years, improving HRQOL has been included as a fundamental component of the nationwide Healthy People 2000, 2010, and 2020 initiatives led by the U.S. Department of Health and Human Services.[10] Self-reported HRQOL questions have been incorporated into many of the CDC's surveillance surveys, such as the Behavioral Risk Factor Surveillance System (BRFSS) and the National Health and Nutrition Examination Survey (NHANES).[10,11] Assessing population-level HRQOL can help public health officials and policy makers identify the groups and areas most in need of HRQOL interventions.

Measuring Health-Related Quality-of-Life in Pediatric Palliative Care

A clear understanding of a patient's HRQOL can lead to identification of physical, psychological, and/or social problems that could be causing distress and may require intervention.[12] Measures of health-related quality of life (HRQOL) should be subjective and multidimensional, and should minimally include physical, psychological, and social dimensions of health.[13] Given that improving quality of life is also one of the main tenets of palliative care, psychometrically sound measurement tools are needed to assess health-related quality-of-life (HRQOL) accurately in a seriously ill population. Regular assessment and intervention upon

identified HRQOL concerns, can improve satisfaction with care, psychosocial and activity-related issues, communication, and clinical decision-making in pediatric populations.[14] Routine clinical assessment of patient reported outcome measures of HRQOL have been shown to improve communication between patients and their health care providers in adult populations by facilitating conversations about psychosocial functioning and other HRQOL issues.[15] Studies have shown that clinicians often underrate functional and psychosocial issues in adult patients.[16,17] Pediatricians have also been shown to underestimate emotional and behavioral problems in children, leading to the labeling of psychosocial issues in pediatric populations as a "hidden morbidity."[18] In pediatric clinical practice, good quality communication between patients and providers is critical since younger patients may lack the cognitive development and language skills necessary to verbally describe HRQOL issues.[14]

Measuring HRQOL in pediatric palliative care is uniquely complex as both serious illness- and pediatric-related conceptual and methodologic challenges must be addressed. Pediatric palliative care covers a wide variety of illnesses and conditions, many of which are rare. Generic and disease-specific quality of life measures have been developed for seriously ill adults and healthy children but may not be suitable for a pediatric palliative care population. HRQOL measures for adults often include questions about activities that may not apply to children such as working, driving, housework, or the ability to perform self-care. Additionally, HRQOL structures for a pediatric palliative care appropriate population may be different from those previously validated in a less ill population. For example, the Pediatric Quality of Life Inventory (PedsQL) 4.0 has been shown to be a reliable and valid measure of HRQOL in a variety of diseases and conditions, including some life-limiting illnesses. However, an attempt to validate the PedsQL in a generic pediatric palliative care population found that hypothesis testing

for construct validity was not supported which suggests that HRQOL factors for a pediatric palliative care population differ from both healthy and less severely ill populations.

Pediatric palliative care measures should also be responsive to various stages of language and cognitive development. Additionally, seriously ill patients may become easily fatigued or may experience disease and/or treatment related cognitive limitations that require careful consideration of measure characteristics such as instrument length, response options and recall periods.

While clinicians who utilize patient-reported HRQOL data with adult patients are more likely to appropriately diagnose and treat psychosocial and functional issues than their counterparts, less is known about how to implement this practice with children.[19] The goal of this paper is to present a systematic review of outcome measures used to assess HRQOL in pediatric palliative care appropriate patients. Previous reviews have been unable to recommend any HRQOL measurement tools suitable for broad use in pediatric palliative care.[1,20] The aim of this systematic literature review is to examine and summarize the quality of the measurement properties of recent patient- and parent-reported HRQOL outcome measures for children and young people up to 18 years of age with serious illness. Building upon the previous review of pediatric palliative care outcome measures conducted by Coombes et al. (2016) this review will explore recent HRQOL literature to identify new studies that evaluated the measurement properties of new or existing outcome measures in a pediatric palliative care appropriate population.[1] The ultimate goal of this study is to improve the quality of life for children and young people with serious illness and palliative care needs

Methods

Literature Search Strategy

A systematic review published by Coombes et al. in 2016 was the first review of HRQOL measures in pediatric palliative care but was unable to identify any high-quality outcome measures for use in this population[1]. Prompted by the growth in the fields palliative medicine and patient-reported outcomes, this search aimed to improve upon the search previously conducted by Coombes et al. by bringing it up to date.[1] EMBASE, Medline, and PsychInfo were searched from December 1st, 2014 to January 12th, 2020 in an effort to identify new instruments or new validation information for existing instruments. Search terms included a combination of palliative care, supportive care, children, adolescents, outcomes, instruments, and related terms (see Appendix 1 for the full search strategy). The results from each database were downloaded into EndNote ® [Thomson Reuters (Scientific) Inc., Carlsbad, CA, U.S.A.] and duplicates were removed.

Inclusion and Exclusion Criteria

A publication was included if it was a full text, English language, peer-reviewed manuscript and met the following additional criteria:

1. published between December 1st, 2014 – January 12th, 2020,
2. the study sample included human infants, children, or young adults aged 0 – 18 years old,
3. at least 25% of the study sample had to be living with a life-limiting, life-threatening, or complex chronic disease associated with high morbidity or mortality [4],
4. examined at least once measurement property (e.g. reliability, validity, or responsiveness) of a patient- or parent-reported outcome measure,
5. clinician-reported HRQOL outcome measures were excluded.

Study Selection and Methodological Quality Assessment Approach

The titles and abstracts of all identified publications were screened for the inclusion criteria. Full text of potentially eligible manuscripts was evaluated based on the previously specified inclusion and exclusion criteria. Data was extracted on the characteristics of each included study and outcome measure, including information about the study sample, interpretability, and feasibility of using the measure in a pediatric palliative care population.

The methodological quality of each included manuscript was assessed using the COnsensus based Standards for the selection of health Measurement INstruments (COSMIN) Risk of Bias Checklist.[21] The COSMIN checklist specifies nine measurement properties to evaluate:

1. Content validity is a measure that the content of an instrument is an appropriate reflection of the construct to be measured. All items should be comprehensible and relevant to the population of interest and comprehensive of the construct of interest. Content validity should be assessed and agreed upon by subject matter experts.
2. Structural validity is a measure of the degree to which scores are an adequate reflection of the dimensionality of the construct of interest. Structural validity is often assessed using confirmatory factor analysis or item response theory. A sufficient (+) rating is given if Comparative Fit Index or Tucker-Lewis Index are greater than 0.95 or the Root Mean Square Error of Approximation is less than 0.06.
3. Internal consistency is a measure of homogeneity or interrelatedness among the items in the scale and subscales and is often assessed using factor analysis. A sufficient (+) rating is given if (a) the sample size is greater than 100 and 7 times the number of items in the measure, and (b) Cronbach's α is greater than 0.70.

4. Measurement invariance and cross-cultural validity are measures of important differences in how the outcome measure performs or is interpreted between cultural or other study groups (e.g., disease severity). Measurement invariance is often assessed using regression analysis or confirmatory factor analysis. A sufficient (+) rating is given if no important differences are found between groups in factor analysis or McFadden's R^2 is less than 0.02.
5. Reliability is a measure of the reproducibility of scores between administrations when measurement conditions remain stable. Reliability measures consistency, not accuracy, and is often assessed by intraclass correlation coefficient or Kappa calculations. A sufficient (+) rating is achieved if (a) the sample size is 50 or more, and (b) an intraclass correlation coefficient or Kappa was 0.70 or higher for each domain.
6. Measurement error is a measure of deviations of the score, or systematic random errors, that are not attributable to changes in the construct of interest. Measurement error is often assessed using standard error of measurement, smallest detectable change, limits of agreement, or percent agreement calculations. A sufficient (+) rating is given if the smallest detectable change or limit of agreement are smaller than the minimum important change.
7. Criterion validity is a measure of how well scores correlate with an existing gold standard. Criterion validity is rarely assessed for patient-reported outcome measures since there is seldom a gold standard measure available for comparison. A sufficient (+) rating is given if correlation with the gold standard is at least 0.70.
8. Hypothesis testing for construct validity is a measure of the degree to which scores are consistent with a previously stated hypothesis. Construct validity is often assessed using

known groups validity, i.e., comparison between subgroups, convergent and/or divergent validity, i.e., comparison with other instruments. A sufficient (+) rating is given if 75% of the pre-specified hypotheses are confirmed.

9. Responsiveness is a measure of sensitivity to change or the ability to detect clinically important changes over time in the construct of interest. Responsiveness is often assessed using effect size calculations. A sufficient (+) rating is given if the area under the curve is at least 0.70 or the 75% of pre-specified hypothesis are confirmed.

Each measurement property was assessed based on how it had been tested during the study and was given a rating of very good, adequate, doubtful, or inadequate.[21,22]

Synthesis of Results

Measurement property evaluations were pooled for each outcome measure and the quality of the evidence was graded using a modified Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach and rated as high, moderate, low, or very low.[22] Quality ratings were downgraded based on four GRADE factors: (1) risk of bias (inadequate quality studies), (2) inconsistency (conflicting results), (3) imprecision (small sample size) , and (4) indirectness (portion of study population is not the population or context of interest). Study results of measurement property assessments were evaluated using the COSMIN criteria of good measurement properties and rated as sufficient (+), insufficient (-), or indeterminate (?).[22,23]

Results

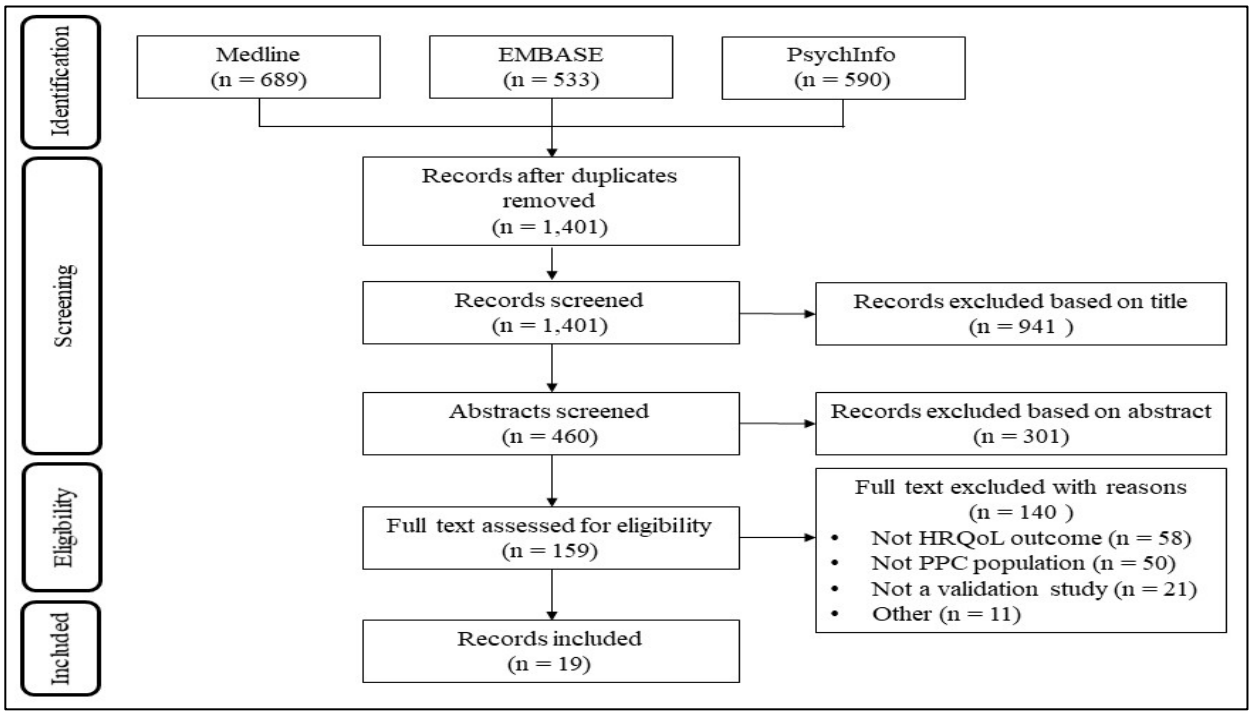
A total of 1,401 unique manuscripts were identified and screened. Figure 1 displays a flowchart describing the process and outcome of each stage of manuscript review and selection for inclusion according to the Preferred Reported Items for Systematic Reviews and Meta-

Analysis (PRISMA) guidelines. After title and abstract screening and exclusion, 159 full text manuscripts were assessed for eligibility. Common reasons for exclusion included studies of non-HRQOL outcomes (e.g., physical symptoms only or utility measures), adult or not palliative care appropriate sample populations (e.g., obesity or scoliosis), and studies that did not evaluate measurement properties (e.g., studies of treatment effects or concept development). After full text exclusion, 19 manuscripts of 18 studies were included that evaluated the measurement properties of 12 patient- or parent-reported HRQOL measures tested in pediatric palliative care appropriate populations. Two manuscripts presented results of the same study and were analyzed together. All further analyses presented here are based on these final 18 studies.

Description of Studies

An overview of the key characteristics of the 18 included studies is presented in Table 1. The study characteristics described are: authorship, publication year, name of patient- or parent-reported outcome measure, age range of patients included in study, if the measure was self

Figure 1. PRISMA flow diagram



and/or parent reported, the potentially palliative care appropriate population, and the number of study participants. No studies of outcome measures for use specifically in specialty pediatric palliative care were identified. Instead, all of the included studies were conducted with a pediatric palliative care appropriate sample population of children and young people with a life-limiting or life-threatening illness. Epilepsy (six studies), cancer (three studies), and sickle cell disease (three studies) were the most common serious illnesses studied. Only five of the 18 studies evaluated both patient- and parent- reported outcome measures with all five representing a version of the Pediatric Quality of Life Inventory (PedsQL).[24-28] Of the remaining studies seven used only patient-reported measures and six used only parent-reported measures. The majority of the studies had sample sizes larger than 100 participants (13/18) with a range of 20 – 2694 participants.

Description of Outcome Measures

The 12 patient- and parent- reported HRQOL outcome measures included were the Experience Sampling (ESM) Diary[29], the Modified Parent Cystic Fibrosis Questionnaire—Revised (mParent CFQ-R)[30], the Neurology Quality of Life Measurement System (Neuro-QoL)[31], the Niemann-Pick type C quality-of-life questionnaires for children (NPCQLQ-C)[32], four versions of the PedsQL: (1) Generic Core Scales (PedsQL GCS)[25,27], (2) PedsQL Epilepsy[28] (3) Neuromuscular Module (PedsQL NMM)[24], (4) Sickle Cell Disease (PedsQL SCD)[26], the Patient Reported Outcomes Measurement Information System (PROMIS)[33-36], the QoL survey for people with disability[37], and two versions of the Quality of Life in Childhood Epilepsy Questionnaire: QOLCE-55[38-40] and QOLCE-16[41,42]. An overview of the key characteristics of included patient- and parent- reported outcome measures, including measure name, if it is a generic, i.e., applicable to numerous diseases or conditions, or disease-specific oriented measure,

the number of HRQOL domains or subscales being measured, number of items or questions in the measure, recall or look back period, response options, and potential range of scale scores are displayed in Table 2.

The majority of the measures were disease-specific, with only two generic, Peds QL GCS and PROMIS, and ten disease-specific measures identified. None of the measures were developed for, or validated in, a pediatric population receiving palliative care. Of the disease-specific measures, three were designed for use in children and young people with epilepsy (PedsQL Epilepsy, QOLCE-55, and QOLCE-16), one for cystic fibrosis (mParent CFQ-R), one for significant disability (QoL survey for people with disability), one for Duchenne Muscular Dystrophy (ESM), one for neurological disorders (Neuro-QoL), one for neuromuscular disorders (PedsQL NMM), one for Niemann-Pick Type C (NPCQLQ-C), and one for sickle cell disease (PedsQL SCD). Recall time was no longer than one month for any measure with five measures using one week/seven days, four measures using one month/four weeks, two measures using a combination of recall periods depending on the item, and one measure using time of administration. All but one of the included measures utilized 4- or 5-point Likert scale response options with the remaining measure utilizing a 100-point visual analogue scale (VAS).[29,43] Number of items ranged from 15 – 107.

Methodological Quality of Included Measures

Of the nine measurement properties outlined in COSMIN risk of bias checklist, content validity, criterion validity, and measurement error were not assessed by any of the identified studies and were therefore not included in the tables. As criterion validity is a measure of how well an instrument's scores reflect the gold standard, the absence of criterion validity analysis was expected since outcome measures typically do not have a gold standard.[21,22] Cross-cultural

Table 1: Characteristics of included studies

Author	Year	Measure	Age Range	Report	Palliative Care Appropriate Population	n
Alpern et al[30]	2015	mParent CFQ-R	4 mo – 5 years	Parent	Cystic Fibrosis	314
Aspesberro et al[25]	2016	PedsQL4.0 GCS	2-18	Parent	Critically ill and admitted to PICU or CICU (50% with Complex Chronic Disease)	367
			5-18	Self		
		PedsQL Infant	1-24 months	Parent		
Aston et al[32]	2019	NPCQLQ-C	0-17	Parent	Niemann-Pick Type C	23
Bray et al[29]	2017	ESM Diary	9-18	Self	Duchenne Muscular Dystrophy	35
Conway et al[38]	2017	QOLCE-55	4-18	Parent	Epilepsy	136
Dampier et al[33]	2016	PROMIS	8-17	Self	Sickle Cell Disease	235
Deroche et al[37]	2015	QoL survey for people with disability	15-24	Self	Fragile X, Spina Bifida, and Muscular Dystrophy	174
Desai et al[27]	2014	PedsQL4.0 GCS	2-18	Parent	Admitted to medical or surgical unit of the hospital; no chronic illness, noncomplex chronic illness, and complex critical illness	2694
			13-18	Self		
		PedsQL Infant	1-24 months	Parent		
Ferro et al[39]	2016	QOLCE-55	4-12	Parent	Epilepsy	373
Goodwin et al[40]	2015	QOLCE-55	4-12	Parent	Epilepsy	373
Goodwin et al[41,42]	2018 2019	QOLCE-16	4-12	Parent	Epilepsy	373
Hinds et al[34]	2019	PROMIS	8-18	Self	Cancer	96
Hinds et al[35]	2017	PROMIS	8-17	Self	Cancer	20
Lai et al[31]	2015	Neuro-QoL	10-18	Self	Epilepsy	61
Landfeldt et al[24]	2018	PedsQL NMM	16†	Self & Parent	Duchenne muscular dystrophy	278
Modi et al	2017	PedsQL Epilepsy	5-18 2-18	Self & Parent	Epilepsy	430
Panepinto et al	2017	PedsQL SCD	4-21	Self & Parent	Sickle Cell Disease	187
Reeve et al	2018	PROMIS	8-17	Self	Cancer, nephrotic syndrome, sickle cell disease	344

Abbreviations: ESM: Experience Sampling; mParent CFQ-R : Modified Parent Cystic Fibrosis Questionnaire—Revised; Neuro-QoL: Neurology Quality of Life Measurement System; NPCQLQ-C: Niemann-Pick type C quality-of-life questionnaires for children; PedsQL: Pediatric Quality of Life Inventory - GCS: Generic Core Scales, NMM: Neuromuscular Module, SCD: Sickle Cell Disease; PROMIS: Patient Reported Outcomes Measurement Information System; QOLCE: Quality of Life in Childhood Epilepsy Questionnaire

validity was also not assessed, but its partner measurement invariance was reported in five studies and included in the tables. Table 3 gives an overview of the methodological quality of identified outcome measures by study. Missing items indicate that the measurement property was not evaluated by the study.

The methodological quality ratings and associated level of evidence quality of each of the included studies by measurement property were pooled for each patient- and parent-reported HRQOL outcome measure. The synthesis of the results for structural validity, internal consistency, and measurement invariance are shown in Table 4 and reliability, hypothesis testing for construct validity, and responsiveness are shown in Table 5.

Quality scores for the remaining six measurement properties ranged from very good to inadequate. Internal consistency was one of the most frequently assessed measurement properties and was reported in 11 of the 18 studies. However, 73% of these studies failed to report if the scale or subscale was unidimensional leading to a score of "doubtful" methodological quality. Hypothesis testing for construct validity was also assessed in 11 studies, all of which received acceptable scores of either very good (73%) and adequate (27%).

Structural validity was tested using appropriate methods of confirmatory or exploratory factor analysis in six of seven studies. The one study that received an inadequate score had a sample size of less than 100 which was not large enough to support the Rasch analysis performed. Measurement invariance and responsiveness were both evaluated in 5 studies. Reliability was only evaluated in three studies.

Table 2. Characteristics of the identified PROMs

Measure	Generic/ Specific	No. of domains	No. of Items	Recall Period	Response options	Range of scores
ESM Diary	Specific	2 (internal and contextual dimensions of experience)	19	Now	100-point VAS	0 – 100
mParent CFQ-R	Specific	5 (respiratory symptoms, treatment burden, vitality, health perceptions, physical functioning)	26	Past week	4-point Likert scale	0-100
Neuro-QoL	Specific	9 (social relations, cognitive function, depression, anxiety, stigma, fatigue, pain, upper and lower extremity function)	107	Past 7 days	5-point Likert scale from 1 (not at all) to 5 (very much)	0-100
NPCQLQ-C	Specific	6 (embodiment, identity, intersubjectivity, mood, spatiality, temporality)	15	Past 4 weeks	5-point Likert from 1 (never) to 5 (always)	15 - 75
PROMIS	Generic	5 general domains (physical function, pain, fatigue, emotional health, and social health)	97-107	Past 7 days	5-point Likert from never to almost always	NR
PedsQL 4.0 GCS	Generic	Child: 4 (physical functioning, emotional functioning, social functioning, school functioning) Infant: 5 (physical functioning, physical symptoms, emotional functioning, social functioning, cognitive)	Child: 23 Infant: 36-45	Past month; Past 7 days; Since admission	5-point Likert from 0 (never a problem) to 4 (almost always a problem)	0-100
PedsQL Epilepsy	Specific	5 (impact, cognitive, Sleep, executive functioning, and mood/behavior)	29	Past month	5-point Likert from 0 (never a problem) to 4 (almost always a problem)	0-100
PedsQL NMM	Specific	3 (about neuromuscular disease, communication, family resources)	25	Past month	5-point Likert from 0 (never a problem) to 4 (almost always a problem)	0-100
PedsQL SCD	Specific	9 (pain and hurt, pain impact, pain management, worry (I & II), emotions, treatment, communication (I & II)	43	Past month	5-point Likert from 0 (never a problem) to 4 (almost always a problem)	0-100

Table 2. (Continued)

Measure	Generic/ Specific	No. of domains	No. of Items	Recall Period	Response options	Range of scores
QOLCE-55	Specific	4 (cognitive functioning, emotional functioning, social functioning, physical functioning)	55	Past week	5-point Likert from 0 (very often) to 4 (never)	0-100
QOLCE-16	Specific	4 (cognitive functioning, emotional functioning, social functioning, physical functioning)	16	Past week	5-point Likert from 0 (very often) to 4 (never)	0-100
QoL survey for people with disability	Specific	5 (emotional health, physical health, independence, activity limitations, community participation)	20	Past month and past week	4-6 point Likert scales	15-199

Abbreviations: ESM: Experience Sampling; mParent CFQ-R : Modified Parent Cystic Fibrosis Questionnaire—Revised; Neuro-QoL: Neurology Quality of Life Measurement System; NPCQLQ-C: Niemann-Pick type C quality-of-life questionnaires for children; PedsQL: Pediatric Quality of Life Inventory - GCS: Generic Core Scales, NMM: Neuromuscular Module, SCD: Sickle Cell Disease; PROMIS: Patient Reported Outcomes Measurement Information System; QOLCE: Quality of Life in Childhood Epilepsy Questionnaire

Discussion

The aim of this systematic literature review was to describe and evaluate the methodological quality of recent patient- and parent-reported HRQOL outcome measures for pediatric palliative care appropriate patients. A systematic review published by Coombes et al. in 2016 was the first review of HRQOL measures in pediatric palliative care but was unable to identify any high-quality outcome measures for use this population.[1] The review summarized here identified 18 studies of 12 outcome measures published after the seminal Coombes et al systematic review.[1] Summaries of the findings from this review are presented in Tables 3-5.

Methodologic Quality of Pediatric Measures

Psychometric evidence was limited, and methodologic quality varied among all of the identified measures. Internal consistency and hypothesis testing were the most commonly assessed measurement properties. The PedsQL NMM and QOLCE-16 were the only measures to have both internal consistency and unidimensional reported. Internal consistency assessments

for the remaining measures should be viewed with caution since it is unknown if the scale is a unidimensional measure of HRQOL as a construct.

Table 3: Methodological quality of identified outcome measures by study

Measure Ref	Structural Validity	Internal Consistency	Measurement Invariance	Reliability	Hypothesis Testing	Responsi-veness
ESM Diary						
Bray et al[29]	Inadequate	Very Good		Inadequate		
mParent CFQ-R						
Alpern et al[30]		Doubtful	Adequate		Adequate	
Neuro-QoL						
Lai et al[31]		Doubtful			Adequate	
NPCQLQ-C						
Aston et al[32]		Doubtful			Very good	
PedsQL 4.0						
GCS						
Aspesberro et al[25]					Very Good	Adequate
Desai et al[27]					Very Good	Very Good
PedsQL Epilepsy						
Modi et al[28]	Very Good	Doubtful	Very Good	Very Good	Very Good	
PedsQL NMM						
Landfeldt et al[24]	Very Good	Very Good				
PedsQL SCD						
Panepinto et al[26]						Very Good
PROMIS						
Dampier et al[33]					Very Good	
Hinds et al[34]		Doubtful			Adequate	Doubtful
Hinds et al[35]		Doubtful				
Reeve et al[36]						Very Good
QOLCE-55						
Conway et al[38]	Adequate	Doubtful	Doubtful	Adequate	Very Good	
Ferro et al[39]			Adequate			
Goodwin et al[40]	Very Good	Doubtful			Very Good	
QOLCE-16						
Goodwin et al[41,42]	Very Good	Very Good	Adequate			
QoL survey for people with disability						
Deroche et al[37]	Adequate				Very Good	

Abbreviations: ESM: Experience Sampling; mParent CFQ-R : Modified Parent Cystic Fibrosis Questionnaire—Revised; Neuro-QoL: Neurology Quality of Life Measurement System; NPCQLQ-C: Niemann-Pick type C quality-of-life questionnaires for children; PedsQL: Pediatric Quality of Life Inventory - GCS: Generic Core Scales, NMM: Neuromuscular Module, SCD: Sickle Cell Disease; PROMIS: Patient Reported Outcomes Measurement Information System; QOLCE: Quality of Life in Childhood Epilepsy Questionnaire

Table 4: Data synthesis: Internal Validity

Measure	Structural Validity		Internal Consistency		Measurement Invariance	
	Rating	Quality	Rating	Quality	Rating	Quality
ESM Diary	-	Low	?	Low	+	Low
mParent CFQ-R			?	Low	+	Moderate
Neuro-QoL			?	Low		
NPCQLQ-C			?	Low		
PedsQL GCS						
PedsQL Epilepsy	+	High	?	Low	+	High
PedsQL NMM	-	Moderate	+	Moderate		
PedsQL SCD						
PROMIS			?	Low		
QOLCE-55	+	Moderate	?	Low	?	Moderate
QOLCE-16	+	Moderate	+	Moderate	+	Moderate
QoL survey for people with disability	+	Moderate				

Abbreviations: ESM: Experience Sampling; mParent CFQ-R : Modified Parent Cystic Fibrosis Questionnaire—Revised; Neuro-QoL: Neurology Quality of Life Measurement System; NPCQLQ-C: Niemann-Pick type C quality-of-life questionnaires for children; PedsQL: Pediatric Quality of Life Inventory - GCS Generic Core Scales, NMM: Neuromuscular Module, SCD: Sickle Cell Disease; PROMIS: Patient Reported Outcomes Measurement Information System; QOLCE: Quality of Life in Childhood Epilepsy Questionnaire

Table 5: Data Synthesis: Other Measurement Properties

Measure	Reliability		Hypothesis Testing		Responsiveness	
	Rating	Quality	Rating	Quality	Rating	Quality
ESM Diary	+	Low				
mParent CFQ-R			+	Moderate		
Neuro-QoL			?	Moderate		
NPCQLQ-C			+	Low		
PedsQL 4.0 GCS			+	Moderate	+	Moderate
PedsQL Epilepsy	+	High	+	High		
PedsQL NMM						
PedsQL SCD					+	Moderate
PROMIS			+	Moderate	+	Low
QOLCE-55	+	Moderate	?	Moderate		
QOLCE-16						
QoL survey for people with disability			+	Moderate		

Abbreviations: ESM: Experience Sampling; mParent CFQ-R : Modified Parent Cystic Fibrosis Questionnaire—Revised; Neuro-QoL: Neurology Quality of Life Measurement System; NPCQLQ-C: Niemann-Pick type C quality-of-life questionnaires for children; PedsQL: Pediatric Quality of Life Inventory - GCS: Generic Core Scales, NMM: Neuromuscular Module, SCD: Sickle Cell Disease; PROMIS: Patient Reported Outcomes Measurement Information System; QOLCE: Quality of Life in Childhood Epilepsy Questionnaire

Responsiveness was only reported in three of the 12 measures: PedsQL GCS, PedsQL SCD, and PROMIS. Children and young people with life-limiting or life-threatening illness often experience frequent symptom and functional status changes that can significantly impact their HRQOL. Since improving quality of life is one of the primary goals of palliative care, it is especially important that pediatric palliative care appropriate measures of HRQOL are responsive to change. Measurement error was not assessed or reported for any of the HRQOL measures therefore instrument scores should be viewed with caution since the amount of systematic random error is unknown.

The PedsQL GSC and PROMIS measures have been tested in several life-limiting illness populations and both had sufficient methodological quality with moderate evidence for hypothesis testing of construct validity and moderate to low evidence, respectively, for responsiveness to change. However, little is known about the internal validity of these measures and future testing of structural validity, internal consistency, and measurement invariance would provide greater insight into the psychometric quality of these instruments.

PedsQL Epilepsy and QOLCE-55 had the highest methodologic quality overall, although given the high number of items, the QOLCE-55 might prove burdensome for children and their parents to complete. The QOLCE-16 shows promise as shorter measure of HRQOL in epilepsy but may require additional psychometric testing before use.

Measurement Considerations and Research Implications

Generic vs. Disease Specific Measures

Pediatric palliative care covers a wide variety of illnesses and conditions. While all of the included HRQOL measures were tested on a sample with potentially palliative care appropriate diseases, none have been validated in children and young people who actually

received palliative care services. Studies of children with chronic illnesses or disabilities reported lower HRQOL than their healthier peers, however the effect size varied by health condition and domain(s) assessed.[44,45] This variation supports the need for a generic serious illness HRQOL measure that is able to be used across conditions enabling use in a heterogenous palliative care population.

Only two of the 12 measures identified in this review were generic measures of HRQOL – PedsQL GCS and PROMIS. A previous study outside the scope of this review attempted to validate the PedsQL in a life-limiting illness population but found that the measure lacked the psychometric properties needed to accurately measure HRQOL in a pediatric palliative care population.[46] Huang et al evaluated the validity and reliability of the PedsQL in a sample of children and young people with a life-limiting illness who met the criteria for an integrated pediatric palliative care hospital admission and a comparison group of children enrolled in Medicaid. Confirmatory factor analysis implied an unacceptable model fit for a serious illness population 5 to 18 years of age with a comparative fit index of 0.69 (CFI > 0.9 satisfactory) and root mean square error of approximation of 0.25 (RMSEA < 0.06 satisfactory).[46] Therefore, construct validity was not supported by confirmatory factor analysis which could suggest that HRQOL factors for children and young people with serious, life-limiting illness and healthier populations may be different further exemplifying the need for a life-limiting illness specific HRQOL measure. Additionally, children with less serious conditions were not more likely to report higher HRQOL than those with more serious conditions. This contradicts the both the hypnotized relationship and existing literature on pediatric HRQOL that demonstrates lower HRQOL and higher physical, functional, psychological, and social burden for seriously ill children and young people.[46-48]

PROMIS measures of HRQOL were tested in sickle cell disease, nephrotic syndromes, and cancer populations and while more testing is needed, show potential for use in a broader pediatric palliative care population.

Disease-specific HRQOL measures are only relevant for the condition of interest and cannot be used to compare HRQOL across illness groups. Furthermore, pediatric palliative care clinicians would have to be aware of, and have access to, a multitude of disease-specific instruments in order to assess HRQOL for all of their patients, which is not feasible. The factors contributing to HRQOL in this seriously ill and heterogeneous population should also be explored.

Validation across age ranges

Reviews of younger children's ability to self-report pain and other physical symptoms have indicated a lack of evidence for children less than five years of age being able to accurately use self-report tools.[49] Another review of self-reported symptom instruments in children with cancer determined that current instruments were not reliable or valid in children younger than 8.[50] Of the studies identified in this review, the PedsQL GCS and PedsQL Epilepsy utilized self-report starting at five years of age, while the remaining studies started at eight years of age or older.

There is also evidence that younger children, 5 to 7 years of age, have trouble interpreting the more nuanced intermediate scores in 5-point Likert style scales and instead typically select the extreme or middle responses while children 8 years of age and older are able to fully understand a 5-point range.[51] This finding suggests that response options should be tailored to age, with younger children receiving less options. Further study should be conducted in children

with life-limiting illness to explore if illness burden plays a role in ability to understand response options.

Patient and proxy reported measures

HRQOL is an individually subjective construct and is best represented through patient report when possible.[52] Studies have shown a lower correlation between parents and children for non-observable constructs, like quality of life and emotional problems, and higher correlations for observable constructs, such as physical aspects.[1,52] Children may have a different understanding of HRQOL than their older parents, and parents may not be privy to a child's social interactions or aware of psychosocial issues.[52] HRQOL measures for use in pediatric palliative care populations should be available in both patient- and proxy-reported versions.

Limitations

This search was limited to three databases and restricted to English language peer-reviewed manuscripts. This could exclude studies of outcome measures in other languages that are relevant to a pediatric palliative care population. Due to project constraints this literature review was conducted by one reviewer. Additional reviewers are needed to increase the reliability of the results.

Conclusion

This review identified 18 studies of 12 HRQOL patient- and parent-reported outcome measures for children and young people with serious illness. Psychometric evidence was limited, and methodologic quality varied among all of the identified measures. Internal consistency and hypothesis testing for construct validity were most commonly assessed. Information on measurement error, content validity, and criterion validity were not available for any instrument. No one instrument was identified as being appropriate for use in a non-disease specific pediatric

palliative care population. The PedsQL Epilepsy and QOLCE-55 showed promise for use in children with epilepsy and palliative care needs.

Future Directions

Patient-reported outcome and experience measures are needed to assess and provide quality care for children and young people with life-limiting illnesses. Generic measures that capture the daily burdens of living with life-limiting illness are needed to compare HRQOL across a variety of diseases and conditions. Given the heterogeneity of a pediatric palliative care population, developing a generic patient-reported HRQOL measure could be difficult because all items may not be relevant to all children. A potential solution to this problem is to utilize individual items validated through item response theory (IRT) administered with content-balanced computerized adaptive testing (CAT) instead of static models. If properly assessed and employed, CAT administration may better assess HRQOL in a diverse serious illness population and could lead to reduced respondent burden.[53]

Additional solutions that may lead to improvements in the future include the development of new outcome measures, modification of existing measures to better assess HRQOL in pediatric palliative care, and additional field testing and cross-cultural validation of the African Palliative Care Association Children's Palliative Outcome Scale (APCA c-POS), The APCA c-POS is a PROM specifically developed to assess HRQOL in pediatric palliative care populations. However, the APCA c-POS was not included in the measure review because an English language version has not been developed and validated.[20,54]

Leadership

Public health leadership skills, such as agenda setting, advocacy, and policy promotion, are needed to accelerate the development and implementation of pediatric palliative care

HRQOL measures. Strong leadership skills are needed to identify and cultivate relationships with key stakeholders at all levels. Palliative care and pediatric coalitions can be leveraged to advocate for the need for methodologically sound outcome measures and to promote policies that allocate funding for instrument development or validation in pediatric palliative care. Leaders in the field can be utilized to set the research agenda to include rigorous psychometric testing of pediatric palliative care measures and to promote including validation of HRQOL instruments as a secondary aim in pediatric palliative care and serious illness research studies.

APPENDIX: DETAILED SEARCH STRATEGY

Database	Strategy	Results
Medline	Search (((((((patient reported outcomes[Title/Abstract]) OR quality of life[Title/Abstract]) OR health status[Title/Abstract]) OR global health[Title/Abstract]) OR health related quality of life[Title/Abstract]) OR outcome measurement[Title/Abstract])) AND ((((((((((classical test theory[Title/Abstract]) OR validity[Title/Abstract]) OR reliability[Title/Abstract]) OR content validity[Title/Abstract]) OR confirmatory factor analysis[Title/Abstract]) OR exploratory factor analysis[Title/Abstract]) OR internal consistency[Title/Abstract]) OR test-retest[Title/Abstract]) OR psychometr*[Title/Abstract]) OR known group[Title/Abstract]) OR Rasch[Title/Abstract]) OR DIF[Title/Abstract])) AND (((((child*[Title/Abstract]) OR neonat*[Title/Abstract]) OR adolescent*[Title/Abstract]) OR pediatric*[Title/Abstract]) OR paediatric*[Title/Abstract]) AND ("2014/12/01"[PDat] : "2020/01/12"[PDat]) AND Humans[Mesh] AND English[lang] AND (infant[MeSH] OR child[MeSH] OR adolescent[MeSH])	689
EMBASE	('patient-reported outcome':ab,ti OR 'quality of life':ab,ti OR 'health status':ab,ti OR 'global health':ab,ti OR 'outcome assessment':ab,ti) AND ('classical test theory':ab,ti OR validity:ab,ti OR reliability:ab,ti OR 'content validity':ab,ti OR 'confirmatory factor analysis':ab,ti OR 'exploratory factor analysis':ab,ti OR 'internal consistency':ab,ti OR 'test retest reliability':ab,ti OR psychometry:ab,ti OR 'known group validity':ab,ti OR 'rasch analysis':ab,ti) AND (child:ab,ti OR newborn:ab,ti OR adolescent:ab,ti OR pediatrics:ab,ti) AND [english]/lim AND ([newborn]/lim OR [infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim OR [young adult]/lim) AND [humans]/lim AND [2014-2020]/py	533
PsychInfo	((patient reported outcomes OR (quality of life or well being or well-being or health-related quality of life) OR health status OR global health OR (outcome measure or outcome tool or outcome assessment)) AND (classical test theory OR (validity or reliability) OR content validity OR confirmatory factor analysis OR exploratory factor analysis OR internal consistency OR test-retest OR psychometric OR known group OR rasch) AND (child or children or paediatric or pediatric or neonatal or adolescent)) TI OR AB	590

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