PedsQL Eosinophilic Esophagitis Module: Feasibility, Reliability, and Validity

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ABSTRACT

Objective: Eosinophilic esophagitis (EoE) is a chronic esophageal inflammatory condition with a paucity of information on health-related quality of life (HRQOL). The objective of the study was to report on the measurement properties of the PedsQL EoE Module.

Methods: The PedsQL EoE Module was completed in a multisite study by 196 pediatric patients with EoE and 262 parents of patients with EoE.

Results: The PedsQL EoE Module scales evidenced excellent feasibility (0.6%–3.1% missing), excellent group comparison reliability across total scale scores (patient α 0.93; parent proxy α 0.94), good reliability for the 7 individual scales (patient α 0.75–0.87; parent proxy α 0.81–0.92), excellent test–retest reliability (patient intraclass correlation coefficient 0.88; parent intraclass correlation coefficient 0.82), demonstrated no floor effects and low ceiling effects, and demonstrated a high percentage of scaling success for most scales. Intercorrelations with the PedsQL Generic Core Scales were in the medium (0.30) to large (0.50) range. PedsQL EoE Module scores were worse among patients with active histologic disease (≥5 eos/hpf) compared with those in remission (patient self-report: 63.3 vs 69.9 [$P < 0.05$]; parent proxy report: 65.1 vs 72.3 [$P < 0.01$]), and those treated with dietary restrictions compared with those with no restrictions (patient self-report: 61.6 vs 74.3 [$P < 0.01$]; parent proxy report: 65.5 vs 74.7 [$P < 0.01$]).

Conclusions: The results demonstrate excellent measurement properties of the PedsQL EoE Module. Patients with active histologic disease and those treated with dietary restrictions demonstrated worse PedsQL scores. The PedsQL EoE Module may be used in the evaluation of pediatric EoE disease-specific HRQOL in clinical research and practice.

Key Words: children, eosinophilic esophagitis, health-related quality of life, patient-reported outcomes, pediatrics, PedsQL

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Eosinophilic esophagitis (EoE) is a chronic esophageal inflammatory condition with an increasing prevalence approaching 1/1000 in the US pediatric population (1,2). Food allergies are a common cause of EoE, and strict dietary antigen elimination is a common treatment (3,4). Pediatric health outcomes in present EoE clinical practice typically focus primarily on histologic and symptomatic improvement (3), and patient health-related quality of life (HRQOL) is not routinely assessed with standardized instruments; however, as our understanding of pediatric EoE is rapidly evolving, so too does the recognition that there are many important components to this chronic condition beyond counting the number of esophageal eosinophils on mucosal biopsies.

Legislative changes during the last several years, including the pediatric exclusivity provision of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, have established voluntary and mandatory guidelines for drug studies in children, which have resulted in a significant growth in clinical trials for pediatric patients (5). Despite these pediatric initiatives that have created the opportunity for children to be included in clinical trials, until relatively recently, pediatric patients have not been provided the opportunity to self-report on matters pertaining to their health and well-being in clinical trials (6). The emerging paradigm shift toward patient-reported outcomes (PROs), including recent guidelines from the US Food and Drug Administration (FDA), has provided the opportunity to further emphasize the value and critical need for pediatric patient self-report measurement as efficacy outcomes in pediatric clinical trials (5,7).

Although pediatric patients with EoE experience significant disease- and treatment-related sequelae, to our knowledge, there is no validated EoE-specific HRQOL instrument to document the effect of EoE on the daily lives of affected pediatric patients, which includes pediatric patient self-report for ages 5 to 18 years and parent proxy report for ages 2 to 18 years. Recently, we used the Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales to investigate the generic HRQOL of patients with eosinophilic gastrointestinal disease (EGID, including EoE) in comparison with several other pediatric chronic conditions and healthy controls (8). Not only did patients with EGID and their parents report significantly lower generic HRQOL than healthy controls but they also reported generic HRQOL lower than pediatric patients with inflammatory bowel disease, epilepsy, type 1 diabetes mellitus, sickle cell disease, postrenal transplantation, cystic fibrosis, and obesity (8). In addition, we have identified that untreated pediatric patients with EoE are at risk for adverse effect on their generic HRQOL an average of 15 years after their initial endoscopy (1).

Even though the PedsQL 4.0 Generic Core Scales (Physical, Emotional, Social, and School Functioning scales) assess generic issues common across healthy and ill pediatric populations, as well as benchmarking with healthy populations, a disease-specific HRQOL instrument is essential to understanding the particular health issues most germane to pediatric patients with EoE from their perspective (9). In addition, an EoE disease-specific HRQOL instrument would be expected to be more sensitive than a generic scale alone to detecting change in health status over time within a population of children with EoE. To better understand differences in health status within the population of pediatric patients with EoE and to enhance the ability to measure the effect of disease-modifying therapies, we developed items for a new EoE disease-specific HRQOL instrument. This new instrument is targeted to pediatric EoE using qualitative methods to support content validity (9,10), and is consistent with recent FDA guidelines on PRO measures in chronic diseases (5).

Given the lack of an empirically validated multidimensional pediatric EoE disease-specific HRQOL instrument in the extant literature, the objective of the present study was to address this significant gap in the EoE literature by describing the measurement properties for both pediatric patient self-report and parent proxy report for the new PedsQL EoE Module. We present the initial feasibility, reliability, and validity of the new PedsQL EoE Module scales. Based on previous PedsQL 4.0 Generic Core Scales disease-specific findings, we hypothesized that pediatric patients with EoE would manifest lower PedsQL 4.0 Generic Core Scales' scores in comparison with a matched healthy children sample, supporting discriminant validity (11–18). We further hypothesized that greater EoE-specific symptoms or problems would be significantly correlated with lower generic HRQOL as measured by the PedsQL 4.0 Generic Core Scales, with medium- to large-effect sizes, based on the conceptualization of disease-specific symptoms as causal indicators of generic HRQOL, supporting construct validity (19). In addition to analyzing these measurement properties, we also sought to test the hypotheses that PedsQL EoE Module scale scores would be lower (worse) in patients with active histologic disease compared with those in remission and in patients treated with dietary elimination compared with those treated with no dietary restrictions.

METHODS

EoE Sample

Families were invited to participate from 6 sites across the United States. A total of 263 families (196 children ages 5–18 years and 262 parents of children ages 2–18 years) completed the questionnaires. The sample consisted of children who had received a physician diagnosis of EoE. Specifically, all of the children had their diagnosis confirmed by an EoE subspecialty physician with an endoscopy with 15 or more eosinophils per high-powered field (eos/hpf) in an endoscopic biopsy of the distal esophagus after being treated with 8 or more weeks of proton pump inhibitor therapy or having a negative pH probe test. Patients with eosinophilic gastrointestinal disorders beyond the esophagus were excluded. Among confirmed patients with EoE, their most recent endoscopy results (range 3 days–9.3 years) were also stratified into those with active disease (using both $\geq$5 eos/hpf and $\geq$15 eos/hpf cutpoints) and those in histologic remission. In addition, parents of patients with EoE who self-reported whether their child used dietary elimination therapy for EoE were dichotomized into those with no dietary restrictions and those with dietary restrictions. The average age of the 177 boys (67.3%) and 70 girls (26.6%) (missing sex values 16 [6.1%]) was 8.75 years (SD 4.50; missing age values 2 [0.8%]). With respect to race/ethnicity, the sample contained 233 (88.6%) self-reported white non-Hispanics, 11 (4.2%) Hispanics, 5 (1.9%) black non-Hispanics, 3 (1.1%) Asian/Pacific Islanders, and 11 (4.1%) others or missing. With respect to parent education in the electronic questionnaire cohort (n = 213), 1.4% of mothers and 2.4% of fathers did not complete high school; 4.7% of mothers and 11.3% of fathers had a high school diploma; 24.4% of mothers and 20.7% of fathers completed some college; 35.7% of mothers and 30.0% of fathers had an undergraduate degree; and 30.0% of mothers and 28.6% of fathers had a graduate degree (missing: 3.8% mothers and 7.0% fathers).

Healthy Children Sample: PedsQL 4.0 Generic Core Scales

The age-, sex-, and race-/ethnicity-matched healthy children sample (n = 1164) was derived from the previously conducted PedsQL 4.0 Generic Core Scales initial field test (20) and a State's Children's Health Insurance Program (SCHIP) evaluation in

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California (21). Children were assessed either in physicians' offices during well-child visits, by telephone, or via a statewide mailing. The average age of the 783 boys (67.3%) and 381 girls (32.7%) was 8.75 years (SD 4.18). With respect to race/ethnicity, the sample contained 1068 (91.8%) white non-Hispanics, 57 (4.9%) Hispanics, 23 (2.0 %) black non-Hispanics, and 16 (1.4%) Asian/Pacific Islanders. Parental level of education was not available for the total sample, although the statewide State's Children's Health Insurance Program sample was representative of low-income families. The healthy sample was randomly matched to the EoE sample by age, sex, and race/ethnicity using SPSS 19.0 (SPSS Inc, Chicago, IL).

Measures

PedsQL EoE Module

The PedsQL EoE Module was developed through a literature review of the relevant research, consultation with EoE health care professionals, focus interviews, cognitive interviews, and pretesting protocols (9,10). Development of the items for the PedsQL EoE Module began in 2008. The child self-report items are listed in Table 1.

The 33-item PedsQL EoE Module encompasses 7 scales: Symptoms I (6 items; chest/throat/stomach pain and nausea/vomiting), Symptoms II (4 items; trouble swallowing), Treatment (5 items; treatment barriers), Worry (6 items; worries about treatment and disease), Communication (5 items; communication with others about EoE), Food and Eating (4 items; food and eating allergies and limitations), Food Feelings (3 items; emotions associated with food allergies). A 1- to-2-item (depending on age) Feeding Tube Scale is included only for clinical purposes and is not included in the quantitative analyses. In addition to a PedsQL, EoE Module Total Scale Score, a PedsQL EoE Module Total Symptom Scale Score was also developed. The format, instructions, Likert response scale, and scoring method for the PedsQL EoE Module are identical to the PedsQL 4.0 Generic Core Scales, with higher scores indicating better HRQOL and lower EoE symptoms and problems (20).

The scales comprise parallel child self-report and parent proxy report formats for children ages 5 to 18 years, and a parent proxy report format for children ages 2 to 4 years. Child self-report forms are specific for ages 5 to 7, 8 to 12, and 13 to 18 years. Parent proxy report forms are specific for children ages 2 to 4 (toddler), 5 to 7 (young child), 8 to 12 (child), and 13 to 18 (adolescent), and assess parents' perceptions of their child's HRQOL. The instructions ask how much of a problem each item caused during the last 1 month. The grammar and syntax of the new items were structurally equivalent to those in the existing PedsQL item bank. Instructions and response scales for the PedsQL EoE Module were created to be consistent with the instructions and response scales of the PedsQL 4.0 Generic Core Scales for ages 2 to 18 years and other PedsQL disease-specific modules (11–18). The PedsQL 5-point Likert-type response scale has been widely used in published PedsQL studies (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem), and has also previously undergone extensive cognitive interviewing for a number of Pediatric Patient Reported Outcomes Measurement Information System scales and were found acceptable and understood by both pediatric patients and parents (23–26). To further increase the ease of use for the young child self-report (ages 5–7), the response scale is reworded and simplified to a 3-point scale (0 = not at all a problem; 2 = sometimes a problem; 4 = a lot of a problem). This simplification to a 3-point scale for the young child self-report is consistent with the PedsQL 4.0 Generic Core Scales as well as with all of the PedsQL disease-specific modules (27). See Table 1 for several age differences across items and scales.

TABLE 1. PedsQL Eosinophilic Esophagitis Module child self-report item content

Symptoms I
I have chest pain, ache, or hurt
I have burning in my chest, mouth, or throat (heartburn)*
I have stomach aches or belly aches
I throw up (vomit)
I feel like I am going to throw up, but don't (nausea)*
When I am eating food comes back up my throat*
Symptoms II†
I have trouble swallowing
I feel like food gets stuck in my throat or chest
I need to drink to help me swallow my food
I need more time to eat than other kids my age
Treatment
It is hard for me to remember to take my medicines*
I do not want to take my medicines
I do not like going to the doctor
I do not like getting an endoscopy (scope, EGD)
I do not like getting allergy testing
Worry
I worry about having EoE*
I worry about getting sick in front of other people
I worry about what other people think about me because of EoE*
I worry about going to the doctor
I worry about getting an endoscopy (scope, EGD)
I worry about getting allergy testing
Communication‡
I have trouble telling other people about EoE*
I have trouble talking to my parents about how I feel
I have trouble talking to other adults about how I feel
I have trouble talking to my friends about how I feel
I have trouble talking to doctors or nurses about how I feel
Food and Eating
It is hard not being allowed to eat some foods
It is hard for me not to sneak foods that I am allergic to§
It is hard for me not to eat the same things as my family
It is hard for me not to eat the same things as my friends
Food Feelings
I worry about eating foods I'm allergic to or not supposed to eat
I feel mad (get upset) about not eating foods I am allergic to or not supposed to eat
I feel sad about not eating foods I am allergic to or not supposed to eat
Feeding Tube‖
It is hard for me to remember to use my feeding tube*
It is hard for me to use my feeding tube

Reproduced with permission from JW Varni, Ph.D. Copyright 1998. The PedsQL is available at *http://www.pedsql.org*. EGD = esophagogastroduodenoscopy; EoE = eosinophilic esophagitis.

* Items not included in young child self-report (ages 5–7) and parent proxy report for young child (ages 5–7) and toddlers (ages 2–4).

† For young child self-report (ages 5–7), scale only for clinical purposes.

‡ Scale not included in parent proxy report for toddlers (ages 2–4).

§ Item not included in parent proxy report for toddlers (ages 2–4).

‖ Scale only for clinical purposes.

Items are reverse scored and linearly transformed to a 0 to 100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicate better HRQOL. Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). If >50% of the items in the scale are missing, the scale score is not computed (28). This accounts for the differences in sample sizes for scales reported in the tables.

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Although there are other strategies for imputing missing values, this computation is consistent with the previous PedsQL peer-reviewed publications as well as other well-established HRQOL measures (20,29,30). To create the PedsQL EoE Module Total Scale Score (33 items), the mean is computed as the sum of the items divided by the number of items answered in the Symptoms I, Symptoms II, Treatment, Worry, Communication, Food and Eating, and Food Feelings scales. To create the PedsQL EoE Module Symptoms Total Scale Score (10 items), the mean is computed as the sum of the items divided by the number of items answered in the Symptoms I and Symptom II scales. The Feeding Tube Scale is not included in the Total Scale Score because this scale is typically completed only by a small subgroup of patients and parents.

The PedsQL 4.0 Generic Core Scales

The 23-item PedsQL 4.0 Generic Core Scales encompass Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items), and School Functioning (5 items) (20,31). The Physical Health Summary Score is the same as the Physical Functioning Scale. To create the Psychosocial Health Summary Score, the mean is computed as the sum of the items divided by the number of items answered in the Emotional, Social, and School Functioning scales.

The PedsQL Family Information Form

Parents completed a modified PedsQL Family Information Form, which contains demographic information, including the child's date of birth, sex, race/ethnicity, and parental education and occupation information (20).

Procedures

Data collection for the field test took place during a 13-month period between January 2011 and February 2012. Participants were children ages 5 to 18 years who had received a physician diagnosis of EoE and parents of children ages 2 to 18 years who had received a physician diagnosis of EoE at 6 clinical centers across the United States (Cincinnati Children's Hospital Medical Center, The Children's Hospital of Philadelphia, Children's Hospital Colorado, Riley Children's Hospital, Texas Children's Hospital, Nationwide Children's Hospital). All of the eligible patients at each clinical site were invited to participate in the study. The human subject institutional review boards at each center approved the study.

Statistical Analysis

Feasibility was determined from the percentage of missing values (32). Cronbach coefficient α was used to determine scale internal consistency reliability (33). Scales with internal consistency reliabilities of ≥0.70 are recommended for comparing patient groups, whereas an internal consistency reliability criterion of 0.90 is recommended for analyzing individual patient scores (34,35). Test–retest reliability was calculated for a subset of the sample (n = 102) using intraclass correlation coefficients (ICCs) (36). Patients and their parents were assessed on average 14 days after baseline. ICCs are designated as <0.40 poor to fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 good agreement, and 0.81 to 1.00 excellent agreement (36). Range of measurement was based on the percentage of scores at the extremes of the scaling range, that is, the maximum possible score (ceiling effect) and the minimum possible score (floor effect). Surveys with small floor or ceiling effects (1%–15%) are considered to meet acceptable measurement standards, whereas surveys with moderate floor or ceiling effects (≥15%) are considered less precise in measuring latent constructs at the extremes of the scale (37). Multitrait scaling analyses were conducted to determine the extent to which individual items correlated with their hypothesized scale construct rather than with other scales (38). Multitrait scaling analyses were summarized via tests of individual item scaling success, defined as the percentage of items correlating equal to or higher with their hypothesized scale construct rather than with another scale using adjusted scale scores for scales in which the item was part of the score (32).

Discriminant validity for the PedsQL 4.0 Generic Core Scales in EoE was determined using the known-groups method (39). The known-groups method compares scale scores across groups known to differ in the health construct being investigated. Generic Core Scales scores in groups differing in known health condition (pediatric patients with EoE and healthy children) were computed using independent samples *t* tests. We hypothesized that the Generic Core Scales would distinguish between healthy children and pediatric patients with EoE based on previous PedsQL findings in other pediatric chronic conditions (14–16,40) and pediatric patients with EGID (8). Effect sizes were calculated to determine the magnitude of the differences (41). Effect size as used in these analyses was calculated by taking the difference between the healthy sample mean and the EoE sample mean, divided by the pooled standard deviation. Effect sizes for differences in means are designated as small (0.20), medium (0.50), and large (0.80) in magnitude (42).

An analysis of the intercorrelations among the PedsQL 4.0 Generic Core Scales and Summary Scores with the EoE Module Scale Scores was used to examine construct validity for the PedsQL EoE Module. Computing the intercorrelations among scales provides initial information on the construct validity of an instrument (35). We hypothesized that greater disease-specific symptoms or problems would correlate with lower overall generic HRQOL as measured by the PedsQL 4.0 Generic Core Scales based on the conceptualization of disease-specific symptoms as causal indicators of generic HRQOL (43). Pearson Product Moment Correlation coefficients' effect sizes are designated as small (0.10), medium (0.30), and large (0.50) (41).

To support additional construct validation for the PedsQL EoE Module Scales and Summary Scores, we performed contrast analyses between patients treated with dietary restrictions and those with no restrictions, and between patients with active histologic disease and those in remission using independent samples *t* tests.

ICCs were used to determine agreement between patient self-report and parent proxy report (36). The ICC provides an index of absolute agreement because it takes into account the ratio between subject variability and total variability (36,44).

RESULTS

Feasibility: Missing Item Responses

The percentages of missing item responses on the PedsQL EoE Module were 0.8% and 0.6% for the first 5 scales for child self-reports 8 to 18 and 5 to 7 years of age, respectively. For parent proxy report, the percentages of missing item responses were 1.0% (ages 8–18), 3.1% (ages 5–7), and 2.8% (ages 2–4) for the first 5 scales on the PedsQL EoE Module. The percentages of missing item responses were not computed for the last 2 scales because they consist of conditional items and individuals were asked to respond to them only if they were allergic to certain foods and could not eat some foods. For child self-report and parent proxy report on the PedsQL 4.0 Generic Core Scales, the percentages of missing item responses were 0.8% and 0.4%, respectively, for all of the scales

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except the parent proxy report School Functioning Scale. The percentages of missing items for the proxy report School Functioning Scale were 1.8% (ages 5–18) and 19.7% (ages 2–4). This large percentage for toddlers (ages 2–4) may exist because instructions on the PedsQL toddler form ask parents to complete the School Functioning Scale if their child attends school or day care and many toddlers do not attend school or daycare.

Range of Measurement

Table 2 contains the percentage of scores at the extremes of the scaling range (floor and ceiling effects) for the PedsQL EoE Module Scales and Summary Scores. For child self-report, there were no significant floor effects for any of the scales or summary scores, and only a ceiling effect for the Communication Scale. For parent proxy report, there were no significant floor effects for any of the scales or summary scores, and marginal ceiling effects for the Symptoms II, Treatment, Worry and Communication Scales.

Internal Consistency Reliability

Internal consistency reliability coefficients for the PedsQL EoE Module summed across the age groups are shown in Table 3. All child self-report and parent proxy report scales on the EoE Module exceed the minimum reliability standard of 0.70 required for group comparisons summed across the age groups. The Total Scale Scores for both child self-report and parent proxy report exceed the reliability criterion of 0.90 recommended for analyzing individual patient scores. Table 3 contains the internal consistency reliability coefficients individually across the age groups. For child self-reports, except for the Symptoms II Scale for 5 to 7 years age group, all of the other scales demonstrated higher values than the minimum reliability standard of 0.70. For parent proxy report, all of the scales exceed 0.70 internal consistency reliability coefficients individually across the age groups.

Online-only Appendix 1 (*http://links.lww.com/MPG/A207*) presents internal consistency reliability coefficients for the PedsQL 4.0 Generic Core Scales for the EoE sample. All child self-report and parent proxy report scales on the Generic Core Scales meet or exceed the minimum reliability standard of 0.70 required for group comparisons, except for child self-report Social Functioning (0.69). The Total Scale Scores for both child self-report and parent proxy report exceed the reliability criterion of 0.90 recommended for analyzing individual patient scores.

Test–Retest Reliability

Table 4 presents ICCs for test–retest reliability. In a subsample (n = 102), patients and their parents were readministered the PedsQL EoE Module on average 12.3 days (SD 4.0) after baseline. All but 1 of the ICCs was in the good to excellent test–retest reliability range for both patients and parents.

Construct Validity

Online-only Appendix 1 (*http://links.lww.com/MPG/A207*) presents the differences between the pediatric patients with EoE and the healthy children sample. For each PedsQL 4.0 Generic Core

TABLE 2. PedsQL Eosinophilic Esophagitis Module Scores, reliability, and percent floor and ceiling effects for child self-report and parent proxy report

EoE Module scales	No. items	n	α	Mean	SD	% Floor	% Ceiling
Child self-report							
EoE Module Total Scale Score	33	196	0.93	65.2	19.1	0	0
Symptoms Total Scale Score	10	139*	0.85*	69.8	19.0	0	1.5
Symptoms I	6	196	0.83	66.7	20.1	0.4	4.6
Symptoms II	4	139*	0.86*	70.9	24.3	0	10.6
Treatment	5	195	0.75	55.5	26.8	1.9	3.4
Worry	6	196	0.85	68.1	26.1	0.8	11.8
Communication	5	196	0.87	74.0	25.7	0.8	23.2
Food and Eating	4	171	0.87	60.3	32.4	4.9	12.9
Food Feelings	3	161	0.81	57.2	32.5	5.7	10.3
Parent proxy report							
EoE Module Total Scale Score	33	262	0.94	67.4	17.6	0	0.4
Symptoms Total Scale Score	10	258	0.89	68.0	20.0	0	3.8
Symptoms I	6	258	0.88	67.8	20.9	0	6.8
Symptoms II	4	258	0.83	68.2	23.9	0.8	15.6
Treatment	5	261	0.81	72.5	22.8	0	18.3
Worry	6	254	0.87	72.1	23.5	0.4	16.3
Communication	5	196	0.92	67.1	27.2	1.5	16.7
Food and Eating	4	227	0.82	59.8	27.1	2.3	12.5
Food Feelings	3	216	0.84	55.6	28.0	3.4	10.6

Higher scores equal better HRQOL. For the calculation of the Cronbach α values for EoE Module Total Scale Score, the sample size was smaller because of list-wise deletion based on all items completed (child = 157, parent = 146). For child self-report (ages 5–7 years), Symptoms I Scale contains 3 items, Treatment Scale contains 4 items, Worry Scale contains 4 items, and Communication Scale contains 4 items. For parent report for toddlers (ages 2–4 years), there is no Communication Scale, and the Food and Eating Scale contains 3 items; for parent proxy report for toddlers and young child (ages 2–4 and 5–7 years), Symptoms I Scale contains 3 items, Treatment Scale contains 4 items, and Worry Scale contains 4 items; for parent proxy report for young child (ages 5–7 years), the Communication Scale contains 4 items. See Table 1 for the child self-report items for ages 8–18 years. α = Cronbach alpha internal consistency reliability; EoE = eosinophilic esophagitis; SD = standard deviation.

* Because of the low Cronbach α value (0.39) for young child self-report (ages 5–7), this age group was not used to calculate the overall Symptoms II score and Symptoms Total Score. For ages 5 to 7 years, this scale is used only for clinical purposes, and is not included in the scale scores.

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TABLE 3. PedsQL Eosinophilic Esophagitis Module Scales Cronbach α internal consistency reliability for child self-report and parent proxy report by age and summary score/scale

EoE Module scales	Age group, y				Total sample
	2–4	5–7	8–12	13–18	
Child self-report	N = 0	N = 56	N = 78	N = 62	N = 196
EoE Module Total Scale Score	NA	0.89*	0.94	0.95	0.93
Symptoms Total Scale Score	NA	0.77*	0.85	0.86	0.85*
Symptoms I	NA	0.90	0.76	0.82	0.83
Symptoms II	NA	0.39*	0.83	0.88	0.86*
Treatment	NA	0.78	0.74	0.73	0.75
Worry	NA	0.82	0.81	0.88	0.85
Communication	NA	0.82	0.87	0.90	0.87
Food and Eating	NA	0.82	0.88	0.93	0.87
Food Feelings	NA	0.73	0.83	0.88	0.81
Parent proxy report	N = 66	N = 56	N = 77	N = 63	N = 262
EoE Module Total Scale Score	0.93	0.94	0.95	0.92	0.94
Symptoms Total Scale Score	0.89	0.91	0.91	0.87	0.89
Symptoms I	0.87	0.94	0.89	0.83	0.88
Symptoms II	0.79	0.75	0.87	0.87	0.83
Treatment	0.83	0.88	0.78	0.82	0.81
Worry	0.89	0.92	0.88	0.84	0.87
Communication	NA	0.94	0.93	0.89	0.92
Food and Eating	0.80	0.82	0.85	0.81	0.82
Food Feelings	0.81	0.79	0.89	0.84	0.84

EoE = eosinophilic esophagitis; NA = not applicable.
* The Cronbach α value for young child self-report (5–7 years old) was not used to calculate the overall Symptoms II and overall Symptoms Total Scale Score Cronbach α because of its low value (0.39). For ages 5 to 7 years, this scale is only used for clinical purposes, and is not included in the scale scores.

Scales and Summary Scores, pediatric patients with EoE and their parents report statistically significant lower generic HRQOL than healthy children. The majority of effect sizes are in the medium range, supporting discriminant validity. The largest effect sizes for individual scales were demonstrated for the Physical Functioning (0.65), Emotional Functioning (0.65), and School Functioning (0.83) scales for child self-report, and for the Emotional Functioning (0.87) and School Functioning (0.75) scales for parent proxy report.

Online-only Appendix 2 (*http://links.lww.com/MPG/A208*) presents the intercorrelations between the PedsQL EoE Module Scales and Total Scale Score, and the Generic Core Scales and Summary Scores. The majority of intercorrelations are in the medium- to large-effect size range, supporting construct validity of the EoE Module Scales for child self-report and parent proxy report. Smaller effect sizes were observed with the Food and Eating and Food Feelings scales.

Item Scaling Tests

For the PedsQL EoE Module patient self-report scales, multitrait scaling analysis for item scaling success for the Symptoms Total Scale Score (ages 8–18), Symptoms I Scale, Symptoms II Scale (ages 8–18), Food and Eating Scale, and Food Feelings Scale was 100.0%; for the Treatment Scale it was 20.0%; for the Worry Scale it was 50.0%; and for the Communication Scale it was 80.0%. For the parent proxy report scales, scaling success was

TABLE 4. PedsQL Eosinophilic Esophagitis Module Scales ICCs for test–retest reliability for child self-report and parent proxy report

	Test–retest agreement child ICCs, n = 61	Test–retest agreement parent ICCs, n = 102
EoE Module Total Scale Score	0.88	0.82
Symptoms Total Scale Score	0.87*	0.82
Symptoms I	0.80	0.83
Symptoms II	0.85*	0.75
Treatment	0.71	0.62
Worry	0.77	0.60
Communication	0.67	0.77†
Food and Eating	0.84	0.79
Food Feelings	0.82	0.75

ICCs are designated as ≤0.40 poor to fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 good agreement, and 0.81 to 1.00 excellent agreement.
ICCs = intraclass correlation coefficients.
* n = 40 (smaller sample sizes as a result of age differences across forms).
† n = 69 (smaller sample sizes as a result of age differences across forms).

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100.0% for the Symptoms Total Scale Score, Symptoms I Scale, Symptoms II Scale, Treatment Scale, Worry Scale, and Communication Scale; it was 75.0% for the Food and Eating Scale and 66.7% for the Food Feelings Scale.

Parent–Child Agreement

ICCs between child self-report and parent proxy report are shown in Table 5. The majority of the ICCs are in the moderate-to-good agreement range for the PedsQL Scales.

Dietary Restrictions and Active Disease

To support additional construct validation for the PedsQL EoE Module Total Scale Scores, we performed contrast analyses between patients treated with dietary restrictions and those with no restrictions, and between patients with active histologic disease and those in remission. As shown in Figure 1, for children with no dietary restrictions, the PedsQL EoE Module Total Scale Scores were better (higher) than those with dietary restrictions (patient self-report: 74.3 [n = 51] vs 61.6 [n = 143], respectively [$P < 0.01$, effect size = 0.71]; parent proxy report: 74.7 [n = 54] vs 65.5 [n = 207], respectively [$P < 0.01$, effect size = 0.53]). Figure 1 also contains the contrasts across the individual scales.

In addition, PedsQL EoE Module Total Scale Scores were better (higher) among patients in remission compared with the patients with active histologic disease when active disease was defined as peak distal eos/hpf of either <5 eos/hpf versus ≥5 eos/hpf (patient self-report: 69.9 [n = 57] vs 63.3 [n = 139], respectively [$P < 0.05$, effect size = 0.36]; parent proxy report: 72.3 [n = 79] vs 65.1 [n = 182], respectively [$P < 0.01$, effect size = 0.43]) or <15 eos/hpf versus ≥15 eos/hpf (patient self-report: 68.4 [n = 85] vs 62.7 [n = 111], respectively [$P < 0.05$, effect size = 0.30]; parent proxy report: 70.4 [n = 120] vs 64.7 [n = 141], respectively [$P < 0.01$, effect size = 0.33]). PedsQL EoE Module Symptoms Total Scale Scores were also lower (worse) with active disease that was defined as peak distal eos/hpf of either <5 eos/hpf versus ≥5 eos/hpf (patient self-report: 71.9 [n = 41] vs 69.0 [n = 98], respectively [$P = 0.41$, effect size = 0.16]; parent

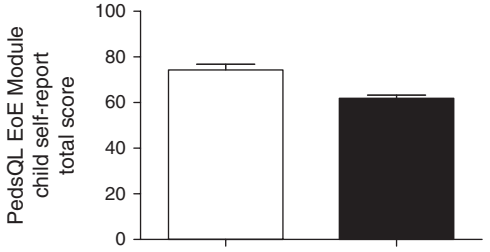
TABLE 5. ICCs between child self-report and parent proxy report on the PedsQL 4.0 Generic Core Scales and PedsQL Eosinophilic Esophagitis Module for pediatric patients with eosinophilic esophagitis sample

PedsQL Scales	Parent–child agreement ICCs
Generic Core Scales	
Generic Core Total	0.67
Physical Health	0.66
Psychosocial Health	0.62
Emotional Functioning	0.54
Social Functioning	0.50
School Functioning	0.70
Eosinophilic Esophagitis Module	
EoE Module Total Scale Score	0.57
Symptoms Total Scale Score	0.58
Symptoms I	0.63
Symptoms II	0.55
Treatment	0.30
Worry	0.45
Communication	0.30
Food and Eating	0.52
Food Feelings	0.54

ICCs are designated as ≤0.40 poor to fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 good agreement, and 0.81 to 1.00 excellent agreement. EoE = eosinophilic esophagitis; ICCs = intraclass correlation coefficients.

A

Child self-reported PedsQL™ EoE Module Total Scale Scores are worse (lower) with dietary elimination therapy

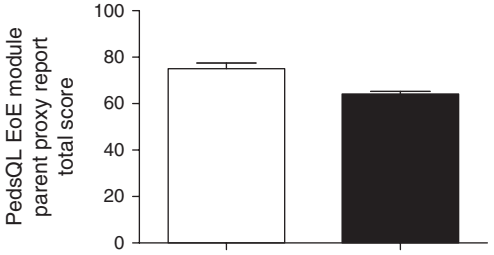


	No restrictions	Dietary elimination therapy
EoE Module Total Scale Score	74.3 (16.8)	61.6 (18.8)**
Symptoms Total Scale	74.7 (18.1)	67.3 (19.0)*
Symptoms I	71.5 (18.1)	64.6 (20.5)*
Symptoms II	76.1 (23.2)	68.4 (24.8)
Treatment	63.3 (26.5)	52.4 (26.4)*
Worry	77.8 (21.5)	64.4 (26.7)**
Communication	79.1 (25.9)	72.1 (25.7)
Food and Eating	85.1 (21.2)	55.0 (32.0)**
Food Feelings	75.0 (28.3)	54.5 (32.4)**

* $P < 0.05$; ** $P < 0.01$

B

Parent proxy reported PedsQL™ EoE Module Total Scale Scores are worse (lower) with diet elimination therapy



	No restrictions	Dietary elimination therapy
EoE Module Total Scale Score	74.7 (18.0)	65.5 (17.0)**
Symptoms Total Scale	68.8 (19.9)	67.9 (20.1)
Symptoms I	67.3 (22.7)	67.9 (20.6)
Symptoms II	70.4 (23.6)	67.9 (23.9)
Treatment	74.7 (24.4)	72.0 (22.4)
Worry	78.2 (21.1)	70.4 (23.9)*
Communication	75.8 (27.6)	64.1 (26.6)**
Food and Eating	85.9 (21.3)	55.8 (25.6)**
Food Feelings	80.0 (30.3)	53.1 (26.6)**

* $P < 0.05$; ** $P < 0.01$

FIGURE 1. PedsQL EoE Module Total Scale Scores, Total Symptom Scores, and individual scale scores among patients with EoE as child self-report (A) and parent proxy report (B) comparing those with no dietary restrictions and those with strict dietary antigen elimination.

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proxy report: 73.3 [n = 79] vs 65.7 [n = 178], respectively [$P < 0.01$, effect size = 0.39]), or <15 eos/hpf versus ≥15 eos/hpf (patient self-report: 72.5 [n = 62] vs 67.7 [n = 77], respectively [$P = 0.13$, effect size = 0.26]; parent proxy report: 70.9 [n = 120] vs 65.6 [n = 137], respectively [$P < 0.05$, effect size = 0.27]). In this cross-sectional study, the time from the last endoscopy to assess histologic disease activity and completion of the questionnaires ranged from 3 days to 9.3 years. Therefore, an exploratory post hoc analysis with regard to histologic disease activity and its relation to symptoms was conducted among a subgroup of patients who underwent endoscopy within 30 days of completing study questionnaires. PedsQL EoE Module Symptoms Total Scale Scores for child self-report (ages 8–18) were lower (worse) with active disease that was defined as peak distal eos/hpf of either <5 eos/hpf (75.0; n = 3) versus ≥5 eos/hpf (57.3; n = 4; $P = 0.34$, effect size = 0.87); or <15 eos/hpf (78.4; n = 4) versus ≥15 eos/hpf (46.9; n = 3; $P \leq 0.05$, effect size = 1.94).

DISCUSSION

These analyses support the feasibility, reliability, and validity of the PedsQL EoE Module scales for pediatric patient self-report for ages 5 to 18 years and parent proxy report for ages 2 to 18 years. Moreover, the findings provide further support for the measurement properties of the PedsQL 4.0 Generic Core Scales in pediatric patients with EoE. The PedsQL EoE Module scales make a significant contribution to the empirical literature by creating a multidimensional EoE-specific instrument that can be integrated with the PedsQL 4.0 Generic Core Scales to provide a comprehensive assessment of patient generic and disease-specific HRQOL.

The PedsQL EoE Module had minimal missing responses, supporting feasibility, suggesting that pediatric patients and their parents were willing and able to provide good-quality data regarding the child's HRQOL. The PedsQL EoE Module scales' internal consistency reliabilities exceeded the recommended minimum α coefficient standard of 0.70 for group comparisons, except for the Symptoms II Scale for child self-report ages 5 to 7 years. This specific scale for the 5 to 7 years age group was not used to calculate the overall Symptoms II and the overall Symptoms Total Scale Score α coefficients or scaling success, and should be used only for clinical or descriptive purposes. The PedsQL EoE Module individual scales may be used to examine specific domains of EoE-specific HRQOL given the requirements of a particular clinical trial, as well as subgroup differences across scales. The PedsQL EoE Module Total Scale and the Symptoms Total Scale scores both exceed the reliability criterion of 0.90 recommended for analyzing individual patient scores, except for child self-report ages 5 to 7 years (α=0.89), which does not include the Symptoms II Scale items for the Total Scale Score calculation. Therefore, with regard to EoE symptom outcome assessments, we suggest that the child self-report PedsQL EoE Module Symptom I, Symptom II, and Symptom Total Scale scores be used only for children ages 8 to 18 years of age, and that parent proxy reports be used for children ages 2 to 7 years.

The PedsQL 4.0 Generic Core Scales differentiated generic HRQOL in pediatric patients with EoE and a matched healthy children sample as hypothesized with medium- to large-effect sizes. Pediatric patients with EoE reported lower HRQOL than did healthy children, with physical, emotional, and school functioning showing the greatest differences between pediatric patients with EoE and healthy children. Differences in school functioning may be related to missing days of school for clinic or laboratory visits, hospitalizations, or other illnesses. The difficulties in school functioning reported by patient and parents suggest that clinicians should attend to the child's academic functioning and should encourage families to advocate for their child's academic support.

Pediatric patients with EoE and their parents showed moderate to good agreement across the scale scores of the PedsQL 4.0 Generic Core and EoE Module Scales, except for the Treatment and Communication Scales on the EoE Module that demonstrated poor to fair agreement. Agreement between child and parent reports on the PedsQL EoE Module Total Scale Score was moderate. These findings are in accordance with the results of the scaling item success. For parent proxy report, all of the first 5 scales of the EoE Module achieved a 100% scaling item success rate, whereas for child self-report, the Treatment, Worry, and Communication Scales demonstrated a lower scaling success rate. The lower percentage of scaling item success on the Treatment and Worry Scales for child self-report suggests that the items of these specific scales are also highly correlated with other EoE scales. These findings are logical because the treatment of EoE is highly related to different EoE disease-specific symptoms and worrying is related to one's symptoms and communications with others about symptoms and problems.

Although the primary focus of the present study was to demonstrate the feasibility, reliability, and validity of the newly developed PedsQL EoE Module, we also explored several hypotheses as further evidence of construct validity. It is notable that the PedsQL EoE Module Total Scale Scores were worse among patients with active histologic disease compared with those in histologic remission using both esophageal histologic disease activity cut-points of 5 and 15 eos/hpf. This provides strong initial evidence that EoE-specific HRQOL may be affected by treatment. It is notable that recent clinical trials have not shown improvements in assessments of HRQOL compared with placebo, even though the treatment intervention (eg, anti-interleukin-5) lowered esophageal eosinophil counts (47). We speculate that the usage of a properly validated EoE-specific HRQOL instrument, such as the PedsQL EoE Module, would improve the ability to identify potential beneficial effects. Furthermore, although in-depth analyses of symptoms at the time of an endoscopy to assess histologic disease activity was beyond the scope of our present study, in the patient subgroup who completed the PedsQL EoE Module within 30 days of their last endoscopy, an exploratory post hoc analysis demonstrated significant trends in the Symptoms I, Symptoms II, and Symptoms Total Scale scores. In particular, the effect sizes of the 30-day subgroup for the PedsQL EoE Symptoms Total Scale Scores for patient self-report scores (ages 8–18) comparing patients with active disease (either defined at ≥5 eos/hpf or ≥15 eos/hpf) with those in histologic remission were in the large-effect size range, with the latter reaching statistical significance despite a small sample size (<15 eos/hpf [78.4; n = 4) vs ≥15 eos/hpf [46.9; n = 3; $P \leq 0.05$, effect size = 1.94]); however, it is important to emphasize that a detailed analysis of EoE Symptoms assessments and their relation to histologic disease status were beyond the scope of the present construct validation study. Future research will seek to answer the important clinical question of whether not only the PedsQL EoE Module Total Scale Score but also the individual PedsQL EoE Module Symptom Scales are worse among patients with EoE at the time of their most recent endoscopy, and whether those patients with active symptoms and active histologic disease who respond histologically to EoE therapies also have symptomatic response using the PedsQL Symptoms Scales. Given that it is widely recognized that EoE symptoms and histologic disease are not a perfect correlation, it is likely that both endpoints will need to be used for clinical trials. The recent FDA Gastroenterology Regulatory and Therapeutic Endpoints (GREAT) workshop (48) has continued to emphasize that all therapies need to be assessed in the context of their clinical benefit (eg, survival, symptoms). Beyond FDA regulatory goals, it is important to emphasize that a patient's global health needs to be the focus for treating disease.

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The World Health Organization has specifically defined health as ''A state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity'' (49).

The Symptoms I, Symptoms II, and Symptom Total Score Scales achieved 100% scaling success across both pediatric patients self-report and parent proxy report. The Symptoms I, Symptoms II, and Symptom Total Score Scales may be indicated for clinical trials targeting symptom reduction in pediatric patients with EoE. The Symptom II Scale is particularly of interest because this scale captures the concepts of dysphagia from the patients' perspective. Clinically, it is well recognized that patients may not realize that they have trouble swallowing, but they do need to drink liquids to help swallow food or take more time to eat food than other children. Our findings support the internal consistency and scaling success of the Symptom II Scale items, that is, that they are associated with one another, represent a unique scale, and these items are not answered the same by all patients. Therefore, it is important to include all of these items to comprehensively evaluate EoE symptoms.

In addition to histologic disease activity status, we were also able to demonstrate that the PedsQL EoE Module Total Scale Scores were predictably worse among patients with more severe dietary restrictions. Although an in-depth analysis of the adverse psychological effect that severe dietary restrictions may have on patients and their families alike was beyond the scope of our present study, it is clear that this is a major area of concern and warrants further investigation. This also further supports the urgent need for novel EoE therapies that keep a focus on patient health that includes QOL assessments and goes beyond esophageal eosinophil counting and only measures of disease status.

In addition to assessment of symptoms relative to histologic disease activity and degree of dietary restriction therapy, medication adherence is often an issue with chronic diseases that require long-term therapy. It is interesting to note that the lowest score was for the child self-reported Treatment Scale when compared with other self-reported module scales and when compared with the parent proxy reported Treatment Scale score. In particular, this scale asks about medication adherence and difficulties with medications, clinic visits, and diagnostic testing. Given that EoE is a chronic disease that requires long-term treatment, issues of adherence to treatment become highly salient, and it is essential that the treatment is acceptable to the patients. This potentially emphasizes the need for behavioral health adherence interventions and additional treatment options because present treatments are a problem for the patients from their perspective. It also suggests that the EoE Module scales will be useful because new treatments are introduced to determine whether adherence is improved.

The present study has several strengths, including the rigorous methods used to construct the measure, the relatively large sample size, the broad age range of participants, and the nationwide representation of the participants (6 clinical sites from across the country). Limitations include the lack of information on families that chose not to participate in the study, and the small sample sizes for the exploratory post hoc analyses. Feasibility in the present study was assessed solely by the percentage of missing values; future investigations should also evaluate the feasibility of these measures with regard to completion time and nonresponse rate. The only measure used to assess construct validity was the PedsQL Generic Core Scales. Other measures assessing such constructs as depression, anxiety, family communication, and adherence to medical regimens were not collected for this study (to reduce participant burden), and future comparisons among these measures may add important information regarding the construct validity of the PedsQL EoE Module scales. The use of historical controls for the PedsQL 4.0 Generic Core Scales comparisons is another potential limitation. It should be noted, however, that the lower socioeconomic status (SES) of the healthy children comparison sample in the present study most likely underestimated the true differences between the EoE sample and healthy children given previous findings on the negative effect of lower SES on children's HRQOL (50). Future studies with the PedsQL 4.0 Generic Core Scales should prospectively recruit an age-, sex-, race/ethnicity-, and SES-matched healthy cohort sample. Last, although the data of the present study provide some initial support toward the use of the PedsQL EoE Module scales and summary scores in clinical trials, prospective longitudinal studies are urgently needed.

The recall period for the PedsQL EoE Module used in the present study was the PedsQL standard ''past 1 month'' recall version. Although there are PedsQL Modules that also offer the acute ''past 7 days'' recall period option, we have found that the data from both recall periods are similar (14). The test–retest reliability data presented in present study demonstrated that the PedsQL EoE Module scales and summary scores did not change to a significant degree over an average interval of ~12 days between instrument administrations in pediatric patients with stable disease. In the adult dysphagia literature, the Mayo Dysphagia Questionnaire was not found to be responsive in a 14-day recall period, but rather performed better during a 1-month recall period (51). Additionally, there have been a number of responsiveness analyses with the PedsQL 4.0 Generic Core Scales in which the 1-month recall period was demonstrated to be sensitive to intervention effects (27). Future research studies may explore using the PedsQL acute 7-day recall with the EoE Module to compare the acute and standard recall period versions. These analyses may help determine whether the PedsQL EoE Module responsiveness is improved by using the 7-day recall period compared with the standard 1-month recall period.

To assess the clinical use of this newly developed multidimensional EoE-specific HRQOL instrument, future studies using the measure in clinical trials would facilitate a more thorough understanding of the multidimensional nature of both the patient's experience and the parents' perceptions of their child's experiences regarding the effect of EoE on generic and disease-specific HRQOL and facilitate medical decision making for these patients. The development of the PedsQL EoE Module should help clinicians identify children at different levels of morbidity, identify the differential effect of various treatment regimens, identify those children at risk for emotional difficulties and school issues, and identify emerging problems over time for individual patients and patient groups.

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