

Journal Pre-proof

Assessing Health-Related Quality of Life in Children with Food Allergy and Eosinophilic Esophagitis

Vibha Szafron, MD, Sara Anvari, MD, MSc, FAAAAI, Grant Pickett, MD, Kristen A. Staggars, MS, Charles G. Minard, PhD, JaLeen Rogers, BS, MPH, Ariel Washington, BS, Carla M. Davis, MD FAAAAI

PII: S2213-2198(21)00172-0

DOI: <https://doi.org/10.1016/j.jaip.2021.01.042>

Reference: JAIP 3419

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 19 December 2019

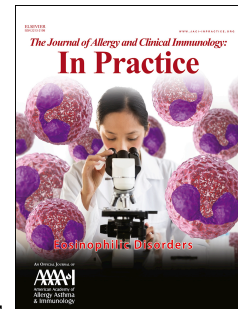
Revised Date: 25 January 2021

Accepted Date: 26 January 2021

Please cite this article as: Szafron V, Anvari S, Pickett G, Staggars KA, Minard CG, Rogers J, Washington A, Davis CM, Assessing Health-Related Quality of Life in Children with Food Allergy and Eosinophilic Esophagitis, *The Journal of Allergy and Clinical Immunology: In Practice* (2021), doi: <https://doi.org/10.1016/j.jaip.2021.01.042>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology



Assessing Health-Related Quality of Life in Children with Food Allergy and Eosinophilic Esophagitis

Vibha Szafron, MD^{1,2}, Sara Anvari, MD, MSc, FAAAAI^{1,2}, Grant Pickett, MD³, Kristen A. Stagg, MS⁴, Charles G. Minard, PhD⁴, JaLeen Rogers, BS, MPH¹, Ariel Washington, BS¹, and Carla M. Davis, MD FAAAAI^{1,2}

(1)Texas Children's Hospital (2) Baylor College of Medicine, Department of Pediatrics, Section of Immunology, Allergy, and Retrovirology (3) Baylor College of Medicine, Department of Internal Medicine (4) Institute for Clinical and Translational Research, Baylor College of Medicine

Corresponding Author: Vibha Szafron

vibha.szafron@bcm.edu

1102 Bates St. Suite 330. Houston, TX 77030. USA

Phone 281-734-0734

Author emails: sara.anvari@bcm.edu, grant.pickett@bcm.edu, kandrews@bcm.edu, minard@bcm.edu, alwashi1@texaschildrens.org, jcrogers@texaschildrens.org, carlad@bcm.edu

Conflict of Interest, Financial Disclosures and Funding Sources:

Drs. Anvari and Davis receive research contract funding from DBV Technologies, Regeneron and Aimmune Therapeutics. Dr. Anvari and Davis receive grant funding from NIH and Food Allergy Research and Education. Dr. Davis is a consultant for Moonlight Therapeutics.

Text Word Count: 1669 words

1 **Clinical Implications:**

2 Children with IgE-mediated food allergy had better HRQOL in parent-perceived physical
3 functioning scores compared to eosinophilic esophagitis. HRQOL was lower in
4 eosinophilic esophagitis patients treated with PPIs versus without PPIs. Privately insured
5 patients had better HRQOL than Medicaid patients.

6

7 IgE-mediated food allergy (FA) and eosinophilic esophagitis (EoE), are chronic, common
8 conditions that affect all aspects of health in pediatric patients^{1,2}. Socioeconomic
9 differences can impact care of these patients. For example, insurance type and race
10 have been shown to influence disease severity and treatment adherence in children with
11 FA³⁻⁴. Various features of health-related quality of life (HRQOL) in FA and EoE have
12 been studied previously^{1,2}, though without direct comparison of the two. Given IgE-FA
13 can co-exist in 24-68%⁵ of patients with EoE and symptoms can differ greatly between
14 FA and EoE, it is important to compare how each of these diseases impact HRQOL.
15 Additionally, effects of treatment strategies on HRQOL have been studied for FA, but not
16 as much for EoE^{1,2}. The aim of this study was to explore differences in HRQOL between
17 children with FA and EoE and assess demographic and treatment factors associated
18 with HRQOL. We hypothesized that EoE patients would have lower HRQOL than FA
19 patients and insurance type would be associated with HRQOL.

20

21 We conducted a retrospective cohort study evaluating HRQOL differences in children
22 aged 2-18 years with FA, EoE or both diagnoses, from 2014-2017 through a
23 Medicare/Medicaid program evaluating healthcare metrics. The Baylor IRB approved
24 this study. Patients were evaluated at their initial visit at Texas Children's Hospital
25 Allergy/Immunology or Eosinophilic Gastrointestinal Disease Clinics. FA cases were
26 diagnosed by allergists, using a combination of clinical history, skin prick testing, specific

IgE-mediated blood testing, and oral food challenges. EoE was diagnosed with a combination of clinical symptoms and endoscopic findings under the care of both allergists and gastroenterologists. Exclusion diagnoses included oral allergy syndrome and eosinophilic gastrointestinal disease without FA/EoE. The validated PedsQL™ (Generic Core Scale) survey⁶ contained 23 questions, scoring 0-100, and averaged towards one total and four subset scores (physical functioning scores (physical-FS), emotional functioning scores (emotional-FS), social functioning scores (social-FS) and school functioning scores (school-FS)). Higher scores indicated better HRQOL. The survey-respondent was child and/or parent, though the subject was always the child.

Simple linear regressions were used to evaluate differences in total or subset scores among child characteristics (for diagnosis FA, EoE, both FA +EoE, insurance type, age, EoE treatment type, gender, race, number of food allergies), with separate analyses for child and parent-perceived scores. Previously validated minimal clinically meaningful differences were used⁶ for child and parent-perceived scores, respectively, as follows: 4.36 and 4.50 points for total scores, 6.66 and 6.92 points for physical-FS, 8.94 and 7.79 points for emotional-FS, 8.36 and 8.98 points for social-FS and 9.12 and 9.67 points for school-FS. Factors significant at $p < 0.05$ level were included in the multiple linear regression analysis. All comparisons of HRQOL were adjusted for diagnosis, age, and insurance type. Intraclass correlation coefficients (ICC) were calculated between parent-perceived and child scores.

Two-hundred-eighty surveys were completed for 174 child subjects. Of 140 children ages 2-12 years, 67(47.9%) had only parent-perceived surveys and 73(52.1%) had child and parent-perceived surveys completed. Of 34 children ages 13-18 years, 1(2.9%) had a child survey only and 33(97.1%) had child and parent-perceived surveys completed.

Subject demographics were divided as follows—by gender: 78 (44.8%) female and 96 (55.2%) male, by diagnosis: 146 (83.9%) with FA-only, 10 (5.7%) with FA-and-EoE and 18 (10.3%) with EoE only, by race: 33 (19.2%) African American, 19 (11.0%) Asian, 79 (45.9%) Caucasian, 41 (23.8%) Hispanic, 2 unknown and by insurance type: 66 (37.9%) with Medicaid and 108 (62.1%) with private insurance. There was moderate agreement between child and parent-perceived total scores (ICC=0.63), emotional-FS (ICC=0.50), physical-FS (ICC=0.53), and school-FS (ICC=0.72) and poor agreement in social-FS (ICC=0.43).

Significant associations between average HRQOL scores and diagnosis, EoE treatment, insurance type and age are described below. There were no significant differences found related to gender, race or number of food allergies. FA-only patients had parent-perceived physical-FS 12.64 points higher than EoE-only patients (95%CI: 4.91, 20.36; $p=0.002$) after adjusting for age and insurance (Table 1). Although not significant at $p<0.05$, parent-perceived physical-FS were 10.68 points higher in FA-plus-EoE patients versus EoE-only patients (95%CI: -0.97, 22.32; $p=0.072$). There were no significant differences related to diagnosis in parent-perceived total, emotional-FS, social-FS, school-FS or any child scores.

In regards to types of treatment, EoE patients were on proton pump inhibitors (PPIs) (17/28), steroids (11/28), elimination diet (23/28), or no treatment (2/28) prior to initial visit. EoE patients treated with PPIs had a child school-FS 16.0 points lower (95%CI: -28.77, -3.23; $p=0.016$) than EoE patients not on PPIs (Supplemental Figure E1), and did not significantly depend on whether a patient had FA. Interactions between treatments were not significant. There were no significant differences related to treatment type in

any parent-perceived scores or child total score, emotional-FS, physical-FS, or social-FS.

After controlling for diagnosis and child age, parent-perceived physical-FS were 6.89 points higher (95%CI:2.18,11.60;p=0.004) among patients with private insurance versus Medicaid. Child total scores, emotional-FS, physical-FS and social-FS were 7.70 (95%CI:1.60,13.87;p=0.014), 9.48 (95%CI:0.79,18.16;p=0.033), 7.82 (95%CI:1.07,14.57;p=0.024) and 8.96 (95%CI:2.28,15.64;p=0.009) points higher, respectively, among privately insured versus Medicaid patients. (Figure 1.) There were no significant differences related to insurance type in parent-perceived total, emotional-FS, social-FS, school-FS or child school-FS.

After controlling for diagnosis and insurance, parent-perceived total scores and physical-FS decreased by 0.71 (95%CI:-1.21,-0.21;p=0.006) and 0.66 (95%CI:-1.21,-0.12;p=0.017) points per year increase in child's age, respectively. Child social-FS increased by 1.30 points per year increase in child age (95%CI:0.33,2.27;p=0.009). (Supplemental Figure E2.) There were no significant differences related to age in parent-perceived emotional-FS, social-FS, school-FS or child total, physical-FS, emotional-FS or school-FS.

Overall, FA-only patients had significantly higher parent-perceived physical-FS than EoE-only patients. Similar differences were not seen in parent-perceived or child total scores or child subset scores, which could be explained by the chronic physical manifestations of EoE versus the more intermittent acute nature of allergic reactions in FA. Symptoms like EoE-related abdominal pain can be more persistent or chronic in nature, and more frequently noticeable to parents, versus episodic features of FA-

associated anaphylaxis. Though not statistically significant at $p < 0.05$, the higher physical-FS of FA-plus-EoE patients versus EoE-only patients could represent improved control of symptoms due to increased adherence to allergen avoidance in patients with FA and EoE compared to EoE-only patients. FA could contribute to immediate symptom feedback with non-adherence. Realizing potential differences in perception of symptoms can help medical professionals provide anticipatory guidance to families.

The decreased child school-FS seen in EoE patients on PPIs can be related to symptom severity, lack of improvement while taking a PPI, or the burden of taking daily medications. Studies have shown that HRQOL in EoE patients can improve when on elimination diet or steroids plus PPI¹. Our data shows PPIs may not contribute heavily to improvement in EoE HRQOL given the lack of improvement in the total score and three subset scores. However, since only school-FS showed significance, this may be a limited finding.

Patients with Medicaid had significantly lower HRQOL than privately insured patients in multiple child scores, but only parent-perceived physical-FS. One possible explanation for the higher parent-perceived scores versus child scores relates to the impact of the relationship of familial socioeconomic status on the burden of disease for the child and strained child-parent relations in the home of families with economic pressure^{7,8}. Even further, child reported HRQOL may be more sensitive to HRQOL differences than parent-perceived HRQOL, in the same way that any self-reported data may be more reliable than outsider observed data, in a population old enough to complete self-reported data. A multitude of socioeconomic factors impact HRQOL⁴, like inability to afford medications or allergen-free food. While studies have shown socioeconomic disparities regarding FA specialty care and ER costs⁴, this is the first study

demonstrating how insurance type, one marker of socioeconomic status, impacts HRQOL among children with FA and EoE.

Lastly, we found that as children age, parent and child reports become more discrepant, especially in the social functioning domain. Parents of older children had significantly lower perceived total and physical-FS, but parallel findings were not seen in the older child scores. However, older children had significantly higher child social-FS, but this was not seen in parent-perceived social-FS. The weakest ICC agreement between parent/child was in social-FS. Parents may become less involved in social settings as children get older and thus have discrepant perceived social HRQOL scores from their adolescents. Child-parent disagreement has also been seen in previous studies² and can be applied well to our population, as teenagers develop autonomy with medication use and activities outside the home. These findings highlight-the need to assess both the parent and child perspectives in medical visits, especially when the patient is a teenager.

Limitations of our study included the generic PedsQL™ survey used. FA/EoE-specific questions may analyze HRQOL more accurately in this population. While all FA patients were physician-diagnosed, there was a lack of consistency in the tests used for FA diagnosis between providers. Additionally, obtaining both child and parent-perceived surveys from all subjects would have resulted in more thorough evaluation. Finally, the number of patients with FA was much higher than the number of patients with EoE. The sample sizes of 156 patients with FA and 28 patients with EoE provide about 90% power to detect a standard effect size of 0.62 using a two-way ANOVA. However, the small number of patients with EoE could provide poor estimates of differences between patients with and without EoE. These results should be validated in the future with a larger cohort.

This study illuminates many important points, from which we hope to create tangible interventions. The decreased parent-perceived physical-FS seen in EoE versus FA patients highlights the need to better prepare families for the scope of symptoms seen in EoE. The decreased HRQOL in patients with Medicaid versus private insurance emphasizes the need to improve support for less resourced families. Lastly, the differences in patient and parent-perceived HRQOL as children get older depicts the importance of addressing possible contributing factors of parental anxiety and patient compliance as adolescents become independent with their medical care. Overall, this was an exploratory study. Larger prospective studies are needed to confirm our results and evaluate comprehensive effects of HRQOL-based interventions. However, incorporating this knowledge into medical care will help comprehensively address illness in children with FA and EoE.

References

1. Mukkada V, Falk GW, Eichinger CS, King D, Todorova L, and Shaheen NJ. Health-Related Quality of Life and Costs Associated With Eosinophilic Esophagitis: A Systematic Review. Clin Gastroenterol Hepatol. 2018;16(4):495-503.
2. van der Velde, JL, Dubois, AEJ and Flokstra-de Blok, BMJ. Food Allergy and Quality of Life: What Have We Learned? Curr Allergy Asthma Rep. 2013;13(6): 651-661.
3. Mahdahvinia M, Fox SR, Smith BM, James C, Palmisano EL, Mohammed A, et al. Racial Differences in Food Allergy Phenotype and Health Care Utilization among US Children. J Allergy Clin Immunol Pract. 2018;5(2):352-357.
4. Bilaver LA, Kester KM, Smith BM, Gupta RS. Socioeconomic Disparities in the Economic Impact of Childhood Food Allergy. Pediatrics. 2016;137(5): e20153678.

5. Capucilli P, Hill DA. Allergic Comorbidity in Eosinophilic Esophagitis: Mechanistic Relevance and Clinical Implications. *Clin Rev Allergy Immunol*. 2019;57(1):111-127.
6. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr*. 2003;3:329 –341.
7. Conger RD, Conger KJ, Martin MJ. Socioeconomic Status, Family Processes, and Individual Development. *J Marriage Fam*. 2010;72(3):685-704.
8. Neppl TK, Senia JM, Donnellan MB. Effects of economic hardship: Testing the family stress model over time. *J Fam Psychol*. 2016;30(1):12-21.

Figure Legends

Figure 1. HRQOL was significantly lower in Medicaid versus privately insured patients with FA and EoE in child total ($p=0.014$), emotional ($p=0.033$), physical ($p=0.024$) and social ($p=0.009$) and parent-perceived physical functioning scores ($p=0.004$) when controlling for age and diagnosis.

Table 1. Differences in HRQOL compared to patients with only EoE controlling for insurance and child age

	Child Scores (n=107)		Parent-perceived Scores (n=173)	
	Difference (95% CI)	p-value	Difference (95% CI)	p-value
<u>Total Score</u>		0.397		0.101
Food allergy only	5.42 (-3.26, 14.10)	0.218	7.55 (0.41, 14.68)	0.038
Food allergy and EoE	7.28 (-5.24, 19.80)	0.252	8.58 (-2.18, 19.34)	0.117
<u>Emotional Score</u>		0.943		0.532
Food allergy only	2.01 (-10.27, 14.29)	0.746	5.46 (-4.12, 15.04)	0.262
Food allergy and EoE	2.36 (-15.35, 20.07)	0.792	4.40 (-10.04, 18.84)	0.548
<u>Physical Score**</u>		0.380		0.006*
Food allergy only	6.49 (-3.05, 16.03)	0.181	12.64 (4.91, 20.36)*	0.002*
Food allergy and EoE	7.21 (-6.56, 20.97)	0.302	10.68 (-0.97, 22.32)	0.072
<u>Social Score</u>		0.751		0.771
Food allergy only	1.70 (-7.75, 11.15)	0.722	-1.45 (-10.69, 7.80)	0.758
Food allergy and EoE	5.20 (-8.44, 18.83)	0.451	2.70 (-11.24, 16.64)	0.702
<u>School Score</u>		0.142		0.129
Food allergy only	10.83 (-0.99, 22.66)	0.072	14.51 (0.40, 28.61)	0.044
Food allergy and EoE	14.39 (-2.66, 31.45)	0.097	12.97 (-8.29, 34.23)	0.230

*overall significant association between HRQOL and diagnosis, and significant difference for individual comparison with EoE only patients

**Parent-perceived physical functioning scores for EoE Only: 75.6, for FA+EoE: 85.9; for FA only: 88.8.

Figure 1