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ORIGINAL PAPER

Applicability of the PedsQL™ 4.0 Generic and Fatigue Modules in Romanian Children with Inflammatory Bowel Disease: Pilot Study

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ABSTRACT

The Pediatric Quality of Life (PedsQL) Inventory is a tool used to measure Health Related Quality of Life (HRQoL) in children aged 2 to 18 years. The aim of the present study was to investigate the feasibility and reliability of the Romanian version of two PedsQL modules, the Generic Core and the Multidimensional Fatigue Scales, in children with inflammatory bowel disease (IBD). Children diagnosed with IBD in our clinic and their parents completed a total of 26 Romanian version PedsQL forms, while a control group of healthy children and their caregiver filled in 86 identical online forms. We compared total and dimensional scores between controls and subjects, along with age, sex, and active versus inactive disease differences. The results indicated that the PedsQL total and summary scores differentiated between subjects and controls, with lower HRQoL and higher levels of fatigue being reported in children with chronic IBD. The Romanian version of the PedsQL was found to be feasible and reliable, with good internal consistency higher than 0.70 and minimum missing responses. However, the limited number of participants meant that clinical activity severity indices correlated poorly with fatigue and generic scores. Further validation of these models requires larger, multi-centric studies.

Keywords: quality of life, fatigue, inflammatory bowel disease, pediatrics.

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INTRODUCTION

In the last 50 years, the incidence of inflammatory bowel diseases (IBD) in the pediatric population has been on the rise, with 10 cases *per* 100,000 children reported in the United States and Canada (1). The incidence is higher in northern European countries, with slightly lower rates for ulcerative colitis (UC) compared to Crohn's disease (CD) (2). While the incidence in Western countries has stabilized, there is a high increase in IBD cases in newly industrialized countries that have adopted a westernized lifestyle (3).

Once diagnosed, the therapeutic goals for IBD include symptom relief, proper growth and complications avoidance by maintaining disease remission. However, optimizing the quality of life (QoL) as well as psychosocial and physical functioning are also key elements of the therapeutic conduct. Studies have shown that adolescents with IBD were more depressed than those suffering from other chronic diseases, with rates as high as 25% based on standardized depressive severity scores (4, 5). Depression or anxiety levels are related to IBD severity through direct IBD-induced inflammation, treatment (exogenous steroids) and sleep disturbances (5).

Patient outcomes in IBD typically focus on disease activity scores, but it is important to also consider the child's perception of the disease and its impact on his/her daily functioning. Health Related Quality of Life (HRQoL) metrics can determine the social impact of the disease, school functioning and economic aspects of living. Therefore, pediatricians should pay close attention to psychosocial factors when evaluating how a child is coping with IBD as it can play an important role in disease control. Usage of general and specific disease-related QoL scores can extend the disease activity scores to better assess patient's response to disease and to implement strategies for increasing the QoL.

One such measurement tool is the Pediatric Quality of Life (PedsQL™) Measurement Model, which was developed by James W. Varni in 1998 (6). This model includes scales and modules designed to describe the health status of children and adolescents at a given time. The model integrates a generic core scale with a four-dimensional structure in accordance with the World Health Organization (WHO) children's health recommendations and a disease-specific module both in one measurement system. These disease-specific forms available for diabetes, rheumatology, cancer and cardiac conditions are highly utilized, and additional forms are currently under development. Translations in various languages are available to validate their usage in different settings. These metrics can be used at regular clinical appointments and can help health providers evaluate daily functioning, social and school behavior, and identify signs of somatization or warning signs of anxiety or depression which require a referral to counsel.

The purpose of this study was to evaluate the applicability of a Romanian version of PedsQL™ Generic Core Scale and Multidimensional Fatigue Scale in a group of pediatric IBD patients from a tertiary center. Our final aim was to inquire about the medical and cultural impact of these scales on this particular geographical area. ❑

MATERIALS AND METHODS

Participants

We conducted a cross-sectional study at a pediatric gastroenterology unit in Romania, which involved examining a database of 46 patients with IBD aged 5 to 18 years, who were evaluated between January-July 2019 (Figure 1). Of the 46 patients, 10 had already been transferred to adult gastroenterology centers and were no longer under our care at the time of the study.

The inclusion criteria for the study required a diagnosis of IBD, which was based on the current criteria defined by ESPGHAN in collaboration with ECCO (7, 8), and was confirmed at least four months prior to the present study. From our database, 13 patients were clinically examined within a six-month period. These patients and their caregivers individually completed the Romanian versions of the PedsQL™ Generic Core and Multidimensional Fatigue Scale questionnaires. Since English was not familiar to all patients and their parents, we decided to adapt a Romanian version of the questionnaire. Age-appropriate paper forms were completed by the patients, while their caregivers completed special paper forms for them.

As controls, we recruited a group of 40 healthy children and 74 parents, who completed an online version of the PedsQL™ forms. Inclusion cri-

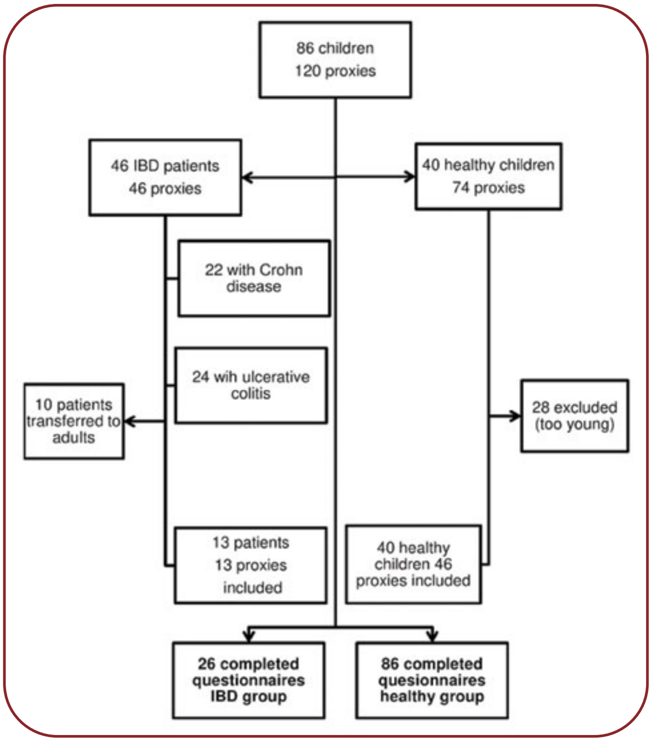


FIGURE 1. Flowchart of the selection of the patients included in the study
(IBD=inflammatory bowel disease)

teria for the control group required participants to be aged between 2 and 18 years old and without a history of chronic diseases. Online forms were disseminated through support groups and organizations dedicated to mothers. Children between 5 and 18 years old also completed age-appropriate online forms, while parents completed special online forms for caregivers. For children younger than five years old, only the caregiver form was completed.

The sample size necessary to evaluate the proportion of IBD patients from our center willing to complete the translated version of the scales with 95% confidence and a margin of error of 5% was 42. In this study, we did not collect the necessary number of responses for statistical significance. However, we consider the included answers valuable and preliminary for the upcoming multicenter study phase. Also, the two groups (study and control) were not similar in terms of number of included subjects, but did not differ in terms of age, gender or living setting. We encounter a large number of healthy children and their parents willing to answer health-related questions over a short period of time encouraging our future efforts of addressing larger samples of subjects.

The present study was carried out in accordance with the Declaration of Helsinki. The Committee on Ethics of Marie S. Curie Emergency Children's Clinical Hospital approved the study on June 1, 2020. Written consent was obtained from parents of all children included in the study.

PedsQL™ Generic Core and Multidimensional Fatigue Scales

The questionnaires used in our study were designed according to participants' age and consisted of four sets: one for parents/caregivers and three sets for children aged 5-7, 8-12, and 12-18 years old, respectively. For children under the age of five, only the caregiver was allowed to complete the form. Each child and their parents received the appropriate set of forms.

The PedsQL™ Generic Core Scale is a four-dimensional questionnaire that assesses physical and psychosocial health, including emotional, social and school functioning. The questionnaire comprises 23 items (21 items for children aged 2-4 years), which are rated on a five-point Likert scale graded from 0 to 4 for children over the age of seven and on a three-point Likert scale for children aged 5-7 years.

The PedsQL™ Multidimensional Fatigue Scale consists of 18 items that also use the same five-point or three-point Likert scale and are divided into general fatigue, sleep *versus* rest fatigue, and cognitive fatigue. The items are reversely scored and transformed to a 0-100 scale, with the scores computed by dividing the sum of items by the number of items answered. Higher scores on the Generic Core Scale indicate a higher health-related QoL, while higher scores on the fatigue scale indicate lower levels of fatigue. The questions in both paper and online forms pertain to subjective experiences and emotions that occurred over the past month. The content and structure of both the paper and online forms were identical.

The original version of the scales was translated into Romanian through a collective effort of medical professionals. Pediatricians with expertise in digestive diseases and a nutrition specialist familiarized with patients and caregivers' practical guidance participated in the translation process. They evaluated for both the conceptualization of sentences and answers and the language accuracy through debriefing sessions. The feasibility and reliability of the scales were than assessed through the current pilot study as an intermediary step to a more extensive research project. We did not test for differences in terms of social and educational status between study and control groups but we consider adding these features to the upcoming versions.

Medical measures

We obtained medical data from the physician's records, including variables such as the type of IBD (CD or UC), current age, age at diagnosis, gender, history of surgical intervention, type of intervention and medication history, with particular focus on the current therapy. We also looked for any adverse reactions to treatment and assessed the development of antibodies to biological treatment to determine treatment resistance. We categorized the current treatment into four groups: biologics, immunosuppressants, 5-aminosalicylates, or no medication. Disease activity was evaluated based on clinical activity scores, including the Pediatric Crohn's Disease Activity Index (PCDAI) (9) and the Pediatric Ulcerative Colitis Activity Index (PUCAI) (10), which classified disease activity as inactive, mild, moderate, or severe. Inactive disease was defined as a clinical activity score of less than 10 points, mild disease was between 10 and 35 points, and moderate to severe disease was defined as a score higher than 35 points.

Data analysis

Dichotomous variables included IBD type, gender, surgical intervention history, adverse reaction to treatment and antibodies to biological treatment. Ordinal categorical data included clinical activity scores, PedsQL^{TM} summary and total scores and current treatment. Continuous variables included current age and diagnosis age. We used a Chi-square test to compare variables and a t-test to evaluate age differences. We analyzed score differences using the Mann-Whitney-U test and determined correlation using Spearman's rank correlation coefficient. Feasibility was assessed based on the percentage of missing values, and internal consistency reliability was determined using Cronbach's alpha coefficient. We used SPSS software for data analysis and considered a p value of <0.05 statistically significant. ❑

RESULTS

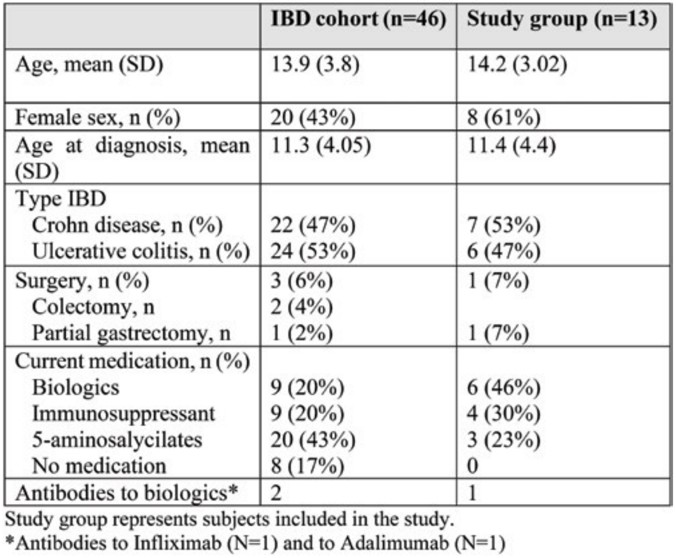
Patients' characteristics

Our local cohort of IBD patients consisted of 46 children (characteristics in Table 1). Both CD and UC were equally represented in our patient population, with the youngest patient being diagnosed at one year of age. In the CD subgroup, there was a male to female ratio of 1.4:1, and two out of three patients who required surgery had CD. Additionally, two out of nine patients who received anti-TNF alpha therapy developed antibodies to the treatment and failed to maintain remission.

From the total IBD cohort, 13 patients (seven with CD and six with UC) and their caregivers completed the PedsQL^{TM} Generic Core and Multidimensional Fatigue Scale questionnaires either in routine evaluations or during flare-ups. At the time of completion, five patients had active disease with high clinical activity scores (PUCAI or PCDAI >35 points), and 38% of subjects were receiving biological treatment. There were no differences in clinical activity scores between boys and girls with IBD.

The control group included 40 children and 46 caregivers, with a median age of 14 (IQR=4), which matched the median age of the IBD subjects (15, IQR=3). The gender distribution did

TABLE 1. Medical and demographic characteristics in IBD patients



	IBD cohort (n=46)	Study group (n=13)
Age, mean (SD)	13.9 (3.8)	14.2 (3.02)
Female sex, n (%)	20 (43%)	8 (61%)
Age at diagnosis, mean (SD)	11.3 (4.05)	11.4 (4.4)
Type IBD		
Crohn disease, n (%)	22 (47%)	7 (53%)
Ulcerative colitis, n (%)	24 (53%)	6 (47%)
Surgery, n (%)	3 (6%)	1 (7%)
Colectomy, n	2 (4%)	
Partial gastrectomy, n	1 (2%)	1 (7%)
Current medication, n (%)		
Biologics	9 (20%)	6 (46%)
Immunosuppressant	9 (20%)	4 (30%)
5-aminosalycilates	20 (43%)	3 (23%)
No medication	8 (17%)	0
Antibodies to biologics*	2	1

Study group represents subjects included in the study.
*Antibodies to Infliximab (N=1) and to Adalimumab (N=1)

TABLE 2. Total and summary median general scores for all completed questionnaires. Comparison in terms of scores between completed questionnaires by subjects (IBD patients and their caregivers or proxies) *versus* controls (healthy children and their caregivers or proxies)

	Subjects (N=26)		Controls (N=86)		z value	p value
	median	IQR	median	IQR		
Physical health	60.9	23.4	81.3	12.5	-4.10	0.000
Psychosocial health*	65.0	23.8	70.0	18.3	-1.51	0.012
Total Generic Core score	59.2	21.2	72.8	13.5	-2.69	0.007

N=total number of completed questionnaires by both children and caregivers (proxies); IQR=interquartile range.
*Includes emotional, social, and school functioning score

not differ significantly between the subjects and controls (female to male ratio of 1.9:1 and 1.6:1, respectively) and all participants lived in urban settings. The control group completed an online-translated version of the PedsQL™ Generic Core and Multidimensional Fatigue Scale questionnaires.

Questionnaire validation

We obtained significantly higher scores on total and summary general core items in the control group compared to subjects (median total score of 72.8 *versus* 59.2, p<0.05, Table 2). This is an indication of lower QoL in our patients with chronic disease, in accordance with data described in the literature (11,12) and a proof of the applicability of the PedsQL™ 4.0 Generic and Fatigue modules in Romanian children with IBD.

The missing response rate was 0.1% in both groups. Children and parents answered most items, achieving great feasibility for the two modules. Internal consistency reliability coefficients across ages show that all scales exceed the minimum reliability of 0.70 for group comparison detailed in Table 3.

We compared fatigue median scores from our subjects with PedsQL values reported in different studies in patients with different chronic diseases. The median total score was 68.1 (IQR=19.9), with the lowest value in the physical activity summary score (62.5, IQR=22.2). Our results state that children with IBD experience levels of fatigue comparable to pediatric patients with rheumatic disease, cancer or obesity, whose mean values in the Multidimensional Fatigue module range from 58.0 to 69.0 (SD=25) in comparison with reported healthy children mean scores higher than 76.0 (SD=16) (13-16). Fatigue levels were not different between CD subjects and UC ones in our pilot study.

Our results were based on a small sample and did not succeed in identifying significant differences in levels of fatigue between patients in remission and those in flare when we analyzed data for the entire IBD group. When assessing for disease subgroup separately, we obtained higher levels of fatigue in patients with acute UC than those in UC remission, especially in terms of sleep *versus* rest fatigue and cognitive fatigue (z score <-1, p<0.05, Table 4).

Caregivers (proxies) and children scored differently in the IBD group. Parents tend to underestimate the QoL of their children, especially in terms of psychosocial health (summary median score of 58.3 *versus* 66.7, p <0.05). On the other hand, caregivers overestimate the level of fatigue their children experience (median total score of 65.3 *versus* 68.1, p<0.05), a lower score indicating higher fatigue levels.

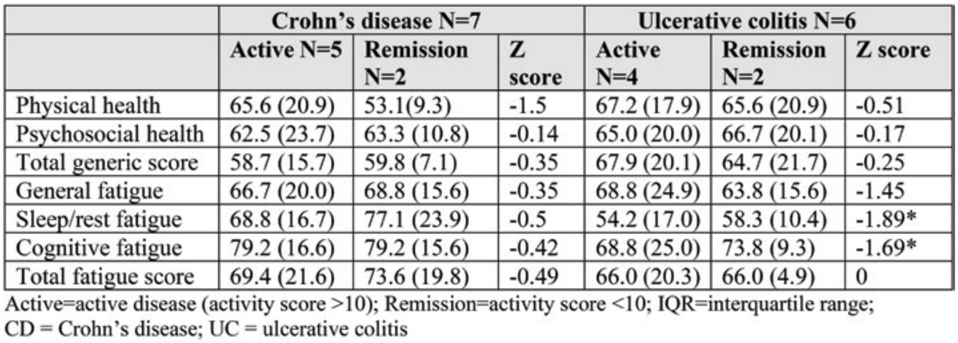
Concurrent validity

We determined correlation between generic and fatigue scores in subjects using Spearman's correlation coefficients to assess concurrent validity as shown in Table 5. We obtained strong correla-

Scale	No. of items	Cronbach's alpha in subjects	Cronbach's alpha in controls
PedsQLTM total score	23	0.88	0.83
Physical health	8	0.73	0.70
Psychosocial health	15	0.84	0.78
Emotional functioning	5	0.70	0.68
Social functioning	5	0.77	0.81
School functioning	5	0.71	0.71
Multidimensional Fatigue total score	18	0.85	0.86
General fatigue	6	0.85	0.83
Sleep *versus* rest fatigue	6	0.79	0.76
Cognitive fatigue	6	0.85	0.79

TABLE 3. Reliability coefficients for total and summary scores of PedsQL™ and Multidimensional Fatigue

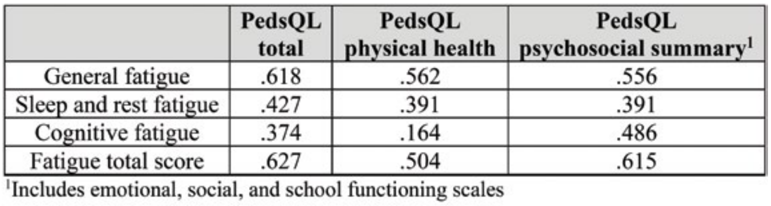
TABLE 4. Total and summary median (IQR) scores of children – only completed questionnaires (caregivers scores excluded) enrolled in the study group (CD and UC in remission or active disease)



	Crohn's disease N=7			Ulcerative colitis N=6		
	Active N=5	Remission N=2	Z score	Active N=4	Remission N=2	Z score
Physical health	65.6 (20.9)	53.1(9.3)	-1.5	67.2 (17.9)	65.6 (20.9)	-0.51
Psychosocial health	62.5 (23.7)	63.3 (10.8)	-0.14	65.0 (20.0)	66.7 (20.1)	-0.17
Total generic score	58.7 (15.7)	59.8 (7.1)	-0.35	67.9 (20.1)	64.7 (21.7)	-0.25
General fatigue	66.7 (20.0)	68.8 (15.6)	-0.35	68.8 (24.9)	63.8 (15.6)	-1.45
Sleep/rest fatigue	68.8 (16.7)	77.1 (23.9)	-0.5	54.2 (17.0)	58.3 (10.4)	-1.89*
Cognitive fatigue	79.2 (16.6)	79.2 (15.6)	-0.42	68.8 (25.0)	73.8 (9.3)	-1.69*
Total fatigue score	69.4 (21.6)	73.6 (19.8)	-0.49	66.0 (20.3)	66.0 (4.9)	0

Active=active disease (activity score >10); Remission=activity score <10; IQR=interquartile range;
CD = Crohn's disease; UC = ulcerative colitis

TABLE 5. Correlation of total fatigue and dimensional scores with generic measures using Spearman's correlation coefficient



	PedsQL total	PedsQL physical health	PedsQL psychosocial summary[1]
General fatigue	.618	.562	.556
Sleep and rest fatigue	.427	.391	.391
Cognitive fatigue	.374	.164	.486
Fatigue total score	.627	.504	.615

[1] Includes emotional, social, and school functioning scales

tion in 50% of paired-median scores (rho>0.5), moderate correlation in 41% (rho>0.3) of paired scores and weak correlation for one association of items (cognitive fatigue and physical health). Comparing domains of Multidimensional Fatigue and Generic Core modules showed high correlation for almost all cases. ❑

DISCUSSION

Through this pilot study, we aimed to observe the willingness of our patients and parents to complete the translated questionnaires, evaluate the response rate, and interpret the total and summary scores to certify the applicability of this model in a larger group of Romanian patients. We expected that the overall HRQoL in IBD patients would be lower than in healthy children, correlated with the disease activity clinical scores. We also expected that children and adolescents with IBD would manifest the same level of fatigue as those with chronic conditions, as reported in the literature. Furthermore, we intended to describe parents' perception of the overall QoL of their children.

In this pilot study, we applied the PedsQL™ modules in a non-randomized sample of our IBD cohort. We addressed the modules to patients that presented on routine evaluation or during flares. 38% of IBD patients included in the pilot study were on biological treatment at completion time. This was due to increased likelihood of hospital visits for treatment administration. Furthermore, this may have influenced our results as patients treated with anti TNF alpha drugs had more severe disease and consequently may have higher levels of fatigue and lower QoL. In controls, we excluded 28 cases of children aged less than four that did not match our IBD group. We targeted support groups and organizations dedicated to mothers for the completion of online forms because the main selection criteria, being a parent, was already fulfilled. We also expected higher response rates from the parents involved in this sort of associations and willingness to involve their children in the process of completing this type of form.

Fatigue is common finding in children and adolescents with IBD. Furthermore, active disease tends to accentuate the level of fatigue due to nocturnal abdominal pain and diarrhea. Active disease in UC patients can produce even higher levels of physical disturbances as it manifests mainly through increased number of nocturnal stools and intense abdominal pain in contrast with active CD patients whose activity score depends on a larger number of items, including the biological profile (9, 10). We did not identify differences in terms of fatigue levels between CD subjects and UC subjects. This is consistent with results from different studies that used questionnaires to assess fatigue levels in IBD patients (11–16). Our results have partial strength to discriminate between active or inactive disease stages. Clinical activity scores correlated with fatigue level indices only in UC subjects, but the number of patients in this subgroup was too small for statistical interpretation. Literature data prove that psychometrics tests correlate with IBD severity and disease flare, and it can complement clinical severity scores for routine evaluation. Moreover, it is important for the medical team to differentiate between short-term distress that is common in disease flare or at diagnosis from more severe symptoms leading to impaired function that needs special psychological attention (5).

We evaluated total and dimensional fatigue scores in subjects and discussed the results in parallel with data reported in distinct studies using the same Multidimensional Fatigue Module. Children with rheumatic disease, type 1 diabetes, or obesity were evaluated using the same self-reported and parent-reported surveys. However, in these studies total and summary scores were defined as continuous variables and results were reported in mean values (13-15). In our study, based on the fact that the answers were structured as a three-point or a five-point Likert scale, we defined total and summary scores as categorical variables and results were reported in median values. Thus, the comparison between our results and reported data cannot be appropriately evaluated, even though we believe that defining total and summary scores as categorical data is statistically correct.

With regard to the feasibility of these two modules, there were minimal missing responses. For both parents and children, the respondent burden was low. The completion time was short: less than five minutes *per* module. However, the number of patients *per* studied subgroup was small (six UC subjects, seven CD subjects). In terms of practices of validating scales in health research, Boateng *et al* describe how to establish the sample size (17). Although they conclude that there is no single item-ratio that works for all survey development scenarios, a large sample size (minimum of 300-450 respondents) or respondent:item ratio of 10:1 is necessary for validation. A larger sample size certifies that the model is replicable and that results are generalizable for a whole population. A smaller sample size or respondent:item ratio may mean that some factors are not replicable and results cannot be generalized. In our study, the small sample size does not allow for module validation. A multicenter patient recruitment will be needed in order to achieve validating sample size and also to increase the reliability coefficient from 0.70 to the preferable 0.90.

Previous studies proved poor to low degree parent-adolescent agreement on psychosocial symptoms (18). Also, parents tend to report more somatic symptoms in their adolescents than the adolescents themselves. Our results illustrated the differences in both parents reported scores when asked specifically about their children's symptoms and overall functioning. This proves the need for dual assessment of self-reported and parent reported surveys especially in adolescents.

This study has several strengths: use of validated methods to evaluate for HRQoL and level of fatigue; minimal missing response rate, with total completion time of less than 15 minutes for both parents and children; inclusion of patients with both active and inactive disease; accessibility of online questionnaires.

To our knowledge, this is the first study to evaluate health-related QoL and level of fatigue in Romanian pediatric IBD patients. Furthermore, this is the first study to extensively describe a Romanian pediatric IBD cohort.

The main limitation of this study represents the small sample size of IBD pediatric patients and the significantly higher number of included healthy children. Further enrollment of subjects from our clinic and other specialized centers will allow further validation of these translated modules. Secondly, we applied different strategies for completing the questionnaire, online *versus* paper form, which can add bias to our data. We did not randomize the patients included in our study. The questionnaires were not disease-specific, and included general psychometrics rather than disease specific questions.

We aim to expand our research by including all patients from our center and from different IBD centers in order to achieve a significant number of participants to further validate the Romanian version of PedsQL™ Generic Core and Multidimensional Fatigue scales. Furthermore, an upcoming objective will be to validate a disease-specific module, the IMPACT III form. The IMPACT III questionnaire is an IBD-specific model that is being increasingly used to assess HRQOL in patients with this condition (19-21). In contrast to non-specific models like the PedsQL™ Generic Core or Multidimensional Fatigue scales, the specific instruments can be more sensitive to changes in HRQOL. We aim to design future research to validate a Romanian version of the IMPACT III module by correlation to the translated version of the generic scales. ❑

CONCLUSIONS

Notwithstanding the small sample size, our study suggests applicability and feasibility of the Romanian versions of PedsQL™ Generic Core and Multidimensional Fatigue Scale in a group of IBD patients and healthy controls, with very low missing response rate and the ability to differentiate between disease-group and healthy-group subjects. Further cross-cultural validation of this translated scales requires enrollment of a larger cohort of IBD patients from our country. ❑

Author contributions: Conceptualization – A.I.; methodology, A.I., F.G., C.B; investigation – A.I., C.B., M.A., A.A.O.; data curation – A.I.; writing, original draft preparation – A.I., M.I.I.; writing, review and editing – M.I.I., F.G.; supervision – F.G. All authors have read and agreed to the published version of the manuscript.

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Institutional review board statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Marie Curie Emergency Children's Hospital on June 1st, 2020.

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

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