Novel Approaches Identifying Relevant Patient-Reported Outcomes in Patients With Inflammatory Bowel Diseases—LISTEN 1

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Background: Several patient-reported outcomes (PROs) have been established and are widely used in the assessment of patients with inflammatory bowel disease (IBD). However, it has never been investigated which PRO items are experienced by and are considered most relevant for IBD patients.

Methods: A review of IBD-related disease scores by a steering committee led to the identification of relevant PRO questions and assignment to 16 different PRO categories (9 symptoms and 7 impacts) that characterize patient's disease burden. In a cross-sectional study, a digital patient survey was carried out to determine the self-reported experience by multiple response, the relevance of these PRO categories by pairwise comparison and the suitability of the respective questions and answer possibilities by yes-or-no-question.

Results: Sixty patients with Crohn's disease (CD) (56.7% women; mean age 40.6 years; mean disease duration 12.4 years) and 60 patients with ulcerative colitis (UC) (51.7% women; mean age 37.3 years; mean disease duration 9.0 years) participated in the patient survey. All predefined symptoms and impacts, with the exception of nausea, were experienced by at least 50% of patients. Stool urgency and pain were rated the 2 most important symptoms in CD patients with similar ratings for relevance. Stool urgency was also the most important symptom in patients with UC, followed by stool frequency. Differences in self-reported experience between CD and UC patients were seen for the symptoms of rectal bleeding, pain, and nausea. Most important impact of symptoms in both patient groups were general wellbeing followed by social activities, while sexual activity was the least relevant impact category.

Conclusions: Stool urgency was the most relevant and most self-reported symptom for both CD and UC. Relevance and self-reported experience of pain and rectal bleeding differed between the 2 diseases. Therefore, the future collection of PROs should take these disease specificities into consideration.

Lay Summary

This study showed that stool urgency, stool frequency, and either pain for Crohn's disease patients or rectal bleeding for patients with ulcerative colitis were considered the most relevant symptoms. Thus, emphasis on patient reporting outcomes with focus on these categories is advised.

Introduction

Inflammatory bowel disease (IBD) is mainly comprised of ulcerative colitis (UC) and Crohn's disease (CD). IBD affects over 2 million individuals in North America, 3.2 million in Europe, and millions more worldwide with an increasing incidence rate in newly industrialized countries experiencing a westernization of lifestyle in the last decades.[1] Several factors influence the incidence of IBD, including gender,[2,3] age,[4] genetics,[5,6] environmental factors,[4,6,7] and geography.[1,8]

Despite many overlapping features, both diseases differ from each other regarding pathologic and clinical characteristics.[9,10] UC is a chronic inflammatory condition characterized by relapsing and remitting episodes of inflammation in the majority of patients. The inflammatory reaction is usually strictly limited to the mucosal layer of the colon. Typically, the disease starts at the rectum and subsequently extends in a proximal and continuous fashion to involve other portions of the colon.[11] The majority of the patients suffer from bloody stool.[10] In contrast, CD is characterized by transmural inflammatory foci affecting the entire bowel wall, and by discontinuous skip lesions. These transmural lesions may occur throughout the entire gastrointestinal tract, and may lead to fibrosis, strictures, and obstructions. The most commonly affected areas in CD are the ileum and the proximal colon.[7] Characteristic symptoms of CD

are diarrhea, abdominal pain, and weight loss.[10] Still, there is often an uncertainty in diagnosis that may lead to disease misclassification and suboptimal therapeutic treatment.

Patient-reported outcome (PRO) items, such as symptoms, health-related quality of life, or disease impact on certain aspects of life, are reported directly by the patient and are powerful tools to inform patients, clinicians, and policymakers about morbidity and burden of disease. For the assessment of IBD patients, several disease activity scores and quality of life questionnaires have been established and are widely used (Mayo-Score, Harvey–Bradshaw Index (HBI), Inflammatory Bowel Disease Questionnaire). Notably, many of the scores vary considerably, ie, while the Mayo-Score only includes the PRO rectal bleeding and stool frequency, symptoms such as stool urgency, pain, and fatigue are not included.

Despite a clear endorsement on the use of PROs in clinical trials on IBD by both the US Food and Drug Administration,[12] and the European Medicines Agency,[13,14] it remains unknown which of the commonly assessed PRO items such as symptoms are considered most relevant by the patients themselves. Therefore, the present study was conducted to fill this data gap and to provide the basis for future observational studies using the most relevant PROs for patients in IBD.

Methods

Study Design and Study Population
In this cross-sectional study, patients with CD and UC were recruited in 3 gastroenterology sites in Germany (Frankfurt, Jena, and Leipzig). All patients were recruited in 2019 in a 3 month period. Adult patients (≥18 years) with a diagnosis of CD or UC according to current German S3 guidelines[15,16] that was made at least 6 months prior to study entry, and with at least 1 prior moderate to severe episode of CD or UC within the last 12 months, defined as requiring systemic steroids and/or treatment with immunosuppressants/biologics, were eligible for inclusion. Patients with prior stoma surgery, prior intestinal resection (except ileocecal resection), short bowel syndrome, current or planned participation in a clinical trial with intake of study treatment for CD or UC, or those not able to give informed consent were excluded from participation. The study was conducted in accordance with the latest version of the Declaration of Helsinki,[17] and was approved by the local ethics committees. Written informed consent was obtained from all participants.

To identify the main sections and their categories, 11 established disease scores or questionnaires which included at least 1 single PRO question, were identified by a literature research and analyzed for the relevance of their respective questions/items: EuroQol (EQ)-5D-5L, Fatigue Assessment Scale (FAS), HBI, IBD Control Questionnaire (IBD Control Q), IBD-Disability Index (IBD-DI), IBD Questionnaire (IBDQ), Mayo-Score, Numeric Rating Scale (NRS), Simple Clinical Colitis Activity Index (SCCAI), and Work Productivity and Activity Impairment (WPAI). Each of the 81 single PRO questions was assessed by a steering committee. They assigned each question to one of the 16 identified categories in 2 main sections "symptoms" or "impact of symptoms" (Table 1), both of which were assessed independently in this study. Some single questions were considered unsuitable and not included. Reasons for excluding a question included the following: (1) Question is part of consecutive group of questions and cannot not be separated from the other questions without major changes/add-

Table 1. Main sections and categories of PRO questions

Symptoms	Impact of symptoms
Stool frequency	Work productivity
Stool urgency	Daily activities
Rectal bleeding	Social activities
Flatulence	Sexual activities
Fatigue	Emotional distress
Pain	Depression/anxiety
Weight	General wellbeing
Night symptoms	
Nausea	

Abbreviation: PRO, patient-reported outcome.

itions, (2) Question is too general and precludes the assignment to a specific category, and (3) Question to be answered by a practitioner only and not foreseen to be answered by a patient.

Data Collection
Data collection was performed by use of a custom-made digital application that was available on site-based computer tablets. Comprehensibility and usability of the application were verified by the steering committee and by a patient before study start. Information on demographics and disease characteristics were documented by the physician (ie, diagnosis, time of diagnosis, age, gender, experiences with biologics intake, and physician's assessment of current disease activity, based on the physician's global assessment).

A 3-step approach was used to identify symptoms and impact of symptoms which affect patients most. Patients evaluated whether and how they are affected by specific symptoms and impact of symptoms as follows. In a first step, the participants answered survey questions by multiple response on their experience since diagnosis with categories of symptoms and impact of symptoms that were selected and categorized as described above. All categories are shown in Table 1.

In a second step, patients identified relevant categories within the 2 sections symptoms and impact of symptoms on daily life by pairwise comparison between all categories in both sections. That is, the app presented pairs of categories asking for the patient's "preference" between the 2 options ("Which of the two symptoms/impact of symptoms is of greater relevance to you"). The category identified as being more relevant in such a comparison was scored with 1, the less relevant category with 0.

In a third step, after identification of the 3 most relevant categories of each section, participants were presented with original single PRO items (questions and answers) taken from original questionnaires with established relevance for IBD. Patients were then asked on their opinion regarding the suitability (yes/no) of the question–answer combination with respect to appropriately describing and assessing the respective symptoms or impact.

Statistical Analysis
Descriptive statistical analyses were performed, stratified by CD and UC. For identifying the relevance of each category in the sections symptoms and impact of symptoms, a score was computed for each category. The relevance of a single category was calculated as the sum of all respective comparisons performed

for this category. The most relevant categories were identified as the categories with the highest sum scores. The scores, ranging from 0 to 8 in the section symptoms (9 categories), and ranging from 0 to 6 in the section impact of symptoms (7 categories), were recalculated as percentages, with higher values indicating higher relevance. Within each category, the absolute and relative frequency of patients rating a specific original PRO item as suitable was determined. Subgroup analyses were performed, stratified by prior treatment with biologics, age, time since diagnosis, and physician's global assessment of disease. All analyses were conducted using the statistical software package SAS 9.4 (SAS Institute).

Ethical Considerations

The study was approved by the ethics committee of the University Hospital of Jena. Informed consent was obtained from every participant prior to study inclusion.

Results

One hundred twenty patients participated in the study, 60 with CD or UC, respectively. Patient recruitment was balanced across the sites. Demographic characteristics of the study population are summarized in Table 2. There was a preponderance of women (54.2% vs 45.8% men), and most participants were between 30 and 60 years of age (62.5%, mean age: 38.9 years, SD: 12.8). Most participants' IBD diagnosis was made more than 2 years ago (88.3% vs 11.7% less than 2 years). No major differences were observed for any demographic or disease characteristic variable between the 2 disorders.

In the section symptoms, all categories except nausea were experienced in the majority of the patients (≥60%). Specifically, rectal bleeding was experienced by 96.7% of UC patients and by 60% of the CD patients; pain was reported by 93.3% of CD and by 73.3% of UC patients; nausea was

experienced by 55% of CD patients and by 31.7% of UC patients only. All categories of the section impact of symptoms were experienced by the majority of patients. Apart from the impact on sexual activities, which was more often mentioned by UC (61.7%) than by CD patients (50.0%), the experience of the impact of symptoms was similar for both patient groups. Table 3 shows the self-reported experience of symptoms and impact of symptoms among participants.

The scores for the assessment of the individual relevance of each symptom and each category for impact of symptoms after pairwise comparisons are shown in Figures 1 and 2. In CD patients, the highest mean scores (indicating highest relevance) for symptoms were found for the categories of pain (72.9% ± 23.9%) and stool urgency (mean: 70.8% ± SD: 28.2%). In UC patients, stool urgency had the highest mean score (84.2% ± 19.0%), followed by stool frequency (71.3% ± 21.1%). For impact of symptoms, mean scores were largely similar between both CD and UC patients and across all categories except for impairment of sexual activities, which was rated markedly less relevant in both groups (CD: 17.8% ± 24.7% and UC: 16.9% ± 23.9%). Highest mean scores were observed for impaired general wellbeing (CD: 65.8% ± 27.0% and UC: 65.6% ± 29.1%) and impaired social activities (CD: 62.5% ± 25.8% and UC: 64.2% ± 25.5%).

In addition, Figures 3 and 4 show only the most relevant voted symptom and impact of symptom category in each CD and UC patient. For the majority of patients stool urgency was the most relevant symptom, both in CD (33.3%) and UC patients (48.3%) followed by pain in CD (26.7%) and rectal bleeding (21.7%) in UC patients. General wellbeing (23.3%) and impaired work productivity (21.7%) were the most relevant impact categories for CD patients. For UC patients, general wellbeing (31.7%) and impaired social activities (21.7%) were regarded as most relevant.

Table 2. Main characteristics of the study population, stratified by disease

	Crohn's disease n (%)	Ulcerative colitis n (%)	Total n (%)
Gender			
Male	26 (43.3)	29 (48.3)	55 (45.8)
Female	34 (56.7)	31 (51.7)	65 (54.2)
Age in categories			
<30 years	15 (25.0)	20 (33.3)	35 (29.2)
≥30 to < 60 years	39 (65.0)	36 (60.0)	75 (62.5)
≥60 years	6 (10.0)	4 (6.7)	10 (8.3)
Age, mean (SD)	40.6 (13.5)	37.3 (12.1)	38.9 (12.8)
Time since diagnosis in categories			
≤2 years	6 (10.0)	8 (13.3)	14 (11.7)
>2 years	54 (90.0)	52 (86.7)	106 (88.3)
Biologic experience			
Naive	15 (25.0)	19 (31.7)	34 (28.3)
Experienced	45 (75.0)	41 (68.3)	86 (71.7)
Physician's global assessment of current disease activity			
Normal	9 (15.0)	14 (23.3)	23 (19.2)
Mild disease	19 (31.7)	14 (23.3)	33 (27.5)
Moderate disease	19 (31.7)	28 (46.7)	47 (39.2)
Severe disease	13 (21.7)	4 (6.7)	17 (14.2)

Table 3. Self-reported experience of symptoms and impact of symptoms

	Crohn's disease n (%)	Ulcerative colitis n (%)	Total n (%)
Total	60 (100.0)	60 (100.0)	120 (100.0)
Symptoms			
Rectal bleeding	36 (60.0)	58 (96.7)	94 (78.3)
Stool urgency	52 (86.7)	55 (91.7)	107 (89.2)
Fatigue	47 (78.3)	51 (85.0)	98 (81.7)
Flatulence	53 (88.3)	45 (75.0)	98 (81.7)
Weight	47 (78.3)	42 (70.0)	89 (74.2)
Night symptoms	36 (60.0)	41 (68.3)	77 (64.2)
Pain	56 (93.3)	44 (73.3)	100 (83.3)
Stool frequency	52 (86.7)	56 (93.3)	108 (90.0)
Nausea	33 (55.0)	19 (31.7)	52 (43.3)
Impact of symptoms			
Impaired daily activities	45 (75.0)	43 (71.7)	88 (73.3)
Depression/anxiety	36 (60.0)	39 (65.0)	75 (62.5)
Impaired work productivity	47 (78.3)	46 (76.7)	93 (77.5)
Impaired general wellbeing	53 (88.3)	55 (91.7)	108 (90.0)
Emotional distress	45 (75.0)	44 (73.3)	89 (74.2)
Impaired sexual activities	30 (50.0)	37 (61.7)	67 (55.8)
Impaired social activities	48 (80.0)	49 (81.7)	97 (80.8)

Figure 2. Mean impact scores in %, stratified by inflammatory bowel disease. Abbreviations: CD, Crohn's disease; UC, ulcerative colitis.

Figure 3. Most relevant symptom, stratified by inflammatory bowel disease. Abbreviations: CD, Crohn's disease; UC, ulcerative colitis.
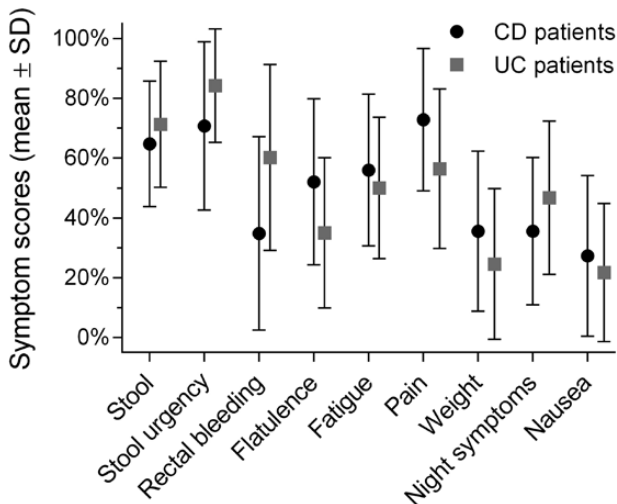

Figure 1. Mean symptom scores in %, stratified by inflammatory bowel disease. Abbreviations: CD, Crohn's disease; UC, ulcerative colitis.

Table 4 shows the suitability of questions for each symptom and impact category. In general, almost all questions of each symptom category showed a high suitability (≥50%), as did almost all questions for each impact category.

Subgroup analyses were conducted for the categories of age, gender, time since diagnosis, biologic experience, and current disease activity as stated in Table 2. No major differences in symptom and impact scores were observed between the subgroups of CD and UC patients (data not shown).
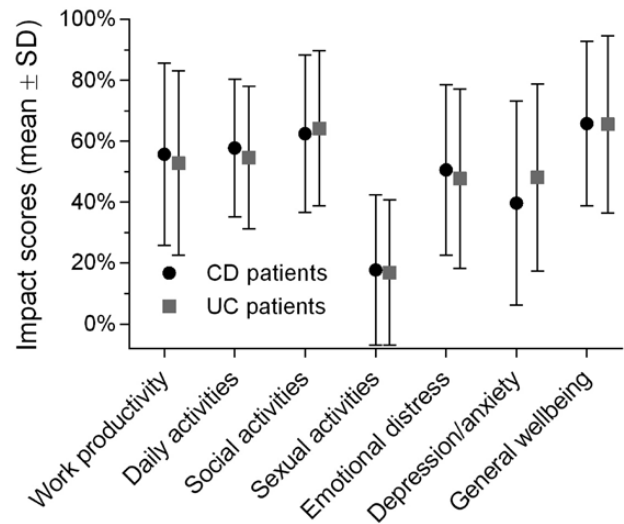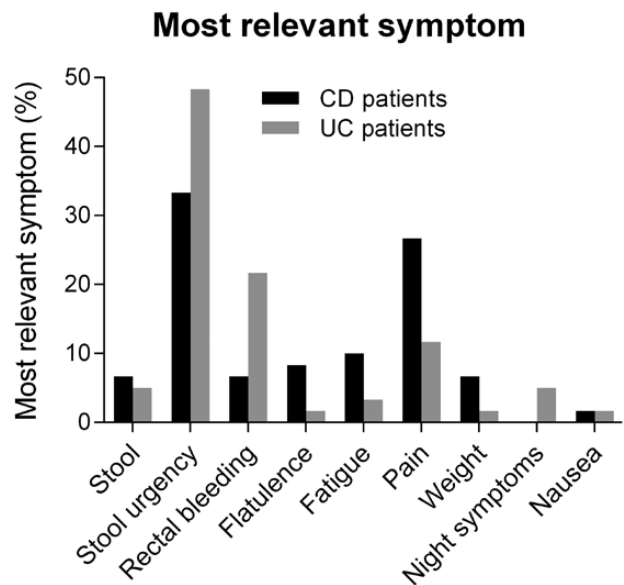
Discussion

PRO measures are commonly used in the assessment of patients with IBD. In this cross-sectional study, we carried out a digital patient survey to determine the self-reported experience and relevance of several PRO categories in patients with CD and UC. To our knowledge, this is the first study to evaluate patients' impairments and identify needs for improvement of PROs in such detail. The most important finding of our study was that stool urgency and pain were rated the 2 most important symptoms in CD patients with similar ratings for relevance. Stool urgency was also the most important symptom in patients with UC, followed by stool frequency.

Many regulatory bodies nowadays emphasize the importance of incorporating PROs in the approval process of new drugs, albeit in combination with more traditional outcome measures such as survival or adverse events.[12–14] However, this

call for the patient perspective must be met with accurate and valid PRO measurements.[18] PROs play a particularly important role in IBD, as there are no known biomarkers or a sufficient set of surrogate parameters to accurately reflect the full spectrum of the disease.[19] For the assessment of IBD patients in clinical trials and the real world, several disease activity

Figure 4. Most relevant impact, stratified by inflammatory bowel disease. Abbreviations: CD, Crohn's disease; UC, ulcerative colitis.

scores and quality of life questionnaires have been established and are widely used.

The disease scores most applied in clinical trials and real-world studies in IBD are the Mayo-Score for UC and the HBI and Crohn's Disease Activity Index for CD. All 3 scores do not include the symptom "stool urgency," which turned out to be one of the most frequently experienced and most important symptoms in both UC and CD patients in our study. Yet, 2 important other disease-specific symptoms ("stool frequency" and "pain" for CD and "stool frequency" and "rectal bleeding" for UC) are included in the respective disease scores.

Most noticeable differences between the diseases were observed in the categories of rectal bleeding and pain: rectal bleeding was much more common in UC (96.7%) than in CD patients (60.0%), which can be considered an expected finding based on the disease's etiology and clinical signs.[20,21] On the other hand, pain was markedly more often experienced in CD (93.3%) than in UC patients (73.3%), which is also in accordance with the literature.[22,23]

Most frequently experienced categories for impact of symptoms in both groups were general wellbeing, followed by reduced social activities. Least frequent categories were impaired sexual activities, and depression/anxiety. A prior study highlighted depression to be an important determinant of low sexual function; thus, these 2 categories are probably associated and cannot be interpreted independently.[24] The category "impaired sexual activities" differed between the groups—it was somewhat less common in CD (50%) compared to UC (61.7%). Given that previous reports emphasized that patients with IBD experience emotional distress relating to factors such as fear of sexual inadequacy,[25] the fact that the
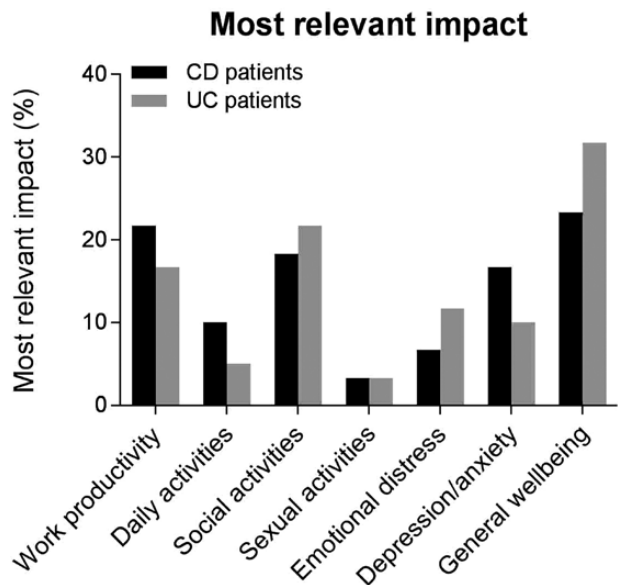
Table 4. Suitability of questions for symptom and impact categories

| | | | CD patients | | | UC patients | |
| | | | Least suitable | Most suitable | | Least suitable | Most suitable |
	N_{quest}	N*	%	%	N*	%	%
Symptom							
Stool frequency	6	30	73.3	96.7	41	73.2	87.8
Stool urgency	4	34	58.8	97.1[1]	45	73.3	86.7[1]
Rectal bleeding	4	15	66.7	86.7	28	71.4	92.9[1]
Flatulence	2	21	81.0	95.2	9	66.7	88.9
Fatigue	14	20	50.0	95.0	14	42.9	85.7
Pain	6	38	73.7	94.7[2]	21	81.0	100.0
Weight	2	8	75.0	75.0	4	50.0	75.0
Night symptoms	4	7	57.1	85.7	13	76.9	100.0
Nausea	1	7	100.0	100.0	5	60.0	60.0
Impact of symptoms							
Impaired work productivity	3	30	66.7	80.0[2]	26	69.2	80.8[4]
Impaired daily activities	4	33	69.7	90.9[3]	30	80.0	86.7[3,5]
Impaired social activities	4	35	68.6	91.4[2]	37	75.7	89.2[6]
Impaired sexual activities	1	5	100.0	100.0	6	83.3	83.3
Emotional distress	11	23	60.9	91.3	20	50.0	95.0
Depression/anxiety	6	16	87.5	93.8	23	73.9	100.0
General wellbeing	7	38	71.1	97.4[2]	38	60.5	94.7[2]

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis. N_{quest}: number of questions per symptom/impact of symptom questionnaire; N*: number of patients for whom the respective symptom/impact of symptom was one of 3 most relevant.
Most suitable score: [1]SCCAI, [2]IBD-DI, [3]EQ-5D-5L, [4]WPAI, [5]IBD-Control Q, [6]IBDQ.

impact category sexual activities were least frequently experienced among all included patients, both among CD and UC, is striking. Notably, not only was the impact of IBD on sexual activity the least frequently experienced category by all participants, but also was rated as least relevant among all impact categories. Previous literature found a positive correlation between sexual functioning and quality of life in patients with IBD,[26] however, and we believe our results do not contradict these earlier findings. Rather, it should be kept in mind that our ranking was based on pairwise comparison and other categories of symptom impact seemed to have been of even more relevance than sexual functioning.

Strengths and Limitations

A potential limitation of the study design lies in the fact that questionnaire items were selected, grouped, and categorized into the 2 sections symptoms and impact of symptoms solely based on clinical judgment by a small steering committee. Thus, different decisions on grouping or categorization may have potentially led to divergent outcomes. Another limitation is the nonsystematic approach for identification of PRO questionnaires that might have led to the identification of even more categories or at least more PRO items.

As usual in observational research, certain limitations in data quality and sources of bias, both on the doctor's and the patient's side, are inherent. In this study, eg, a certain degree of selection bias and acquiescence bias must be taken into account. Inclusion criteria included diagnosis of either CD or UC at least 6 months before study inclusion. Even though most participants were diagnosed for a considerably longer time, ie, more than 2 years prior to study participation, it is possible that some patients with a relatively short disease duration might not have experienced all aspects of the burden of the respective chronic disease and thus provided insufficient feedback. Moreover, location of disease was not taken into account which also might influence the type of symptoms patients experience. The sample size of 120 IBD patients was calculated to allow for sufficient power of the pairwise comparisons between all categories of symptoms and between all categories of impact of symptoms. However, identification of possible differences in the relevance of categories or differences in the subgroups might not have been possible due to sample size restrictions.

A key strength of this study is the strictly patient-centered approach with which IBD patients received a voice to declare self-reported experience, relevance of PRO items as well as usability of PRO questionnaires. As our patient cohort was comparable to other IBD studies in terms of age, gender, or disease activity,[27] the strict digital application on site-based computer tablets causes obviously no selection bias of the participating patients.

Conclusions

The results of this study show that many symptoms and their impact are experienced universally in many patients with IBD, regardless of the underlying disease. Stool urgency, stool frequency, and either pain for CD patients or rectal bleeding for UC patients were considered the most relevant symptoms. Thus, emphasis on PROs with focus on these categories is advised. However, disease-specific differences do exist and warrant individual adjustment of PROs. While this study gives good insight in which symptoms and impact of symptoms affect IBD patients most, larger studies are warranted to confirm these findings.

Data Availability

The datasets generated during the current study are not publicly available but are available from the corresponding author on reasonable request.

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