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Alimentary Tract

Lower urinary tract symptoms in patients with inflammatory bowel diseases: A cross-sectional observational study

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ABSTRACT

Background: Inflammatory Bowel Diseases (IBD), Crohn's Disease (CD), and Ulcerative Colitis (UC) may have extraintestinal manifestations, including disorders of the urinary tract. The prevalence of lower urinary tract symptoms (LUTS) in IBD patients remains unclear.
Aims: Assess the prevalence of LUTS in patients with CD or UC, evaluate the variables implicated in any difference in LUTS prevalence between CD or UC, and assess any relationship between disease activity and LUTS
Methods: LUTS were evaluated in 301 IBD patients through standardised questionnaires: Bristol Female Lower Urinary Tract Symptoms (BFLUTS), NIH-Chronic Prostatitis Symptom Index (NIH-CPSI), and International Prostate Symptom Score (IPSS). IBD activity was determined through the Crohn's Disease Activity Index (CDAI), Partial Mayo Score (PMS), and Total Mayo Score (TMS).
Results: BFLUTS total score for females was 6 (3–11). Patients with a higher age at diagnosis had worse filling symptoms ($p = 0.049$) and a worse quality of life ($p = 0.005$). In males, 67.1% had mild, 28.5% moderate, and 4.4% severe IPSS symptom grades. The overall NIH–CPSI prevalence of chronic prostatitis-like symptoms was 26.8%. The questionnaires revealed some significant differences in the subgroups analysed.
Conclusion: LUTS should be evaluated in IBD patients by urologic-validated questionnaires for prompt diagnosis and early treatment.

1. Introduction

Inflammatory Bowel Diseases (IBD) mainly consist of Crohn's disease (CD) and ulcerative colitis (UC) [1]. IBD can be associated with several extraintestinal manifestations, including urogenital ones [2]. The urinary impairment in IBD is multifactorial and may depend on the type of IBD (i.e., CD or UC), other associated comorbidities, or the kind of therapy. In CD patients, for example, there is a tendency for urinary oxalate or uric acid stone formation [3]. The incidence of nephro-urolithiasis is drastically higher in the IBD population than in the general population (8–19% versus 0.1%, respectively) [4]. Moreover, 5-aminosalicylates (5-ASA), a mainstay of IBD therapy, may cause kidney damage [5]. The mechanism of 5-ASA-associated nephrotoxicity is not completely clear. However, the lack of a clear relationship between 5-ASA dose and the risk of nephrotoxicity suggests that this complication is an idiosyncratic rather than a dose-related event [5].

Symptoms of urinary incontinence are also often a problem that IBD patients encounter, especially with other comorbidities (i.e., cerebrovascular events, diabetes, and obesity) [6,7].

Several IBD patients present with lower urinary tract symptoms (LUTS), often without diagnosed urinary disorders. In a recent

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meta-analysis, the prevalence of kidney or urinary tract disorders ranged from 4% to 23% [8]. LUTS are known to impact the quality of life (QoL) in general [9–11].

LUTS prevalence in IBD has never been investigated systematically through validated questionnaires. Therefore, this cross-sectional study was designed to define through well-validated questionnaires if IBD patients complain of urinary symptoms. A secondary endpoint was to assess if there was any difference between CD and US in the prevalence of LUTS. Finally, we aimed to evaluate whether any subgroups were at a higher risk for LUTS.

2. Material and methods

2.1. Study design

This is a cross-sectional multicentric observational study conducted from January 2021 to May 2022 at the Gastroenterology Unit of the University of Campania "Luigi Vanvitelli", of "Umberto I" Hospital in Nocera Inferiore and of "S. Anna and S. Sebastiano" Hospital in Caserta.

The following inclusion criteria were set: patients with IBD aged at least 18 years. We excluded patients who met at least one of the following conditions: neoplasm, psychiatric conditions, previous surgery involving the urogenital compartment, and clinically significant infections within the six months before enrolment.

The following variables were collected: age and age at diagnosis of IBD and duration of disease, gender, type of IBD, *Montreal* classification, extraintestinal manifestations, IBD-specific and concomitant treatments, comorbidities, smoking status, alcohol consumption, Crohn's Disease Activity Index (CDAI) score for CD [12], Partial Mayo Score (PMS) and/or the Total Mayo Score (TMS) for UC [13].

According to the CDAI, a score less than or equal to 150 indicates clinical remission, between 151 and 219 mild disease activity, 220–450 moderate, and >450 severe disease activity [14]. According to the PMS, a score <2 implies a state of clinical remission, between 2 and 4 of mild disease activity, 5–7 of moderate disease activity, and finally >7 of severe disease activity [14].

Moreover, with TMS, UC was defined as in remission for a score <3, in mild activity for a score between 3 and 5, moderate between 6 and 10, and, finally, severe if >10 [15].

Concerning smoking status, we considered the status of current smokers, previous smokers (defined as those who reported having smoked at least 100 cigarettes in their lifetime and quit smoking within the last five years [16]), and absolute non-smokers (defined as those who have never smoked cigarettes in their lives). For alcohol consumption, we considered the Alcoholic Unit (AU, considering 1 AU equal to 12 g of ethanol) as the unit of measurement. We thought non-drinkers, those who did not consume any AU, occasionally those who drank no more than 2 AU per week, those who had an alcohol consumption declared as "*often*" consumed more than 2 AU alcohol per week, and as frequent those who consumed at least 1 AU per day.

According to Montreal's classification for the CD, we considered a diagnosis before the age of 16 years (A1), between 17 and 40 years (A2), over 40 years (A3), ileal localization (L1), colic (L2), ileocolic (L3), isolated upper gastrointestinal (L4) and finally, stricturing, nonpenetrating (B1), stricturing (B2), penetrating (B3), perineal (p) disease. For UC, we considered proctitis (E1), left colitis distal to the splenic flexure (E2), and extensive/pancolitis (E3), in clinical remission (S0) as mild (S1), as moderate (S2) or as severe (S3) [17]. All patients received the administration of a questionnaire aimed at collecting the variables identified for the study and administered, organised, and processed anonymously. The study was conducted following the principles of the Declaration of Helsinki. It received approval from the Ethics Committee of our University Department (i.e., Department of Precision Medicine).

2.2. Female urinary symptoms evaluation

Female patients with IBD were anonymously administered the Bristol Female Lower Urinary Tract Symptoms (BFLUTS) questionnaire [18] consisting of several domains. The F domain (F1-F4) evaluates *filling symptoms*. The V domain (V1–V3) evaluates *voiding symptoms*. The I (I1–I5) evaluates *incontinence symptoms*, the S domain evaluates *sexual symptoms* (S, S1, S2), and finally, *symptoms related to the quality of life* are also assessed (QoL1–QoL5). No specific cut-off defines whether a patient has a urinary disorder [19].

2.3. Male urinary symptoms evaluation

The following two questionnaires were administered anonymously for the assessment of male urinary function:

- National Institute of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) questionnaire [20]. A patient with a pain subscore $\geq$ 4 in different experiences is defined as having similar chronic-prostatitis symptoms [21].
- International Prostatic Symptoms Score (IPSS) [22], a 7-item questionnaire, also consisting of an additional question on urinary-related quality of life (IPSS QoL) and exploring, respectively: incomplete bladder emptying (IPSS 1), urinary frequency (IPSS 2), urinary intermittency (IPSS 3), urinary urgency (IPSS 4), weak stream (IPSS 5), straining (IPSS 6), and nocturia (IPSS 7) symptoms. A score between 0 and 7 implies mild symptoms, between 8 and 19 moderate symptoms, and between 20 and 35 severe symptoms.

2.4. Outcomes

The primary outcome of our study was to assess the LUTS levels in IBD patients assessed by BLUFTS, NIH-CPSI, and IPSS. The secondary outcomes were to determine any differences in urinary symptoms according to the clinic-demographic characteristics of CD and UC patients and finally to assess any relationships between disease activity (set by CDAI for CD and PMS/TMS for UC) and urinary symptoms levels evaluated by the BFLUTS, NIH-CPSI, and IPSS.

2.5. Statistical analysis

Descriptive statistics were used to present the data. Continuous variables were expressed as median (interquartile range), while ordinal and categorical variables were expressed as numerosity (percentage of total) for each degree of freedom. The distribution of variables was tested by a Kolmogorov–Smirnov test to see if it was normal and to set the choice between parametric and nonparametric tests. Two categorical variables were compared using the chi-square test to pursue the study outcomes. In contrast, continuous and ordinal variables were differentiated between groups and subgroups using the Mann–Whitney *U test* or the Kruskal–Wallis's test, depending on the degrees of freedom of the variable related to the group/subgroup. The chi-square or the Fisher exact test was used to compare two categorical variables. The strength of the correlation between the two variables was assayed by Kendall's tau-b test, also showing the correlation coefficient tau (τ) and the relative p-value. The *p*-value accepted as significant was less than 0.05. A *p*-value less than 0.01 was defined as highly significant. Statistical analyses were performed with IBM SPSS® software.

Table 1
Clinical and demographic characteristics of the patients considered in the study. The table is stratified by type of Inflammatory Bowel Disease (IBD), i.e., Crohn's Disease (CD) or Ulcerative Colitis (UC), as well as by gender in the total sample.

Variable	CD *N = 99*	UC *N = 202*	p-value[a]	Males *N = 161*	Females *N = 140*	*p*-value[b]
Male	48 (48.5%)	113 (55.9%)	0.226	161 (100%)	–	–
Female	51 (51.5%)	89 (44.1%)		–	140 (100%)	
CD	99 (100%)	–	–	48 (29.8%)	51 (36.4%)	0.226
UC	–	202 (100%)		113 (70.2%)	89 (63.6%)	
Age (y)	39 (30–55)	46 (34–58)	0.078	47 (34.5–60)	41.5 (30–55)	0.062
Age at IBD diagnosis (y)	28 (20–43)	32 (22–45.2)	0.283	32 (21–45.5)	30 (21–43)	0.398
IBD duration			0.928			0.898
<5 years	34 (34.3%)	66 (32.7%)		52 (32.3%)	48 (34.3%)	
5–10 years	25 (25.3%)	49 (24.3%)		37 (23%)	37 (26.4%)	
>10 years	40 (40.4%)	87 (43.1%)		72 (44.7%)	55 (39.3%)	
Montreal[c]			–			0.190
A1	6 (6.1%)	–		2 (1.2%)	4 (2.9%)	
A2	64 (64.6%)	–		36 (22.4%)	28 (20%)	
A3	29 (29.3%)	–		10 (6.2%)	19 (13.6%)	
L1	44 (44.4%)	—	–	19 (11.8%)	25 (17.9%)	0.475
L2	12 (12.1%)	—		7 (4.3%)	5 (3.6%)	
L3	39 (39.4%)			20 (12.4%)	19 (13.6%)	
L4	4 (4%)			2 (1.2%)	2 (1.4%)	
B1	32 (32.3%)	—	–	15 (9.3%)	17 (12.1%)	0.904
B2	47 (47.5%)	—		23 (14.3%)	24 (17.1%)	
B3	4 (4%)			2 (1.2%)	2 (1.4%)	
p	16 (16.2%)			8 (4.9%)	8 (5.7%)	
E1	—	32 (15.8%)	–	13 (8.1%)	19 (13.6%)	**0.007**
E2	–	102 (50.5%)		54 (33.5%)	48 (34.3%)	
E3		68 (33.7%)		46 (28.6%)	22 (15.7%)	
S0	—	72 (35.6%)	–	41 (25.5%)	31 (22.1%)	0.581
S1	—	62 (30.7%)		37 (23%)	25 (17.9%)	
S2		60 (29.7%)		30 (18.6%)	30 (21.4%)	
S3		8 (4%)		5 (3.1%)	3 (2.1%)	
Smoker	34 (34.3%)	35 (17.3%)	0.423	34 (21.1%)	35 (25%)	**0.015**
Non-smoker	39 (39.4%)	103 (51%)		68 (42.2%)	74 (52.9%)	
Past smoker	26 (26.3%)	64 (31.7%)		59 (36.6%)	31 (22.1%)	
Alcohol						
Non-drinker	52 (52.5%)	80 (39.6%)		57 (35.4%)	75 (53.6%)	
Occasional	40 (40.4%)	101 (50%)	**0.026**	86 (53.4%)	55 (39.3%)	**0.003**
Often	6 (6.1%)	20 (9.9%)		16 (9.9%)	10 (7.1%)	
Frequent	1 (1%)	1 (0.5%)		2 (1.2%)	–	

[a] Comparison between patients with CD and UC.
[b] Comparison between females and males regardless of IBD type. Significant *p*-values (<0.05) are highlighted in bold.
[c] Montreal classification percentages are relative to each parameter.

3. Results

3.1. General characteristics

Three hundred fifty-one patients were considered, of whom 50 were later excluded because they refused to participate. Three hundred and one patients were then included. Of these, 161 (53.5%) were male and 140 (46.5%) females. Concerning IBD, 99 (32.9%) had CD, and 202 (67.1%) had UC. We did not collect the IPSS questionnaire in 3 patients and the NIH-CPSI in 1 patient who declared no time to complete all the questionnaires. The overall median age was 45 (32–57) years, and the age at diagnosis of IBD was 32 (21–44) years. Table 1 summarises the clinical and demographic characteristics of the included patients. Data on comorbidities and specific therapy patients practice for their IBD are presented in Table 2. Data on extraintestinal manifestations and concomitant treatments are in the supplementary material. There was no correlation between therapy or comorbidities and LUTS in our clinical setting.

3.2. Female LUTS assessment

LUTS in the female sample, as assessed by BFLUTS, showed a median filling symptoms (BFLUTS-F) score of 3 (2–5), voiding symptoms (BFLUTS-V) score of 1 (0–2), incontinence symptoms (BFLUTS-I) score of 0 (0–1), sexual symptoms (BFLUTS-S) score of 0 (0–0) and finally a quality of life-related symptoms (BFLUTS-QoL) score of 0 (0–3). The total BFLUTS score, on the other hand, was 6 (3–11). Most females (88, 62.85%) were sexually active when completing the questionnaire. Although there is no well-defined and precise threshold of BFLUTS to define if a female patient has or does not have a urinary disorder [19], we compared to see if the distribution of scores was statistically different among different subgroups.

We did not observe a different distribution of BFLUTS subscores and BFLUTS total score and sexual activity between patients with CD and UC (Table 3). In each case, several subgroup analyses were subsequently conducted beyond the type of IBD. We compared all the clinical-demographic parameters, already shown in Table 1, to see if any of these were significantly differently distributed than the BFLUTS scores. According to the duration of IBD, the BFLUTS-S sub-score was differently expressed ($p = 0.009$). In detail, 23.7% of patients with an IBD diagnosis for more than ten years reported a negative influence on sex life by urinary symptoms (i.e., had a BFLUTS-S sub-score greater than 0) versus 2.7% of patients diagnosed between 5 and 10 years and 10.4% of those diagnosed for less than five years.

We also wanted to examine the impact of the *Montreal* classification on BFLUTS scores. We saw that scores related to filling symptoms (BFLUTS-F) were significantly worse in A3 patients than in A2 and A1 patients ($p = 0.049$). Respectively, in the three Montreal groups mentioned, the medians were 4 (2–7), 2 (1–3.75), and 1.5 (1–2). Therefore, the higher the age at a diagnosis, the worse the filling symptoms. Quality of life related to urinary symptoms

Table 2
Inflammatory Bowel Disease (IBD) specific therapy, comorbidities, and concomitant therapies in the patient sample.

Variable	CD *N* = *99*	UC *N* = *202*	*p*-value[a]	Males *N* = *161*	Females *N* = *140*	*p*-value[b]
IBD-specific therapy						
Adalimumab	26 (26.3%)	13 (6.4%)	**0.027**	17 (10.6%)	22 (15.7%)	0.708
Infliximab	13 (13.1%)	27 (13.4%)		27 (16.8%)	13 (9.3%)	
Certolizumab	1 (1%)	–		1 (0.6%)	–	
Ustekinumab	19 (19.2%)	2 (1%)		9 (5.6%)	12 (8.6%)	
Vedolizumab	10 (10.1%)	37 (18.3%)		26 (16.1%)	21 (15%)	
Tofacitinib	–	2 (1%)		2 (1.2%)	–	
Combo therapy	1 (1%)	1 (0.5%)		2 (1.2%)	–	
Prednisone *alone*	2 (2%)	–		1 (0.6%)	1 (0.7%)	
Mesalamine *alone*	12 (12.1%)	62 (30.7%)		40 (24.8%)	34 (24.3%)	
Mesalamine *plus* budesonide	1 (1%)	23 (11.4%)		11 (6.8%)	13 (9.3%)	
Mesalamine *plus* prednisone	5 (5.1%)	22 (10.9%)		15 (9.3%)	12 (8.6%)	
Sulfasalazine	–	6 (3%)		3 (1.9%)	3 (2.1%)	
Topical budesonide	–	1 (0.5%)		–	1 (0.7%)	
None	9 (9.1%)	6 (3%)		6 (3.7%)	8 (5.7%)	
Comorbidities						
Mediterranean anaemia	2 (2%)	–	0.068	–	2 (1.4%)	**0.008**
Aortal aneurysm	1 (1%)	–		1 (0.6%)	–	
Arthrosis	1 (1%)	1 (0.5%)		1 (0.6%)	–	
Bronchial asthma	2 (2%)	1 (0.5%)		2 (1.2%)	1 (0.7%)	
Diabetes mellitus	1 (1%)	1 (0.5%)		2 (1.2%)	–	
Colic diverticulosis	1 (1%)	–		1 (0.6%)	–	
Chronic HBV hepatopathy	1 (1%)	1 (0.5%)		–	2 (1.4%)	
Epilepsy	1 (1%)	2 (1%)		1 (0.6%)	2 (1.4%)	
Hypercholesterolemia	1 (1%)	5 (2.5%)		5 (3.1%)	1 (0.7%)	
Hypertension	10 (10.1%)	36 (17.8%)		32 (19.9%)	14 (10%)	
Hyperthyroidism	1 (1%)	–		–	1 (0.7%)	
Hypothyroidism	4 (4%)	1 (0.5%)		1 (0.6%)	4 (2.9%)	
Osteopenia	1 (1%)	–		–	1 (0.7%)	
Osteoporosis	1 (1%)	2 (1%)		1 (0.6%)	2 (1.4%)	
Chronic pericarditis	1 (1%)	–		–	1 (0.7%)	
Psoriasis	1 (1%)	–		–	1 (0.7%)	
Liver steatosis	2 (2%)	2 (1%)		1 (0.6%)	3 (2.1%)	
Peripheral thrombophlebitis	1 (1%)	–		–	1 (0.7%)	
Urolithiasis	4 (4%)	5 (5%)		5 (3.1%)	4 (2.9%)	
Alopecia	–	1 (0.5%)		1 (0.6%)	–	
Chronic obstructive pulmonary disease	–	1 (0.5%)		1 (0.6%)	–	
Ischemic heart disease	–	3 (1.5%)		3 (1.9%)	–	
Celiac disease	–	1 (0.5%)		1 (0.6%)	–	
Primary biliary cholangitis	–	1 (0.5%)		1 (0.6%)	–	
Cholelithiasis	–	2 (2%)		2 (1.2%)	–	
Vitamin D insufficiency	–	4 (2%)		1 (0.6%)	3 (2.1%)	
Fibromyalgia	–	3 (1.5%)		–	3 (2.1%)	
Pervious foramen of Botallo	–	1 (0.5%)		1 (0.6%)	–	
Gout	–	1 (0.5%)		–	1 (0.7%)	
HPV	–	1 (0.5%)		–	1 (0.7%)	
Irritable Bowel Syndrome	–	1 (0.5%)		1 (0.6%)	–	
Lower extremity venous insufficiency	–	1 (0.5%)		1 (0.6%)	–	
Mitral prolapse	–	1 (0.5%)		–	–	
Rosacea	–	1 (0.5%)		1 (0.6%)	–	
Wolf-Parkinson-White Syndrome	–	1 (0.5%)		1 (0.6%)	–	

[a] Comparison between patients with CD and UC.
[b] Comparison between females and males regardless of IBD type. Significant *p*-values (<0.05) are highlighted in bold.

(BFLUTS-QoL) was also worse in patients with higher age at diagnosis (A3) compared with those diagnosed at younger ages (A2, A1) ($p = 0.005$). The medians were the same for A1 and A2 patients, i.e., 1.5 (0–3) and higher in A3 with 3 (1–6). Finally, total BFLUTS was also higher in A3 patients ($p = 0.025$).

In addition, while smoking did not seem to affect urinary symptoms, occasional alcohol consumption was associated with a lower prevalence of urinary incontinence symptoms (BFLUTS-I). In detail, 38.7% (29/75) of non-alcohol drinkers showed positivity for incontinence symptoms compared to 18.1% (10/55) of patients with occasional consumption ($p = 0.034$).

Ultimately, our data showed that several female subgroups (patients diagnosed with IBD for 5–10 years, patients diagnosed with CD for less than 40 years, and finally, patients with occasional alcoholic beverage consumption) had fewer LUTS, as assessed by the BFLUTS questionnaire.

3.3. Male LUTS assessment

As assessed using the NIH-CPSI, LUTS in males showed a median total score of 6 (3–11). Following the NIH-CPSI, the prevalence of chronic prostatitis-like symptoms was 26.8%. Comparing UC and CD, symptoms did not tend to differ between CD and UC, based on NIH-CPSI scores either as sub-scores or as total score ($p > 0.05$, Table 3). However, if for the pain sub-score, we use a cut-off value of ≥4 [21], the prevalence of chronic prostatitis-like symptoms was significantly different between CD (21.3%) and UC patients (29.2%) ($p < 0.01$) (*data not shown*). By subgroup analysis, we tested the possible significant distribution of NIH-CPSI scores. In detail, disease duration was found to impact pain NIH-CPSI scores. Specifically, the group of patients with a course of IBD between 5 and 10 years had a lower frequency of painful urinary symptoms with a median of 1 (1–1.25) compared to those with a disease duration of

Table 3
Female urinary symptoms assessed using the Bristol Female Lower Urinary Tract Symptoms (BFLUTS) questionnaire and male urinary symptoms were evaluated by the NIH-Chronic Prostatitis Symptom Index (NIH-CPSI) and the International Prostate Symptom Score (IPSS) questionnaires stratified by Crohn's Disease (CD) and Ulcerative Colitis (UC).

Sub scores	CD	UC	Min–Max	*p*-value[a]
Bristol Female Lower Urinary Tract Symptoms (BFLUTS)				
BFLUTS-F	2 (1–4)	3 (2–5)	0–15	0.144
BFLUTS-V	1 (0–2)	1 (0–3)	0–16	0.730
BFLUTS-I	0 (0–1)	0 (0–1)	0–20	0.926
BFLUTS-S	0 (0–0)	0 (0–0)	0–6	0.548
BFLUTS-QoL	1 (0–3)	0 (0–3)	0–18	0.452
BFLUTS total	6 (3–11)	7 (3–11)	0–75	0.556
Sexually active	30 (58.8%)	58 (65.2%)	0–100%	0.172
NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)				
Pain symptoms	1 (1–3)	1 (1–5)	0–22	0.413
Urinary symptoms	1 (0–2)	1 (0–2)	0–10	0.352
QoL symptoms	3 (1–6)	3 (1–6)	0–12	0.869
Total score	7 (3–9)	6 (3–11)	0–43	0.603
International Prostate Symptom Score (IPSS)				
IPSS 1 (incomplete emptying)	0 (0–1)	0 (0–1)	0–5	0.153
IPSS 2 (frequency)	1 (0–2)	1 (0–2)	0–5	0.841
IPSS 3 (intermittency)	0 (0–1)	0 (0–2)	0–5	0.529
IPSS 4 (urgency)	0 (0–1)	0 (0–1)	0–5	0.133
IPSS 5 (weak stream)	0 (0–1)	0 (0–1)	0–5	0.225
IPSS 6 (straining)	0 (0–0)	0 (0–0)	0–5	0.119
IPSS 7 (nocturia)	1 (0–1)	1 (0–2)	0–5	**0.023**
IPSS QoL	1 (0–1)	1 (0–2)	0–6	0.389
IPSS total score	4 (1–7)	5 (2–10)	0–35	0.070

F: filling symptoms; V: voiding symptoms; I: incontinence symptoms; S: sexual function symptoms; QoL: Quality of Life symptoms.
[a] Comparison of BFLUTS, NIH-CPSI, and IPSS sub-scores and total scores between UC and CD.

fewer than five years, i.e., 1 (1–5), or to those with disease duration longer than ten years, 1 (1–6) ($p = 0.049$). Moreover, patients with UC E1 (i.e., proctitis according to the Montreal classification) had higher NIH-CPSI scores. In detail, E1 patients had a pain subscore of 6 (1.5–10), those with left colitis (E2) showed a pain subscore of 1 (1–6), and finally, those with pancolitis (E3) showed a pain sub-score of 1 (1–3) ($p = 0.004$). In addition, we observed that as the NIH-CPSI score worsened, so did the S-parameter of UC patients. In other words, there was a reduced percentage of UC patients in remission in the subgroup of patients with worse NIH-CPSI ($p = 0.005$).

Male IBD patients had an IPSS median total score of 4 (1–9) with a stratification of 106 (67.1%) patients with mild symptomatology, 45 (28.5%) with moderate symptomatology, and finally, 7 (4.4%) with severe symptomatology. There were no differences between CD and UC in terms of IPSS scores ($p > 0.05$, Table 3), except, however, for the IPSS-7 score (nocturia), which was significantly worse in UC patients ($p = 0.023$).

IPSS-2 (i.e., frequency) and IPSS-4 (i.e., urgency) in patients with an IBD duration longer than five years were significantly higher than those recorded in patients with an IBD duration of fewer than five years ($p < 0.05$, *data not shown*). This is significantly different compared to patients with an IBD duration of fewer than five years

In patients with CD, moreover, those diagnosed at ages younger than 16 years (A1) were the most impacted in terms of IPSS-QoL, with a median of 2.5 (2–2.5) ($p = 0.017$). In addition, the distribution of IPSS severity differed according to disease location in patients with UC ($p = 0.039$).

In detail, a more distal extent of UC corresponded to a worse level of LUTS. Specifically, patients with pancolitis (E3) had a 73.91 % rate of mild LUTS, those with left colitis (E2) at 59.25 %, and, finally, those with proctitis (E1) at 33.3 %.

3.4. Inflammatory bowel disease activity and LUTS

The median CDAI score was 60 (30–110), and, in detail, 82 patients (82.82%) were in remission, 7 (7.07%) had mild CD, 9 (9.09%) had moderate CD, and finally, 1 (1.01%) had severe CD. In the UC sample, however, PMS was calculated in all patients and was equal to 2 (0–4). On the contrary, the TMS was estimated in 176 (87.12%) patients and was 3 (1–6). By adopting PMS as a reference, 124 (61.4%) UC patients were in remission, 33 (16.3%) with a mild grade, 37 (18.31%) with a moderate grade, and finally, 8 (4%) with a severe grade. In the sample of UC patients with the availability of TMS, stratification allowed to distinguish 77 (43.8%) with UC in remission, 54 (30.68%) with mild UC, 38 (21.59%) with a moderate UC, and 7 (3.91%) with severe UC.

Starting with the female sample, we tested whether the distribution of BFLUTS scores differed by CDAI, PMS, or TMS. We observed no differences or correlations at BFLUTS, as the total score or sub-scores, for either CDAI, PMS, or TMS ($p > 0.05$, *data not shown*).

In males, examining the NIH-CPSI score in patients with CD, the CDAI did not distribute differentially according to urinary symptom severity ($p = 0.142$). In contrast, this was the case for PMS in male UC patients in whom urinary symptom severity paralleled the severity of the disease.

The rate of patients with PMS compatible with remission was 76.38% (55/72) in patients with mild urinary symptoms, 53.57% (15/28) in patients with moderate urinary symptoms, and 46.15% (6/13) in patients with severe urinary symptoms ($p = 0.024$). In addition, we tested whether the PMS showed any correlation with the NIH-CPSI scores. We observed a correlation with the pain subscore ($\tau = 0.209$; $p = 0.006$), the QoL sub-score ($\tau = 0.236$; $p = 0.001$) as well as the NIH-CPSI total score ($\tau = 0.213$; $p = 0.003$). A significant correlation was demonstrated between TMS and NIH-CPSI QoL scores ($\tau = 0.196$; $p = 0.008$) and NIH-CPSI total score ($\tau = 0.177$; $p = 0.014$).

The same analysis was performed with the IPSS questionnaire. We observed a relationship between IPSS-6 (straining) and CDAI ($p = 0.036$). Specifically, as the severity of CDAI worsened, so did urinary straining. Patients with CD and CDAI compatible for remission and mild disease had a median of 0 (0–0) IPSS-6 score, while those with moderate of 0.5 (0–0.5) and those with severe of 1 (1–

1). The PMS and the IPSS total score showed a significant relationship when stratified by the severity of UC ($p = 0.049$). 67.14% of patients with UC in remission had mild urinary symptoms versus 32.35% of patients with mild UC, 17.14% of patients with moderate UC, and 0% of those with severe UC. This trend was confirmed for TMS ($p = 0.003$, *data not shown*).

4. Discussion

This multicentre cross-sectional study showed that IBD patients have a non-negligible prevalence of urinary complaints. Many women showed an impaired BFLUTS score, more than half of the male IBD patients had at least mild prostatic symptoms, and about 30% had an NIH-CPSI score compatible with chronic prostatitis-like symptoms. No significant differences in the score of questionnaires assessing LUTS were observed between UC and CD patients. However, a subgroup analysis showed that higher age at diagnosis of IBD was associated with worsening urinary symptoms in both the female and male samples. This agrees with epidemiological evidence that increasing age is associated with a higher likelihood of detecting a higher prevalence of urinary symptoms [11,23,24]. An additional finding in the male sample was a worsening of score levels in patients with E1 compared with other disease topographies (i.e., E2 and E3). In addition, S0 UC patients were found to be less affected by LUTS than patients with active disease. The worsening of LUTS score in male E1 UC patients might be attributed to the anatomical proximity between the rectum and prostate and by the knowledge of the connections between the lower urinary tract and the rectum. In this regard, cross-organ sensitization refers to the ability of a given organ to influence the health and disease condition of an adjacent or distant organ through the transmission of noxious stimuli. In particular, a cross-organ sensitization between the genitourinary tract and the gut has been associated with the pathophysiology of several chronic urogenital conditions, such as interstitial cystitis/bladder pain syndrome or chronic prostatitis/chronic pelvic pain syndrome [25]. Pelvic organ cross-sensitization has also been demonstrated between experimentally induced colitis, bladder overactivity, and painful sensation in the rat [26]. A putative link between the genitourinary tract and gastrointestinal tract mainly relies upon the gut microbiome and its ability to modulate intestinal permeability [27,28]. In particular, short-chain fatty acids, one of the leading products of intestinal bacteria, can affect gut permeability by strengthening tight junctions and stimulating mucus and IgA production. Also, indole, a product of *E. coli*, stimulates the protein synthesis of tight and adherence junctional complexes of intestinal epithelial cells. Therefore, a qualitative or quantitative alteration of gut microbiota may cause an increased intestinal permeability (i.e., leaky gut), which in turn may favour the transmission of noxious agents to the genitourinary tract. Moreover, cross-sensitization in the pelvis may also occur via shared sensory neural pathways at the prespinal, spinal and supraspinal levels [29], thus causing an impairment of the bladder sensory pathway [25]. Finally, glutamate and glutamate receptors, capsaicin, and its receptor, TRPV1, have been pathogenically associated with cross-organ sensitization [30].

We also found that female patients had a more favourable BFLUTS score if they had occasional alcohol consumption. Indeed, these data agree with several studies already conducted (in the general population) where it was already observed that alcohol consumption could be associated with improved LUTS [31]. Possible mechanisms for the relationship between alcohol intake and LUTS include increased sympathetic tone activity, diuretic effect, and changed androgen levels [31]. The diuretic effect and low androgen levels could explain the positive impact of alcohol intake on LUTS. In contrast, the negative effect could be explained by an increased sympathetic tone activity [31]. Therefore, we hypothesize that their low androgen levels might contribute to the favourable impact of occasional drinking on LUTS prevalence in women. However, we do not have data on diuresis, androgen levels or sympathetic tone activity in our cohort of patients.

Moreover, it is conceivable that the type of alcoholic beverage might have a different influence on the prevalence of LUTS in alcoholic drinkers. However, in this study, we did not evaluate whether various alcoholic beverages had distinct effects on the prevalence of LUTS. Finally, Suh et al. [32] showed that the protective effect of low alcohol consumption becomes much more attenuated when the serum concentration of high-density lipoprotein (HDL) is included as a confounding factor in the analyses. This should be considered in interpreting our findings because our study did not assess HDL serum levels.

The literature on LUTS in patients with IBD has not been pervasive. Yumura et al. [33], in a male sample of Japanese IBD patients, retrospectively examined the frequency of urogenital complications. They observed that out of 75% of patients with UC, 17.3% had LUTS. However, this study focused more on urologic complications (i.e., fistulas, hydronephrosis, and urolithiasis). To our knowledge, our study is the only one conducted on a large sample of well-standardised questionnaires assessing LUTS.

Although there were no marked differences between CD and UC patients, there was a specific difference in chronic prostatitis-like symptoms percentage between CD and UC (21.3 % vs 29.2%, respectively). Such evidence reinforces the need to rule out, in such patients, the presence of real chronic prostatitis, recognised as a risk factor for prostate cancer [34]. Evidence from a systematic review points to the fact that patients with UC appear to have a higher risk of developing prostate cancer (and should therefore undergo an earlier screening for prostate cancer), while the data in patients with CD are less definitive [35]. Accordingly, our data confirm the need to examine male patients with IBD for prostate cancer risk [36], and we postulate that non-invasive questionnaires could be a complementary tool in identifying which subgroups of IBD patients deserve to be addressed in a urological setting and screened earlier. The use of non-invasive questionnaires addressing urogenital disorders has already been applied in the gastroenterological environment [37].

Our study has some limitations. First, it is a cross-sectional, non-longitudinal study and therefore does not have a randomized controlled design toward other diagnostic tools. Moreover, we did not have detailed urological evaluations in patients with altered scores. Consequently, we cannot reach conclusions on the sensitivity, specificity, and negative and positive predictive value of the questionnaire score to predict urological diseases in our clinical setting of IBD patients.

Our data suggest that IBD patients frequently complain of LUTS as assessed through validated questionnaires. Older female IBD patients have worse filling symptoms, whereas male UC patients with active proctitis experience more frequently severe LUTS than those in remission. Finally, UC patients have a higher prevalence of chronic prostatitis-like symptoms than those with CD, possibly through the mechanism of cross-organ sensitization.

Author contributions

Study concept and design: LR, RP, DA, AGG, and MR; Acquisition of data: LR, RP, DA, AGG, AM, KP, NDG, AS, GP, FC, BB, AC, AF, CM, LS, CS, MDS, MR, and LN; Formal analysis: LR, RP, and DA; Interpretation of data: LR, RP, DA, AGG, AM, KP, NDG, AS, GP, FC, BB, AC, AF, CM, LS, CS, MDS, MR, and LN; Drafting of the manuscript: LR, RP, DA, AGG, and MR. All authors revised the manuscript for important intellectual content.

Conflict of interest

The authors declare that they have no conflicts of interest to disclose.

Data availability

The data providing the results of this study are entirely derivable from what is written in this manuscript. Other information can be asked to the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2023.10.010.

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