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Short communication

Fatigue in inflammatory bowel disease beyond intestinal inflammation: A cross-sectional study

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ABSTRACT

Background and aims: Fatigue is one of the most common and burdensome extraintestinal manifestations of inflammatory bowel disease (IBD) with a multifactorial aetiology that may extend beyond inflammatory activity. This study aimed to clarify the relative contribution of biological, psychological and central sensitization-related factors to fatigue in outpatients with IBD.

Methods: A cross-sectional study was conducted in a sample of 106 adult consecutive outpatients with IBD. Participants completed questionnaires assessing fatigue, central sensitization, depressive and anxiety symptoms. Laboratory data including fecal calprotectin (FC), C-reactive protein (CRP), and hemoglobin (Hb) levels were retrieved from medical records. A hierarchical regression analysis assessed the contribution of biological markers (Block 1) and psychological and central sensitization-related symptoms (Block 2) to fatigue severity.

Results: Clinically significant fatigue was present in 42.5% of patients. Biological markers explained a small, non-significant proportion of variance in fatigue severity. In the full model, central sensitization-related symptoms ($\beta = 0.54$, $p < .001$) were the strongest independent correlates of fatigue, followed by depressive symptoms ($\beta = 0.30$, $p = .006$) and FC ($\beta = 0.26$, $p = .001$). Anxiety, CRP, and hemoglobin were not independently associated with fatigue. The full model explained 55.5% of the variance in fatigue severity. In a sensitivity analysis removing fatigue-related items from the psychological scales, central sensitization-related symptoms and FC remained independently associated with fatigue, whereas depressive symptoms did not.

Discussion: Although intestinal inflammation contributed independently, fatigue was more closely related to central sensitization-related symptoms than to depressive symptoms, inflammatory or hematological markers. These findings support a multidimensional assessment of fatigue, extending beyond inflammation-focused care toward an integrated, multidisciplinary approach.

1. Introduction

Inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders of the gastrointestinal tract characterized by alternating periods of active inflammation and remission [1]. Beyond intestinal symptoms, IBD patients frequently report extraintestinal manifestations, including fatigue [2]. The potential causes of fatigue in IBD involve a complex interplay of factors [3], with growing evidence on an association with depression, both in active disease and in remission [4,5]. Another mechanism that may account for fatigue is central sensitization (CS), characterized by heightened central nervous system excitability. CS has been associated with IBD and IBS symptom severity, depression, and a broader range of persistent somatic symptoms [6,7]. In non-IBD populations, CS has been shown to predict fatigue severity independently of mood disorders [8]. No study has examined the relative contribution of CS-related symptoms, alongside psychological factors and biomarkers, to fatigue severity in IBD. The present study therefore addressed this gap, hypothesizing that psychological and CS-related variables would account for a substantial proportion of variance in fatigue severity beyond inflammation and anemia.

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2. Material and methods

2.1. Study design and participants

In this cross-sectional study, consecutive outpatients were recruited at the G.I. unit of San Salvatore Hospital, L'Aquila, Italy, between July 2025 and May 2026. Inclusion criteria: a) Confirmed diagnosis of IBD based on clinical, endoscopic, histological and radiological criteria; b) Age 18–75 years; c) Fluency in Italian; d) Signed informed consent. Exclusion criteria: a) Outdated laboratory data (over 30 days before/after recruitment); b) Incomplete psychological assessment. Data were collected through medical record review and self-report questionnaires. Ethical Committee Approval was obtained from the CEtRA Abruzzo Region (IT) (Protocol ID 228/2025).

2.2. Measures

2.2.1. Demographics and clinical data

Demographic and clinical data were collected from medical records. Variables included age (years), sex (male or female), disease type (CD or UC), and disease duration (months). Smoking habit (yes/no), physical activity (yes/no) were also collected.

2.2.2. Laboratory parameters

Fecal calprotectin (FC) was used as a marker of intestinal inflammation, (≥200 mg/kg) [9]. C-reactive protein (CRP) as a marker of systemic inflammation, (≥0.5 mg/dl) [10]. Finally, hemoglobin (Hb) as a marker of anemia (male: <13 g/dl; female: <12 g/dl) [11].

2.2.3. Psychological assessments

Four questionnaires were administered. Fatigue severity was assessed using the Fatigue Severity Scale (FSS) [12], with higher total scores indicating greater severity and a cutoff of ≥36 defining clinically significant fatigue. Depressive, anxiety and CS-related symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9) [13], the Generalized Anxiety Disorder-7 (GAD-7) [14], and the Central Sensitization Inventory (CSI) [15], respectively.

2.2.4. Statistical analysis

Patient characteristics were summarized for the whole sample and by fatigue status. Symmetric continuous variables (age, Hb) were reported as mean (SD) and compared with Student's or Welch's *t*-test; non-normal continuous variables (disease duration, FC, CRP, PHQ-9, GAD-7, CSI) as median (IQR) and compared with Mann-Whitney *U* test; categorical variables as frequencies and percentages and compared with chi-square test. Bivariate correlations were calculated with Spearman's rank correlation. Given their high skewness, FC and CRP were $\log_{10}$-transformed prior to the hierarchical regression [16,17]. The regression examined the incremental contribution of psychological and CS-related variables to fatigue severity beyond objective patient characteristics. Block 1 included age, disease duration, Hb, FC $\log_{10}$, CRP $\log_{10}$; Block 2 included PHQ-9, GAD-7, and CSI. A sensitivity analysis repeated the regression after removing PHQ-9 and CSI items overlapping with the FSS. Assumptions were verified with Shapiro-Wilk test, Breusch-Pagan test, Variance Inflation Factor (VIF), and Cook's distance. A priori power analysis (GPower 3.1.9.6) indicated that at least 77 participants were required to detect a small-to-moderate effect ($f^2 = 0.15$). All analyses were performed using Jamovi (version 2.7.9.0), with significance set at $p < .05$.

3. Results

Of 116 screened patients, 9 were excluded for missing or outdated laboratory data, and 1 for incomplete psychological assessment. The final sample included 106 patients (50.9% female; mean age 47.6 years). UC was the most frequent diagnosis (57.5%). At enrollment, 86 patients (81.1%) were on advanced therapies (biologics or small molecules) and 20 (18.9%) were on 5-aminosalicylic acid (5-ASA), while no patient was receiving systemic corticosteroids. A minority of patients showed active intestinal inflammation (32.1%), elevated systemic inflammation (25.5%), or anemia (17.9%). Overall, 45 patients (42.5%) were fatigued, of whom 66.7% had no active intestinal inflammation (See Table 1).

FC and CRP showed highly skewed distributions (1.73 and 3.60), which $\log_{10}$-transformation substantially reduced (−0.03 and 0.71). Psychological and CS-related variables correlated with fatigue severity, specifically CSI ($\rho = 0.690$, $p < .001$), PHQ-9 ($\rho = 0.597$, $p < .001$), and GAD-7 ($\rho = 0.426$, $p < .001$). Biological and demographic variables did not show correlations with FSS scores (Supplementary Table 1). The hierarchical regression is presented in Table 2. All assumptions were satisfied in the final model, with all VIF values between 1.24 and 2.45, indicating no multicollinearity. Block 1 was not significantly associated with FSS scores, while Block 2 yielded a substantial increment, with the full model explaining 55.5% of variance ($R^2 = 0.555$). CSI scores showed the strongest association ($\beta = 0.538$), followed by PHQ-9 ($\beta = 0.298$) and FC $\log_{10}$ ($\beta = 0.263$), while age, disease duration, CRP $\log_{10}$, Hb, and anxiety were not significant. The sensitivity analysis showed that CSI

Table 1
Patient's characteristics.

Variable	Total *n* = 106	Fatigued *n* = 45	Non-fatigued *n* = 61	*p*-value
Sex, *n (%)*	Male = 52 (49.1%), Female = 54 (50.9%)	19 (42.2) 26 (57.8)	33 (54.1) 28 (45.9)	0.227
Age (years), *Mean (SD)*	47.6 (±15.8)	49.2 (±14.3)	46.4 (±16.8)	0.366
Disease type, *n (%)*	UC = 61 (57.5%), CD = 45 (42.5%)	23 (51.1) 22 (48.9)	38 (62.3) 23 (37.7)	0.250
Disease duration (months), *Median (IQR)*	100 (41.3–232)	104 (41.0–238)	100 (42.0–221)	0.865
Tobacco use, *n (%)*	Yes = 36 (34%), No = 70 (66%)	18 (40.0) 27 (60.0)	18 (29.5) 43 (70.5)	0.260
Physical activity, *n (%)*	Yes = 34 (32.1%), No = 72 (67.9%)	9 (20.0) 36 (80.0)	25 (41.0) 36 (59.0)	**0.022**
Fecal calprotectin (mg/kg), *Median (IQR)*	75.5 (19.3–288)	107 (40.0–346)	47.0 (15.0–268)	0.148
Intestinal inflammation (FC ≥200 mg/kg) *n (%)*	Yes = 34 (32.1%), No = 72 (67.9%)	15 (33.3) 30 (66.7)	19 (31.1) 42 (68.9)	0.812
C-reactive protein (mg/dl), *Median (IQR)*	0.18 (0.07–0.48)	0.16 (0.06–0.51)	0.18 (0.07–0.43)	0.858
Systemic inflammation (CRP ≥0.5 mg/dl), *n (%)*	Yes = 27 (25.5%), No = 79 (74.5%)	13 (28.9) 32 (71.1)	14 (23.0) 47 (77.0)	0.488
Hemoglobin (g/dl), *Mean (SD)*	13.8 (±1.55)	13.7 (±1.55)	13.8 (±1.56)	0.731
Anemia (Male <13 g/dl / Female <12 g/dl) *n (%)*	Yes = 19 (17.9%), No = 87 (82.1%)	10 (22.2) 35 (77.8)	9 (14.8) 52 (85.2)	0.322
PHQ-9 score, *Median (IQR)*	6.00 (3.0–9.0)	7.0 (5.0–11.0)	3.0 (2.0–7.0)	**<0.001**
GAD-7 score, *Median (IQR)*	5.00 (3.0–10.0)	8.0 (5.0–12.0)	5.0 (2.0–7.0)	**0.002**
CSI score, *Median (IQR)*	29.0 (19.3–43.0)	43.0 (34.0–52.0)	21.0 (14.0–29.0)	**<0.001**
FSS score, *Median (IQR)*	29.0 (16.3–44.8)	45.0 (41.0–53.0)	18.0 (11.0–26.0)	n.a.

CD: Crohn's disease; CSI: Central sensitization inventory; FSS: Fatigue Severity Scale; GAD-7: Generalized anxiety disorders – 7; PHQ-9: Patient health questionnaire – 9; UC: ulcerative colitis.

Table 2
Hierarchical linear regression predicting FSS score.

Predictor	B	SE	β	95% CI	*p*-value
Block 1					
Intercept	26.35	17.29		[−7.95, 60.65]	0.131
Age	0.110	0.118	0.106	[−0.124, 0.343]	0.354
Disease duration	−0.008	0.014	−0.069	[−0.036, 0.019]	0.550
FC $\log_{10}$	5.041	2.554	0.220	[−0.026, 10.107]	0.051
CRP $\log_{10}$	−4.431	3.061	−0.162	[−10.503, 1.641]	0.151
Hemoglobin	−0.828	1.109	−0.079	[−3.029, 1.372]	0.457
Block 2					
Intercept	−13.87	12.823		[−39.320, 11.578]	0.282
Age	0.013	0.083	0.013	[−0.151, 0.178]	0.871
Disease duration	0.004	0.010	0.033	[−0.016, 0.024]	0.688
FC $\log_{10}$	6.005	1.789	**0.263**	[2.456, 9.555]	**0.001**
CRP $\log_{10}$	−3.495	2.162	−0.128	[−7.785, 0.795]	0.109
Hemoglobin	0.556	0.793	0.053	[−1.017, 2.130]	0.484
PHQ-9 score	1.104	0.393	**0.298**	[0.324, 1.883]	**0.006**
GAD-7 score	−0.214	0.327	−0.064	[−0.863, 0.434]	0.513
CSI score	0.548	0.092	**0.538**	[0.366, 0.730]	**<0.001**

Model Fit		
	Block 1	Block 2
R^2	0.059	0.555
Adjusted R^2	0.012	0.518
F	1.26	15.12***
ΔR^2	–	0.496***
$\Delta F(3, 97)$	–	36.0***

CRP: C-reactive protein; CSI: Central sensitization inventory; FC: Fecal calprotectin; FSS: Fatigue Severity Scale; GAD-7: Generalized anxiety disorders – 7; PHQ-9: Patient health questionnaire – 9.
*** $p < .001$.

scores ($\beta = 0.303$, $p = .004$) and FC $\log_{10}$ ($\beta = 0.293$, $p = .002$) remained independently associated with fatigue severity, whereas PHQ-9 scores were no longer significant ($\beta = 0.228$, $p = .083$) (Supplementary Table 2).

4. Discussion

The study examined the relative contribution of biological, psychological, and CS-related variables to fatigue severity in outpatients with IBD, yielding three findings. First, fatigue was highly prevalent in IBD. Second, CS-related symptoms showed the strongest independent association with fatigue severity, followed by depressive symptoms. Third, FC showed a modest association. Prevalence of fatigue was 42.5%, in line with prior studies [5]. The use of laboratory data allowed a more accurate assessment of disease activity than the symptom-based indices [5,18]. Entered as Block 1, biological markers explained only a small and non-significant proportion of variance. Specifically, CRP was not associated with fatigue severity. FC did not differ between fatigued and non-fatigued patients but reached significance in the full regression model and was confirmed in the sensitivity analysis. This can be explained by two features of the regression. First, fatigue was treated as a continuous measure, whereas the group comparison dichotomized it, reducing the power to detect differences. Second, the regression estimated the contribution of FC independently of psychological and CS-related symptoms. This suggests that intestinal inflammatory activity was associated with the severity of fatigue rather than with its presence, since fatigue was equally prevalent in patients with and without active inflammation. Hb was not associated with fatigue severity, in line with previous research [19,20]. CS symptoms showed the strongest independent association with fatigue severity, in line with results from non-GI populations [8], supporting models proposing gut-brain axis dysfunctions as central in IBD-related fatigue [21]. This association was confirmed in the sensitivity analysis, although attenuated, indicating that it was not merely driven by content overlap. However, results should be interpreted with caution, as the CSI doesn't directly assess the neurophysiological mechanisms of CS [6,22], and its scores should be regarded as a symptom profile that may reflect CS-related processes [23]. Depressive symptoms were independently associated with fatigue severity in the primary model, consistent with previous evidence in IBD [24–26]. However, this association should be interpreted with caution, as it did not persist in the sensitivity analysis once items overlapping with the FSS were removed, indicating that it was partly driven by content overlap. This does not exclude a genuine link between depression and fatigue, which may reflect their frequent coexistence and a possible shared biological substrate [19,21]. Although anxiety has been reported as a correlate of fatigue in IBD, it did not show an independent association in our model [25,27]. Several limitations should be acknowledged. First, the cross-sectional design precludes inference about the direction of these associations, which longitudinal studies would help clarify. Second, our findings on biological markers refer to a predominantly quiescent and non-anemic population, and their role may differ in patients with active disease or higher anemia prevalence. Third, the CSI includes 3 items overlapping in content with the FSS [28]. Although addressed through the sensitivity analysis, future studies incorporating quantitative sensory testing would help clarify the association [6]. Fourth, the self-report instruments are susceptible to recall and response bias, so future studies should integrate semi-structured interviews for a more in-depth assessment of psychological features. Fifth, additional potentially relevant factors, including sleep disturbance, pain, and IBS-like symptoms, were not assessed, and physical activity, despite differing between groups, was not included in the theory-driven model. These should be incorporated in future research. Finally, recruitment was limited to a single Italian tertiary IBD center, which may have selected more complex patients and inflated results. Race and ethnicity were not collected, as not available in medical records. Replication in other settings and more diverse populations is needed to improve generalizability of findings. These findings carry clinical implications. Since fatigue severity was more closely related to CS symptoms than to inflammatory markers or hemoglobin levels, relying on disease-activity indices alone risks overlooking fatigue, especially in patients in remission. While screening for depression is already recommended in IBD, our findings suggest that CS-related symptoms may represent a distinct and clinically relevant dimension of fatigue in IBD, warranting specific assessment. In conclusion, assessing this dimension, alongside inflammatory and psychological factors, would support a more accurate, multidimensional and multidisciplinary approach to fatigue, extending beyond inflammation-focused care.

CRediT authorship contribution statement

Alberto Caruso: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Angelo Viscido:** Writing – review & editing, Methodology, Conceptualization. **Dina Di Giacomo:** Writing – review & editing, Methodology. **Giovanni Latella:** Writing – review & editing, Methodology. **Federica Galli:** Writing – review & editing, Methodology, Conceptualization.

Ethics

Ethical Committee Approval was obtained from the CEtRA Abruzzo Region (IT) (Protocol n° 243,773/24; ID 228/2025).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2026.112960.

Data availability

Requests to access the data can be made by contacting the study team. Proposals to access the data must be reviewed and approved by the CEtRA Abruzzo Region (IT) Ethical Committee.

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