Irritable bowel syndrome is related to small fibre pathology in patients with fibromyalgia

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Abstract

Objective

Fibromyalgia (FM) is a multisystem disorder frequently associated with functional gastrointestinal disorders, particularly irritable bowel syndrome (IBS). Diet-related factors and gut microbiota alterations, key elements in IBS pathophysiology, may disrupt the gut-brain axis, promoting immune activation, altered pain processing, and peripheral nerve dysfunction, including small fibre involvement, which has been consistently reported in FM. The study investigated whether IBS symptom severity in FM is associated with clinical and psychological features and with neuropathological evidence of small fibre involvement.

Methods

In this monocentric cross-sectional observational study, 89 FM patients underwent clinical and psychological assessments. IBS severity was assessed using the IBS Severity Scoring System (IBS-SSS). Skin biopsy with quantification of intraepidermal nerve fibre density (IENFD) at proximal and distal sites was performed in 57 patients. Patients were classified into mild-moderate and severe IBS groups. Between-group differences were analysed using Mann-Whitney U and χ^2 tests. Spearman's rank correlation served to assess associations between IBS severity, clinical variables, and IENFD.

Results

Severe IBS symptoms were present in 47.1% of patients. Compared with patients with mild–moderate IBS, those with severe IBS showed higher widespread pain index (WPI) and symptom severity scale (SSS) scores, indicating greater fibromyalgia severity, as well as increased anxiety and depressive symptoms, reduced sleep duration, and greater functional impairment (all $p<0.05$ after FDR correction). Skin biopsy revealed a higher prevalence of reduced IENFD, particularly at proximal sites, in severe IBS patients. Notably, IBS-SSS scores were negatively correlated with proximal IENFD ($r=-0.34$, $p=0.01$).

Conclusion

IBS severity identifies a clinically more severe FM phenotype with small fibre pathology. These findings are consistent with a possible interaction between gastrointestinal dysfunction and peripheral nerve involvement in FM, although mechanistic pathways require further investigation.

Key words

fibromyalgia, irritable bowel syndrome, small fibre neuropathy, gut-brain axis, central sensitisation

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Introduction

Fibromyalgia (FM) is a chronic condition characterised by a wide range of symptoms, including widespread pain, fatigue, sleep disturbances, cognitive difficulties, and increased pain sensitivity (1). Although traditionally considered a disorder of central pain processing, accumulating evidence indicates that peripheral mechanisms may also contribute to its pathophysiology (2-7). In particular, several studies have reported abnormalities of small nerve fibres in a substantial proportion of patients with FM, involving both somatic and autonomic components (8-14). These fibres include both somatic fibres, involved in pain and thermal perception, and autonomic fibres, which regulate involuntary bodily functions such as cardiovascular activity, sweating, and gastrointestinal motility (15). A recent meta-analysis of more than 900 patients estimated that approximately 49% showed abnormalities consistent with small fibre pathology, as measured by skin biopsy or corneal confocal microscopy (16).

In addition to musculoskeletal pain, FM is frequently associated with a range of systemic and extra-musculoskeletal symptoms (17). Among these, functional gastrointestinal disorders (FGIDs) are particularly common. FGIDs are symptom-based conditions characterised by abdominal pain, altered bowel habits, bloating, nausea, or vomiting in the absence of identifiable structural abnormalities (18, 19). Within this group, irritable bowel syndrome (IBS), defined by recurrent abdominal pain and altered bowel habits (18, 20, 21), is one of the most frequently reported comorbidities in patients with FM.

The relationship between FM and IBS has been documented in several studies (22-25). In a cohort of patients with FM, approximately one-third met the diagnostic criteria for IBS, while among patients with IBS, the prevalence of FM was significantly higher than in healthy controls (22). Furthermore, IBS patients have an 80% increased risk of developing FM (25, 26). Clinically, this strong association underscores the importance of systematically assessing gastrointestinal symptoms in patients with FM, given their substantial impact on quality of life and disease burden (27, 28). Emerging evidence also suggests that modifiable lifestyle factors, particularly diet, may influence symptom severity and overall functioning in FM, reinforcing the need for integrated and individualised management strategies in patients with concomitant gastrointestinal symptoms (29).

The frequent co-occurrence of FM and IBS suggests shared pathophysiological mechanisms, including central sensitisation, altered nociceptive processing, and autonomic nervous system dysregulation (5, 30, 31). Emerging evidence further indicates that gut microbiota alterations may contribute to IBS pathophysiology through gut-brain interactions, immune modulation, and altered pain processing (32-34).

Despite growing evidence of the FM-IBS link, the mechanisms underlying the relationship between intestinal symptom severity and neurological, psychological and neuropathological manifestations in FM remain poorly understood (35, 36). In particular, it is unclear whether the severity of IBS symptoms reflects the extent of peripheral nerve involvement, including small fibre pathology. Addressing this gap may help clarify disease mechanisms and support more comprehensive treatment strategies, including dietary and microbiota-targeted interventions (37-39). The aim of the present study is therefore to evaluate, in a cohort of patients with FM, whether the presence and severity of IBS symptoms are associated with clinical variables and skin biopsy results as indicators of small fibre pathology involvement.

Materials and methods

Participants

This monocentric observational, cross-sectional study was conducted at the Neurophysiopathology of Pain Unit, University Hospital Policlinico of Bari. All participants, including women and men, were consecutive patients diagnosed with FM according to the American College of Rheumatology (ACR) criteria (40), who attended our centre for the first time between January 2022 and December 2024. Clinical data were

recorded in an electronic database (https://neuroclinic.thcs.it/login/login.html), authorised by our ethical committee. Patients signed informed consent for the inclusion of their clinical data in the electronic database and for the use of clinical and neurophysiological data for research purposes. Eligibility required a confirmed FM diagnosis and the ability to complete clinical and psychological evaluations. Exclusion criteria included major neurological disorders, uncontrolled psychiatric conditions, general medical conditions (except mild hypertension), unstable or newly initiated centrally acting treatments, and inability to participate in assessments. All patients were receiving stable symptomatic treatments for pain management, including gabapentinoids, antidepressants, and dietary supplements. The main comorbidities of the patients are detailed in Supplementary Table S1.

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the General Hospital of the Aldo Moro University of Bari (protocol no. 7173 2022 01 22). Informed consent was obtained from all subjects involved in the study.

Clinical assessment

Demographic information, including age and disease duration, was collected for all participants. Data on family medical history, past medical conditions, and current therapies were recorded. Clinical severity and symptom characteristics were evaluated using standardised assessment instruments (8, 41-43). Pain distribution was quantified using the Widespread Pain Index (WPI), a numeric rating scale widely used in chronic pain settings, while the Symptom Severity Scale (SSS), part of the ACR criteria for FM diagnosis (44), was used to quantify the burden of somatic symptoms. Pain intensity was assessed using the Numeric Rating Scale (NRS) (45). Neuropathic pain features were assessed using the Douleur Neuropathique 4 questions (DN4) (46), a validated 10-item instrument distinguishing neuropathic from non-neuropathic pain. The presence of associated symptoms, including fatigue, cognitive problems, and somatic complaints, was assessed. The IBS Severity Scoring System (IBS-SSS) (47) was used to assess the severity of gastrointestinal symptom burden and additional clinical data were collected, including bowel function (*i.e.* the number of daily evacuations reported by patients) and body mass index (BMI).

Psychological assessment and patient-reported outcomes

All participants underwent a structured psychological interview conducted by trained clinicians, supplemented by validated self-report questionnaires. Pain intensity and its interference with daily activities were assessed using the Brief Pain Inventory (BPI) (48). Anxiety and depressive symptoms were evaluated with the Self-Rating Anxiety Scale (SAS) and Self-Rating Depression Scale (SDS) (49, 50). Fatigue severity and characteristics were measured using the Multidimensional Assessment of Fatigue (MAF) (51). Sleep disturbances were assessed with the Medical Outcomes Study Sleep Scale (MOS-Sleep) (52). Functional impairment due to FM was measured using the Fibromyalgia Impact Questionnaire (FIQ) (53). Quality of life was evaluated with the Short Form-36 Health Survey (SF-36), analysing the Physical Health (PH) and Mental Health (MH) domains (54).

Skin biopsy

Consistent with established protocols (55-57), 3-mm punch samples were obtained from the proximal thigh and distal leg after local anaesthesia with 1% xylocaine. Tissue specimens were placed in a fixative solution containing 2% paraformaldehyde-lysine-periodate and kept at 4°C overnight, after which they were cryoprotected, cut into serial sections using a cryostat, and processed with immunohistochemistry employing a polyclonal antibody against protein gene product 9.5 (PGP 9.5; Ultraclone Ltd).

The intraepidermal nerve fibre density (IENFD) was determined from three non-adjacent central sections using bright-field microscopy and a dedicated stereology workstation (Olympus BX50, PlanApo oil objective 40×/NA 1.0). Biopsy-derived IENFD values were compared with age- and sex-adjusted normative reference data (58, 59), and classification into reduced proximal IENFD (P), reduced distal and proximal IENFD (D), or normal IENFD (N) was then performed according to validated diagnostic thresholds (60).

Statistical analysis

Descriptive statistics were used to characterise the study sample. Because no sex differences were observed in the preliminary analyses, men and women were analysed together in the subsequent analyses. Patients were classified into subgroups according to IBS-SSS scores (47). Specifically, mild, moderate and severe IBS cases were indicated by scores of 75 to 175, 175 to 300 and >300 respectively (47). The Mann-Whitney U-test and the Chi-square (χ^2) test were used to compare clinical and demographic variables between patients with mild-moderate *versus* severe IBS symptoms. Effect sizes were reported for group comparisons using the rank-biserial correlation (r) for Mann-Whitney U-tests and Cramér's V for χ^2 analyses. Spearman's rank correlation coefficients were calculated to assess potential associations between clinical scores and demographic measures, as well as between FM and IBS severity indices; correlation coefficients were interpreted as measures of effect magnitude. To reduce the risk of type I error due to multiple comparisons, false discovery rate (FDR) correction according to the Benjamini-Hochberg procedure was applied where appropriate. Data were expressed as mean values ± 1 standard deviation (SD). A p-value <0.05 was considered statistically significant. Data analysis was performed using STATISTICA® (TIBCO Software Inc., Palo Alto, California, USA).

Results

Whole sample characteristics

A total of 89 patients were enrolled in the study. The sample consisted predominantly of women (n=85, 95.5%), with four men (4.5%). The mean age ± SD was 51.3±11.1 years. The mean

disease duration was 12.2±9.78 years. Fifty out of 89 participants (56.2%) reported a family history of neurological disorders (Table I).

WPI scores were 14.01±3.4 in patients, indicating extensive pain distribution, while the mean SSS score was 6.99±2.12 (Table I), reflecting a substantial severity of associated symptoms such as fatigue, sleep disturbance, and cognitive complaints. Pain intensity, as measured by the NRS, was markedly elevated, with an average score of 9.40±1.36, consistent with severe ongoing pain. Furthermore, neuropathic pain features were prominent in this cohort, as assessed by the DN4 questionnaire, which yielded a mean score of 4.4±2.02, exceeding the commonly used threshold for neuropathic pain (Table I).

Regarding bowel movements, data from 58 patients showed that 7 (12.1%) reported no daily evacuations, 32 (55.2%) reported one per day, and 19 (32.7%) reported more than one per day. For BMI, 49 patients (55%) had values above the normal thresholds. Specifically, 40 patients (44.9%) were of normal weight, 28 (31.5%) were overweight, and 21 (23.6%) were obese. Other clinical scores are reported in Table I.

Overall, abdominal pain was reported by 53 of 89 patients (59.6%). The severity of IBS, assessed using the IBS-SSS, had a mean score of 285.17±128. Forty-seven patients (52.9%) had mild-to-moderate IBS symptoms, while 42 patients (47.1%) had severe IBS symptoms.

Table I. Demographic, clinical and neuropathological characteristics of patients with fibromyalgia (FM). Data are presented as mean ± standard deviation (SD) or number (percentage), as appropriate.

Demographic and clinical data	FM sample (89)
Sex (F:M)	85:4
Age	51.27 ± 11.1
Disease duration	12.2 ± 9.78
Familiarity [n (%)]	50 (56.2%)
WPI	14.01 ± 3.4
SSS	6.99 ± 2.12
NRS	9.4 ± 1.36
DN4	4.4 ± 2.02
Fatigue	
- None [n (%)]	1 (1.1)
- Mild [n (%)]	11 (12.4)
- Moderate [n (%)]	60 (67.4)
- Severe [n (%)]	17 (19.1)
Sleep problems	
- None [n (%)]	0 (0)
- Mild/intermittent [n (%)]	26 (33.3)
- Moderate [n (%)]	42 (53.8)
- Severe [n (%)]	10 (13.5)
Cognitive disorders	
- None [n (%)]	16 (18)
- Mild [n (%)]	37 (41.6)
- Moderate [n (%)]	31 (34.8)
- Severe [n (%)]	5 (5.6)
Reported somatic abdominal pain [n (%)]	53 (59.6)
IBS-SSS	285.17 ± 128
- Mild to moderate [n (%)]	47 (52.9%)
- Severe [n (%)]	42 (47.1%)
BMI	26.2 ± 5.25
- Normal [n (%)]	40 (44.9%)
- Overweight [n (%)]	28 (31.5%)
- Obesity [n (%)]	21 (23.6%)
Bowel movement 58	
- No daily evacuation [n (%)]	7 (12.1%)
- 1 evacuation per day [n (%)]	32 (55.2%)
- >1 evacuation per day [n (%)]	19 (32.7%)
BPI	
- Severity	7.19 ± 1.93
- Interference	6.08 ± 2.21
SAS	42.49 ± 9.57
SDS	43.57 ± 10.3
MAF	36.6 ± 10.8
MOS-Sleep	48.47 ± 7.14
FIQ	62.76 ± 15.6
SF-36	
- PH	33.75 ± 6.72
- MH	40.28 ± 8.63

WPI: Widespread Pain Index; SSS: Symptom Severity Scale; NRS: Numeric Rating Scale; DN4: Douleur Neuropathique en 4 Questions; IBS-SSS: Irritable Bowel Syndrome Severity Scoring System; BMI: Body Mass Index; BPI: Brief Pain Inventory; SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale; MAF: Multidimensional Assessment of Fatigue; MOS-Sleep: Medical Outcomes Study Sleep Scale; FIQ: Fibromyalgia Impact Questionnaire; SF-36 PH: Short Form-36 Physical Health score; SF-36 MH: Short Form-36 Mental Health score.

Subgroup analysis - IBS symptoms and clinical variables

Age and disease duration did not differ between mild-to-moderate IBS and severe IBS subgroups (p=0.81 and 0.24, respectively) (Table II). The occurrence of a positive family history did not differ between subgroups (χ^2=0.03, df=1, p=0.86).

Patients with severe IBS reported higher WPI (p=0.001, FDR-adjusted p=0.033) and greater symptom severity as expressed by the SSS scores (p=0.007, FDR-adjusted p=0.030) compared to patients with mild-to-moderate IBS, with both variables showing moderate effect sizes (r=0.31 and r=0.33, respectively) (Table II).

Patients with severe IBS also showed higher anxiety (SAS) and depressive symptoms (SDS) than those with mild-to-moderate IBS, both with moderate effect sizes (p<0.001, FDR-adjusted p=0.009, r=0.42, and p=0.001, FDR-adjusted p=0.033, r=0.31, respectively). Sleep duration was significantly reduced in the severe IBS group (MOS hours of sleep, p=0.002, FDR-adjusted p=0.012, r= -0.37, moderate effect size), whereas the difference in overall sleep quality (MOS total score, p=0.041, r= -0.25) did not remain significant after FDR correction (FDR-adjusted p=0.088). The functional impact of fibromyalgia was higher in patients with severe IBS compared to those with

Table II. Statistical comparison of demographic and clinical characteristics between patients with fibromyalgia (FM) and mild-moderate or severe irritable bowel syndrome (IBS), classified according to IBS Severity Scoring System (IBS-SSS) scores.

Demographic and clinical data	*p*	FDR-adjusted p	r
Age	0.815	0.863	0.02
Disease duration	0.245	0.340	0.14
WPI	**0.010**	**0.033**	**0.31**
SSS	**0.007**	**0.030**	**0.33**
DN4	0.377	0.509	-0.10
Proximal site IENFD	**0.003**	**0.018**	**-0.45**
Distal site IENFD	0.522	0.626	-0.12
BPI Severity	0.227	0.340	0.15
BPI Interference	0.084	0.137	0.21
SAS	**<.001**	**0.009**	0.42
SDS	**0.011**	**0.033**	**0.31**
MAF	0.080	0.137	0.21
MOS	0.041	0.088	-0.25
Hours of sleep	**0.002**	**0.012**	**-0.37**
FIQ	**0.001**	**0.009**	**0.40**
NRS	0.803	0.863	-0.01
SF-36 PH	0.738	0.831	-0.05
SF-36 MH	0.638	0.766	-0.04

p values refer to unadjusted between-group comparisons, whereas FDR-adjusted *p* values were calculated using the Benjamini-Hochberg false discovery rate correction for multiple comparisons. r indicates the rank-biserial correlation effect size for Mann-Whitney U-test comparisons. Values shown in bold indicate results that remained statistically significant after FDR correction.
WPI: Widespread Pain Index; SSS: Symptom Severity Scale; DN4: Douleur Neuropathique en 4 Questions; BPI: Brief Pain Inventory; SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale; MAF: Multidimensional Assessment of Fatigue; MOS-Sleep: Medical Outcomes Study Sleep Scale; FIQ: Fibromyalgia Impact Questionnaire; NRS: Numeric Rating Scale; SF-36 PH: Short Form-36 Physical Health score; SF-36 MH: Short Form-36 Mental Health score.

milder IBS symptoms (FIQ, p=0.001, FDR-adjusted p=0.009, r=0.40, moderate effect size) (Table II). Finally, fatigue (p=0.08) and the occurrence of cognitive disturbances (χ^2=1.67, df=4, p=0.79) did not differ significantly between groups. Overall, severe IBS identified a subgroup of FM patients with greater symptom burden and functional impairment.

Skin biopsy

Skin biopsy was performed in 57 patients (Fig. 1). The mean IENFD was 11.15±3.50 fibres/mm at the proximal site and 8.82±3.42 fibres/mm at the distal site (Table III). In details, 16 patients (28.1%) showed normal IENFD, 34 (59.64%) exhibited proximal reduced IENFD, and 7 (12.3%) had combined proximal-distal reduced IENFD (Table III). Notably, none of the enrolled patients had a reduced distal IENFD only.

Subgroup analysis - IBS symptoms and skin biopsy

Statistical analysis revealed significant differences in skin biopsy results between patients across subgroups (χ^2=15.4, df=2, p<0.001, FDR-adjusted p=0.009, Cramér's V=0.52, indicating a large effect size). Among patients with mild-to-moderate IBS severity, 14 of 27 patients (51.9%) had normal IENFD at both proximal and distal sites, 12 patients (44.4%) showed proximal fibre reduction, and only 1 patient (3.7%)

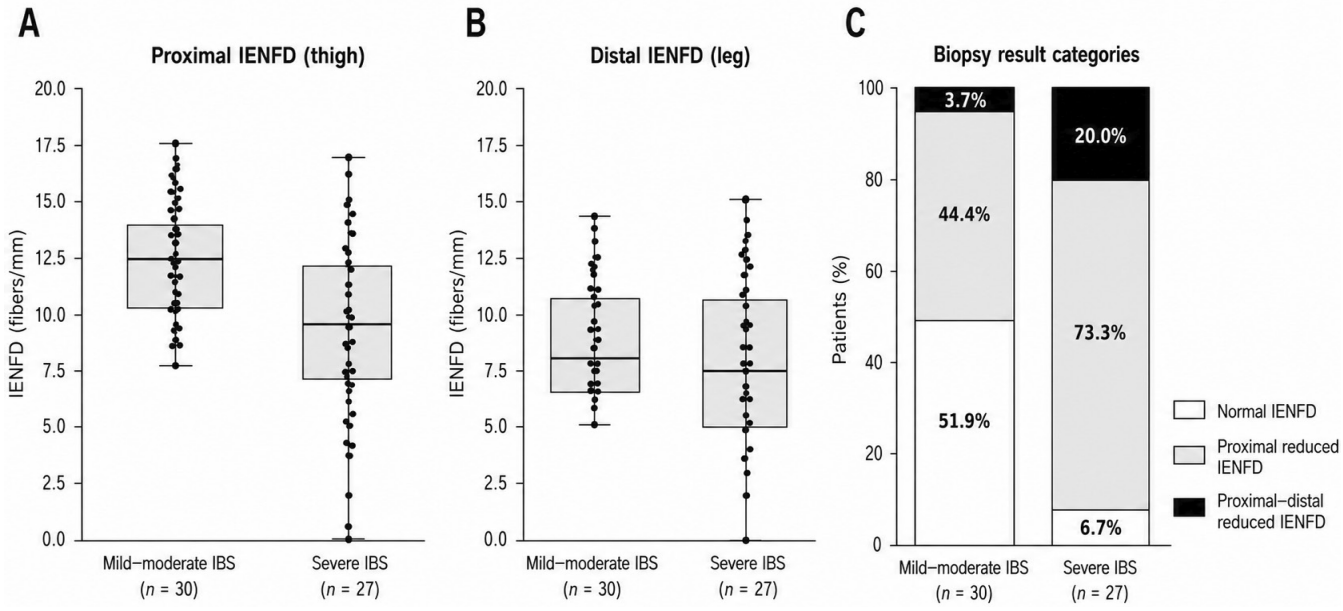


Fig. 1. Intraepidermal nerve fibre density (IENFD) according to irritable bowel syndrome (IBS) severity in patients with fibromyalgia (FM). (**A**) Box-and-whisker plot of proximal (thigh) IENFD (fibres/mm) in patients with mild–moderate and severe IBS. (**B**) Box-and-whisker plot of distal (leg) IENFD (fibres/mm) according to IBS severity. Individual data points are superimposed. Boxes represent the median and interquartile range (IQR), while whiskers indicate 1.5×IQR. (C) Distribution of skin biopsy categories according to IBS severity. White bars indicate normal IENFD, grey bars indicate reduced proximal IENFD with preserved distal values, and black bars indicate reduced IENFD at both proximal and distal sites. Percentages are calculated within each IBS severity group. IBS severity was classified according to the IBS Severity Scoring System (IBS-SSS).

Table III. Skin biopsy findings in patients with fibromyalgia (FM). Data are presented as mean ± standard deviation (SD) or number (percentage), as appropriate.

Skin biopsy results	FM sample (57)
IENFD	
- Proximal site	11.16 ± 3.50
- Distal site	8.82 ± 3.42
IENFD categories	
- Normal [n (%)]	16 (28.1%)
- Proximal reduced [n (%)]	34 (59.64%)
- Proximal-distal reduced [n (%)]	7 (12.3%)

IENFD: Intraepidermal Nerve Fiber Density (fibres/mm). Proximal-distal reduced indicates reduced IENFD at both proximal and distal sites.

presented with combined proximal-distal small fibre involvement (Fig. 1). In the severe IBS group, only 2 patients (6.7%) had normal IENFD at both proximal and distal sites, whereas 22 patients (73.3%) showed proximal alterations, and 6 patients (20.0%) displayed combined proximal-distal small fibre changes (Fig. 1). *Post-hoc* analyses based on standardised residuals (SR) indicated that patients with severe IBS had a significantly higher probability of proximal IENFD reduction (SR=2.22) and a significantly lower probability of normal biopsy findings (SR= -3.79) compared with patients with mild-to-moderate IBS. In contrast, the probability of combined proximal-distal small fibre alterations did not differ significantly between groups (SR=1.87 and -1.87, respectively). These findings were further supported by the comparison of raw IENFD values between patients with mild-to-moderate and severe IBS. Specifically, patients with severe IBS showed significantly lower proximal IENFD values (p=0.003, FDR-adjusted p=0.018, r=–0.45, moderate-to-large effect size), whereas distal IENFD values did not significantly differ between groups (p=0.522, r= -0.12) (Table II).

Correlation analysis

IBS-SSS scores were significantly correlated with WPI (r=0.22, p=0.039), SSS (r=0.25, p=0.018), SAS (r=0.4, p<0.001), SDS (r=0.27, p=0.01), and FIQ scores (r=0.39, p=0.003). A negative correlation was observed with MOS-hours of sleep (r= -0.29, p=0.005) (Fig. 2). Notably, a significant negative correlation was also found between IBS-SSS scores and IENFD at the proximal site (r= -0.34, p=0.01), indicating a moderate association between gastrointestinal symptom severity and reduced small fibre density at the proximal site (Fig. 3), whereas no significant associations emerged between disease duration and either IBS-SSS scores (r=0.16, p=0.120) or proximal IENFD (r= -0.21, p=0.118). Moreover, to account for potential confounding by age, disease duration, BMI, psychological distress, sleep disturbances, and overall disease burden, a multivariable linear regression analysis was performed including age, disease duration, BMI, IBS-SSS, SAS, SDS, MOS hours of sleep, and FIQ scores as predictors of proximal IENFD. IBS symptom severity remained independently associated with reduced proximal IENFD (β= -0.01, p=0.023), whereas disease duration, anxiety, depressive symptoms, sleep disturbances, and disease burden were not significant predictors (all p>0.19).

Discussion

This study investigated the relationship between IBS symptoms and clinical, psychological and neuropathological features in patients with FM. Although the association between FM and IBS has been consistently reported, the mechanisms linking gastrointestinal symptom severity to the multisystem manifestations of FM remain incompletely understood (22-25). By integrating clinical phenotyping, validated psychological assessments, and objective measures of small fibre pathology, we explored whether IBS severity identifies a distinct clinical and biological phenotype within FM.

Our findings confirm that gastrointestinal symptoms, particularly IBS, are highly prevalent among patients with FM and are associated with a more severe disease burden. More than half of the sample reported abdominal pain and altered bowel habits, and nearly half of the patients who completed the IBS-SSS were classified as having severe IBS. This prevalence is consistent with previous epidemiological studies reporting a strong overlap between FM and functional gastrointestinal disorders, reinforcing the concept that IBS is one of the most frequent and clinically relevant comorbidities in FM (22-24). Beyond confirming the frequent coexistence of these conditions, our findings suggest that IBS severity identifies a distinct clinical and neuropathological phenotype within FM.

A key finding of this study is that greater IBS severity was associated with higher WPI and SSS scores, indicating more widespread pain and a greater overall symptom burden. These findings support the hypothesis that IBS severity is linked to a broader amplification of symptoms in FM. The coexistence of severe IBS and more extensive pain distribution is consistent with shared pathophysiological mechanisms, likely involving central sensitisation, whereby visceral and somatic pain may represent different manifestations of altered pain modulation (30, 31). In this context, visceral and somatic pain are not distinct entities but rather different manifestations of a common dysfunction in pain modulation. At the same time, the observed associations between IBS severity and anxiety, depression, sleep disturbances, and functional impairment may partly reflect a generalised severity phenotype of FM rather than a specific contribution of gastrointestinal symptoms alone.

Beyond pain, patients with severe IBS showed significantly higher levels of anxiety and depressive symptoms. This association highlights the close interplay between gastrointestinal symptoms and psychological distress in FM. Psychological factors influence symptom perception, pain modulation, and coping strategies, and their role is especially prominent in conditions involving the gut-brain axis (30). Anxiety and depression may exacerbate visceral

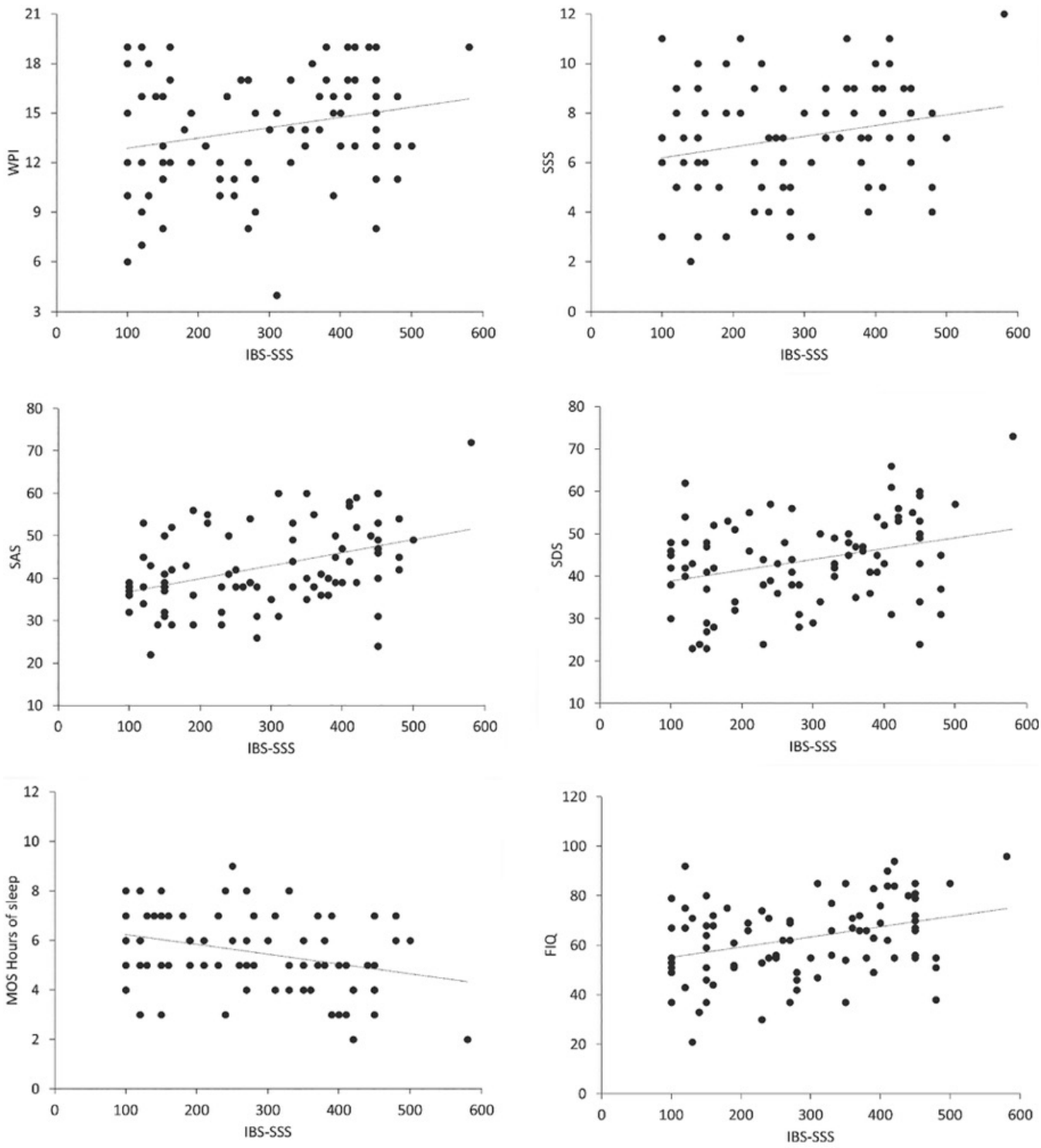


Fig. 2. Correlation between clinical data and Irritable Bowel Syndrome Severity Symptoms Scale (IBS-SSS) scores in patients with fibromyalgia (FM). WPI: Widespread Pain Index; SSS: Symptom Severity Scale; SAS: Self-Rating Anxiety Scale; SDS: Self-Rating Depression Scale; MOS-Sleep: Medical Outcomes Study Sleep Scale; FIQ: Fibromyalgia Impact Questionnaire.

hypersensitivity and alter gastrointestinal motility (61, 62), whereas chronic gastrointestinal symptoms may further reinforce psychological distress, creating a self-perpetuating cycle. The present data suggest that IBS severity may identify a subgroup of FM patients in whom this bidirectional interaction is particularly pronounced. Sleep disturbances and functional impairment were also more severe in patients with a higher IBS symptom burden. Reduced sleep duration and increased functional impact, as measured by the FIQ, indicate that severe IBS contributes substantially to overall disability. Sleep disruption is a well-established feature of FM and plays a crucial role in pain amplification, fatigue, and cognitive dysfunction (63, 64). Gastrointestinal symptoms such as abdominal pain,

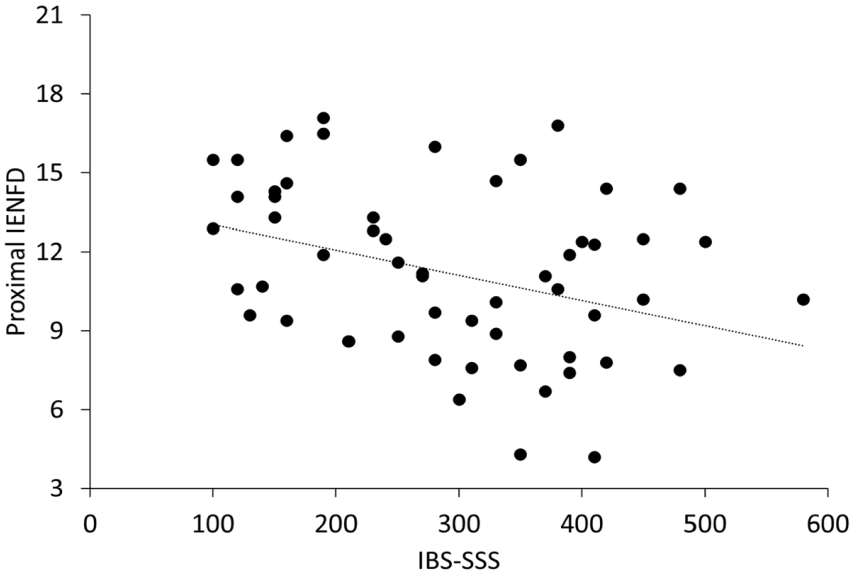


Fig. 3. Correlation between proximal site Intraepidermal Nerve Fiber Density (IENFD) at skin biopsy and Irritable Bowel Syndrome Severity Symptoms Scale (IBS-SSS) scores in patients with fibromyalgia (FM).

bloating, and altered bowel habits can further impair sleep quality, thereby worsening FM-related symptoms.

One of the most novel and clinically relevant aspects of this study is the association between IBS severity and objective markers of small fibre pathology. Skin biopsy showed that patients with severe IBS were significantly more likely to have reduced IENFD, particularly involving proximal fibres. The association remained significant after adjustment for potential confounding factors, including age, disease duration, BMI, psychological distress, sleep disturbances, and overall disease burden, supporting the robustness of this relationship. This finding provides biological support for a role of peripheral small fibre involvement in the clinical expression of both FM and IBS. Small fibre pathology has been increasingly recognised in FM, with previous studies reporting abnormalities in approximately half of patients (10, 11, 57, 65, 66), predominantly at proximal sites, supporting a non-length-dependent pattern of involvement. The present results extend this concept by suggesting that small fibre damage may be more pronounced in FM patients with severe gastrointestinal symptoms.

The involvement of small fibres provides a plausible mechanistic link between somatic and visceral symptoms, particularly given the significant correlation we found between reduced proximal IENFD and IBS symptoms. Small unmyelinated and thinly myelinated fibres play a critical role in nociception and autonomic regulation, including gastrointestinal function (67, 68). Damage or dysfunction of these fibres could result in altered visceral sensitivity, dysmotility, and impaired autonomic control, thereby contributing to IBS symptoms (15). At the same time, small fibre pathology may amplify somatic pain and sensory disturbances characteristic of FM. Emerging evidence further suggests that gut microbiota alterations may contribute to the overlap between FM and IBS through immune modulation, altered intestinal permeability, and gut-brain signalling (31, 69). Although these mechanisms may plausibly contribute to symptom amplification in FM, the present study did not directly assess microbiota composition or gut permeability; therefore, mechanistic interpretations should remain cautious.

Interestingly, while small fibre pathology was associated with IBS severity, not all patients with severe IBS showed distal fibre loss, suggesting heterogeneity in the pattern of nerve involvement. Proximal alterations were particularly frequent, which may reflect a non-length-dependent neuropathic process, consistent with immune-mediated or metabolic mechanisms rather than classical length-dependent neuropathy (66). This observation aligns with emerging evidence that small fibre involvement in FM may follow atypical patterns and may be driven by systemic factors such as inflammation, immune dysregulation, or neurotrophic imbalance.

The high prevalence of overweight and obesity observed in the cohort may also be relevant in this context. Metabolic factors may contribute to both FM and IBS, as obesity has been associated with low-grade inflammation, altered gut microbiota, and increased pain sensitivity. Although BMI was not directly associated with IBS severity in this study, metabolic status may act as a background modifier of both gut microbial ecology and peripheral nerve health. Future studies should further explore the interaction between metabolic factors, gut microbiota alterations, and small fibre pathology in FM.

Taken together, these findings support a multidimensional model of FM in which IBS severity reflects the convergence of central sensitisation, psychological distress, sleep disruption, and peripheral small fibre involvement. Rather than representing a simple comorbidity, IBS appears to identify a more severe FM phenotype. This perspective has important clinical implications, as it suggests that gastrointestinal symptoms should be systematically assessed in FM patients. Identifying this phenotype may help clinicians anticipate a higher risk of severe pain, psychological distress, functional impairment, and underlying small fibre pathology. Although our study did not directly assess gut microbiota or dietary interventions, these mechanisms remain a plausible interface between gastrointestinal dysfunction and systemic pain amplification. In practice, integrating evaluation of gastrointestinal symptoms into FM management may guide more comprehensive, multidisciplinary treatment approaches, including tailored pharmacologic strategies, lifestyle modifications, and supportive therapies targeting the gut-brain-nerve axis (19, 37, 70-72). In addition, our findings suggest that prominent gastrointestinal symptoms,

particularly severe IBS, may help clinicians identify a subgroup of patients with FM who could benefit from further evaluation of small fibre pathology, including skin biopsy.

Limitations

Several limitations should be acknowledged. First, the IBS-SSS was used to assess the severity of gastrointestinal symptom burden within the FM population rather than to establish a formal diagnosis of IBS according to Rome IV criteria (21). Second, although unstable or newly initiated centrally acting therapies were excluded, all patients were receiving stable symptomatic treatments for pain management, including gabapentinoids, antidepressants and dietary supplements. Thus, the potential influence of ongoing pharmacological treatments on symptom severity and clinical heterogeneity cannot be completely excluded. Although major comorbidities were recorded, lifestyle-related variables (*e.g.* diet, physical activity, sleep habits) were not systematically assessed and may have influenced both gastrointestinal symptoms and small fibre function. Third, the cross-sectional design precludes causal inferences regarding the relationship between IBS severity and small fibre pathology. Longitudinal studies are needed to determine whether gastrointestinal symptoms precede or follow the development of peripheral nerve abnormalities. Moreover, skin biopsy was available only in a subgroup of patients, potentially introducing selection bias and reducing statistical power for subgroup analyses. The absence of a healthy control group may further limit the interpretability of the observed prevalence of small fibre abnormalities. However, the primary aim of the study was to investigate whether IBS symptom severity identifies distinct clinical and neuropathological phenotypes within FM rather than to perform a case–control comparison. Accordingly, skin biopsy findings were interpreted according to validated age- and sex-adjusted normative reference values for IENFD. In addition, the monocentric design and the predominance of female participants may limit the generalisability of the findings, although this sex distribution is largely consistent with the epidemiology of fibromyalgia, which predominantly affects women. Furthermore, no direct microbiota, dietary, or gut permeability measures were collected. Therefore, gut microbiota-related mechanisms should be regarded as plausible explanatory hypotheses rather than processes directly demonstrated in the present study. Future multicentre studies including matched controls and biological markers of gut-brain interactions are needed to further clarify the relationship between gastrointestinal dysfunction, peripheral nerve involvement, and pain processing in FM. Finally, psychological and gastrointestinal symptom measures rely entirely on self-reported questionnaires. Given the known overlap between somatic symptoms, anxiety, and gastrointestinal symptom reporting in FM, reporting bias may contribute substantially to the observed correlations.

In conclusion, this study provides evidence that IBS severity in FM identifies a clinically more severe phenotype characterised by greater symptom burden and objective signs of small fibre pathology. These findings are consistent with the concept of FM as a multidimensional disorder potentially involving gut-brain-nerve interactions and underscore the importance of comprehensive assessment and personalised management strategies in patients with prominent gastrointestinal symptoms.

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