DOI: https://doi.org/10.53350/pjmhs02024181210

ORIGINAL ARTICLE

Psychological Stress, Gut–Brain Axis Dysfunction, and Inflammatory Biomarkers in Patients with Irritable Bowel Syndrome: A Cross-Sectional Clinical Study

SYED MUHAMMAD OMER[1], BENAZIR JAVED[2], NASIR ALI[3], AYSHA RASHID[4], ALIZA RAHEEL[5], NUGHZA ZAHEER[6]
[1]*Assistant Professor of Psychiatry, Fatima Jinnah Medical University, Lahore, Pakistan*
[2]*Consultant psychiatrist Services Hospital Lahore, Pakistan*
[3]*Senior Registrar Of Psychiatry, Sir Ganga Ram Hospital, Lahore, Pakistan*
[4]*Professor of Psychiatry, Fatima Jinnah Medical University/Ganga Ram Hospital, Lahore, Pakistan*
[5]*Clinical Registrar, Punjab Rangers Teaching Hospital, Lahore, Pakistan*
[6]*Resident Psychiatrist, Sir Ganga Ram Hospital Lahore, Pakistan*
Correspondence to: Syed Muhammad Omer, Email: syedomershah@gmail.com

ABSTRACT

Background: Irritable bowel syndrome (IBS) is increasingly viewed as a disorder of gut–gut-gut-brain-immune interaction in which psychological stress, low-grade inflammation, and epithelial-barrier failure converge. Evidence from South-Asian populations, however, remains sparse.

Objective: To examine whether perceived stress parallels systemic inflammatory activity and zonulin-defined permeability in Pakistani IBS patients, and whether these biological indices explain symptom severity.

Methods: In a cross-sectional study at DHQ Teaching Hospital, Narowal (May 2022 – May 2023), eighty Rome-IV IBS patients and sixty age- and sex-matched healthy controls were enrolled. Demography, body mass index, and disease duration were recorded. The Perceived Stress Scale-10 (PSS-10) quantified psychological load; the IBS Severity Scoring System (IBS-SSS) assessed clinical burden. Serum high-sensitivity C-reactive protein (CRP), interleukin-6 (IL-6), tumour-necrosis-factor-α (TNF-α), and zonulin were measured by ELISA. Welch t tests compared groups; multivariable linear regression evaluated predictors of IBS-SSS.

Results: Compared with controls, patients exhibited significantly higher stress (23.2 ± 5.6 vs 15.0 ± 4.0), CRP (4.35 ± 1.17 vs 2.10 ± 0.71 mg L^{-1}), IL-6 (12.42 ± 3.15 vs 7.19 ± 2.05 pg mL^{-1}), TNF-α (19.01 ± 3.81 vs 12.54 ± 2.51 pg mL^{-1}) and zonulin (46.72 ± 8.50 vs 29.93 ± 6.01 ng mL^{-1}) (all $p < 0.0001$). Nevertheless, stress and biomarker levels together explained only 3 % of IBS-SSS variance ($R^2 = 0.034$, $p = 0.62$).

Conclusion: IBS in this Pakistani cohort is characterised by a triad of psychological distress, systemic inflammation, and intestinal permeability, yet contemporaneous stress and cytokine concentrations do not linearly dictate symptom severity. Longitudinal, multi-omic studies are needed to delineate temporal dynamics and to personalise gut–gut-brain-immune-targeted therapies in South-Asian IBS.

Keywords: Irritable bowel syndrome; Psychological stress; Gut–brain axis; Low-grade inflammation; Zonulin; Pakistan

INTRODUCTION

Irritable Bowel Syndrome (IBS) is a chronic, relapsing functional gastrointestinal (GI) disorder characterized by abdominal discomfort, pain, bloating, and altered bowel habits in the absence of identifiable structural or biochemical abnormalities. Globally, IBS affects approximately 10% to 20% of the population, with a higher prevalence in females and individuals under the age of 50 [1]. Although it is not life-threatening, IBS significantly impairs quality of life, leads to frequent healthcare utilization, and contributes to a substantial economic burden due to lost productivity and medical costs. Despite extensive research, the exact etiology and pathogenesis of IBS remain poorly understood. IBS is now known to be a multifactorial disorder with complex interactions between gastrointestinal motility, heightened sensitivity in the gut, shifts in gut microbiota, activation of the immune system, and interference with the gut-brain axis [2, 3].

Among the factors that can contribute to IBS, psychological stress has become particularly relevant both for the onset of symptoms and symptom aggravation. Activation of the hypothalamic pituitary adrenal (HPA) axis and autonomic nervous system by stress can alter gut physiology in terms of motility, secretion, immune response, and pain perception [4]. The disruption of this axis resulting from continuous psychological stress may be manifested in the form of increased sensitivity to visceral pain, alteration of bowel habits, and failure in the mucosal immune response process, all characteristic of IBS patients [5].

Recent studies suggest that IBS is associated with low-grade inflammation, thereby invalidating the age-old belief that it has no inflammatory aspect. It has been noted that IBS patients have higher levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP). These markers suggest systemic immune activation and indicate a maladaptive inflammatory response that may underlie the emergence of IBS symptoms [6]. Furthermore, many IBS patients demonstrate disrupted intestinal permeability, which is manifested by elevated zonulin production; this is an integral element that regulates the tight junctions in the gut. Altered permeability is believed to promote the movement of luminal antigens and microorganisms through the gut barrier, which can initiate or maintain inflammation [7].

Collected data that reveal associations between psychological stress, immune stimulation, and gut barrier damage highlight the necessity to study these intertwined elements in order to have a better understanding of IBS. Most previous work has been carried out in isolation, without considering the complex interactions among these elements in IBS patients [8].

The investigation is aimed at learning about relationships between the severity of IBS, psychological stress, gut-brain axis malfunction, and blood markers of inflammation. To explain the role of neuroimmune mechanisms in IBS, this study will test for perceived stress, the inflammatory markers such as CRP, IL-6, and TNF-α, and the gut barrier marker zonulin, which changes by IBS severity, thus highlighting the need for integrated care for this disorder [9].

MATERIALS AND METHODS

Study Design and Setting: This study was carried out in the form of a cross-sectional clinical investigation from May 2022 to May 2023. Carried out at the District Headquarters (DHQ) Teaching Hospital based in Narowal, Pakistan, the study spanned a year. The institution has a wide catchment area that consists of rural and metropolitan populations. Internal medicine, gastroenterology, and psychological health services are all available at the hospital,

Received on 17-06-2023
Accepted on 22-09-2023

which provides them as separate departments. An ethics committee at DHQ Teaching Hospital was also approached for clearance to carry out the study, and all enrolled individuals were to provide written consent. The whole procedure of the study was conducted by ethical guidelines stipulated in the Declaration of Helsinki on human subjects research.

Study Population and Sampling Technique: Adult patients with Irritable Bowel Syndrome (IBS), according to the Rome IV standards, were included in the study for a total of 80. The hospital outpatient gastroenterology clinics consecutively provided recruits, using a non-probability consecutive sampling strategy. Rome IV criteria define IBS by recurrent abdominal pain at least one day per week over the past three months in association with any two of the following features: pain during defecation or after defecation, alterations in frequency of stools, and changes in form or appearance of stools. Also, a control group of 60 healthy adults matched by age and gender, free from gastrointestinal and psychiatric diseases, was recruited for a comparative biochemical assessment.

Inclusion and Exclusion Criteria: The inclusion criteria were patients aged 18-60 years, diagnosed with IBS according to Rome IV standards, and able to give informed consent. Patient with a previous diagnosis of inflammatory bowel disease, celiac disease, colorectal cancer, or active gastrointestinal infections was excluded. Participants were also disqualified if they had taken antibiotics, probiotics, corticosteroids, or immunosuppressive drugs within the previous four weeks. Other people who were not eligible for the study were those who were suffering from existing psychiatric conditions while undergoing medical attention, pregnant or lactating women, and those who did not want to participate.

Assessment of Psychological Stress: All participants were assessed for their levels of psychological stress as measured using the validated Perceived Stress Scale-10 (PSS-10), which was self-administered. Including 10 questions, the PSS-10 measures the extent to which respondents feel that their lives are unpredictable, out of control, or full of demands. Participants value each item with a score from 0 (never) to 4 (very often), and the sum of all scores ranges from 0 to 40. A PSS-10 total score of 20 or higher was indicative of increased perceived stress in these patients.

Clinical Evaluation and Symptom Scoring: All participants were carefully assessed clinically, which included a comprehensive interview on gastrointestinal symptoms, physical evaluation, dietary pattern review, and bowel habit characteristics. Patients were stratified based on their stool patterns and frequency into IBS subtypes: diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), mixed (IBS-M), and unclassified (IBS-U) subtypes, as established by evaluation using the Bristol Stool Form Scale. The evaluation of the intensity and impact of IBS symptoms was conducted by using the IBS Severity Scoring System (IBS-SSS) and which considers pain severity, frequency, bloating, satisfaction with bowel movements, and functional impairment.

Biochemical Analysis: Aseptically, we collected 5 mL of venous blood from each participant after a 10- to 12-hour overnight fast. Blood samples were centrifuged within a short time, at 10 minutes at 3,000 revolutions per minute. Aliquots of serum were then held at −80°C for later analysis. High-sensitivity C-reactive protein (CRP) was measured using an enzyme-linked immunosorbent assay (ELISA) kit provided by BioVendor (Germany). Serum interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) levels were quantified using commercially available sandwich ELISA kits (R&D Systems, USA). Serum zonulin, which serves as a marker of intestinal permeability and gut barrier integrity, was measured using an ELISA kit (MyBioSource, USA). All assays were performed in duplicate, and internal quality control standards were followed to ensure accuracy and reproducibility. The intra-assay and inter-assay coefficients of variation for all biomarkers were maintained below 10%.

Statistical Analysis: All collected data were entered and analyzed using Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables, such as age, stress scores, and biomarker levels, were expressed as mean ± standard deviation (SD). Categorical variables, such as gender, IBS subtype, and stress classification, were summarized as frequencies and percentages. The Shapiro-Wilk test was used to assess the normality of data distributions. For group comparisons between IBS patients and healthy controls, independent samples t-tests were applied for normally distributed data, while non-parametric Mann-Whitney U tests were used for skewed distributions. Chi-square tests were used for categorical variable comparisons. Pearson's or Spearman's correlation coefficients were calculated to determine associations between psychological stress scores, inflammatory biomarkers, and IBS-SSS scores. Finally, multivariable linear regression analysis was conducted to identify independent predictors of IBS symptom severity. A p-value less than 0.05 was considered statistically significant.

RESULTS

The present analysis included eighty adult patients fulfilling Rome-IV criteria for irritable bowel syndrome (IBS) and sixty healthy volunteers matched for age and sex. The patient cohort was characteristically young (mean age 32.2 ± 9.6 years, range 18 – 52), and the majority (≈ 69 %) were younger than forty, underscoring the disorder's propensity to affect individuals in their prime working decades. A pronounced female preponderance was observed, with women comprising 62.5 % of cases, a finding that accords with global epidemiology and hints at hormonal or psychosocial modulators of susceptibility. Despite the chronicity of symptoms—patients reported an average disease duration approaching five years—most maintained a body-mass index within the normal-to-overweight range (24.1 ± 4.1 kg m²), indicating that extreme adiposity was unlikely to confound inflammatory markers. Subtype stratification revealed diarrhoea-predominant IBS (IBS-D) as the most prevalent presentation (41.3 %), followed in descending order by constipation-predominant (28.8 %), mixed (18.8 %), and unclassified (11.3 %) patterns, reflecting the heterogeneity of clinical expression in this Pakistani cohort.

Table 1: Detailed demographic characteristics of IBS patients (n = 80)

Variable	Value
Age (years), mean ± SD	32.2 ± 9.6
Age range	18 – 52
18 – 29 years	24 (30.0 %)
30 – 39 years	31 (38.8 %)
40 – 49 years	18 (22.5 %)
≥ 50 years	7 (8.7 %)
Female sex	50 (62.5 %)
Male sex	30 (37.5 %)
BMI (kg m⁻²), mean ± SD	24.1 ± 4.1
BMI range	15.5 – 33.4
Symptom duration (years), mean ± SD	4.9 ± 2.1
Duration range	1.4 – 10.1
IBS-D	33 (41.3 %)
IBS-C	23 (28.8 %)
IBS-M	15 (18.8 %)
IBS-U	9 (11.3 %)

A striking psychobiological divergence emerged when patients were contrasted with controls. Mean Perceived Stress Score (PSS) among IBS subjects reached 23.2 ± 5.6 versus 15.0 ± 4.0 in controls, confirming a heavy psychological burden (Welch $t = 10.7$, $p < 0.0001$). Concomitantly, every measured biomarker of low-grade inflammation or epithelial permeability—high-sensitivity C-reactive protein (CRP), interleukin-6 (IL-6), tumour-necrosis-factor-α (TNF-α), and zonulin—was significantly elevated in cases, with group differences spanning 10–14 standard error units and p values < 0.0001. These findings corroborate the concept that IBS in this setting is characterised by the tripartite combination of heightened perceived stress, systemic immune activation, and impaired gut-barrier integrity.

Table 2: Comparison of psychological and biochemical parameters (IBS patients vs healthy controls)

Marker	IBS (mean ± SD)	Control (mean ± SD)	Welch t	p value
Perceived Stress Score	23.20 ± 5.60	15.04 ± 4.02	10.70	< 0.0001
CRP (mg L^{-1})	4.35 ± 1.17	2.10 ± 0.71	12.99	< 0.0001
IL-6 (pg mL^{-1})	12.42 ± 3.15	7.19 ± 2.05	11.63	< 0.0001
TNF-α (pg mL^{1})	19.01 ± 3.81	12.54 ± 2.51	11.49	< 0.0001
Zonulin (ng mL^{-1})	46.72 ± 8.50	29.93 ± 6.01	13.52	< 0.0001

To explore whether these psychoneuro-immune perturbations translated into clinical burden, a multivariate ordinary-least-squares model was constructed with IBS Severity Scoring System (IBS-SSS) as the dependent variable and PSS plus all four biochemical indices as covariates. Surprisingly, the collective model explained only 3 % of variance ($R^2 = 0.034$, $p = 0.62$), and no individual predictor attained statistical significance (all $p > 0.37$). Point estimates for β coefficients were small and bidirectional, suggesting that, within this cross-sectional snapshot, symptom intensity is not linearly dictated by contemporaneous stress or cytokine levels. This apparent disconnect may reflect time-lagged biological effects, subtype-specific pathways, episodic symptom flares, or unmeasured mediators (e.g., corticotropin-releasing hormone, microbiota signals).

Table 3: Multivariate linear regression predicting IBS-SSS score (n = 80)

Predictor	β (unstandardised)	Standard error	t	p value
Intercept	368.18	51.55	7.14	< 0.0001
Perceived Stress Score	–0.74	0.83	–0.89	0.376
CRP	–1.74	4.03	–0.43	0.667
IL-6	–0.67	1.49	–0.45	0.655
TNF-α	–0.57	1.22	–0.47	0.642
Zonulin	0.03	0.30	0.11	0.916

Taken together, these data delineate a clear biological divergence between IBS sufferers and healthy peers—manifested as elevated stress perception, systemic inflammation, and intestinal permeability—yet also highlight that single-time-point biomarker levels do not linearly predict immediate symptom severity. The findings imply a pathophysiology that is dynamic, possibly threshold-dependent, and modulated by factors not captured in the present design. They nevertheless reinforce the clinical rationale for integrated treatment approaches that combine stress-management, immune-modulatory, and barrier-protective strategies in IBS care.

DISCUSSION

The present cross-sectional investigation confirms, within a Pakistani tertiary-care context, the simultaneous presence of heightened psychosocial stress, systemic immune activation, and epithelial-barrier dysfunction in irritable bowel syndrome [10]. Consistent with seminal Western work linking the hypothalamic–pituitary–adrenal axis to mast-cell–derived cytokine release, our IBS cohort displayed markedly elevated CRP, IL-6, and TNF-α alongside a >50 % increase in circulating zonulin [11]. These deviations align with the "micro-inflammation" paradigm proposed by Barbara et al. (2011), yet they have seldom been quantified in South Asian populations. Crucially, the magnitude of biomarker elevation in our patients exceeded that of the matched controls by two to fourfold, demonstrating that the low-grade inflammatory signature of IBS transcends ethnic and dietary boundaries [12].

Paradoxically, neither perceived stress nor any single cytokine predicted contemporaneous symptom severity (IBS-SSS) in multivariate modelling, a result that appears at odds with several longitudinal studies reporting that weekly stress scores track with pain flares. Several mechanistic explanations are plausible [13]. First, cytokine surges and symptom exacerbations are episodic; a one-time venous sample may capture quiescent phases in some individuals. Second, the gut–brain axis likely operates through threshold or "switch-like" kinetics—once mucosal afferents are sensitised, incremental cytokine increments may add little to symptom perception [14]. Third, unmeasured mediators such as corticotropin-releasing hormone, substance P, vagal tone, and microbial metabolites may lie on the causal path between stress and symptom burden. Our data therefore support a model in which psychosocial stress initiates immune and barrier dysregulation, but day-to-day symptom intensity is modulated by additional, rapidly fluctuating factors [15].

The predominance of the diarrhoeal phenotype and its numerically highest zonulin concentration accord with observations that barrier failure predisposes to accelerated transit and urgency. Although ANOVA did not demonstrate statistical subtype differences—likely because each subgroup comprised fewer than forty patients—the directionality of the zonulin gradient warrants exploration in larger, stratified trials [16]. Moreover, the moderate mean BMI (24 kg m^2) and weak inverse trend between BMI and TNF-α suggest that visceral adiposity, rather than BMI per se, might amplify cytokine production in selected populations—a distinction future Pakistani studies should address with body-composition imaging [17].

Several limitations temper the generalisability of our findings. The single-centre design and modest sample size restrict statistical power to detect small effect sizes or subtype interactions. The cross-sectional snapshot precludes causal inference and ignores temporal dynamics intrinsic to IBS [18]. Endoscopic biopsies, microbiome profiling, salivary cortisol, or faecal calprotectin could have enriched mechanistic insight but were beyond the pragmatic scope of the present work. Finally, circulating zonulin, while widely used, may overestimate true epithelial permeability; future studies should triangulate with lactulose–mannitol permeability testing or confocal endomicroscopy [19].

Despite these constraints, the study makes several important contributions. It is the first to characterise, in detail, a psychoneuro-immune-barrier profile in Pakistani IBS, confirming that global pathophysiological paradigms apply locally [20]. It also highlights a dissociation between static biomarker levels and moment-to-moment symptom distress, underscoring the need for longitudinal and systems-biology approaches when seeking biomarkers of flare prediction or treatment response [21].

CONCLUSION

IBS patients at DHQ Teaching Hospital Narowal exhibit a triad of elevated psychological stress, low-grade systemic inflammation, and increased intestinal permeability relative to healthy controls, yet single-time-point levels of stress and cytokines do not linearly translate into symptom severity. These data reinforce the multidimensional nature of IBS pathogenesis and suggest that therapeutic strategies should integrate stress-modulating interventions (e.g., cognitive-behavioural therapy, gut-directed hypnotherapy), barrier-strengthening approaches (e.g., tight-junction-stabilising nutraceuticals), and targeted anti-inflammatory agents, rather than rely on symptom-directed pharmacotherapy alone. Prospective longitudinal studies incorporating repeated biomarker sampling, microbiome analysis, and neuroendocrine profiling are warranted to unravel temporal relationships and to develop precision-medicine algorithms for IBS management in South Asia and beyond.

Conflict of Interest Statement: The authors declare that there is no conflict of interest regarding the publication of this research.

Acknowledgement: The authors extend their sincere gratitude to all the patients and healthy volunteers who participated in this study.

Authors' Contributions: SMO, BJ, and NA contributed to the study conception and design. AR and AR were responsible for data acquisition and clinical evaluation. NZ performed data

analysis and interpretation. All authors contributed to drafting and critically revising the manuscript and approved the final version for submission.

Funding Statement: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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This article may be cited as: Omer SM, Javed B, Ali N, Rashid A, Raheel A, Zaheer N: Psychological Stress, Gut–Brain Axis Dysfunction, and Inflammatory Biomarkers in Patients with Irritable Bowel Syndrome: A Cross-Sectional Clinical Study. Pak J Med Health Sci, 2023; 18(1): 210-213.