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# Association Between Systemic Interleukin-1β Levels and Irritable Bowel Syndrome: A Systematic Review and Meta-Analysis

## IL-1β Levels and IBS

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**ABSTRACT:** **Background**: Abdominal pain or discomfort, inconsistent stools, and bloating are the hallmarks of irritable bowel syndrome (IBS), a functional bowel condition. Although interleukin-1β (IL-1β), a significant pro-inflammatory cytokine implicated in immunological activation and visceral hypersensitivity, has been thoroughly studied in IBS, published results are still conflicting.

**Aim**: To compare systemic IL-1β levels between patients with IBS and healthy controls

**Patients and Methods**: Using PubMed, Scopus, Cochrane, and Web of Science databases, a thorough literature search was carried out for articles published from inception to May 2026, with an emphasis on clinical studies comparing IBS patients with healthy controls. Pooled effect sizes and statistical significance were computed using meta-analytical techniques, and the methodological quality and risk of bias of the included observational studies were evaluated using the Newcastle–Ottawa Scale (NOS).

**Results**: The IBS group's serum IL-1β was noticeably higher than healthy control group's (MD= 0.77, 95% CI= 0.61:0.92, P value<0.001, I2=99) while a single study evaluating plasma IL-1β reported significantly lower levels in patients with IB.

**Conclusion**: Patients with IBS had considerably higher serum IL-1β levels than healthy controls, which may indicate a role for low-grade systemic immune activation in the pathophysiology of IBS. However, its current usefulness as a stand-alone biomarker is limited by the significant heterogeneity and contradictory plasma findings, which call for additional standardized research.

## INTRODUCTION

A common disorder that affects the gut and the brain, irritable bowel syndrome (IBS) is characterized by persistent discomfort in the abdomen and changes in bowel movements, which can include diarrhea, constipation, or a combination of both. Although IBS is not associated with the structural abnormalities typically seen in organic gastrointestinal diseases, it can substantially impair quality of life and increase healthcare burden [1].

IBS was traditionally considered a functional disorder related to altered intestinal motility, visceral hypersensitivity, psychological stress, and dysregulation of the gut–brain axis [2]. However, growing evidence suggests that biological abnormalities, including increased intestinal permeability, altered gut microbiota, neuroimmune dysfunction, and low-grade mucosal and systemic immune activation, may contribute to its pathophysiology. Inflammatory mediators may disrupt epithelial barrier integrity, influence gastrointestinal motility and secretion, and sensitize visceral afferent nerves, thereby contributing to abdominal pain and altered bowel habits. These mechanisms may be particularly relevant in postinfectious IBS but have also been reported in other IBS subtypes [3].

After inflammasome activation, active monocytes and macrophages create interleukin-1 beta (IL-1β), a powerful pro-inflammatory cytokine. It promotes inflammatory signaling, leukocyte recruitment, epithelial barrier dysfunction, and neuronal sensitization. Accordingly, excessive IL-1β activity may contribute to mucosal inflammation, visceral hypersensitivity, and altered gastrointestinal motility. Although some studies have reported increased IL-1β production, expression, or circulating levels in patients with IBS, findings remain inconsistent [4].

Differences in diagnostic criteria, IBS subtypes, participant characteristics, specimen types, laboratory assays, and sample-processing methods may explain the variability across studies. Moreover, IL-1β has been assessed in serum, plasma, whole blood, mucosal tissue, stool, and peripheral blood mononuclear cell cultures, limiting direct comparability. Consequently, a systematic review and meta-analysis were conducted with the objective of assessing the relationship between IBS and IL-1β levels by integrating the findings from research that measured IL-1β in individuals with IBS and in healthy controls.

## METHODS

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards were followed when conducting a systematic review.

Studies published from inception till May 2026 were included in the systematic review and meta-analysis as comparative observational studies. The PECO framework was used to organize this systematic review and meta-analysis. Population (P): Patients who are adults (>18 years old). IBS group exposure (E) and control group comparison (C). Result (O): Systemic interleukin-1β levels are linked to irritable bowel syndrome.

### Search strategy

Using the PubMed, Scopus, Cochrane, and Web of Science databases, a thorough literature search was carried out to find papers comparing the IBS group and control group that had been published from inception until May 2026. The search method employed the following phrase combination: (("irritable bowel syndrome" OR "IBS" OR "irritable colon" OR "spastic colon") AND ("Cytokine" OR "interleukin-1 beta" OR "interleukin 1 beta" OR "IL-1β" OR "IL1β" OR " biomarker") AND ("serum" OR "plasma" OR "blood" OR "circulating" OR "systemic"))

Preferred Reporting Items for Systematic Reviewers and Meta-Analyses (PRISMA) criteria were used in this systematic review.

**Inclusion Criteria:** Criteria for inclusion included the following: (a) Clinical studies comparing the IBS group with the control group; and (b) adults older than 18 years.

**Exclusion Criteria:** 1. Dealing with poorly specified or non-existent main endpoints. 2. Studies using animals or cadavers. 3. Editorials and case studies. 4. Non-English studies.

### Study Selection

Two reviewers manually screened the studies based on the abstract and title before going on to screen them based on the full text. After that, an impartial reviewer confirmed the findings to ensure accuracy and resolve any disagreements.

### Data Extraction

From each included study, two reviewers retrieved pertinent material, which was then confirmed by a third reviewer to guarantee correctness.

The extracted data included patient demographics, study design, sample size, country of origin, and publication year. The extracted data included patient demographics, study design, sample size, country of origin, and publication year. Systemic interleukin-1β levels and irritable bowel syndrome were linked to outcomes.

### Quality assessment

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The Newcastle-Ottawa Scale (NOS), which was adjusted for cross-sectional research when needed, was used by two reviewers to assess the methodological quality of the included observational studies independently. By assessing three domains—outcome/exposure ascertainment (maximum 3 points), comparability of study groups (maximum 2 points), and study participant selection (maximum 4 points)—the NOS can receive up to nine points. A score of seven to nine was assigned to high-quality research, five to six to moderate-quality studies, and less than five to low-quality studies. When the reviewers were unable to reach a consensus through debate, a third reviewer acted as an adjudicator.

**Outcomes**

The outcome was a systematic evaluation of interleukin-1β levels.

**Data Synthesis and statistical analysis**

Statistical analysis was performed using Review Manager (REV-Man) Version 5.4. The mean difference (MD) and 95% confidence intervals (CIs) were combined for continuous outcomes, while the risk ratio (RR) was used for dichotomous outcomes. The techniques suggested by **Wan et al. 2014** [5] and **Luo et al. 2018** [6] were used to convert continuous data provided in studies as median and interquartile range to mean and standard deviation (SD). For overall effect estimates, a P value of less than 0.05 was deemed statistically significant. The random-effects model developed by DerSimonian and Laird was used. Heterogeneity was measured using the Cochran Q test and I2 statistics; under Cochrane's guidelines, significant heterogeneity was defined as $p < 0.10$ and $I2 > 50\%$. A P value of less than 0.05 was considered statistically significant.

**RESULTS**

**Study Selection**

Articles from 1947 were first discovered. 1168 papers were examined using their titles and abstracts after 779 duplicate studies were eliminated. 31 of these studies were found to be eligible for full-text review. After full-text review, twenty-three publications were removed due to inadequate outcome data, incorrect comparator, incorrect population, or non-comparative design. This review ultimately comprised eight papers **(Figure 1).**

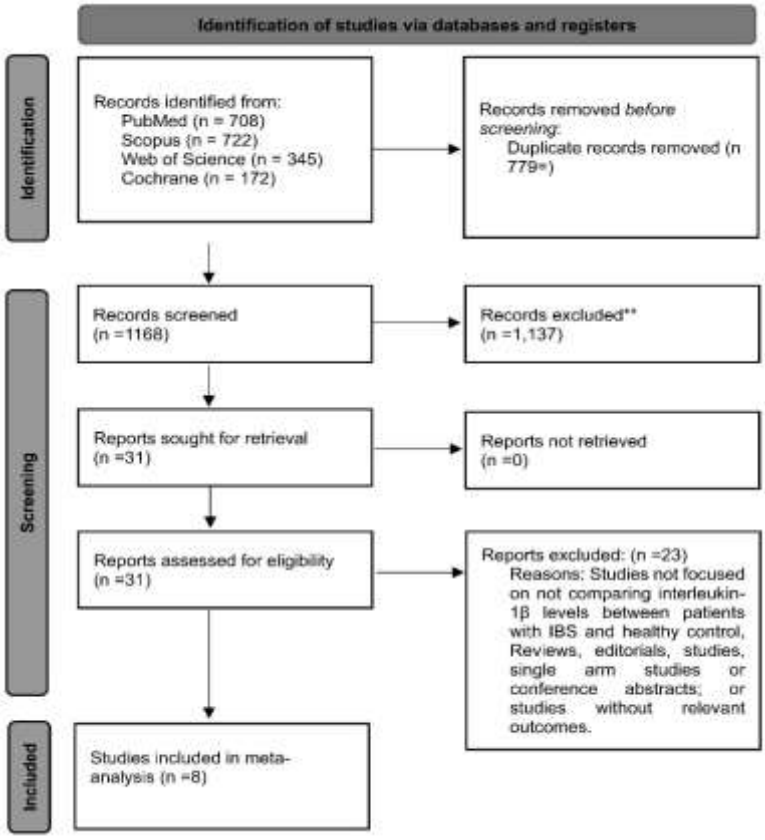



Figure 1: PRISMA flow diagram depicting the selection of the included articles

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**Quality assessment**

Using a modified Newcastle–Ottawa Scale for cross-sectional research, two reviewers independently evaluated the methodological quality of the included comparative observational studies. The scale evaluated three domains: participant selection, with a maximum of four points; comparability of the study groups, with a maximum of two points; and outcome ascertainment, with a maximum of three points. The maximum total score was nine points. High-quality studies received a score of 7–9, moderate-quality studies received a score of 5–6, and low-quality studies received a score of less than 5. Discussion and, when required, interaction with a third reviewer were used to settle disagreements between the reviewers **Table 1.**

**Table 1:** Methodological quality assessment of the included studies using the Newcastle–Ottawa Scale

| Study | Selection / 4 | Comparability / 2 | Outcome ascertainment / 3 | Total /9 | Quality |
|---|---|---|---|---|---|
| **Stankiewicz et al., 2011** [7] | 3 | 0 | 2 | 5 | **Moderate** |
| **Chang et al., 2012** [8] | 3 | 2 | 2 | 7 | **High** |
| **Gao, 2013** [9] | **2** | **1** | **2** | **5** | **Moderate** |
| **Darkoh et al., 2014** [10] | 2 | 1 | 1 | 4 | **Low** |
| **Mujagic et al., 2016** [11] | 3 | 2 | 2 | 7 | **High** |
| **Bennet et al., 2018** [12] | **3** | **1** | **3** | **7** | **High** |
| **Katsumata et al., 2018** [13] | 3 | 1 | 2 | 6 | **Moderate** |
| **Vara et al., 2018** [14] | 2 | 0 | 2 | 4 | **Low** |

**Characteristics of included studies**

The included studies were seven case–control studies and one cross-sectional study, and their characteristics are shown in **Table 2.** Eight research studies contrasted IBS patients with healthy controls. There were 1142 patients in all, 762 of whom had IBS and 380 of whom were healthy controls. The mean Age did not differ statistically significantly amongst the six trials ($I2=0\%$, $P=0.1$). None of the four studies showed a significant difference in sex between the two groups ($I^2=83\%$, $P=0.09$).

**Table 2:** Characteristics of the included studies

| Study | Country | IBS Type | Sample Size (IBS / Control) | Mean Age (years) | | Gender (M/F) | | IL-1β Outcomes |
|---|---|---|---|---|---|---|---|---|
| | | | | IBS group | Control group | IBS group | Control group | |
| **Stankiewicz et al., 2011** [7] | Poland | IBS-D<br>IBS-C<br>IBS-M | 17 IBS /<br>20 controls | -- | -- | M= 2<br>F= 15 | | Serum IL-1β |

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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Chang et al., 2012** [8] | USA | IBS-C<br>IBS-D<br>IBS-A/M | 45 IBS / 41 controls | -- | -- | M=19<br>F=26 | M=19<br>F=22 | Serum IL-1β |
| **Gao, 2013** [9] | China | IBS-D | 28 IBS-D / 15 controls | 39±9.2 | 38.5±10.6 | M=12<br>F=16 | M=6<br>F=9 | Serum IL-1β |
| **Darkoh et al., 2014** [10] | USA | ID-IBS<br>PI-IBS | 60 IBS / 40 controls | 54±12.5 | 53±14.1 | M=8<br>F=36 | M=17<br>F=23 | Serum IL-1β |
| **Mujagic et al., 2016** [11] | Netherlands | IBS (IBS-D, IBS-C, IBS-M, IBS-U) | 196 IBS / 160 controls | 44.8±16.4 | 43.9±19.2 | M=58<br>F=138 | M=62<br>F=98 | Plasma IL-1β |
| **Bennet et al., 2018** [12] | Sweden | IBS-C<br>IBS-D<br>IBS-MI | 244 IBS / 20 controls | 34.4±14.91 | 33.6±13.56 | -- | -- | Serum IL-1β |
| **Katsumata et al., 2018** [13] | Japan | IBS-D | 60 IBS / 32 controls | 47.9±20.5 | 42.5±11.2 | M=18<br>F=42 | M=26<br>F=6 | Serum IL-1β |
| **Vara et al., 2018** [14] | Norway | IBS-SSS | 38 IBS / 22 controls | 34.7±12.2 | 32±4.9 | M=32<br>F=6 | M=5<br>F=17 | Serum IL-1β |

PI-IBS: Postinfectious IBS, M: Male, F: Female, SSS: Severity Scoring System, IBS-C: constipation along with IBS, IBS-D: IBS accompanied by diarrhea, Interleukin (IL), and IBS-M (IBS with mixed constipation and diarrhea).

**Outcomes**

**Serum IL-1β**

According to four studies [7, 9, 12, 13], the IBS group's serum IL-1β was noticeably higher than that of the healthy control group (MD= 0.77, 95% CI= 0.61:0.92, P-value < 0.001, $I^2$=99).

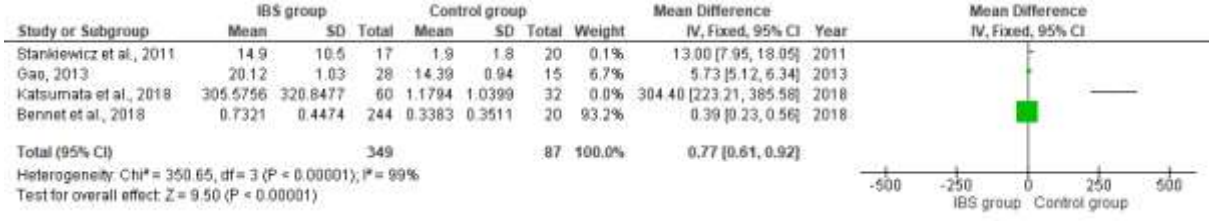



**Figure 1:** Forest plot of serum IL-1β in IBS group versus healthy control

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**Sensitivity analysis**

According to two studies [7, 9], serum IL-1β was substantially higher in the IBS group than in the healthy control (MD= 8.91, 95% CI= 1.84:15.98, P-value = 0.01, $I^2$=87).

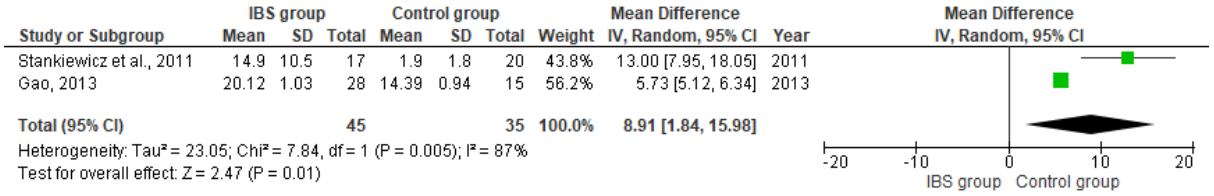



**Figure 2:** Forest plot of serum IL-1β in IBS group versus healthy control

In **Vara et al.** [14], serum levels of IL-1β were significantly higher in the control group (p=0.03).

**Plasma IL-1β**

In **Mujagic et al.** [11], the IBS group's plasma IL-1β was considerably lower than that of the healthy control group (P value=0.01).

## DISCUSSION

Irritable bowel syndrome (IBS) is now understood to be a disorder of gut-brain interaction with a complicated and multifactorial pathophysiology that includes changes in microbiota, altered gastrointestinal motility, visceral hypersensitivity, epithelial barrier dysfunction, psychological factors, and neuroimmune interactions. [15]. Cytokines are important mediators of this neuroimmune interaction, and alterations in their circulating or mucosal concentrations may reflect disturbances in the balance between pro-inflammatory and regulatory immune pathways [16].

Changes in the circulating or mucosal amounts of cytokines, which are crucial mediators of this neuroimmune interaction, may indicate imbalances between pro-inflammatory and regulatory immune pathways. IL-1β may influence epithelial barrier integrity, gastrointestinal motility and secretion, immune-cell recruitment, and nociceptive signaling. Accordingly, dysregulated IL-1β activity provides a biologically plausible mechanism linking subtle immune activation to visceral hypersensitivity and abdominal symptoms in IBS [17].

The current systematic review and meta-analysis aimed to evaluate the association between systemic IL-1β levels and IBS by comparing circulating IL-1β concentrations in adult IBS patients with those in healthy controls.

Serum IL-1β concentrations were considerably greater in IBS patients than in healthy controls, according to four studies [7, 9, 12, 13] (MD=0.77, 95% CI=0.61:0.92, P value<0.001, I2=99). **Vara et al.** [14] reported significantly higher serum IL-1β concentrations in healthy controls than in IBS patients (P=0.03), while **Mujagic et al.** [11] revealed that plasma IL-1β, found significantly lower concentrations in IBS group than in healthy controls (P=0.01). Thus, although the overall serum findings support an association between IBS and increased circulating IL-1β, this association does not appear to be uniform across all populations or biological specimens.

Several mechanisms may explain the observed elevation in serum IL-1β. Increased activation of innate immune cells and inflammasome-related pathways may enhance IL-1β production in susceptible patients. Increased intestinal permeability may also facilitate exposure of mucosal immune cells to luminal antigens and microbial products, thereby promoting inflammatory signaling [17]. IL-1β can further influence epithelial tight-junction integrity and amplify local immune responses, potentially establishing a bidirectional relationship between impaired barrier function and immune activation. In addition, its ability to enhance neuronal excitability and sensitization of visceral afferent pathways provides a potential mechanism through which low-grade inflammation may contribute to abdominal pain and visceral hypersensitivity. Therefore, elevated IL-1β should probably be considered part of a broader interaction among immune activation, intestinal barrier dysfunction, the microbiota, and gut–brain signaling rather than an isolated pathogenic abnormality [18].

Several earlier studies corroborate the current findings. **Liebregts et al.** [19] found that peripheral blood mononuclear cells from IBS patients generated higher pro-inflammatory cytokines. Compared to healthy controls, IBS patients exhibited significantly

higher baseline levels of IL-1β, TNF-α, and IL-6 production; abnormalities were particularly evident in diarrhea-predominant IBS (IBS-D). These results are generally consistent with the elevated serum IL-1β seen in the current meta-analysis and support the idea that some IBS symptoms may be characterized by heightened immunological activation.

Nevertheless, evidence supporting increased IL-1β in IBS is not universal. **Chang et al.** [8] investigated both systemic and colonic mucosal immune markers in patients with non-post-infectious IBS and healthy controls. They found no significant elevation in most measured serum or mucosal inflammatory cytokines, with the main group difference involving reduced mucosal IL-10 mRNA expression in female IBS patients. These findings suggest that overt activation of inflammatory pathways is not consistently detectable in all IBS populations and further support considerable biological heterogeneity within the disorder.

Similarly, a direction in opposition to the pooled serum finding was described by **Vara et al.** [14]. While IBS patients had considerably greater quantities of serum IL-1β, healthy controls had significantly higher concentrations of serum IL-1β. This finding is important because it demonstrates that cytokines may not change uniformly in IBS, and that elevation of other inflammatory mediators does not necessarily imply a parallel increase in IL-1β. Differences in patient phenotype, atopic status, environmental exposure, sample handling, and laboratory methodology could contribute to this discrepancy.

The very high heterogeneity observed in both serum analyses represents an important consideration when interpreting the present findings. Analytical heterogeneity is another particularly important explanation. Different included studies measured IL-1β using ELISA, radioimmunoassay, Luminex multiplex platforms, and other immunoassay techniques. Such methods differ in analytical sensitivity, detection limits, calibration procedures, dynamic range, antibody characteristics, and susceptibility to matrix effects. These differences are especially relevant for IL-1β because circulating concentrations can be low and therefore particularly sensitive to methodological and pre-analytical variation. Consequently, the statistically significant pooled serum findings should be interpreted in the context of considerable clinical and methodological heterogeneity.

Several limitations should be considered. The number of eligible studies was relatively small, most studies were observational, and their methodological quality varied. Considerable heterogeneity was present, while differences in IBS subtype, specimen type, cytokine assay, sample processing, diagnostic criteria, and participant characteristics limited direct comparability. In addition, the available evidence was insufficient for robust subgroup analyses according to IBS phenotype, postinfectious status, psychological comorbidity, or analytical technique. The finding for plasma IL-1β was derived from only one study and should therefore not be considered equivalent to a pooled estimate.

## CONCLUSION:

This thorough review and meta-analysis show that serum IL-1β levels are significantly higher in IBS patients than in healthy controls, indicating that low-grade systemic immune dysregulation may contribute to the pathophysiology of IBS. However, the confidence and generalizability of this connection are limited by the significant between-study heterogeneity, variation in IBS characteristics and laboratory techniques, and contradictory results across serum and plasma measures. Therefore, rather than being a recognized stand-alone diagnostic biomarker for IBS, circulating IL-1β should currently be considered a potential mechanistic marker.

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