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META-ANALYSIS OPEN ACCESS

Cytokine-Mediated Intestinal and Systemic Immune Dysregulation in Inflammatory Bowel Disease, Celiac Disease, and Autoimmune Hepatitis: A Systematic Review and Meta-Analysis of Biomolecular Mechanisms and Therapies

Asmat Ullah Khan[1] | Hina Murtaza[2] | Raheela Khawar[2]

[1]Center of Excellence in Molecular Biology, University of the Punjab, Lahore, Pakistan | [2]Department of Allied Health Sciences, University of Lahore, Pakistan

***Correspondence:** AsmatUllah Khan (ahspreparations512@gmail.com)

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Abstract

Background: Cytokine-mediated immune dysregulation is important in the pathogenesis of autoimmune and inflammatory diseases, such as inflammatory bowel disease, celiac disease, and autoimmune hepatitis. This paper set out to undertake a systematic review of cytokine-mediated immune mechanisms, especially IL-17, in these conditions. **Methods:** PRISMA 2020 was used in this systematic review. Up to March 2026, the electronic databases such as PubMed, Scopus, Web of Science, and Google Scholar were searched. Articles that reported cytokine levels or immune biomarkers in patients with inflammatory bowel disease, celiac disease, or autoimmune hepatitis versus those without any disease or animal studies, reviews, case reports, and studies for which quantitative cytokine levels were not measured were excluded. Certainty of evidence was measured bt Grade. The synthesis of data was done qualitatively and quantitatively, and meta-analysis was done on the synthesized data using a random-effects model to estimate pooled standardized mean differences. **Results:** 443 articles were found, out of which 15 articles were eligible to be included in the systematic review, and a subset of them was added to the meta-analysis. The combined findings showed very high levels of circulating IL-17 in celiac disease patients in comparison with healthy controls, but no significant differences were found between Crohn's disease patients and autoimmune hepatitis patients. In a number of the observational studies, the risk of bias was moderate and was assessed.The overall level of confidence was rated as low to moderate using the GRADE approach. **Conclusion**: IL-17–mediated immune dysregulation is significantly elevated in celiac disease but not consistently in Crohn's disease or autoimmune hepatitis, while IL-23 is significantly increased in autoimmune hepatitis. These findings highlight disease-specific roles of IL-23/Th17-related pathways and the need for larger, standardized studies.

Keywords: Interleukin-17; Hepatitis, Autoimmune; Celiac Disease; Crohn Disease; Cytokines; Th17 Cells

Introduction

There are immune-mediated gastrointestinal and hepatic diseases, including inflammatory bowel disease (IBD), celiac disease, and autoimmune hepatitis (AIH). These conditions involve chronic inflammation with disregard to cytokine networks [1]. These diseases have a common immunopathogenic pathogenesis that includes abnormal T-cell activation, immune tolerance, and sustained synthesis of pro-inflammatory cytokines [2,3]. The balance between the effector T helper (Th17) cells and regulatory T (Treg) cells is controlled by cytokines, such as interleukin, tumor necrosis factor-a (TNF-a), and transforming growth factor-b (TGF-β). Alteration of this balance has helped to cause intestinal injury in IBD and celiac disease and hepatocellular inflammation in AIH [4,5].

The current research concentrates on the main biomolecular parameters of immune dysregulation mediated by cytokines such as the presence of circulating and tissue-based levels of Th17-associated cytokines, anti-inflammatory cytokines (IL-10, TGF-β), and proof of Th17/Treg imbalance [6]. The biomarkers are compared with the disease activity, severity, and therapeutic response in the three conditions to explain the common and disease-specific mechanisms of inflammation [7]. Despite the several studies that have been carried out to evaluate the cytokine pattern in these disorders, the results are inconclusive because of differences in study design, characteristics of patients, laboratory procedures,

and measurements of outcomes. The majority of the literature assesses the separate diseases, and thus, restricts comparative knowledge of systemic and intestinal immune dysregulation. There is a need, therefore, to do a quantitative synthesis of the available.
The goal of this systematic review and meta-analysis is to assess the intestinal and systemic immune changes mediated by cytokines in IBD, celiac disease, and AIH, and to see their relation with disease activity, disease severity, and treatment response.

Methodology

The PRISMA 2020 guidelines were used to carry out this systemetic review. Statement as a methodological rigor, and reproducibility of all steps [8].

Inclusion and Exclusion Criteria: The studies had to be included when they explored the mechanisms of immune dysregulation induced by cytokines in IBD, celiac disease, or AIH. The designs that were eligible were randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies that reported quantitative biomolecular data. The studies had to give extractable data on Th17/ Treg imbalance, circulating or tissue cytokine levels (e.g., IL-17, IL-6, IL-21, IL-23, IL-10, TGF-β), or the response of immune cells or the response to cytokine therapy. Research had to provide extractable evidence on cytokine or immune pathway (e.g., Th17, Treg, B-cell axis), or targeted therapy response(s). Cases in case reports, narrative reviews, editorials, and conference abstracts without the complete dataset and studies of animals only, lack of quantitative outcome (mean ± SD or effect estimate[29]), and non-English articles were excluded.

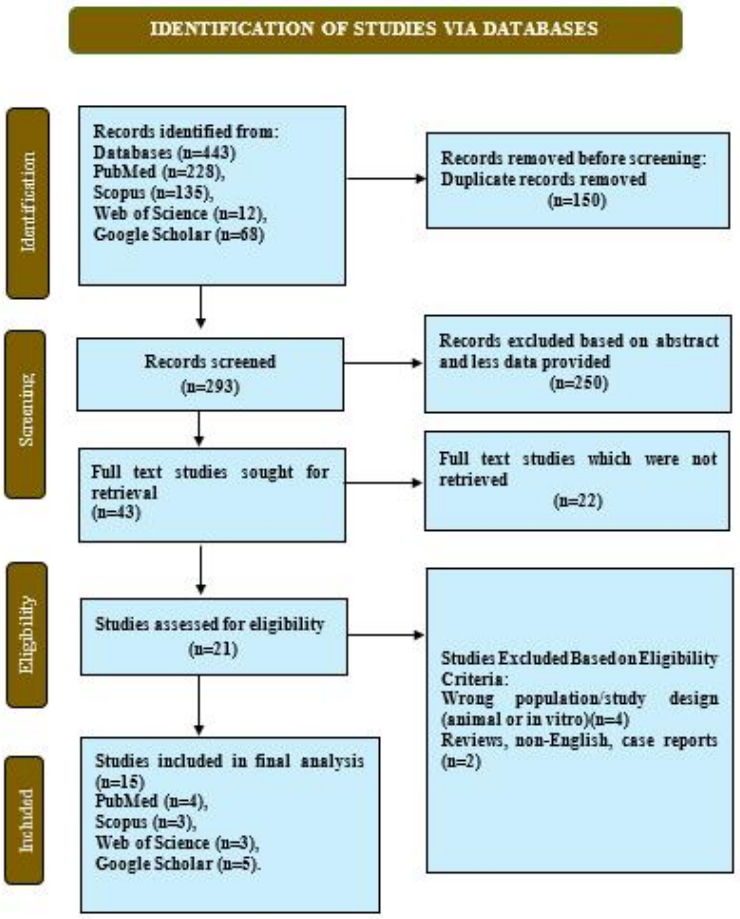

Figure 1: (PRISMA flow diagram) summarizes the overall study selection process.

Data Sources: The search was done in PubMed, Scopus, Web of Science, and Google Scholar. Articles published as early as January 2011 to February 2025 were taken into account.

Search Strategy: The search plan was a combination of MeSH idetified headings and free-text search terms concerning immune-mediated gastrointestinal and hepatic diseases. Specific disease names were included in such terms as inflammatory bowel disease, Crohn's disease, ulcerative colitis, celiac disease, and autoimmune hepatitis. Immunologic terminologies were cytokines, IL-17, IL-6, IL-21, IL-23, IL-10, TGF-beta, Th17, and Treg. Sensitivity and specificity were maximized using the AND/OR operators. Additional relevant publications were manually screened from the reference lists of the eligible studies. The representative search string was:
("Inflammatory Bowel Disease" OR IBD OR "Crohn's Disease" OR "Ulcerative Colitis" OR "Celiac Disease" OR "Coeliac Disease" OR "Autoimmune Hepatitis") AND ("Cytokines" OR "IL-17" OR "Interleukin-17" OR "IL-6" OR "Interleukin-6" OR "IL-21" OR "Interleukin-21" OR "IL-23" OR "Interleukin-23" OR "IL-10" OR "Interleukin-10" OR "TGF-beta" OR "Transforming Growth Factor-beta" OR "Th17" OR "T Helper 17 Cells" OR "Treg" OR "Regulatory T Cells")

Study Selection: Selection of the studies was done in multiple steps: It was identified by searching databases, screened by title and abstract, and filtered by full-text. Each stage was done by two independent reviewers. Any conflict of interest was sorted out by discussion and with the help of third reviewer.

Data Extraction: The extraction of the data was based on a standardized form. The variables that were gathered were author, year, country, study design, sample size, disease subtype (IBD, celiac disease, or AIH), cytokines measured, source of the sample (serum, plasma, or tissue), mean ± SD, disease status of activity, therapeutic intervention, and clinical outcomes measured.

Outcome Measures: The major end points were the variations in the Th17-related cytokines (IL-17, IL-6, IL-21, IL-23), anti-inflammatory cytokines (IL-10, TGF-β), and Th17/Treg imbalance markers. The second outcome was the relationship with the disease activity, severity indices, and cytokine-targeted therapy response.

Quality Assessment: Two reviewers carried out risk of bias assessment independently. RCT were appropriated by Cochrane Risk of Bias 2.0 tool and JBI Critical Appraisal of Case-Control Human Observational Studies [9,10]. The general confidence of evidence was measured using the GRADE methodology.

Data Synthesis: The meta-analysis was conducted in the form of a random-effects model with inverse-variance weighting because of anticipated clinical and methodological variations. Effect sizes were used in the form of standardized mean differences (SMDs) using a 95% confidence interval. Statistical heterogeneity was assessed using the I^2 statistic. Subgroup analysis was done in terms of disease type, cytokine profile, and status of disease activity. The sensitivity tests, such as leave-one-out tests, were conducted to understand the strength of results. The synthesis of studies that were not suitable to quantitatively pool was done as a narrative and included in structured summary tables.

Results

Among the four sources and electronic databases searched, 443 research papers were first identified, with 228 articles in PubMed, 135 in Scopus, 12 in Web of Science, and 68 articles in Google Scholar. Screening of the studies was done after elimination of duplicate records, which left 293 studies. In the screening of the title and abstract, 250 articles were filtered out since they did not meet the objective of the review or had insufficient information on the expression of cytokines, immune pathways, or biomolecular mechanisms involved in inflammatory bowel disease, celiac disease, or autoimmune hepatitis. After that, 43 full-text articles were pursued to be extracted. Of these, 22 articles were not able to be accessed, and 21 full-text papers were eligible to be assessed. Among them, 6 articles were eliminated based on full-text review due to lack of fulfilment of the predefined inclusion criteria, such as articles that were carried out on an animal or in-vitro model, a review article, a case report, studies that failed to provide the results of the relevant cytokine or immunological biomarker, or articles that were not in English. Lastly, 15 articles were used in all the inclusion criteria and thus were incorporated into the systematic review and meta-analysis. These papers examined how immune dysregulation through cytokine mediation and the underlying biomolecular processes are involved in IBD, celiac disease, and AIH, and how the findings may be used in therapeutic targeting.

The included studies evaluating cytokine-mediated immune dysregulation in inflammatory bowel disease, celiac disease and autoimmune hepatitis are summarized in Table 1. The table presents the main study characteristics, cytokine profiles, quantitative findings, key outcomes and therapeutic implications across the selected studies.

Table 1: Summary of Original Human and Preclinical Studies Investigating IL-17/Th17 Pathways in IBD, Celiac Disease, and Autoimmune Hepatitis

Author & Year Contry	(Disease studied)	Study Design	Sample Size / Population characteristics	Key cytokines measured	Quantitative finding Mean± SD(pg/ml)	Key Outcomes	Therapeutic implications
Menesy et al., 2014[11] Egypt	IBD (Crohn's disease)	Observational study	24 patients with Crohn's disease, and 21 were HC.	IL-17 measured via ELISA	IL 17: Patients: 24.29 ± 11.03 Controls: 27.93 ± 12.07	Serum IL-17 level was increased significantly in patients of IBD with Crohn's disease versus controls	Elevated serum IL-17 in IBD suggests that targeting IL-17 or the Th17 pathway could be a potential therapeutic strategy to reduce intestinal inflammation, even though it may not directly reflect disease activity.
Lucaciu et al., 2021[12] Romania	IBD (Crohn's disease	Observational study	16 patients diagnosed with Crohn's disease and 15 HC	Serum IL-17 and IL-23 levels were determined using sandwich ELISA	IL- 17: Patients: 1197.6 ± 1364.9 Controls: 395 ± 312 IL- 23: Patients: 1062.7 ± 521.6 Controls: 371.5 ± 12.8	Disease severity was associated with increased IL-17 values. IL-23 levels were also significantly higher in IBD with Crohn's disease patients with intestinal complications	Both IL-17 and IL-23 correlate with IBD severity, and IL-23 might be a promising novel biomarker for severe Crohn's disease. Identifying the dominant IL pathway involved in IBD severity could serve as guidance for clinical decision-making on biologic therapy.
Krawiec et al., 2020[13] Poland	Pediatric IBD(Crohn's disease)	Observational study	25 patients 20 Healthy controls	Serum interleukin 17A and interleukin 17F was measured via ELISA	IL- 17A Patients: 13.83 ± 15.26 Controls: 6.93 ± 7.33	No significant differences in IL-17A among patients with active and inactive IBD with Crohn's disease.	Targeting IL-17A could be limited therapeutic utility in Crohn's disease.
Cho et al., 2018[14] Korea	Pediatric IBD(Crohn's disease)	Observational study	9 children diagnosed with Crohn's disease and 7 healthy controls	IL-17A was measured via multiplex assay	IL-17A Patients: 64.2 ± 17.2 Controls: 28.3 ± 10.0	Mucosal immunity analysis showed increased FOXP3+ T reg cells in the LP with Crohn's	Modulating the Th17/Treg balance and targeting IL-17A/IL-22–mediated pathways enhancing Treg function may benefit Crohn's disease.

						disease, while Th17 cell polarizing and signature cytokines were decreased in the serum samples of Crohn's disease...	
Sahin et al., 2022[15] Turkey	IBD (Crohn's disease)	Observational study	50 patients with Crohn ,'s disease and 40 HC	IL17 levels of samples were assayed via ELISA	IL-17: Patients: 23.82 ± 11.12 HC: 27.93 ± 12.07	The mean serum IL17 level of Crohn's disease patients did not differ from those of healthy controls.	Serum IL17 was not correlated with inflammatory markers (ESR, CRP, white blood count, platelet count, and albumin) and CDAI. Peripheral IL17 measurement is not a useful tool for detecting and monitoring Crohn's disease
Madi et al., 2024[16] Saudi Arabia	CD	Observational study	23 patients of CD having a gluten-free diet (GFD) and 23 HC	IL-17A level measured via ELISA	IL-17A CD: 2.020±1.887, HC: 2.06±1.56	No significant differences were found in salivary IL-17A level between celiac disease patients and control subjects. Increased levels of salivary IL-17A, was associated with periodontitis.	In treated Celiac disease, normalized salivary IL-17A suggest limited value of systemic cytokine-targeted therapy, as elevations are primarily linked to local periodontal inflammation rather than ongoing autoimmune activity.
Khudair et al., 2025[17] Iraq	CD	Observational study	80 CD patients and 48 HC	The levels of IL-17A were measured using a sandwich ELISA	IL- 17A CD: 264.99 ± 169.10 , HC: 227.78 ± 140.73	IL-17A levels were elevated in patients with CD for >1 year and in those adhering to GFD, indicating that IL-17A may have a role in the inflammatory mechanisms associated with celiac disease, especially in those with prolonged disease duration.	IL-17A may contribute to persistent inflammatory activity and could represent a potential immunomodulatory target requiring further investigation.
Goel et al. 2019[18] Australia and the USA	CD	Interventional Clinical Challenge Study	25 patients with CD and 25 HC	IL-17A and IL-22 were measured via electrochemiluminescence immunoassay assays	IL-17A : Patients: 2.09±3.07 Controls: 0.025±0.0089	IL-17A release following gluten challenge in coeliac disease patients significantly increased.	Early elevations of IL-17A after gluten in patients with coeliac disease implicates rapidly activated T cells as their probable source. Cytokine release after gluten could aid in monitoring experimental treatments and support diagnosis.
Nafari et al., 2022[19]	CD	Observational study	40 CD patients under GFD	mRNA expression of IL-17A was	IL-17A: Patients: 11.9 ± 9 Controls:	High IL-17A levels in CD patients	Persistent IL-17A despite GFD suggests: careful consideration of IL-17A-

Iran			and 40 HC	assessed using quantitative polymerase chain real-time qPCR	6.79 ± 7	despite dieting, which may be related to the protective effect of this cytokine on intestinal tight junctions,	targeted therapy; ; GFD alone may not normalize Th17-related immune activation
Ali et al., 2019[20] Iraq	CD	Observational study	40 patients with CD and 20 HC	IL-17A was assessed via ELISA	IL-17A: Patients: 88.25±40.72 HC: 37.08±10.55	The serum level of IL-17A in the patients was higher as compared to control group in the patients comparing with control group.	Persistent Th17/IL-17A activation suggests potential for Th17-targeted therapies; IL-17A could serve as a biomarker for monitoring interventions
Gutkowski et al., 2018[21] Poland	AIH	Observational study	44 patients with confirmed AIH and 30 HC	Serum IL-17, Level was measured by a quantitative sandwich enzyme immunoassay.	IL- 17: Patients: 30.8±18.5 Controls: 16.4±6.7	Serum IL--17 levels was higher in treatment-naive AIH patients compared with controls.	Serum IL-17 could be used as a biomarker to guide monitoring and optimize immunosuppressive therapy in autoimmune hepatitis.
Dupont et al., 2016[22] Mexico	AIH	Observational case control study	46 patients with AIH and 44 HC	IL-17A, IL-23and TNF-α were assessed via ELISA	IL- 17A: Patients:18±10 Controls:20 ± 12 IL-23: Patients: 30±25 Controls:1 ± 0.5 TNF-α: Patients:150±90 Controls:70 ± 40	Compared to healthy controls, serum levels of IL-23 and TNF-α, but not IL-17A were significantly increased in AIH patients	Therapies targeting the IL-23/IL-17 axis or TNF-α signaling may help suppress immune-mediated liver inflammation and represent potential immunomodulatory treatment strategies.
Xue, et al., 2017[23] China	AIH	Experimental Study	30 female Wistar rats HC, AC, CC	ELISA double antibody sand-wich method to measure IL-17A, cytokine levels.	IL-17 HC=39.84 ± 21.04 CC=238.11 ± 132.80	Th17 cell levels were significantly lower, and Treg cell levels were significantly higher in the CC group, compared with those in the AC group. The Th17/Treg ratio was increased in the acute immune liver injury model and decreased in the chronic liver injury model.	Modulating the Th17/Treg balance could be a strategy to prevent acute liver injury and manage disease progression in autoimmune hepatitis.
Wang et al., 2015[24] China	AIH	Experimental preclinical study	Adult male **C57/BL6 mice**	TGF-β1, IL-10, and IL-17 were assessed via ELISA	IL- 17: M=298.7 ± 79.5 G=154.7 ± 63.0	Mice with AIH have a Treg/Th17 ratio imbalance. The Bu Xu Hua Yu method was able to restore the cellular balance of Treg/Th17 through the	The "Bu Xu Hua Yu" method may treat autoimmune hepatitis by restoring the Treg/Th17 balance, reducing IL-17–mediated inflammation, and enhancing regulatory immune responses.

						regulation of the expression of ROR t and Foxp3, and can play an important role in the treatment of AIH	
Zhao et al., 2011[25] China	AIH	Observational case control study	29 AIH patients, and 28 HC	Serum IL-17A and IL-23 were measured by ELISA	IL-17: Patients:300± 13 Controls:270±5 IL-23 Patients:1050±65 Controls: 900±40	IL-17 elevated in active AIH. Th17 cells are key effector T cells that regulate the pathogenesis of AIH, via induction of MAPK-dependent hepatic	Targeting the Th17/MAPK signaling pathway could interrupt the positive feedback loop and serve as a potential therapy for autoimmune hepatitis.

Footnotes: Healthy controls (HC), celiac disease (CD), inflammatory bowel disease (IBD), and autoimmune hepatitis (AIH) are indicated where applicable. Cytokine levels are reported as mean ± standard deviation in pg/ml unless otherwise specified. IL-17 measurements include IL-17A and IL-17F depending on the study, and IL-23 and TNF-α are reported when assessed. Therapeutic interventions reflect standard clinical management, gluten-free diet, or experimental and preclinical treatments. Immune pathways denote the primary T-helper cell subset or axis involved, such as Th17, Th1, or Treg. Preclinical studies were conducted in animal models to explore mechanistic or therapeutic effects. Quantitative findings are extracted directly from the original studies, noting that differences in assay methods, including ELISA, multiplex, qPCR, and electrochemiluminescence, may contribute to variability. Values for pediatric and adult populations are presented separately when available.

Table 1 shows a summary of the research that was incorporated in the meta-analysis which includes observational human studies, interventional clinical challenge trials and preclinical experimental models on IL-17 and Th17-mediated immune responses. It includes a summary of the critical details; country, disease under investigation, study design, size of the sample, the cytokines that were measured, quantitative results (mean +- SD), the pathways of immunology, therapeutic interventions, the primary findings of the study, and possible therapeutic benefits. In IBD (especially Crohn disease), celiac disease, and autoimmune hepatitis (AIH), IL-17/Th17 dysregulation has been reported inconsistently where increased levels of IL-17 were reported to be linked to severity of disease or immune activation and in other studies there were minimal differences between patients with the diseases and the controls. These data demonstrate the applicability of Th17-driven pathways in the pathophysiology of diseases and also them as biomarkers or therapeutic targets but context-specific differences (e.g., the pediatric versus the adult population, treatment status, and preclinical models) were observed.

The majority of observational human studies (*Table 2*) were moderate risk because of incomplete reporting or uncertainty in the cohort on the possibility of confounders like medication use, duration of disease or variability between cohorts. Some of the studies that were well documented had a low risk. The overall certainty of evidence was rated as low to moderate using the GRADE approach.

Table 2: JBI Critical Appraisal of Case-Control Human Observational Studies

Study	Case definition	Control selection	Comparability	Exposure measurement	Same measurement	Confounders addressed	Statistical analysis	Overall Risk
Menesy et al., 2014[11]	Yes	Yes	Yes	Yes (ELISA)	Yes	**Unclear**	Yes	**Moderate** (confounders not reported)
Lucaciu et al., 2021[12]	Yes	Yes	Yes (matched)	Yes (duplicate ELISA)	Yes	**Yes** (recorded)	Yes	**Low**(well documented)
Krawiec et al., 2020[13]	Yes	Yes	Yes	Yes (ELISA)	Yes	**Unclear**	Yes	**Moderate** (pediatric confounders unclear
Cho et al., 2018[14]	Yes	Yes	**Unclear** (very small)	Yes (IHC + multiplex)	Yes	**Unclear**	Yes	**Moderate** (very small sample)
Sahin et al., 2022[15]	Yes	Yes	Yes	Yes (ELISA)	Yes	**Unclear**	Yes	**Moderate** (meds/duration unclear)
Madi et al., 2024[16]	Yes	Yes	Yes	Yes (saliva ELISA)	Yes	**Unclear**	Yes	**Moderate** (small sample, confounders)
Khudair et al., 2025[17]	Yes	Yes	Yes	Yes (ELISA)	Yes	**Unclear**	Yes	**Moderate** (multi-center but confounders)

Nafari et al., 2022[19]	Yes	Yes	Yes	Yes (qPCR)	Yes	**Unclear**	Yes	**Moderate** (molecular assay, confounders)
Ali et al., 2019[20]	Yes	Yes	Yes	Yes (ELISA)	Yes	**Unclear**	Yes	**Moderate** (limited adjustment)
Gutkowski et al., 2018[21]	Yes	Yes	Yes	Yes (ELISA)	Yes	**Unclear**	Yes	**Moderate** (treatment differences)
Dupont et al., 2016[22]	Yes	Yes	Yes	Yes (ELISA)	Yes	**Unclear**	Yes	**Moderate** (serotype groups confounding)
Zhao et al., 2011[25]	Yes	Yes	Yes	Yes (ELISA/RT-PCR)	Yes	**Unclear**	Yes	**Moderate** (mixed clinical/lab methods)

The reported animal studies (*Table 3)* were sufficiently randomized, but no information was provided regarding whether caregivers or outcome measures were blinded, which led to a moderate overall risk despite full data of outcomes.

Table 3: SYRCLE Risk of Bias Assessment of Preclinical Animal Studies

Study	Randomization	Deviations from Intended Intervention	Missing Data	Outcome Measurement	Selective Reporting	Overall Risk
Xue et al., 2017[23]	Low (randomized)	**High** (blinding not reported)	Low (data presented)	Unclear (assessor blinding not described)	Unclear (protocol not available)	**Moderate** (randomization ok; blinding missing)
Wang et al., 2015[24]	Low (block randomization)	**High** (caregiver blinding not reported)	Low (data reported)	Unclear (outcome assessor not described)	Unclear (protocol not available)	**Moderate** (good design; poor reporting of blinding)

The gluten-challenge study (*Table 4*) is a good study with full outcome reporting; however, non-random selection of volunteers and cohort recruitment moderately increased the risk of confounding and selection bias.

Table 4: ROBINS-I Risk of Bias Assessment for Non-Randomized Human Interventional Study

Study	Confounding	Selection of Participants	Classification of Interventions	Deviations from Intended Intervention	Missing Data	Outcome Measurement	Selective Reporting	Overall Risk
Goel et al., 2019[18]	Moderate (non-random volunteers)	Moderate (selected cohorts)	Low (gluten challenge defined)	Low (protocol followed)	Low (no missing data)	Low (validated assays)	Low (preplanned analyses)	**Moderate**

Meta–Analysis

An extensive literature review was used to find articles that examined the role of cytokine-mediated immune dysregulation in Inflammatory Bowel Disease (IBD), Celiac Disease (CD), and Autoimmune Hepatitis (AIH). Screening of titles, abstracts, and full texts as per the predetermined criteria formed the basis of eligibility made the relevant studies that provided cytokine levels in patients and healthy controls in the systematic review. The meta-analysis was, however, not able to quantitatively synthesize all the eligible studies. It eliminated studies in the meta-analysis when no or un-calculable mean and standard deviation values were provided, cytokine measurements were not in serum but in salivary or tissue samples, and inadequate statistical data were not available to calculate standardized mean differences. Thus, only articles that had similar levels of quantitative serum cytokines (Mean ± SD) in both patients and healthy controls were incorporated into the final meta-analysis.

Five articles with 124 patients with Crohn's and 103 healthy controls were chosen to assess the level of circulating IL-17 in patients with Crohn's. The random-effects model was used because there was anticipated variation between studies. The pooled analysis demonstrated a standardized mean difference (SMD) of 0.47 (95% CI: −0.35 to 1.29)**.** The general analysis was not statistically significant ($Z = 1.11$, $p = 0.27$), which implied that there was no significant difference in the circulating IL-17 levels between patients with Crohn disease and healthy controls when combined with other studies. Considerable heterogeneity was observed among the included studies ($I^2 = 82\%$**,** $\chi^2 = 22.22$, $p = 0.0002$),

suggesting substantial variability in effect sizes. Tau2 (between-study variance) was 0.731, which was also in favor of a random-effects model. In other studies, although some individual studies showed high levels of IL-17 in Crohn disease patients, others showed similar or even lower levels compared to the controls, which led to the observed heterogeneity (*Figure 2a*).

Visualization of the funnel plot indicated slight asymmetry whereby most of the studies fit around the pooled effect, and one study had a relatively higher positive effect size. This trend along with the large heterogeneity recorded in the meta-analysis (I^2 = 82%), indicates the presence of the potential small-study effects or methodological variation across studies. Nevertheless, few studies limit the conclusive evaluation of publication bias (Figure 2b).

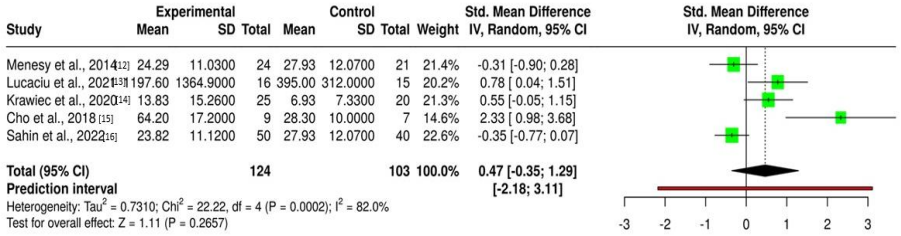

Figure 2a: Forest plot of Meta-analysis of IL-17 in Crohn's Disease (Inflammatory Bowel Diseases

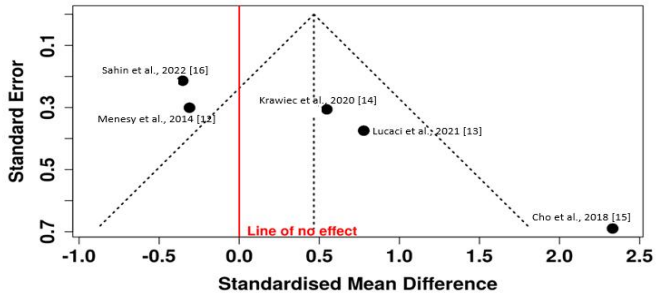

Figure 2b: Funnel Plot Assessing Publication Bias in Studies Reporting Circulating IL-17 Levels in Crohn's Disease (Inflammatory Bowel Diseases

A total of three studies of 119 patients with autoimmune hepatitis and 102 healthy controls were incorporated in the quantitative synthesis. The pooled standardized mean difference using a random-effects model was −14.38 (95% CI: −43.61 to 14.84)**.** The overall effect was not statistically significant (Z = −0.96, p = 0.33)**.** Substantial heterogeneity was observed **(**I^2 = 98%**,** χ^2 = 119.38, p < 0.00001), indicating very high variability between studies. Tau2 was estimated to be 660.8652 and indicates a high level of dispersion in effect sizes. The broad-range of confidence interval and high level of heterogeneity indicate that disparity in the study designs, patient characteristics, severity of disease and methods of measurements could have contributed to the results observed. All in all, the pooled analysis failed to show statistically significant difference in circulating IL-17 between patients of autoimmune hepatitis and healthy controls *(Figure 3a).*

The funnel plot of autoimmune hepatitis indicated a significant asymmetry, which was mainly caused by a single study that had a high negative effect size. Such observation is in line with the extremely high heterogeneity identified in the pooled analysis (I^2 = 98%), and indicates the existence of influential outliers and significant variability between studies. The evaluation of publication bias is also not extensive because of a limited number of incorporated studies *(*Figure 3b*).*

Twenty-four participants in the experimental group and 24 in the control group were included in the two studies that were used to conduct the meta-analysis. A random effects model was used and the standardized mean difference (SMD) was estimated using the inverse variance method. There was also a significant difference in the serum IL-23 levels between patients with autoimmune hepatitis (AIH) and healthy controls in the pooled analysis, with an overall SMD of 2.13 (95% CI: 1.04–3.23). The difference between the overall effect of patients with AIH and controls was statistically significant (p < 0.05) with elevated levels of IL-23. But there was some important variation between the studies that had been included (p = 0.01). The I2 value was 84% indicating that the differences in results between studies were likely to be real, suggesting substantial differences in the effect size estimates (Figure 4a). Pooled estimate publication bias was assessed using a funnel plot, which indicated that the funnel plot did not show any evidence of publication bias for the two studies included.[23],[26] However, due to limited number of studies included, publication bias assessment is limited and should be taken with a grain of salt (Figure 4b).

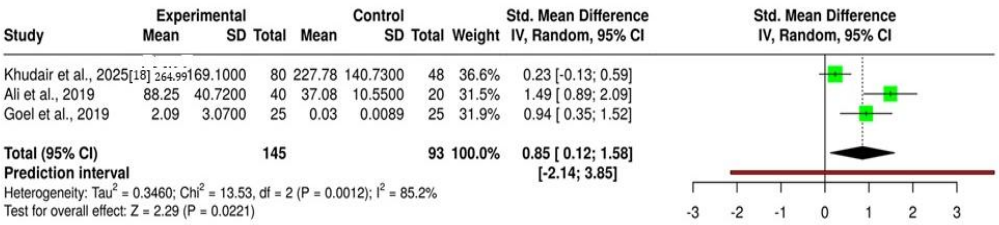

Figure 3a: Forest Plot of Circulating IL-17 Levels in Patients with Autoimmune Hepatitis Compared with Healthy Controls

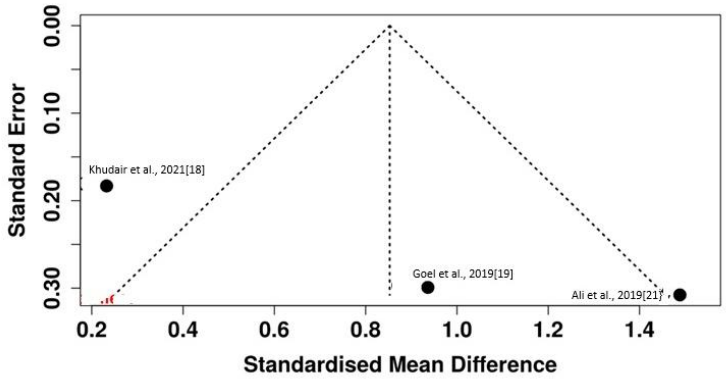

Figure 3b: Meta-analysis Forest Plot Showing the Standardized Mean Difference of Serum IL-17 Levels in Autoimmune Hepatitis Patients Versus Healthy Controls

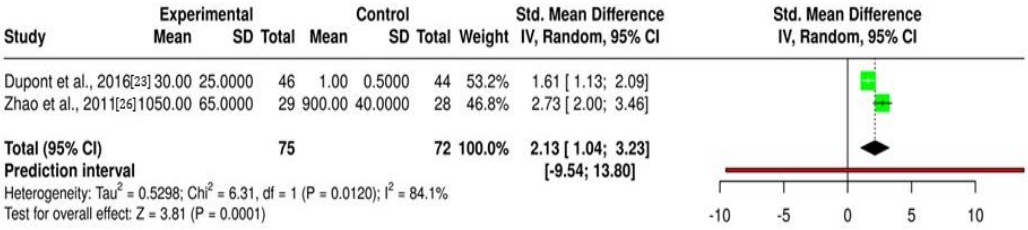

Figure 4a: Forest plot showing the meta-analysis of serum IL-23 levels in patients with autoimmune hepatitis (AIH) compared With healthy controls (HC) based on included case–control studies.

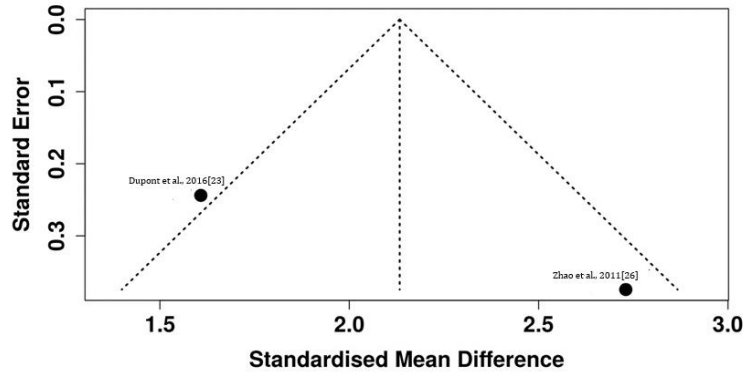

***Figure 4b: Funnel plot assessing** publication bias among the studies included in the meta-analysis of serum IL-23 levels in autoimmune hepatitis (AIH).*

The meta-analysis involved 3 studies that included 145 celiac disease patients and 93 healthy controls. Applying a random-effects model the pooled standardized mean difference was 0.85 (95% CI: 0.12 to 1.58). The entire effect was significant (Z = 2.29, p = 0.022) meaning that the amount of IL-17 in patients with celiac disease is significantly higher than in healthy individuals. Moderate to high heterogeneity was observed (**I^2 = 85.2%**, χ^2 = 13.53, p = 0.0012), suggesting substantial variability among studies. The between-study variance (Tau^2) was **0.346**. The between-study (Tau2) variance was 0.346. Although heterogeneous, the aggregated findings propose that the IL-17-mediated immune activation can be significant to the inflammatory processes related to celiac disease *(Figure 5a).*

The funnel plot of celiac disease was slightly asymmetrical, with the studies being concentrated on the positive effect side. Though the pooled analysis showed that the level of IL-17 was significantly high in the patients with celiac disease, the heterogeneity (I^2 = 85.2) is so high, indicating variability among the studies. With such a limited number of studies included, it is impossible to draw definite conclusions about publication bias *(Figure 5b).* Two studies that were incorporated in the systematic review were not eligible for quantitative meta-analysis because they differed in the manner of outcome measurements. Madi et al. (2024) sampled salivary IL-17A, with the meta-analysis of only studies that reported serum cytokine concentration, which does not allow direct comparison of the results. Moreover, Nafari et al. (2022) measured IL-17A mRNA expression, but not the protein concentration in the bloodstream, with the help of qRT-PCR. Because the meta-analysis was limited to studies that had serum IL-17 concentrations recorded as mean ±- SD, this had excluded this study out of the pooled statistical analysis but included in the qualitative review.

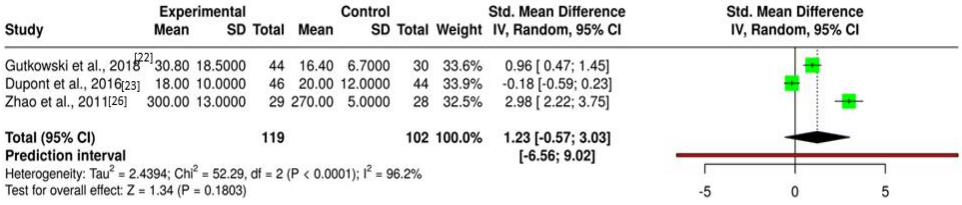

Figure 5a: Forest Plot of the Pooled Standardized Mean Difference of Circulating IL-17 Levels in Patients with Celiac Disease Compared with Healthy Controls

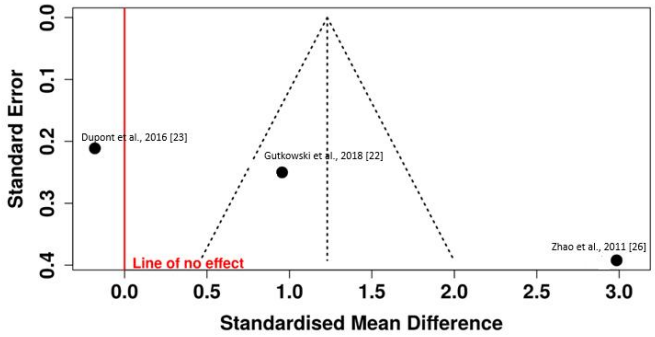

Figure 5b: Funnel plot evaluating potential publication bias among studies included in the meta-analysis of circulating IL-17 levels in celiac disease.

When the findings were combined, there was no significant change due to sensitivity analysis. Some minor changes occurred in the effect size and the heterogeneity of the pooled studies with the exclusion of the individual studies, but the overall direction and interpretation of the results did not change. However, the overall findings were deemed to be fairly consistent with some potential caution about the findings as this was a highly heterogeneous study with limited numbers of studies. The subgroups were analyzed for disease type and cytokine profile. The results revealed disease-specific cytokine profiles: In celiac disease, levels of IL-17 were found to be significantly higher, while there were no significant pooled differences in levels of IL-17 in Crohn's disease or autoimmune hepatitis. Unlike other autoimmune diseases, the level of IL-23 was significantly raised in AIH indicating the activation of the IL-23/Th17 axis may be distinct in gastrointestinal and hepatic autoimmune conditions.

Discussion

This meta-analysis summarized the results of studies that had assessed the level of circulating IL-17 with regard to inflammatory bowel disease (Crohn's disease), celiac disease, and autoimmune hepatitis. The major findings of current study include there was no statistically significant difference between pooled IL-17 in Crohn disease and controls (SMD = 0.47, 95% CI 0.35 to 1.29; I2 = 82%), with an extremely high between-study heterogeneity; whereas IL-17 was significantly higher in celiac disease (SMD = 0.85, 95% CI 0.12-1.58), it was highly heterogeneous [26,27] and (In some analyses, the funnel-plot inspection indicated the possibility of small-study effects, than the limited number of studies restricted the ability of the tests to test bias. Collectively, these findings provide evidence of a disease-specific pattern of IL-17 dysregulation: a steady rise in the case of celiac disease and inconclusive results in the case of Crohn's disease and very inconsistent results in the case of autoimmune hepatitis [28]. According to the meta-analysis of IL-23 levels, the mean concentration of the cytokine in patients with autoimmune hepatitis (AIH) is much higher than it is in healthy controls, and the pooled standardized mean difference (SMD) is 2.13.

These findings have two aspects that support and elaborate the literature. First, the high IL-17 levels in celiac disease are in line with mechanistic models that state rapid, gluten-induced Th17-activation in a subgroup of patients, a trend observed in experimentally gluten-challenged and clinical cohort studies where mucosal and peripheral IL-17 increase in response to antigen-exposure [29, 30]. The combination of all these signals enhances our effect, indicating that IL-17 has a moderate standardized effect size in independent cohorts, indicating that IL-17 could be utilized as a biomarker in the context of challenges or diagnostics [31, 32]. Second, the mixed reports of IL-17 in Crohn and AIH are in agreement with the previous heterogeneous results: some clinical cohorts indicate high Th17 signatures in active disease or complications, but other studies do not show peripheral elevation or even normativity [33]. This discrepancy is likely due to heterogeneity in disease stage (active vs. quiescent), exposure

to treatment (biologics, immunomodulators, gluten-free diet), or source of sample (serum versus saliva or tissue), or assay systems (ELISA, multiplex, electrochemiluminescence) - all of which have been repeatedly identified in the literature of cytokine biomarkers as the cause of inconsistent between-study variation [34, 35]. These findings support the context-specificity of IL-17 biology: in the acute, antigen-driven context of celiac disease, the peripheral IL-17 image is more clearly visible, whereas in Crohn's disease and AIH the peripheral IL-17 image is obscured due to methodological and clinical heterogeneity [36]. Furthermore, the increasing level of IL-23 is in line with increasing evidence that Th17 cells differentiate and persist through the action of IL-23, an essential cytokine, which is central to the immunopathogenesis of AIH. High concentrations of IL-23 can play a role in the activation and proliferation of Th17 cells, which induces hepatic inflammation by downstream secretion of pro-inflammatory cytokines including IL-17 and TNF-α [37].

This systematic review has certain limitations, which should be taken into account. First, despite the thorough search in four databases, almost half of the found full texts were not accessible (22/43), which might have caused selection bias and reduced representativeness. Second, the outcomes had few studies each, which lowers power, the validity of funnel-plot-based bias measures, and the ability to perform subgroup and meta-regression analyses that can be used to describe heterogeneity. Third, only studies with a mean + SD were included because studies with medians, semiquantitative data, or exclusively graphical data were excluded in case they could not be converted to estimates and thus affected the quantitative synthesis. Fourth, pooled estimates could have been influenced by language restriction and the possible publication bias. Lastly, there is a high degree of heterogeneity in a number of pooled analyses, which reduces the level of confidence with which pooled point estimates can be understood [38].

Inclusion of primary research studies is also limited which further limits inference. A number of them were small, single center observational studies with little control on confounders including medication intake, disease duration, comorbidity, and time relative to disease activity. Assay heterogeneity was intense: measurement in different analytical platforms, calibrators and in different units was made and some studies measured cytokines in non-serum (saliva, tissue) or reported mRNA and not protein-levels in these situations this is incomparable. These few studies were not detailed about laboratory blinding or quality control, and some of them were heterogeneous patient subgroups (pediatric/adult; active/inactive disease) that were not stratified in their reporting. Lastly, pooled estimates and inflated Tau2 (between-study variance) were affected by a small number of influential outliers with extreme means/SDs, further decreasing the accuracy of the belief in pooled effects.

On the basis of these limitations, it is evident where research should go further. Primary researches are supposed to use standardized assays and present harmonized units and complete statistical information (means, SDs, or convertible summary statistics) to allow to integrate them in meta-analyses. To distinguish disease-phase and treatment effects, larger, multi-center cohorts with timed protocols (e.g., sample at specific phases of disease) and scrupulous monitoring of treatment status are required. The meta-analysis of individual patient data (IPD-MA) or prospective harmonization of the data would allow the use of strong subgroup and meta-regression analyses to discover the moderators (age, activity, therapy) [39]. The cause and effect and applicability of biomarkers will be explained by mechanistic longitudinal research of IL-17 kinetics following antigen challenge or therapy [40]. Lastly, because of the feasible therapeutic implication, randomized trials or translational researches that would synchronize IL-17 dynamics and clinical outcome in the case of Th17- targeting intervention would be worthwhile [41].

Conclusion

This systematic review and meta-analysis assessed whether IL-17-mediated immune dysregulation plays a role in Crohn's Disease, Celiac Disease, and Autoimmune Hepatitis. These findings indicated that the levels of IL-17 were significantly higher in celiac disease than in healthy controls, which supported the role of Th17-driven inflammation in the pathogenesis of celiac disease. Conversely, pooled analyses of both Crohn disease and autoimmune hepatitis were ineffective in statistically showing differences in the levels of IL-17, perhaps because of the heterogeneity in study design, patient characteristics, and methods of cytokine measurements. Little evidence also suggested higher IL-23 levels in autoimmune hepatitis, implying the stimulation of the IL-23/Th17 inflammatory pathway, but the human data were not enough to meta-analyze. Altogether, these results demonstrate that the IL-17 and IL-23-associated immune pathways play different roles in the multitude of autoimmune diseases, and these studies should be done on a larger and more standardized scale to elucidate their biomarker and therapeutic opportunities.

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Conflict of Interest

None

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Use of Artificial Intelligence

The corresponding author declared that no artificial intelligence or AI-assisted tools were used in this manuscript.

Authors' Contribution

AUH, HM and RK contributed significantly and equally as per ICMJE. All authors gave their final approvals to publish this article.

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