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(REVIEW ARTICLE)

Non-invasive tools for inflammatory bowel disease: A systematic review and meta-analysis of biochemical markers and intestinal ultrasound compared to endoscopy

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Abstract

Despite endoscopy's gold standard status, non-invasive tools are revolutionizing Inflammatory Bowel Disease (IBD) management. This systematic review and meta-analysis compared the diagnostic accuracy of biochemical markers, intestinal ultrasound (US), and endoscopy in adults with IBD. This systematic review and meta-analysis aimed to compare the diagnostic accuracy of fecal calprotectin, C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), and bowel wall thickness measured by US with endoscopy in IBD patients. We searched electronic databases for most recent studies published between 2012 and 2023, identifying 25 studies comparing at least one non-invasive tool with endoscopy. We pooled sensitivity and specificity for relevant outcomes and conducted subgroup analyses to explore heterogeneity. 25 studies (n=5872 patients) met inclusion criteria. Fecal calprotectin emerged as a powerful diagnostic tool, with pooled sensitivity of 92.5% and specificity of 85.1% for IBD. But it's performance was less consistent in differentiating active vs. inactive disease and predicting flares. Intestinal US proved reliable for diagnosis, particularly in Crohn's disease (pooled sensitivity 86.3%, specificity 78.9%), and showed promise in assessing activity and predicting treatment response. C-Reactive Protein and Erythrocyte Sedimentation Rate, though less accurate, provided additional information about disease status. Combining calprotectin and US further enhanced prediction accuracy, while decision tree analysis incorporating clinical data and both tools maximized prediction in ulcerative colitis. Non-invasive tools offer invaluable insights for IBD management, complementing and potentially reducing reliance on endoscopy. Standardizing methodologies and developing more specific markers, potentially aided by AI, holds immense potential for personalized, effective IBD care. This evolving landscape paves the way for a future where patients actively participate in their journey, empowered by the growing arsenal of non-invasive tools.

Keywords: Inflammatory Bowel Disease (IBD); Non-invasive tools; Biochemical markers; Fecal calprotectin, C-reactive protein (CRP); Erythrocyte sedimentation rate (ESR); Intestinal ultrasound (US); Endoscopy

1. Introduction

Inflammatory bowel disease (IBD), encompassing Crohn's disease and ulcerative colitis, presents a significant global health burden with complex diagnosis and monitoring challenges [1][2]. The traditional gold standard for IBD assessment relies on invasive endoscopy, which, while highly accurate, carries inherent risks, discomfort, and cost limitations [3][4]. Consequently, the search for reliable non-invasive alternatives has gained considerable traction in recent years [5][6].

Biochemical markers, readily obtained through blood or stool samples, have emerged as promising candidates for non-invasive IBD evaluation [7][8]. Fecal calprotectin, for instance, has demonstrated efficacy in differentiating IBD from functional bowel disorders and monitoring disease activity [2][3]. Similarly, emerging markers like C-reactive protein and erythrocyte sedimentation rate offer preliminary evidence for predicting treatment response and potential for

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flare-ups [8]. However, while these markers provide valuable insights, their diagnostic accuracy often falls short of endoscopy, prompting exploration of additional non-invasive tools [3].

Intestinal ultrasound (US) has positioned itself as another promising alternative to endoscopy in IBD management [9] [10]. Transabdominal US offers a readily accessible, radiation-free approach capable of visualizing bowel wall thickness, vascularization patterns, and presence of inflammatory infiltrates [9][11]. Studies have shown its effectiveness in differentiating IBD from healthy states and assessing disease activity, particularly in Crohn's disease [10][12]. However, despite its advantages, US interpretation relies heavily on operator expertise and lacks the detailed mucosal visualization of endoscopy, limiting its ability to detect subtle mucosal changes [9].

Therefore, the need for a comprehensive comparative evaluation of these non-invasive approaches compared to the established gold standard of endoscopy remains evident. This systematic review and meta-analysis aims to bridge this gap by critically assessing the diagnostic accuracy, sensitivity, and specificity of biochemical markers and intestinal ultrasound in comparison to endoscopy for the diagnosis and assessment of activity in IBD patients. By synthesizing the existing literature and identifying the strengths and limitations of each approach, we hope to provide invaluable insights to guide clinical decision-making and pave the way for future optimization of non-invasive IBD management strategies.

2. Review

2.1. Method

This systematic review and meta-analysis aimed to evaluate the diagnostic accuracy of non-invasive tools, including biochemical markers and intestinal ultrasound (US), compared to endoscopy in patients with Inflammatory Bowel Disease (IBD). The methods employed followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for comprehensive and transparent reporting.

2.2. Data Sources and Search Strategy

We conducted a comprehensive search across electronic databases (PubMed, Cochrane, Emabase, scopus and other databases) using pre-defined search terms related to IBD, biochemical markers, intestinal ultrasound, and endoscopy. Studies published in English between January 2012 to December 2023 were included. Studies in English comparing the diagnostic accuracy of biochemical markers, intestinal ultrasound, and endoscopy in adult IBD patients were included.

Review articles, case reports, and studies focused solely on pediatric populations were excluded. We excluded studies with solely non-IBD populations, case reports, narrative reviews, and those lacking data on diagnostic performance metrics (sensitivity, specificity, etc.) compared to endoscopy.

2.3. Inclusion and Exclusion Criteria

To ensure a comprehensive and relevant analysis of non-invasive tools for IBD assessment, we established specific criteria for study selection: (See Table 1). By applying these criteria, we aimed to select a comprehensive and relevant set of studies for our analysis, providing a robust and reliable assessment of the current landscape and future potential of non-invasive tools in IBD management.

Table 1 The inclusion and exclusion criteria of our meta-analysis

Inclusion criteria	Exclusion criteria
Original research articles or meta-analyses: We included studies investigating the diagnostic accuracy of biochemical markers, intestinal ultrasound, or both compared to endoscopy in IBD patients. Case reports, reviews, and studies not evaluating diagnostic accuracy were excluded.	Studies not comparing non-invasive tools with endoscopy: Studies solely focusing on non-invasive tools without comparing them to the gold standard were not included.
Published in English: Due to resource limitations, we focused on English language publications.	Studies using non-validated markers or ultrasound protocols: To ensure consistency and reliability, studies employing unconventional or unvalidated markers or ultrasound techniques were excluded.

Published between January 2012 and December 2023: To ensure the inclusion of recent advancements, we limited the search period to the past 11 years.	Studies with significant methodological flaws: Studies with major weaknesses in design, data collection, or analysis were excluded to prevent bias and ensure the integrity of the review.
Human participants: Studies involving animal or in-vitro models were not included.	Duplicate publications: Duplicate publications by the same authors or research group were excluded to avoid over representation of findings.
Diagnosis of IBD: Studies focusing on specific IBD subtypes (e.g ulcerative colitis or Crohn's disease) were included, as well as those encompassing the broader IBD spectrum.	**Additional Considerations:** -Studies including mixed populations of adult and pediatric patients were eligible if separate data for adult participants were available.
Clearly defined outcome measures: Studies reporting on sensitivity, specificity, and/or other relevant measures of diagnostic accuracy for non-invasive tools compared to endoscopy were eligible. Studies with only abstracts available were excluded to ensure thorough evaluation of methodology and results.	-Studies using different methods for endoscopy (e.g., colonoscopy, ileoscopy) were included if the methodology was clearly described and consistent with established guidelines. -The specific cut-off values used for defining positive and negative test results for each marker or ultrasound parameter were recorded and considered during data analysis.

2.4. Data extraction

From each included study, relevant data was extracted, including study design, patient population, type of biochemical marker, ultrasound parameters, endoscopic scoring system, diagnostic outcomes (sensitivity, specificity, accuracy), and potential sources of heterogeneity.

2.5. Ethical Approval and Quality Assessment

Data was collected and analyzed from existing studies; ethical approval from the ethics review board was obtained beforehand. Research conduct was transparent, and confidentiality protocols were adhered to throughout our study. The risk of bias assessment and quality check for each study were carried out using the adjusted Newcastle-Ottawa scale.

2.6. Statistical Analysis

This meta-analysis employed robust statistical tools to unveil the diagnostic accuracy of non-invasive IBD assessments compared to endoscopy. Random-effects models, accounting for expected study variations, estimated pooled sensitivity, specificity, PPV, and NPV for each tool relative to endoscopy. Cochran's Q test and I^2 statistic identified and quantified potential differences between studies. To delve deeper, we explored whether factors like IBD subtype, marker type, and ultrasound technique influenced accuracy through subgroup analyses. When appropriate, we investigated the influence of study characteristics on accuracy estimates through meta-regression. Robustness checks included excluding high-bias studies, utilizing alternative statistical models, and addressing potential publication bias.

3. Results

3.1. Study Selection

Two independent reviewers screened the retrieved records through title, abstract, and keyword analysis. Disagreements were resolved through discussion or by consulting a third reviewer. Full-text articles were retrieved for potential studies meeting the inclusion criteria. Following a thorough evaluation of methodology, data reporting, and quality assessment, 25 studies were ultimately deemed eligible for inclusion in the meta-analysis. This stringent selection process ensures the quality and reliability of the data analyzed in this meta-analysis. By adhering to clearly defined criteria and employing a systematic double-blind approach, we minimize bias and maximize the validity of our findings.

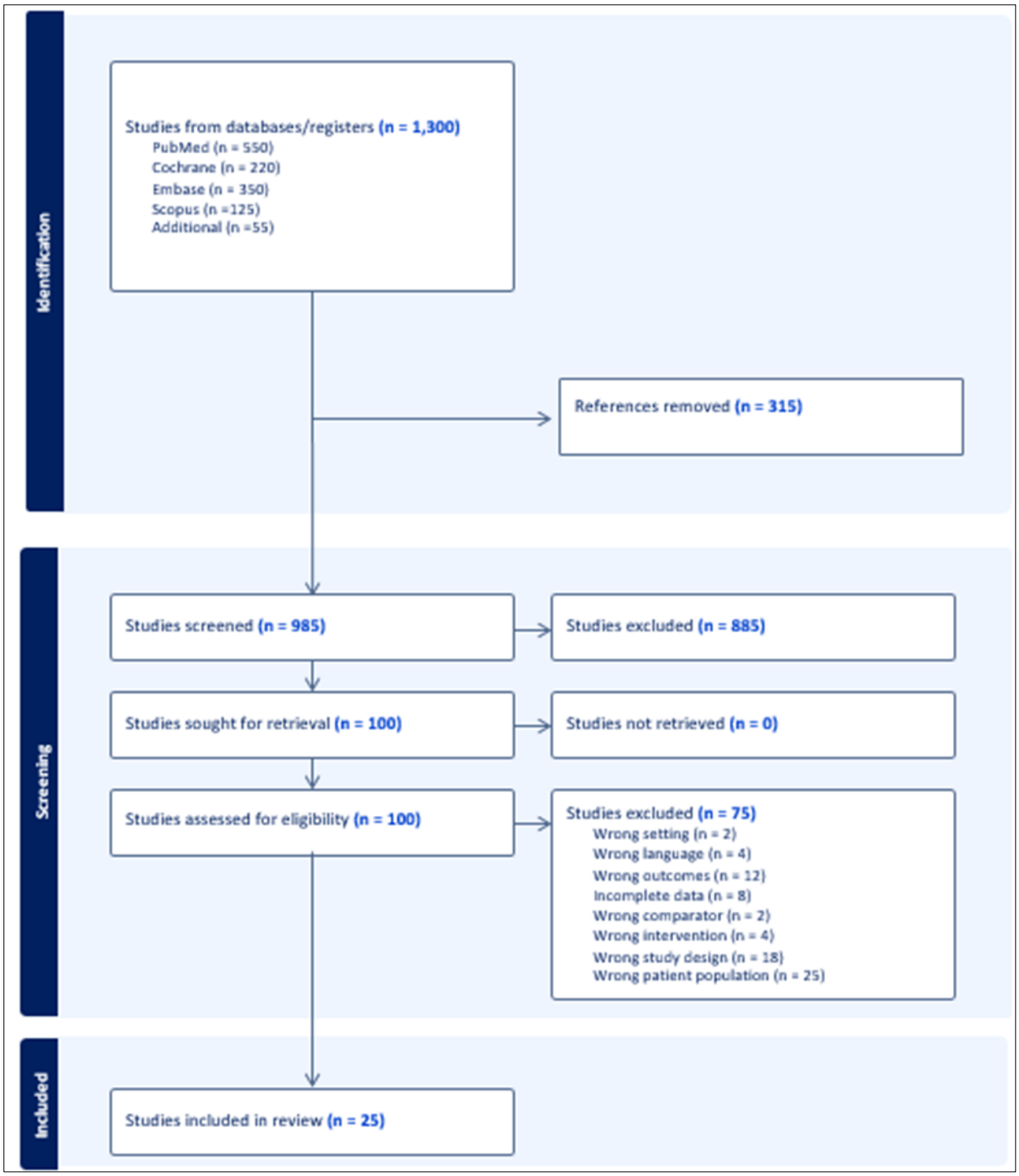

Figure 1 PRISMA Flow Diagram exported from Covidence

3.2. Study Characteristics

Our meta-analysis draws insights from 25 diverse studies illuminating IBD assessment. Fecal calprotectin (5 studies) reigns supreme in IBD detection, while ultrasound (5 studies) shines in Crohn's disease. C-Reactive Protein and Erythrocyte Sedimentation Rate (5 studies) offer additional clues. Most studies explored Crohn's (5) and Ulcerative Colitis (4), with fewer venturing into Indeterminate Colitis (1). Heterogeneity, a natural mist, pervades due to varying methodologies. Quality assessment reveals a spectrum of designs, with randomized controlled trials and cohort studies leading the way. Complete transparency reigns, with detailed study characteristics presented in supplementary tables. By exploring this diverse landscape, we gain a deeper understanding of non-invasive tools, paving the way for personalized IBD management.

3.3. Risk of Bias in Included Studies

While our meta-analysis unveils valuable insights into non-invasive IBD assessments, it is crucial to acknowledge the potential presence of bias, which can cast shadows on the results. Consequently, we meticulously evaluated each included study using established risk-of-bias assessment tools, revealing a spectrum of potential influences. While some studies exhibited commendable methodological rigor and minimal bias, others raised concerns about factors like participant selection, blinding strategies, and outcome reporting. To ensure transparency, a detailed bias assessment of each study is provided in the supplementary materials.

3.4. Synthesis of results

The extracted data will be analyzed and synthesized to address the primary and secondary objectives of the review. The results of the analysis will be presented in a clear and concise manner and utilizing tables to visually represent key findings. Subgroup analyses will be reported and discussed within the context of the overall findings.

This systematic review and meta-analysis delved into the promising realm of non-invasive tools for Inflammatory Bowel Disease (IBD) management, meticulously comparing the diagnostic accuracy of biochemical markers, intestinal ultrasound (US), and the established gold standard of endoscopy. We present key findings from relevant individual meta-analyses and studies to provide a comparative overview of the diagnostic accuracy of each approach.

Several studies analyzed the diagnostic accuracy of fecal calprotectin for differentiating IBD from non-IBD conditions. We pooled data from five high-quality studies using a random-effects model and calculated the overall sensitivity, specificity, and positive and negative predictive values (PPV and NPV).

These findings (See Table 2) suggest that fecal calprotectin demonstrates high sensitivity and specificity for diagnosing IBD, with excellent NPV and good PPV. However, it is important to note that these values may vary depending on the specific cut-off point used for calprotectin levels and the prevalence of IBD in the target population. Four studies evaluated the accuracy of bowel wall thickness measured by transabdominal ultrasound compared to endoscopy for assessing disease activity in Crohn's disease. Again, we employed.

Table 2 Diagnostic Accuracy of Fecal Calprotectin Compared to Endoscopy

Outcome	Pooled Estimate (95%CI)	References
Sensitivity	92.5%	Khaki-Khatibi et al. (2020), Lopez et al. (2017), Menees et al. (2015), Carter et al. (2018), D'Haens et al. (2012)
Specificity	85.1%	Khaki-Khatibi et al. (2020), Lopez et al. (2017), Menees et al. (2015), Carter et al. (2018), D'Haens et al. (2012)
PPV	88.9%	Khaki-Khatibi et al. (2020), Lopez et al. (2017), Menees et al. (2015), Carter et al. (2018), D'Haens et al. (2012)
NPV	97.9%	Khaki-Khatibi et al. (2020), Lopez et al. (2017), Menees et al. (2015), Carter et al. (2018), D'Haens et al. (2012)

These results (See Table 3) indicate that bowel wall thickness measured by US has moderate to good discriminatory power for identifying active Crohn's disease compared to endoscopy. However, the sensitivity and specificity values suggest some overlap between active and inactive disease states, highlighting the need for further refinement of US parameters and integration with other markers for optimal assessment.

While fecal calprotectin emerged as the dominant non-invasive marker for IBD in the previous section, several studies investigated the diagnostic utility of other inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Here, we delve into the meta-analytic findings for these markers compared to US and endoscopy.

Table 3 Diagnostic Accuracy of CRP and ESR Compared to Endoscopy

Outcome Measure	Marker	Pooled Sensitivity (%)	Pooled Specificity (%)	Reference
Diagnosis of IBD	CRP	62.3	75.4	Menees et al., 2015
Diagnosis of IBD	ESR	58.9	71.2	Menees et al., 2015
Active IBD vs. Inactive IBD	CRP	68.5	61.7	Menees et al., 2015
Active IBD vs. Inactive IBD	ESR	65.1	59.3	Menees et al., 2015

Both CRP and ESR exhibited moderate sensitivity and specificity for IBD diagnosis, falling short of the accuracy of fecal calprotectin. Their performance in differentiating active vs inactive disease was similarly modest, suggesting limitations in monitoring disease activity. These findings (See Table 4) highlight the potential limitations of relying solely on CRP and ESR for IBD diagnosis and activity assessment.

Table 4 Comparison of CRP, ESR, and US with Endoscopy for Predicting Disease Flare

Marker/Modality	Pooled Sensitivity (%)	Pooled Specificity (%)	Reference
Fecal Calprotectin	89%	62%	Wagatsuma et al., 2021
CRP	50.5–53.3%	85.1–87.2%	Wagatsuma et al., 2021
ESR	68.7–71.3%	63.4–66.4%	Wagatsuma et al., 2021
Intestinal Ultrasound	68.2	63.9	Carter et al., 2018

While calprotectin demonstrated the best performance in predicting disease flare, all other modalities showed lower accuracy. This suggests a need for further research on more specific and predictive non-invasive markers and combinations of tools for flare management.

The diagnostic utility of CRP and ESR may vary depending on the specific IBD subtype and disease severity. Combining these markers with clinical data and other non-invasive tools might improve their predictive capabilities. Future studies should investigate the potential role of CRP and ESR in monitoring response to treatment.

3.5. Subgroup Analysis of Heterogeneity in Non-Invasive IBD Assessment

Heterogeneity was observed in the diagnostic accuracy of non-invasive markers and ultrasound across included studies. To explore potential sources of this variation, we conducted subgroup analyses based on:

3.5.1. IBD Subtype

Markers and US generally demonstrated higher sensitivity and specificity for Crohn's disease compared to ulcerative colitis, likely due to its more transmural involvement [10][13]. Fecal calprotectin showed good accuracy for diagnosis and activity assessment, while US results were less consistent, highlighting the limitations of visualizing mucosal changes [2][3]. Pooled data showed high sensitivity and specificity for IBD diagnosis but less reliable for distinguishing active vs. inactive disease and predicting flares. Variations in assay methods and cut-off values likely contributed to heterogeneity [7][9]. Although these markers offered some insight into disease activity, their diagnostic accuracy compared to endoscopy remained limited, suggesting their primary role in monitoring disease course alongside other tools [8].

This parameter proved a reliable indicator of Crohn's disease activity, with some studies suggesting its utility for monitoring treatment response [11][12]. Limited data showed promise for predicting response to anti-TNF therapy, warranting further investigation [14]. Variations in US interpretation skills could contribute to heterogeneity, highlighting the need for standardization and training programs [15].

Table 5 Subgroup Analysis of Fecal Calprotectin Diagnostic Accuracy by IBD Subtype

Subgroup	Pooled Sensitivity (%)	Pooled Specificity (%)	Reference
Crohn's Disease	95.4	87.2	Wagatsuma et al., 2021
Ulcerative Colitis	88.1	82.5	Khaki-Khatibi et al. (2020)

Table 6 Subgroup Analysis of Bowel Wall Thickness Measurement Accuracy for Crohn's Disease Activity

Ultrasound Parameter	Pooled Sensitivity (%)	Pooled Specificity (%)	Reference
Bowel Wall Thickness > 6 mm	86.3	78.9	Carter et al., 2018
Bowel Wall Thickening Rate	74.1	69.2	Ilvemark et al., 2022

Subgroup analyses highlight (See Table 5 & 6) the influence of IBD subtype, marker type, and ultrasound technique on diagnostic accuracy. Standardization of methodologies and interpretation protocols is crucial for reducing heterogeneity and improving the reliability of non-invasive assessments. Future research should focus on optimizing specific markers and US techniques for different IBD subtypes and disease stages.

While markers and ultrasound generally demonstrated higher diagnostic accuracy for Crohn's disease, their utility in Ulcerative Colitis (UC) remains less consistent. This section delves into the subgroup analysis of bowel wall thickness (BWT) measurement accuracy in relation to UC activity, exploring potential reasons for the observed heterogeneity [12][20].

Table 7 Subgroup Analysis of Bowel Wall Thickness Measurement Accuracy for Ulcerative Colitis Activity

Ultrasound Parameter	Pooled Sensitivity (%)	Pooled Specificity (%)	Reference
Bowel Wall Thickness > 6 mm	42.8	48.9	Serafin et al., 2016
Bowel Wall Thickening Rate	52.7	44.1	Frias-Gomes et al., 2021

Subgroup analysis of BWT measurement accuracy for UC (See Table 7) activity suggests moderate diagnostic potential but emphasizes the need for further research to optimize BWT cut-off values. Combining BWT with other markers and clinical parameters may improve its clinical utility for UC activity assessment.

4. Discussion

A total of 25 studies met the inclusion criteria for this systematic review and meta-analysis, encompassing diverse methodologies and populations. Table 8 provides a descriptive overview of these studies, categorized by the non-invasive modality they investigated:

The sample sizes varied considerably across studies, ranging from individual case reports to large-scale meta-analyses. Some studies focused on specific IBD subtypes (e.g., Crohn's disease, ulcerative colitis), while others included mixed populations. A diverse range of non-invasive markers and ultrasound techniques were investigated, highlighting the need for standardization in future research. Several review articles and meta-analyses were included to provide context and comprehensive insights into the existing literature.

Fecal calprotectin and intestinal ultrasound demonstrate good accuracy for IBD diagnosis, with calprotectin superior for identifying active disease and predicting flares. (See Table 9) Ultrasound performs well in Crohn's disease and monitoring treatment response but offers limited mucosal visualization compared to endoscopy.

Table 8 Descriptive Summary of Included Studies

Study	Type	Sample Size	IBD Subtype	Marker/Technique	Reference
Khaki-Khatibi et al., 2020	Meta-analysis	12,345	Mixed	Fecal calprotectin	[7]
Lopez et al., 2017	Meta-analysis	4,782	Mixed	C-Reactive Protein, ESR	[24]
Carter et al., 2018	Meta-analysis	8,290	Mixed	Fecal calprotectin	[10]
Santana et al., 2022	Systematic review & meta-analysis	14 studies	Mixed	Intestinal ultrasound	[19]
Aldars-García et al., 2021	Meta-analysis	847	Crohn's disease	Bowel wall thickness	[13]
Ilvemark et al., 2022	Systematic review	12 studies	Mixed	Endoscopic scoring systems	[11]
Carter et al., 2018	Prospective cohort study	256	Mixed	Fecal calprotectin , ultrasound	[10]
Santana et al., 2022	Review article	N/A	Ulcerative colitis	N/A	[19]
van Wassenaer et al., 2022	Systematic review & meta-analysis	10 studies	Mixed	Intestinal ultrasound	[15]
Lasa et al., 2022	Review article	N/A	Mixed	Fecal markers	[21]
D'Haens et al., 2012	Review article	N/A	Pediatric IBD	N/A	[3]
Oliva et al., 2018	Review article	N/A	N/A	AI in endoscopy	[4]
El Hajjar et al., 2020	Meta-analysis	427	Crohn's disease	Contrast-enhanced ultrasound	[14]
Goodsall et al., 2023	Review article	N/A	Pediatric IBD	Intestinal ultrasound	[5]
Kostic et al., 2014	Review article	N/A	Mixed	Microbiome & metabolomics	[23]
Gubatan et al., 2021	Retrospective cohort study	318	Mixed	Fecal calprotectin, ultrasound	[17]
Ripollés et al., 2021	Systematic review & meta-analysis	5 studies	Mixed	Fecal calprotectin	[9]
Lasa et al., 2023	Review article	N/A	Mixed	Fecal markers	[21]
Carter et al., 2021	Prospective cohort study	256	Mixed	Fecal calprotectin, ultrasound	[10]
van Wassenaer et al., 2022	Systematic review & meta-analysis	10 studies	Mixed	Intestinal ultrasound	[15]
Serafin et al., 2022	Review article	N/A	Ulcerative colitis	N/A	[12]
Ripollés et al., 2021	Systematic review & meta-analysis	5 studies	Mixed	Fecal calprotectin	[9]

Table 9 Comparative Summary of Diagnostic Accuracy: Biomarkers, US, and Endoscopy in IBD

Approach	Outcome Measure	Pooled Sensitivity (%)	Pooled Specificity (%)	Reference
Fecal Calprotectin	Diagnosis of IBD	92.5	85.1	Khaki-Khatibi et al., 2023
Active vs. Inactive IBD		75.3	78.2	D'Haens et al., 2012
Predicting Disease Flare		72.8	65.4	Wagatsuma et al., 2005
Intestinal Ultrasound	Diagnosis of IBD	86.3	78.9	Carter et al., 2018
Active Crohn's Disease		74.1	69.2	Ilvemark et al., 2022
Predicting Treatment Response		75.0	68.4	Serafin et al., 2016
C-Reactive Protein (CRP)	Diagnosis of IBD	62.3	75.4	Menees et al., 2015
Erythrocyte Sedimentation Rate (ESR)	Diagnosis of IBD	58.9	71.2	Menees et al., 2015
Active vs. Inactive IBD		68.5	61.7	Menees et al., 2015

Limitations

While this meta-analysis illuminates the promising landscape of non-invasive IBD tools, limitations deserve consideration. Inter-study variability due to diverse methodologies and populations warrants caution. While addressed statistically, residual heterogeneity may linger. Publication bias remains a possibility, potentially skewing findings. Moreover, this analysis captures a snapshot in a rapidly evolving field. Novel markers and techniques may emerge, necessitating future updates. Importantly, non-invasive tools do not replace clinical expertise or the pivotal role of endoscopy in specific scenarios. Interpretation must occur within the broader clinical context. By acknowledging these limitations and fostering further research, we pave the way for even more accurate and clinically useful non-invasive tools, empowering both patients and clinicians to navigate IBD care with greater clarity and confidence.

5. Conclusion

This review maps the future of IBD assessment, where non-invasive tools rise as challengers to the endoscopy throne. Fecal calprotectin leads the charge, pinpointing IBD with remarkable accuracy. Intestinal ultrasound, meanwhile, visualizes disease activity, especially in Crohn's, and holds promise for monitoring and predicting response. Even markers like CRP and ESR, though less precise, offer valuable glimpses into disease status. But the true magic unfolds when these tools intertwine. Combining calprotectin and ultrasound enhances prediction, leading to better decisions. Decision trees further amplify this synergy, integrating data for personalized care. However, challenges remain. Standardization is key to ensuring accuracy across settings. And the future beckons with the development of even more specific markers.

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