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Review

Microplastics and Inflammatory Bowel Disease: From Environmental Exposure to Clinical Uncertainty

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Abstract

Microplastics and nanoplastics are persistent environmental contaminants of increasing relevance to human health, particularly because ingestion places the gastrointestinal tract at the center of exposure. In inflammatory bowel disease (IBD), in which epithelial barrier dysfunction, dysbiosis, immune activation, and environmental factors intersect, these particles represent a biologically plausible but incompletely characterized exposure. This narrative review summarizes the current evidence on microplastics, intestinal inflammation, and IBD, including exposure routes, particle definitions, measurement challenges, biological mechanisms, experimental data, and human studies. Experimental evidence suggests that microplastics may disrupt the mucus–epithelial barrier, promote oxidative stress, alter microbial and metabolite profiles, and amplify inflammation in susceptible or inflamed intestinal environments. Human evidence remains limited and observational, with fecal, serum, and tissue-based studies reporting associations between microplastic burden and IBD-related features, including disease activity, fecal calprotectin levels, and fibrostenotic tissue changes. Current data do not establish microplastics as causal drivers of IBD or clinically useful biomarkers. The most balanced interpretation is that they may act as environmental disease modifiers or markers of altered intestinal handling rather than as primary initiators of IBD. Standardized analytical methods and longitudinal human studies are needed to clarify their clinical relevance.
Keywords: Inflammatory bowel diseases, intestinal mucosa, microplastics, nanoplastics.

INTRODUCTION

Plastics have become integral to modern life because of their low cost, durability, and versatility, with widespread use in packaging, textiles, and consumer products. However, the physicochemical stability that makes plastics useful also contributes to their environmental persistence, as plastic debris progressively fragments into smaller particles that disperse throughout terrestrial, aquatic, and atmospheric environments.[1,2] Microplastics and nanoplastics are increasingly recognized not only as environmental contaminants but also as potential human health hazards, with the gastrointestinal tract representing a principal interface of exposure through ingestion and, indirectly, inhalation.

Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, is a chronic immune-mediated disorder arising from interactions among genetic susceptibility, epithelial barrier dysfunction, alterations in the microbiota, and environmental exposures. Its rising incidence in newly industrialized regions has drawn attention to environmental triggers associated with urbanization and dietary westernization.[3] Compared with acute or predominantly functional gastrointestinal disorders, IBD provides a particularly informative model for studying environmental pollutants because it is characterized by chronic mucosal inflammation, measurable disease activity, and opportunities for longitudinal assessment using stool, blood, endoscopic, and tissue samples. Within this context, microplastics represent a biologically plausible but incompletely characterized exposure. Whether these particles act as causal contributors to IBD, consequences of intestinal inflammation, or modifiers of disease activity remains unresolved, and the available human data remain limited.

Several recent reviews have summarized the analytical challenges, experimental findings, and potential gastrointestinal effects of microplastics and nanoplastics, including their possible relationship with intestinal inflammation and IBD.[4-6] However, the rapid emergence of human and disease-relevant translational data warrants an updated, clinically oriented appraisal that more clearly distinguishes biological plausibility from evidence of causation.

Accordingly, this review updates the evidence through August 2026 and organizes it around a three-part interpretive framework: whether microplastics may represent causal contributors to IBD, consequences or markers of altered intestinal handling, or modifiers of established disease. The review also considers recent human and translational evidence, the possibility of reverse causality, clinically relevant confounding factors, and the implications of current uncertainty for patient counseling and future research.

METHODS

This narrative review aimed to synthesize the most relevant evidence regarding human exposure to microplastics and nanoplastics, their measurement in gastrointestinal samples, and their relationship with intestinal inflammation and IBD. Relevant literature was identified through searches of major electronic databases, including PubMed/MEDLINE, Scopus, and Web of Science, from inception through August 2026. The search strategy used a combination of Medical Subject Headings (MeSH) terms and free-text keywords, including but not limited to "microplastics," "nanoplastics," "polystyrene," "polyethylene," "plastic particles," "inflammatory bowel disease," "Crohn's disease," "ulcerative colitis," "intestinal barrier," "intestinal permeability," "mucus layer," "gut microbiota," and "intestinal inflammation." Reference lists of relevant articles and previous reviews were hand-searched to identify additional sources, and ClinicalTrials.gov was searched to identify registered ongoing studies.

The literature was selected based on its relevance to the central question of whether microplastics and nanoplastics act as causal contributors to IBD, represent consequences of altered intestinal handling, or function as environmental disease modifiers. Selected sources included human observational studies reporting microplastic burden in stool, serum, or intestinal tissue; in vitro and organoid-based epithelial models; animal models of intestinal injury and colitis; and methodological reports addressing particle detection, polymer identification, and contamination control. Environmental and production-related data were incorporated selectively to establish the scale and routes of human exposure. Priority was given to recent, high-quality, peer-reviewed articles, while earlier methodological and mechanistic studies were retained when they provided foundational context for current analytical and biological interpretations. Conference abstracts and registered studies were considered selectively when they provided recent IBD-specific human evidence not yet available as full peer-reviewed publications. Sources without clear relevance to gastrointestinal exposure or intestinal inflammation, as well as duplicate or less complete reports of the same study, were excluded. Study selection and thematic organization were based on author consensus, consistent with a narrative review design rather than a formal systematic review process.

Global Plastic Burden and Routes of Human Exposure

The global burden of plastic pollution has increased in parallel with the expansion of plastic production and consumption. Since the mid-20th century, plastics have been produced at an accelerating rate, and a substantial proportion of cumulative plastic waste has either been landfilled or released into the environment rather than effectively recycled.[1,7] Global emissions inventories indicate that mismanaged plastic waste remains an important source of environmental leakage, with marked regional variation related to consumption patterns, waste management capacity, and disposal practices.[8]

Plastic pollution is not restricted to marine environments. Fragmented plastic particles have also been documented in freshwater and polar systems, illustrating their environmental persistence and capacity for long-range transport.[9] Larger plastic items may fragment through mechanical, photochemical, and thermal degradation into smaller particles that persist and circulate within environmental systems, providing the basis for recurrent human exposure to microplastics and nanoplastics.[2,10]

Human exposure occurs through multiple pathways, of which ingestion is the most directly relevant to the gastrointestinal tract (Figure 1). Microplastics have been reported in drinking water, including tap and bottled water, seafood, salt, and other food products, and food processing and packaging may further contribute to dietary exposure.[11-14] Studies of commercially available table salts further illustrate that microplastic contamination may affect everyday dietary products, including sea, lake, and rock salts.[15] Particle release from plastic containers may increase with heat, prolonged storage, mechanical stress, and repeated use, although the extent of exposure varies according to polymer type and handling conditions. Inhalation represents an additional indirect route, as airborne fibers and fragments from synthetic textiles, household dust, urban air pollution, and cigarette smoke-related exposure may undergo respiratory deposition and, in part, mucociliary clearance followed by swallowing.[16,17]

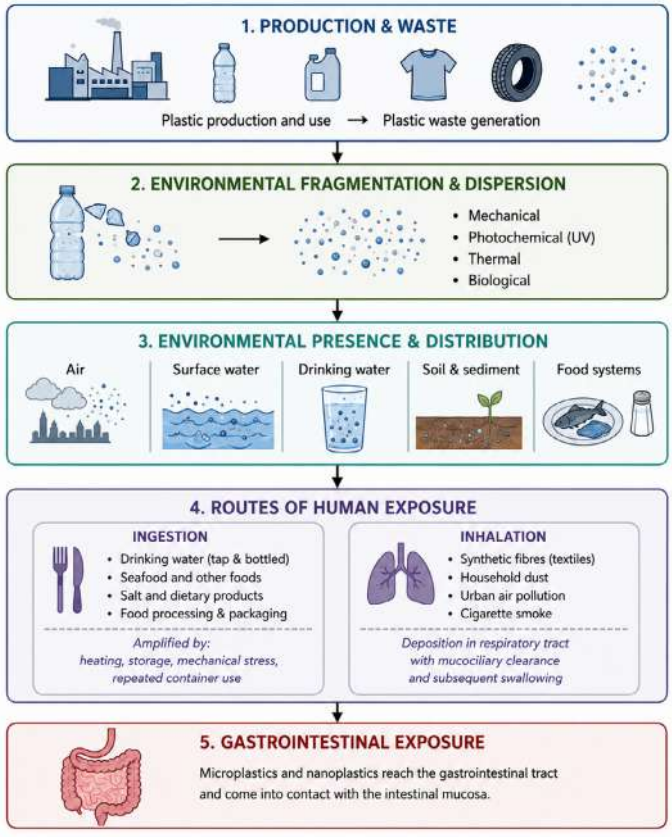

Figure 1. Routes of human exposure to microplastics and nanoplastics through the gastrointestinal tract. Ingestion and inhalation represent two major exposure pathways. Dietary exposure may occur through water, seafood, salt, processed foods, and packaged foods, whereas inhaled particles from textile fibers, household dust, urban air, or cigarette smoke may reach the gut through mucociliary clearance and swallowing. Particle release from food-contact materials may increase with heating, prolonged storage, mechanical stress, and repeated container use.

This exposure landscape is particularly relevant to gastroenterology because the intestinal mucosa represents a chronically exposed biological surface. In IBD, the parallel increase in environmental plastic exposure and disease incidence in industrializing regions should not be interpreted as evidence of causality; however, it supports the rationale for examining microplastics within the broader environmental context in which intestinal inflammation develops and persists.[4,5]

Definitions and Classification of Microplastics and Nanoplastics

Microplastic research has long been limited by inconsistent terminology and the absence of a universally accepted classification framework.[18]

The most widely used consensus definition characterizes microplastics as synthetic solid particles ranging from 1 µm to 5 mm in size, of either primary or secondary origin.[19] Nanoplastics generally refer to plastic particles smaller than 1 µm, although some nanomaterial-based frameworks restrict the term to particles between 1 and 100 nm.[18,20] In this review, we use the term nanoplastics in the broader sense to describe plastic particles smaller than 1 µm, while acknowledging that analytical detection becomes increasingly challenging within this size range.

Beyond size, particles are classified according to origin, shape, and polymer composition, with polymer type influencing density, surface chemistry, and degradation behavior.[18] Primary microplastics are manufactured at small dimensions, such as industrial pellets and microbeads, whereas secondary microplastics arise from the fragmentation of larger plastic items through mechanical, photochemical, and thermal degradation.[19] Shape—whether fragment, fiber, film, or bead—is not merely descriptive: experimental studies have demonstrated shape-dependent gut accumulation, with fibers retained to a greater extent than fragments or beads and associated with more pronounced mucosal damage and increased intestinal permeability.[21] Shape may also influence analytical detectability because fibers and fragments may be identified with different sensitivities across analytical methods.

Plastic particles should not be considered inert materials. They may contain additives such as plasticizers and stabilizers, and their surfaces can adsorb environmental pollutants or microorganisms.[18] Therefore, their potential intestinal effects may reflect not only the physical presence of the particles but also the chemical and microbial exposures they carry. This composite nature provides an important bridge to the mechanistic pathways discussed in the following sections.

Measurement of Microplastics in Gastrointestinal Samples

Measuring microplastics in gastrointestinal samples is technically challenging. Stool and intestinal tissues contain complex organic material, mucus, and cellular debris, whereas the near-ubiquitous presence of plastic in laboratory environments creates a substantial risk of contamination. Therefore, contamination control is a critical methodological concern regardless of sample type. Rigorous protocols require the use of glass or metal labware rather than plastic, cotton laboratory garments, procedural and airborne blanks, and blank-corrected reporting; without these precautions, reported particle concentrations are difficult to interpret.[22,23]

Several analytical techniques are available for microplastic analysis and polymer identification, each with distinct strengths and limitations in terms of sensitivity, size range, and chemical specificity.[24] Fourier-transform infrared (FTIR) spectroscopy is widely used for polymer identification but loses resolution for very small particles. Raman spectroscopy can detect smaller particles with chemical specificity but may be affected by fluorescence and matrix interference. Pyrolysis–gas chromatography/mass spectrometry provides robust polymer mass quantification but does not preserve information on particle count, size, or morphology (Table 1).

Two biological matrices are commonly used in gastrointestinal research. Stool sampling is noninvasive and allows repeated measurements, making it the most feasible approach for clinical cohorts, although its composition is influenced by diet and intestinal transit time.[25-27] Tissue-based assessment using endoscopic biopsy or surgical specimens provides more direct information on mucosal or tissue-associated particles but is invasive and more susceptible to procedural contamination.[28,29] In IBD research, stool sampling has been the more practical approach to date, whereas tissue-based evidence remains comparatively limited.

These findings highlight the need to interpret gastrointestinal microplastic measurements in relation to the biological matrix being analyzed. Stool-based recovery may be confounded by diarrhea, mucus, blood admixture, diet, and transit time, whereas tissue-based detection may be influenced by sampling site, disease activity, fibrosis, and procedural contamination. This raises an interpretive question central to this review: does a measured microplastic burden reflect ambient exposure, altered intestinal handling, or a downstream consequence of active disease? Disentangling these possibilities requires longitudinal studies pairing fecal and tissue sampling with disease activity indices, an issue revisited in later sections.

Biological Mechanisms Linking Microplastics to Intestinal Inflammation

The biological link between microplastics and intestinal inflammation

Table 1. Comparison of analytical techniques for microplastic detection and polymer identification in gastrointestinal samples

Technique	Principle	Effective size range	Polymer/chemical identification	Key strengths	Key limitations
Fourier-transform infrared (FTIR) spectroscopy	Vibrational absorption spectroscopy	Generally limited to particles ≳20 µm	Yes—established polymer spectral libraries	Widely available and well validated for polymer identification	Reduced resolution and sensitivity for particles smaller than approximately 20 µm
Raman spectroscopy	Vibrational/inelastic light scattering	Can resolve particles down to approximately 1 µm	Yes—high chemical specificity	Detects smaller particles than FTIR and provides polymer-specific signals	Susceptible to fluorescence interference and signal masking by organic or biological matrices
Pyrolysis–gas chromatography/mass spectrometry (Py-GC/MS)	Thermal decomposition followed by chromatographic and mass spectrometric analysis	Not particle-resolved; bulk sample analysis	Yes—robust polymer mass and chemical quantification	Provides quantitative data on polymer mass and composition	Destructive; does not preserve information on particle count, size, or morphology

FTIR: Fourier-transform infrared; Py-GC/MS: pyrolysis–gas chromatography/mass spectrometry.

is best interpreted in terms of plausibility rather than established causality. Current evidence suggests that microplastics and nanoplastics may interact with several pathways already central to IBD pathogenesis, including mucus and epithelial barrier function, oxidative stress, dysbiosis, mucosal immune activation, and exposure to plastic-associated chemicals.[4,5]

The mucus–epithelial interface is the first major barrier encountered by ingested particles and is increasingly recognized as a key determinant of whether such particles interact with the mucosal surface, are retained, or cross the epithelial barrier.[30] Human intestinal mucus appears to limit particle migration and cellular damage, while organoid-derived epithelial models, including systems incorporating microfold cells, and gut barrier platforms suggest that particle size, surface characteristics, epithelial context, and specialized particle-sampling pathways may further influence uptake, toxicity, and inflammatory responses.[31]

Experimental evidence also indicates that ingested nano- and micro-sized polystyrene particles can cross the intestinal barrier and accumulate systemically, and advanced epithelial barrier models have similarly demonstrated particle passage across lung and gut systems.[32,33] These findings are relevant to IBD because the mucus layer and epithelial barrier are frequently disrupted during active inflammation. However, barrier passage in experimental models should not be interpreted as evidence of clinically meaningful translocation in humans.

Oxidative stress and epithelial injury represent additional plausible pathways. Experimental studies suggest that microplastics, particularly polystyrene particles, can induce reactive oxygen species generation, mitochondrial stress, and cytotoxicity.[34] Importantly, aged or contaminant-loaded particles, such as benzo[a]pyrene-loaded aged polystyrene microplastics, may exert greater biological effects than pristine particles, promoting colonic barrier injury through oxidative stress-mediated Notch signaling.[35] In IBD, such epithelial stress may amplify existing mucosal injury rather than act as an independent disease trigger.

The gut microbiota provides another mechanism through which microplastics may influence intestinal inflammation. Microplastics may alter the intestinal microenvironment, interact with microbial communities,

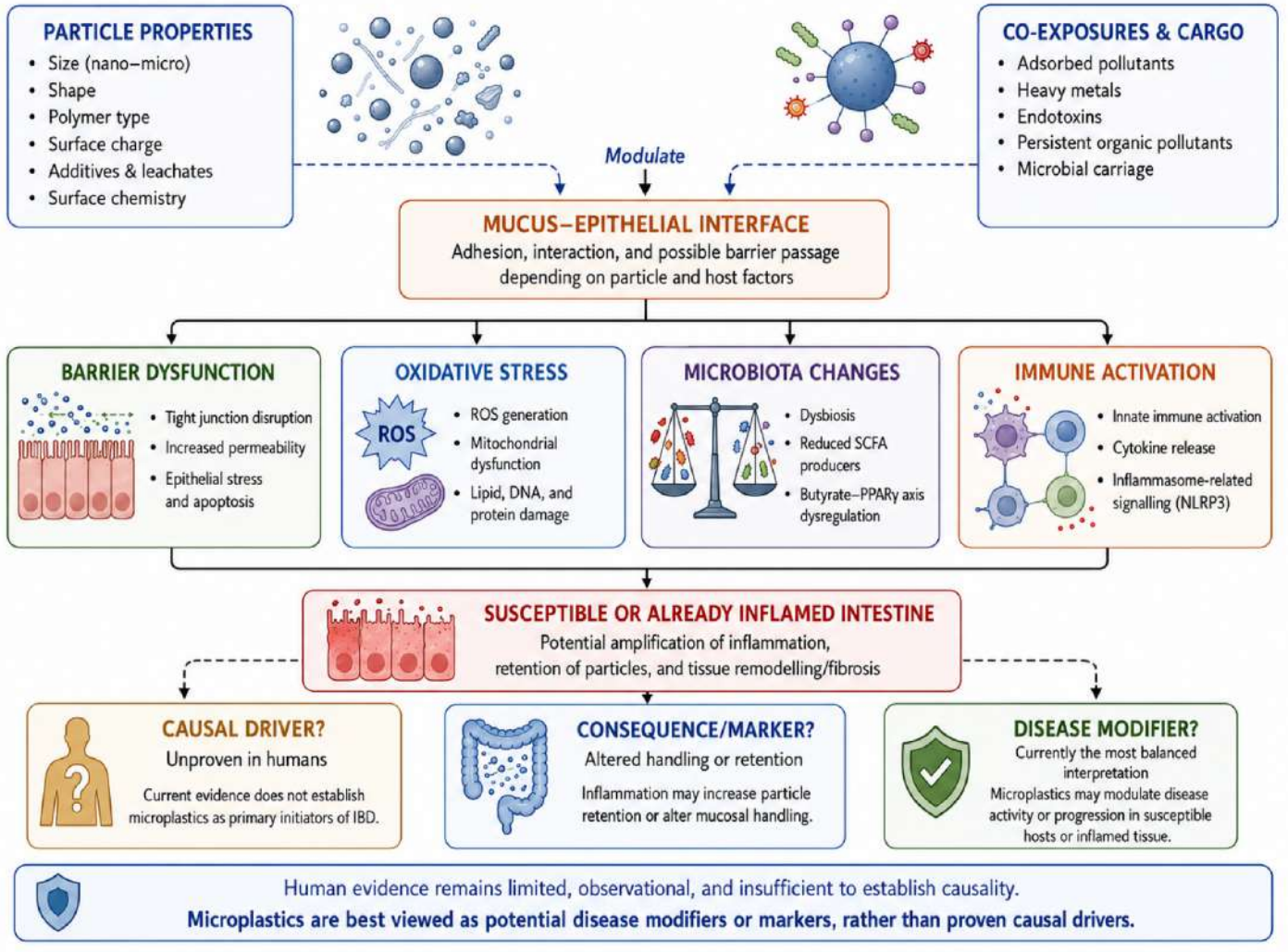

Figure 2. Proposed mechanisms linking microplastics to intestinal inflammation and IBD. Particle properties and co-exposures may influence interactions at the mucus–epithelial interface, contributing to barrier dysfunction, oxidative stress, alterations in the microbiota, and immune activation. In susceptible or already inflamed intestinal tissue, these pathways may amplify inflammation, particle retention, and tissue remodeling. Current evidence supports a disease-modifier model rather than a primary causal role for microplastics in IBD.

Table 2. Representative experimental studies linking micro- and nanoplastics to intestinal inflammation

Mechanistic domain	Representative studies	Model and exposure	Main experimental findings	Relevance to IBD
Mucus–epithelial barrier interaction	van Wijngaarden et al[31] Donkers et al.[33] Lehner et al.[42]	Human intestinal mucus model; advanced epithelial lung/gut barrier models; 3D intestinal barrier model	Human intestinal mucus model; advanced epithelial lung/gut barrier models; 3D intestinal barrier model Human intestinal mucus limited microplastic migration, uptake, and cellular damage; advanced barrier systems demonstrated particle passage under experimental conditions; 3D models enabled evaluation of epithelial and immune responses	Supports the mucus–epithelial interface as a key determinant of particle exclusion retention, and barrier interaction
Human-derived epithelial models	Cortes et al.[43] Chen et al.[44] Kharaghani et al.[45]	Human Caco-2 intestinal epithelial cells; human intestinal organoid-derived epithelial models and without M cells; with healthy and Crohn's disease-derived human duodenum-chip models exposed to polystyrene microplastics and nanoplastics	Polystyrene microplastics and nanoplastics showedsize- and concentration-dependent epithelial uptake or injury, inflammatory cytokine induction, and differential responses between healthy and disease-relevant epithelial systems	Provides human-relevant evidence that particle size, epithelial model complexity, and disease-associated epithelial context may influence toxicity and absorption
Epithelial barrier injury and junction disruption	Luo et al.[46] Sung et al.[47] Xie et al.[48]	DSS-induced colitis mouse models exposed to polystyrene or polyethylene modifying	Microplastics worsened colitis severity, shortened colon length, increased histological injury, impaired epithelial junctions, reduced mucus-related protection, and increased intestinal permeability	Supports a disease-modifying effect in an already inflamed intestine rather than a purely disease-initiating role
Inflamed-tissue susceptibility and particle retention	Lamprecht et al.[49] Busch et al.[50]	TNBS-induced colitis model exposed to fluorescent polystyrene particles; triple-culture in vitro model (Caco-2/HT29-MTX-E12/THP-1) under healthy versus inflamed conditions	Particles preferentially accumulated in ulcerated and inflamed colonic mucosa compared with healthy tissue, with greater retention of smaller particles; in vitro, particle-associated cytotoxicity and cytokine responses were more evident under inflamed culture conditions	Provides experimental support for the disease-modifier hypothesis, suggesting that the inflamed inflamed intestinal environment may alter alter particle retention and biological responses
Oxidative stress, apoptosis, and epithelial injury	Jia et al.[51] Zeng et al.[52] Shaoyong et al.[35] Hwang et al.[34]	Mouse and cellular models exposed to polypropylene or polystyrene microplastics, including aged or contaminant -loaded particles	Microplastics induced oxidative stress, mitochondrial injury, colonic apoptosis, cytotoxicity, and barrier dysfunction; benzo[a]pyrene-loaded aged particles promoted colonic barrier injury through oxidative stress-mediated Notch signaling; polystyrene microplastics activated NF-κB/NLRP3/IL-1β-related pathways	Links microplastics to epithelial stress pathways, inflammasome-related signaling, and barrier damage relevant to intestinal inflammation
Mucus secretion and microbiota–metabolite alterations	Li et al.[53] Sun et al.[54] Qiao et al.[55] Huang et al.[36] Ghosal et al.[37] Zhai et al.[38]	Mice orally exposed to polyethylene or polystyrene microplastics/nanoplastics; in vitro gut simulation/ Caco-2 models; IBD-like experimental models; murine colitis models	Microplastic exposure altered gut microbiota composition, reduced colonic mucin release, affected microbial metabolism, induced dysbiosis-like shifts, impaired gut barrier function, and disrupted the gut microbiota–butyrate –PPARγ axis	Connects particle exposure to dysbiosis, mucus barrier dysfunction, microbial metabolites, and short-chain fatty acid-related pathways central to IBD biology
Immune activation and host susceptibility	Liu et al.[56] Schwarzfischer et al.[57] Choi et al.[58]	Mice with intestinal immune imbalance; nanoplastic exposure in an IBD mouse model; mice exposed to polystyrene microplastics	Microplastics aggravated inflammatory damage in immune-imbalanced mice, affected macrophage-mediated inflammation inflammation and intestinal health, and induced inflammatory responses in the colon	Suggests that host immune status may modify the biological effects of microplastic and nanoplastic exposure
Particle size, polymer type, and exposure context	Li et al.[59] Schwarzfischer et al.[32] Xu et al.[60]	IBD-like zebrafish and mouse models; mice exposed to nano- and microsized polystyrene particles; nanoplastic exposure models	Microplastics and nanoplastics produced distinct adverse effects; particles crossed the intestinal barrier and accumulated in tissues; surface-labeled nanoplastics induced Crohn's ileitis-like features through epithelial injury pathways	Highlights that biological effects depend on particle size, surface properties, polymer type, and experimental context
Environmental aging and co-exposure	Shaoyong et al.[35] Huang et al.[36]	Aged polystyrene microplastics loaded with benzo[a]pyrene; co-exposure to microplastics and tetrabromobisphenol A in human gut simulation /Caco-2 models	Contaminant-loaded particles or co-exposures produced barrier injury, oxidative stress, altered epithelial responses, or gut microbiota-related effects	Emphasizes that real-world microplastic toxicity may reflect mixed exposure to particles, additives, and adsorbed pollutants

3D: three-dimensional; DSS: dextran sodium sulfate; IBD: inflammatory bowel disease; IL-1β: interleukin-1β; M cell: microfold cell; NF-κB: nuclear factor kappa B; NLRP3: NOD-like receptor protein 3; PPARγ: peroxisome proliferator-activated receptor gamma; TNBS: 2:4:6-trinitrobenzenesulfonic acid.

or deliver adsorbed chemicals that affect bacterial composition and function. In vitro gut simulation and experimental studies have linked microplastic exposure to dysbiosis-like shifts and impaired epithelial–microbial homeostasis.[36,37] More recent work has implicated disruption of the microbiota–butyrate–PPARγ axis as a potential pathway through which microplastics may exacerbate colitis-like inflammation.[38] Conversely, certain gut bacteria may also contribute to the degradation or biological mitigation of ingested microplastics, suggesting a dynamic and potentially bidirectional host–microbiota–microplastic relationship.[39] These findings are biologically relevant because reduced microbial diversity and altered short-chain fatty acid metabolism are common features of IBD; however, their translation to human disease remains uncertain.

Microplastics may also modulate mucosal immune responses indirectly through barrier injury and dysbiosis or directly through interactions with epithelial and immune cells. Such interactions may promote innate immune activation, cytokine production, epithelial–immune signaling, and inflammasome-related pathways, particularly in susceptible hosts.[40] The extent to which this occurs in human IBD is unknown, but the concept is consistent with the broader model of IBD as an exaggerated immune response to luminal and microbial stimuli.

Finally, microplastics should not be considered inert particles. They may contain plastic additives and adsorb pollutants, metals, and microorganisms onto their surfaces.[13] Upon contact with biological fluids, plastic particles may acquire a coating of proteins, lipids, and other biomolecules, often termed a biocorona, which can alter their surface properties, cellular recognition, and biological effects in ways not fully captured by studies using pristine particles.[41]

In addition, microorganisms carried on environmentally exposed plastic surfaces may potentially influence the local microbial balance independently of the particles themselves.[39] Therefore, intestinal effects attributed to microplastics may reflect a combination of particle-related injury, polymer-specific properties, biocorona formation, environmental aging, chemical co-exposures, and microbial carriage. Taken together, these mechanisms provide biological plausibility for microplastics as potential modifiers of intestinal inflammation in susceptible or already inflamed mucosal environments, although direct clinical causality remains unproven (Figure 2).

Experimental Evidence from Cellular and Animal Models

Experimental studies have provided most of the mechanistic evidence linking microplastics and nanoplastics to intestinal inflammation. These studies include intestinal epithelial cell systems, mucus and barrier models, organoid-derived epithelial tissues, gut-chip platforms, and animal models, which are summarized by mechanistic domain in Table 2.[31-38,42-60] Overall, these findings support biological plausibility but should not be interpreted as direct evidence that microplastics cause IBD in humans.

In vitro and translational models suggest that microplastics and nanoplastics can interact with intestinal epithelial surfaces and, under certain experimental conditions, cross epithelial barriers.[31,33,44] Disease-relevant human duodenum-chip models further suggest that healthy and Crohn's disease-derived epithelial systems may differ in their absorption and toxicity responses to polystyrene microplastics and nanoplastics.[45] These models provide useful human-relevant information on mucus and epithelial barrier function, but they do not fully reproduce the chronic immune, microbial, vascular, and treatment-related complexity of IBD.

Animal studies, most commonly using DSS-induced colitis models, have primarily examined whether microplastic exposure can aggravate an already inflamed intestine. Across these models, exposure has been associated with more severe colitis, increased intestinal permeability, impaired epithelial junctions, reduced mucus-related protection, and greater inflammatory injury.[46-48] Similar effects have been reported with different polymer types, including polystyrene, polyethylene, and polypropylene, suggesting that intestinal toxicity is not restricted to a single type of plastic.[47,51,54] Overall, these findings are more consistent with the amplification of pre-existing inflammation than with microplastics acting as isolated initiating causes.

Across animal and in vitro models, microplastic exposure has also been associated with dysbiosis, altered microbial metabolism, reduced mucin-related protection, oxidative stress, epithelial apoptosis, and NF-κB/NLRP3/IL-1β-related signaling.[37,38,51,52,56,57] These converging pathways are relevant to IBD but remain dependent on experimental context, dose, polymer type, and host susceptibility.

Experimental evidence nevertheless has important limitations. Many studies use selected polymers, defined particle sizes, high concentrations, short exposure periods, or pristine particles that may not reflect mixed real-world exposures. Animal colitis models reproduce only selected features of Crohn's disease and ulcerative colitis. Therefore, experimental data support biological plausibility and disease-modifying potential but do not establish clinical causality.

Human Evidence in IBD

Experimental and mechanistic data support the biological plausibility of microplastic-related intestinal injury; however, direct human evidence in IBD remains limited and predominantly observational (Table 3). Only a small number of studies have measured microplastics in the stool, serum, or intestinal tissue of patients with IBD.

The principal stool-based evidence in IBD builds on the broader observation that microplastics can be detected in human stool under controlled analytical conditions.[25] This methodological foundation was extended to an IBD population in a case-control study of 52 patients with IBD and 50 healthy controls, which reported significantly higher fecal microplastic concentrations in patients with IBD, with polyethylene terephthalate and polyamide among the most abundant polymers. Particles smaller than 50 μm were disproportionately enriched in the IBD group, and fecal microplastic burden was positively correlated with clinical disease activity.[26] However, this was a cross-sectional study using a nitric acid-based extraction protocol that may alter or degrade certain particles, and causality cannot be inferred from the results. A key limitation is that fecal microplastic burden may reflect ambient exposure, altered intestinal transit, disease-related retention, or active inflammation itself rather than a causal exposure–disease relationship. Complementary pilot data from the ongoing PLANET Study similarly link fecal microplastic burden to fecal calprotectin, independent of IBD status (Spearman's r=0.65, P=.04), although this finding is based on a small sample (n=11) and has been reported only in abstract form to date.[61]

Although more limited, tissue-based evidence provides a complementary line of investigation. Microplastics have been detected in fibrotic intestinal tissue and adjacent mesenteric adipose tissue from patients with Crohn's disease, with particle concentrations reported to correlate with the severity of intestinal fibrosis.[28] A subsequent 2026 pilot study found higher mucosal microplastic concentrations in patients with ac-

Table 3. Summary of human studies evaluating microplastics and nanoplastics in IBD and related intestinal inflammation

Study	Study design and population	Sample type	Analytical method	Main findings	Key limitations
Yan et al.[26]	Cross-sectional case-control study; 52 patients with IBD and 50 healthy controls	Feces	Multistep Fenton reagent and nitric acid digestion followed by micro-Raman spectroscopy	Mean fecal MP concentration was higher in patients with IBD than in healthy controls (41.8 vs. 28.0 particles/g dry weight). Smaller particles were enriched in the IBD group, and MP burden correlated positively with clinical disease activity.	Cross-sectional design and single fecal measurement; acid-based processing may alter some particles; residual confounding and reverse causality
Lykkemark et al.[61]	Pilot analysis within the prospective PLANET Study; 11 pregnant women, including 4 with CD	Feces collected during the third trimester	Plastic-free collection; multistep enzymatic and oxidative treatment; μ-FTIR imaging for particles >10 μm; fecal calprotectin measured by ELISA	MPs were detected in all samples. MP count correlated with fecal calprotectin after adjustment for IBD status (Spearman's r=0.65, P=.04), whereas the association with total MP mass was not statistically significant.	Pilot sample of 11 pregnant women, only 4 of whom had CD; pregnancy-specific population and single-time-point analysis
Wu et al.[28]	Cross-sectional paired-tissue study; 10 patients undergoing surgery for fibrostenotic CD	Involved and adjacent uninvolved ileum; creeping fat and adjacent mesenteric adipose tissue	Laser direct infrared imaging spectroscopy	MPs were detected in intestinal and mesenteric adipose tissues. Concentrations were higher in affected regions and correlated positively with the severity of intestinal fibrosis.	Phenotype-selected surgical cohort restricted to fibrostenotic CD; no non-IBD control group; possible inflammation-related particle retention
Cui et al.[62*]	Pilot cross-sectional study; 20 patients with active CD, 20 with CD in remission, and 10 healthy controls	Colonoscopic mucosal biopsies	High-resolution digital imaging, μ-FTIR spectroscopy, and Raman imaging	Median mucosal MP concentration was higher in active CD than in remission and healthy controls (162.7 vs. 87.31 and 61.28 particles/g, respectively) and correlated with SES-CD in active disease (r=0.628, P<.01).	Cross-sectional pilot design with limited subgroup sizes; possible sampling contamination and inflammation-related particle retention
Du et al.[63†]	Exploratory paired-tissue study; 6 individuals with colonic or terminal ileal erosions	Inflamed erosive tissue and adjacent noninflamed tissue	Histopathological confirmation of inflammation followed by Py-GC/MS quantification of PE, PVC, and PS	Total MNP mass was higher in inflamed tissue than in adjacent noninflamed tissue (1758.15 vs. 611.49 mg/kg, P<.05).	Exploratory paired-tissue study involving 6 non-IBD participants; no healthy control group; Py-GC/MS does not provide particle count, size, or morphology.
Huang et al.[64*]	Two-center prospective observational study; 241 patients with CD and 43 healthy controls; 167 patients with nonstricturing, nonpenetrating CD and no prior intestinal resection followed for a mean of 27 months	Serum	Py-GC/MS quantification of 11 MNP polymers	Serum MNP burden was higher in patients with CD than in healthy controls. Among prospectively followed patients, a higher baseline total MNP burden was independently associated with subsequent disease progression (HR 2.95, 95% CI 1.57–5.57).	Selected follow-up population; residual confounding and reverse causality; serum measurements require validation and do not establish temporality for IBD onset

*Currently reported as a conference abstract. †Supportive non-IBD-specific human study. CD: Crohn's disease; CI: confidence interval; ELISA: enzyme-linked immunosorbent assay; HR: hazard ratio; IBD: inflammatory bowel disease; MP: microplastic; MNP: microplastic and nanoplastic; PE: polyethylene; PS: polystyrene; PVC: polyvinyl chloride; Py-GC/MS: pyrolysis–gas chromatography/mass spectrometry; SES-CD: Simple Endoscopic Score for Crohn's Disease; μ-FTIR: micro-Fourier-transform infrared spectroscopy.

For clinicians, the main practical implication is communication rather than intervention. Questions about whether plastic exposure contributes to IBD may increasingly arise in clinical practice as public awareness of microplastics grows. The most accurate response is that microplastics are being investigated as potential environmental modifiers of intestinal inflammation, but they are not established causes of IBD. There is currently no evidence that reducing plastic exposure improves IBD outcomes; therefore, microplastics cannot be considered a validated therapeutic target.

Specific microplastic-avoidance measures, particularly burdensome or restrictive strategies, currently have no evidence-based role in IBD management, either as adjuncts to or alternatives to established treatment. Nevertheless, general exposure-reduction measures may be reasonable from a broader environmental and public health perspective, particularly when they are low-cost and low-risk. These may include avoiding heating food in plastic containers, reducing unnecessary use of single-use plastics, and using glass or stainless steel containers when feasible. Two existing guideline-based recommendations provide an additional complementary rationale in this context. Smoking cessation is already recommended for all patients with IBD by current national guidelines, and emerging evidence of smoking-associated microplastic exposure in the lower respiratory tract provides a further environmental rationale for avoiding tobacco exposure.[17,66] Similarly, IOIBD dietary guidance recommends limiting ultra-processed foods and selected additives, including nanoparticles, independent of any microplastic-specific concern, and highly processed or heavily packaged foods may also contribute to dietary microplastic exposure through packaging and processing.[12,13,67] However, in both cases, these associations do not demonstrate that plastic-derived particles directly influence IBD outcomes.

Evidence in pediatric IBD is particularly limited, and current data do not support pediatric-specific microplastic testing, dietary restriction, or avoidance strategies. Counseling for children and their families therefore remains centered on established nutritional and disease-management principles rather than unproven microplastic-focused restrictions. Importantly, these discussions should not distract from established IBD management, including objective monitoring of inflammation, adherence to prescribed therapy, nutritional optimization, smoking cessation, and timely treatment escalation when necessary. Currently, microplastics remain a research question rather than a clinical management tool for IBD.

Knowledge Gaps and Future Directions

Several important knowledge gaps limit the interpretation of the current literature. First, human data remain sparse, largely cross-sectional, and heterogeneous in terms of sampling and analytical protocols. Standardized methods are needed for the collection and processing of stool, blood, and intestinal tissue; sample digestion; polymer identification; particle counting; size reporting; and contamination control, including more robust approaches to quantifying inhalational exposure, which remains particularly poorly standardized.[24,68] Without harmonized protocols, comparisons across studies and populations will remain difficult.

Second, clinically integrated longitudinal designs are essential for moving beyond simple detection. Prospective cohorts are needed to determine whether microplastic burden precedes disease onset, increases during flares, decreases during remission, or reflects altered intestinal handling during active inflammation. Where clinically feasible, paired stool, blood, and intestinal tissue samples collected at the same time points would permit comparison of luminal, systemic, and mucosal particle burdens and their integration with endoscopic activity, histology, fecal calprotectin, CRP, disease phenotype, medication exposure, diet, smoking status, and environmental exposure assessments. Newly diagnosed, treatment-naïve patients may be particularly informative because they allow assessment before long-term treatment, dietary adaptation, and disease-related behavioral changes.

Encouragingly, this field is beginning to move in this direction. Registered and ongoing studies are assessing multi-matrix microplastic burden in pediatric IBD populations, segmental distribution in inflamed and noninflamed Crohn's disease biopsy samples (the OPTIC study), and integrated microbial, immune, and barrier function profiles (ClinicalTrials.gov identifiers: NCT07141238 and NCT07630883). These efforts represent an important step toward pairing exposure measurements with clinical and immunological outcome data, although the findings remain emerging and hypothesis-generating.

Third, the relationship between microplastics and specific IBD phenotypes requires further clarification. Current human evidence suggests possible associations with disease activity and fibrostenotic Crohn's disease; however, it remains unknown whether microplastic burden differs between Crohn's disease and ulcerative colitis, inflammatory and stricturing phenotypes, active and quiescent disease, or treatment-responsive and treatment-refractory patients.

A broader unanswered question is whether microplastics represent one of the unintended environmental costs of modernization. Industrial development, urbanization, and dietary westernization have improved many aspects of human life while introducing persistent synthetic materials into food systems, water sources, and air. Future reductions in plastic use may provide a natural experiment for evaluating whether lower environmental exposure has measurable effects on gastrointestinal or immune-mediated diseases. Such ecological trends should be interpreted cautiously; however, they may help generate hypotheses for IBD and other chronic inflammatory disorders.

Fourth, experimental models should better reflect real-world exposure. Many studies have used pristine particles, selected polymers, high concentrations, or short exposure periods. Two decades of broader microplastic research have underscored that methodological rigor, rather than additional descriptive detection studies alone, is now the primary need for translating environmental plausibility into clinically actionable evidence.[69] Future models should incorporate environmentally aged and mixed-polymer particles under chronic, low-dose exposure conditions that more closely approximate human exposure, ideally using disease-relevant human organoid, gut-chip, or mucosal biopsy-based systems.

Finally, intervention research requires a staged approach. After analytical validity and longitudinal associations have been established, initial feasibility studies can test whether predefined, low-risk exposure-reduction measures produce measurable changes in biological particle burden. Subsequent controlled studies, if justified, may evaluate effects on objective inflammatory biomarkers, endoscopic activity, and clinical outcomes. A reduction in measured particle burden alone would not establish therapeutic benefit. Until such evidence becomes available, microplastics remain a research target rather than an established clinical determinant of IBD.

Limitations

Several limitations should be considered when interpreting this narra-

tive review. Although the search followed a predefined strategy in terms of databases, terminology, and time frame, it was not conducted as a systematic review; source selection ultimately reflected author consensus rather than formal eligibility scoring, which introduces the possibility of selection bias and means that the emphasis placed on individual reports may not correspond to the weight they would receive in a formal evidence synthesis. The search was restricted to English-language publications, and relevant work published in other languages may have been missed. In a field expanding as rapidly as this one, positive and mechanistically striking findings are also more likely to be published and cited than null results, and this asymmetry cannot be excluded from the evidence summarized here. Furthermore, the methodological heterogeneity described above constrains not only comparisons among individual studies but also any attempt to synthesize them collectively, and the small, predominantly cross-sectional human evidence base does not permit inferences about temporality. The interpretations advanced in this review should therefore be regarded as provisional and are likely to require revision as standardized analytical methods and longitudinal human data become available.

CONCLUSION

Microplastics and nanoplastics are widespread environmental exposures with plausible relevance to intestinal inflammation. Experimental evidence suggests that these particles may disrupt the mucus–epithelial barrier, promote oxidative stress, alter microbial and immune homeostasis, and amplify inflammation, particularly in susceptible or inflamed intestinal environments. In contrast, human evidence in IBD remains limited, observational, and insufficient to establish microplastics as causal drivers or clinically useful biomarkers.

The most balanced interpretation is that microplastics may represent environmental disease modifiers or markers of altered intestinal handling rather than primary initiators of disease. As microplastic detection methods become more standardized, accessible, and integrated into human studies, their relationship with IBD may be clarified with greater precision. Until stronger longitudinal human evidence becomes available, microplastics should be regarded as an important research priority rather than a basis for disease-specific clinical recommendations.

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Journal of Enterocolitis

Review

Efficacy and Safety of Mirikizumab for Induction and Maintenance of Remission in Ulcerative Colitis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Objective: Mirikizumab, a p19-directed anti-interleukin-23 monoclonal antibody, has been evaluated as induction and maintenance therapy for moderately to severely active ulcerative colitis (UC). We conducted a systematic review and meta-analysis of randomized, placebo-controlled trials to quantify its efficacy and safety.

Methods: PubMed, Web of Science, and Scopus were searched for randomized controlled trials of mirikizumab versus placebo in UC. Two independent RCT programs met the eligibility criteria: the Phase 2 trial (Sandborn et al.,10; comprising a 12-week double-blind induction period and a double-blind 52-week maintenance re-randomization of induction responders, with the latter reported through its ClinicalTrials.gov registry record) and the Phase 3 LUCENT program (D'Haens et al.11;LUCENT-1 induction and LUCENT-2 maintenance). Outcome data (clinical remission, clinical response, endoscopic remission/response, symptomatic remission, histologic remission, and serious adverse events [SAEs]) were extracted from the primary ClinicalTrials.gov results records (NCT02589665, NCT03518086, and NCT03524092) and pooled using random-effects (DerSimonian–Laird) meta-analysis of risk ratios (RRs).

Results: During induction (12 weeks), mirikizumab increased clinical remission (RR 2.45, 95% CI 1.03–5.83; I^2=56%), clinical response (RR 1.98, 95% CI 1.05–3.73), and endoscopic remission (RR 1.72, 95% CI 1.36–2.18; I^2=0%) compared with placebo. During maintenance (weeks 40–52), mirikizumab increased clinical remission (RR 1.98, 95% CI 1.51–2.61) and endoscopic remission (RR 2.03, 95% CI 1.59–2.59; I^2=0%). Serious adverse events were numerically less frequent with mirikizumab than with placebo during both induction (RR 0.56, 95% CI 0.32–0.99) and maintenance (RR 0.36, 95% CI 0.19–0.70).

Conclusion: Mirikizumab is significantly more effective than placebo in inducing and maintaining clinical, endoscopic, symptomatic, and histologic remission in moderately to severely active UC, with a favorable serious adverse event profile relative to placebo. The evidence base remains limited to two independent RCT programs; the wider confidence intervals and moderate-to-high heterogeneity observed for some induction outcomes reflect the small Phase 2 sample and should be interpreted cautiously.

Keywords: Biologic therapy, interleukin-23, meta-analysis, mirikizumab, systematic review, ulcerative colitis.

INTRODUCTION

Ulcerative colitis (UC) is a chronic immune-mediated inflammatory disease of the colon whose global incidence and prevalence have risen steadily in recent decades.[1] A growing number of biologic and small-molecule therapies are now available for its treatment. Interleukin-23 (IL-23), through its p19 subunit, is a key driver of Th17-mediated mucosal inflammation in UC, and selective p19 blockade has emerged as an effective therapeutic strategy.[2] Mirikizumab is a humanized IgG4 monoclonal antibody that selectively binds to the p19 subunit of IL-23, thereby blocking its interaction with the IL-23 receptor.[3]

Mirikizumab was evaluated in a randomized, placebo-controlled Phase 2 dose-ranging study and subsequently in the Phase 3 LUCENT program (LUCENT-1 induction and LUCENT-2 maintenance), leading to regulatory approval for moderately to severely active UC in adults. Several narrative reviews and at least one prior systematic review/meta-analysis conducted by Abu Elainein et al.[4] have summarized this evidence base. The present analysis independently re-extracts arm-level data directly from the primary trial registry records (ClinicalTrials.gov), rather than relying solely on published summary statistics, to provide a fully transparent and reproducible data-extraction table and updated pooled estimates of clinical, endoscopic, histologic, and safety outcomes, separately for the induction and maintenance phases.

Objectives (PICO)

Population: Adults with moderately to severely active ulcerative colitis.

Intervention: Mirikizumab (any studied intravenous induction dose or subcutaneous maintenance dose).

Comparator: Placebo.
Outcomes: Clinical remission, clinical response, endoscopic remission, endoscopic improvement/response, symptomatic remission, histologic remission, and serious adverse events.

Study design: Randomized, double-blind, placebo-controlled trials.

METHODS

This review followed the PRISMA 2020 reporting guidelines.5
This review was registered with PROSPERO (registration number CRD420261485281).

Search strategy

PubMed was searched using combinations of "mirikizumab," "LY3074828," "ulcerative colitis," and randomized controlled trial filters. Web of Science Core Collection was searched using the topic-field query: TS=(mirikizumab OR LY3074828) AND TS=("ulcerative colitis") AND TS=(randomi* OR placebo) AND TS=("phase 2" OR "phase 3" OR LUCENT) NOT TS=(subgroup OR "post hoc" OR "post-hoc" OR "real-world" OR "case report" OR "case series" OR review OR editorial), which was iteratively narrowed from an initial unrestricted search of 344 records to 30 records after applying randomized controlled trial and exclusion terms. Scopus was searched on August 22, 2026, using an analogous query restricted to the title, abstract, and keywords: TITLE-ABS-KEY(mirikizumab OR "LY3074828") AND TITLE-ABS-KEY("ulcerative colitis") AND TITLE-ABS-KEY(randomi* OR placebo) NOT TITLE-ABS-KEY(subgroup OR "post hoc" OR "post-hoc" OR "real-world" OR "case report" OR "case series" OR review OR editorial OR pharmacovigilance OR Crohn), returning 35 records; every record corresponded to one of the four already identified primary trial reports or was a secondary, mechanistic, or commentary analysis of those reports, confirming that no additional eligible randomized controlled trial was identified. As a further supplementary check, the Cochrane Central Register of Controlled Trials (CENTRAL) was also searched for "mirikizumab AND ulcerative colitis," returning 246 trial records; every record corresponded to one of the four already identified primary trial reports, a conference abstract or biomarker subanalysis of those reports, or an unrelated combination-therapy trial (e.g., mirikizumab plus tirzepatide or eltrekibart), confirming that no eligible placebo-controlled RCT had been missed.

Eligibility criteria

Randomized, double-blind, placebo-controlled trials of mirikizumab in adults with moderately to severely active UC reporting at least one efficacy or safety outcome of interest were eligible. Conference abstracts were included only when no corresponding full-text publication existed; when data from an abstract were superseded by a full-text report of the same trial, only the full-text data were extracted. Studies of mirikizumab in Crohn's disease, pharmacokinetic/exposure–response modeling studies, nonrandomized or open-label extension studies without a placebo comparator, and secondary, subgroup, or post hoc analyses of already included trials were excluded from quantitative pooling.

Data extraction

Arm-level participant counts and outcome event counts were extracted directly from the sponsor-submitted results records on ClinicalTrials.gov for each trial (NCT02589665, NCT03518086, and NCT03524092), which report exact per-arm percentages and denominators from which integer event counts were derived for all prespecified efficacy outcomes and adverse-event tables. This source was used in preference to secondary journal figures because it provides complete arm-by-arm denominators for every dose group, including doses not carried forward to Phase 3. Baseline demographic and disease characteristics (Table 1), which are not reported in the ClinicalTrials.gov registry records, were instead extracted directly from the original peer-reviewed trial publications.[6]

Risk of bias assessment

Risk of bias was assessed using the Cochrane RoB 2.0 tool across five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selective reporting. Assessments are summarized in Table 2.[7]

Table 1. Baseline demographic and disease characteristics of the induction-phase trials. *NR, not reported. Table 1a presents baseline characteristics for only the placebo and mirikizumab 200-mg arms of the Phase 2 trial—the two arms included in the pooled induction analyses (Table 3a)—and for both randomized arms of LUCENT-1. Baseline characteristics for the Phase 2 50-mg and 600-mg induction arms, which were not carried forward to Phase 3 and were not included in the pooled analyses, are available in the original publication (Sandborn et al.,10 Table 1).*

	Sandborn 2020 Placebo (n=63)	Sandborn 2020 Mirikizumab 200 mg (n=62)	LUCENT-1 Placebo (n=294)	LUCENT-1 Mirikizumab 300 mg (n=868)
Age, years, mean (SD)	42.6 (13.5)	43.4 (14.7)	41.3 (13.8)	42.9 (13.9)
Female sex, n (%)	27 (42.9)	25 (40.3)	129 (43.9)†	338 (38.9)
Disease duration, years, mean (SD)	9.5 (9.6)	9.0 (9.0)	6.9 (7.0)	7.2 (6.7)
Modified Mayo score (9-point), mean (SD)	6.7 (1.2)	6.4 (1.4)	NR	NR
Severe modified Mayo score, n/N (%)	NR	NR	155/293 (52.9)	463/868 (53.3)
Endoscopic subscore indicating severe disease, n/N (%)	47/63 (74.6)	41/62 (66.1)	200/293 (68.3)	574/868 (66.1)
C-reactive protein, median (IQR), mg/L	3.9 (1.1–11.2)	3.6 (1.4–13.7)	4.2 (1.2–9.5)	4.1 (1.5–9.6)
Fecal calprotectin, median (IQR), µg/g	1353 (618–2481)	1560 (399–2443)	1471.5 (626.5–2944.5)	1559.0 (634.0–3210.0)
Corticosteroid use at baseline, n (%)	33 (52.4)	25 (40.3)	113 (38.4)	351 (40.4)
Previous biologic/tofacitinib treatment failure, n (%)	NR	NR	118 (40.1)	361 (41.6)
IBDQ score, mean (SD)	124.1 (29.8)	133.0 (34.7)	NR	NR

IBDQ, Inflammatory Bowel Disease Questionnaire; IQR, interquartile range; NR, not reported; SD, standard deviation.

Table 2. Cochrane RoB 2.0 domain-level risk-of-bias assessment

Study	D1	D2	D3	D4	D5	Overall
Sandborn 2020 (Phase 2)	Low	Low	Some concerns	Low	Low	Some concerns
Phase 2 maintenance re-randomization (ClinicalTrials.gov record only)	Low	Low	Some concerns	Low	Low	Some concerns
D'Haens et al.11 2023, LUCENT-1 (induction)	Low	Low	Low	Low	Low	Low
D'Haens et al.11 2023, LUCENT-2 (maintenance)	Some concerns	Low	Low	Low	Low	Some concerns

D1, randomization process; D2, deviations from intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selective reporting; RoB, risk of bias.

Table 3. Characteristics of the included trial reports

Trial (report)	Registry ID	Phase	Randomized arms (mirikizumab dose)/route vs placebo	Duration	Primary endpoint
Sandborn10 2020 (Phase 2, induction)	NCT02589665	Induction	Placebo (n=63); mirikizumab 50 mg (n=63), 42.9 (13.9) 200 mg (n=62), or 600 mg (n=61) IV at weeks 0, 4, and 8	12 weeks	Clinical remission (Mayo score)
Phase 2 maintenance re-randomization (ClinicalTrials.gov record only)	NCT02589665	Maintenance	Re-randomized induction responders: placebo (n=13); mirikizumab 200 mg SC Q4W (n=47) or Q12W (n=46)	52 weeks	Endoscopic/ symptomatic remission
D'Haens et al.11 2023, LUCENT-1 (Phase 3, induction)	NCT03518086	Induction	Randomized 3:1 to mirikizumab 300 mg IV (n=868) or placebo (n=294) at weeks 0, 4, and 8	12 weeks	Clinical remission (Mayo score)
D'Haens et al.,11 LUCENT-2 (Phase 3, maintenance)	NCT03524092	Maintenance	LUCENT-1 responders re-randomized 2:1 to mirikizumab 200 mg SC Q4W (n=365) or placebo (n=179)	40 weeks	Clinical remission (Mayo score)

Statistical analysis

For each outcome, study-level risk ratios (RRs) with 95% confidence intervals were calculated on the log scale; a continuity correction of 0.5 was applied to any study with a zero cell. When two independent trials contributed data for the same phase (induction or maintenance) and a comparable dose, estimates were pooled using the DerSimonian–Laird random-effects model.[8] This approach was selected because of the anticipated clinical heterogeneity in dose (200 mg vs 300 mg intravenous induction; 200 mg subcutaneous maintenance schedules) and design between the Phase 2 and Phase 3 programs. Heterogeneity was quantified using the I^2 statistic and τ^2. When only a single trial reported an outcome (e.g., histologic remission, reported only in the LUCENT program), the unpooled study-level RR is presented. All pooled estimates and forest plots were generated using Cochrane RevMan 5.4 (Review Manager, The Cochrane Collaboration), with the inverse-variance method for the random-effects model described above.

Certainty of evidence

The certainty of evidence for each outcome was rated using the GRADE framework.[9] Randomized evidence was initially rated as "high" and downgraded for risk of bias, inconsistency ($I^2 \geq 50\%$), indirectness, and imprecision according to prespecified rules detailed in Supplementary Table S1.

RESULTS

Study selection

The search and screening process is summarized in Figure 1 (PRISMA flow diagram). After removing records concerning Crohn's disease, pharmacokinetic bridging in healthy volunteers, a mismatched drug (guselkumab), nonrandomized pediatric studies, or secondary/subgroup analyses of already identified trials, two independent randomized, placebo-controlled RCT programs met the inclusion criteria: the Phase 2 trial (with induction reported by Sandborn et al.[10] and the double-blind maintenance re-randomization of induction responders reported only in the trial's ClinicalTrials.gov registry record, NCT02589665.10, rather than in a dedicated maintenance-phase journal publication) and the Phase 3 LUCENT program (D'Haens et al.11; comprising LUCENT-1 induction and LUCENT-2 maintenance.10,11).

Study characteristics

Table 3 summarizes the four trial reports arising from the two included RCT programs. The Phase 2 trial (NCT02589665) randomized 249 participants to placebo or mirikizumab 50, 200, or 600 mg intravenously every 4 weeks for a 12-week induction period; induction responders were re-randomized to placebo, 200 mg subcutaneously every 4 weeks, or 200 mg subcutaneously every 12 weeks for a 52-week maintenance period (n=13 in the placebo group, because only responders were re-randomized). LUCENT-1 (NCT03518086) randomized 1,281 participants in a 3:1 ratio to mirikizumab 300 mg intravenously or placebo for a 12-week induction period. LUCENT-2 (NCT03524092) re-randomized LUCENT-1 induction responders in a 2:1 ratio to continue mirikizumab 200 mg subcutaneously or switch to placebo for an additional 40 weeks. A related open-label substudy of the Phase 2 program, reporting rescue extended-induction and extended-maintenance treatment for the subset of patients who did not respond to blinded induction therapy (Sandborn et al.10), was identified but excluded from the quantitative synthesis because of its nonblinded, non-placebo-controlled design, consistent with the eligibility criteria in Section 2.2.

Baseline demographic and disease characteristics for the two induc-

Table 4. Pooled induction-phase efficacy outcomes (mirikizumab vs placebo, week 12). *Endoscopic improvement/response combines two nonidentically named endpoints (Phase 2 "endoscopic improvement" vs LUCENT "endoscopic response"). Both are based on a reduction in the Mayo endoscopic subscore; however, this definitional difference is a source of indirectness.*

Outcome	k	Mirikizumab (events/N)	Placebo (events/N)	RR (95% CI)	I^2
Clinical remission	2	224/930	42/357	2.45 (1.03–5.83)	56%
Clinical response	2	588/930	137/357	1.98 (1.05–3.73)	82%
Endoscopic remission	2	317/930	63/357	1.72 (1.36–2.18)	0%
Symptomatic remission	2	431/930	95/357	2.02 (1.20–3.41)	72%
Endoscopic improvement/response	2	500/930	110/357	2.43 (0.81–7.28)	79%
Histologic remission (Geboes)	1	254/868	46/294	1.87 (1.41–2.49)	N/A

CI, confidence interval; I^2, heterogeneity statistic; k, number of studies; N, total number of participants; RR, risk ratio.

Table 5. Pooled maintenance-phase efficacy outcomes (mirikizumab vs placebo, weeks 40–52). *Endoscopic improvement/response combines two nonidentically named endpoints (Phase 2 "endoscopic improvement" vs LUCENT "endoscopic response"). Both are based on a reduction in the Mayo endoscopic subscore; however, this definitional difference is a source of indirectness.*

Outcome	k	Mirikizumab (events/N)	Placebo (events/N)	RR (95% CI)	I^2
Clinical remission	1	182/365	45/179	1.98 (1.51–2.61)	N/A
Endoscopic remission	2	234/458	53/192	2.03 (1.59–2.59)	0%
Symptomatic remission	2	325/458	78/192	1.70 (1.35–2.13)	14%
Clinical response	1	293/365	88/179	1.63 (1.40–1.91)	N/A
Endoscopic improvement/response	2	314/458	75/192	1.80 (1.50–2.17)	0%
Histologic remission (Geboes)	1	177/365	44/179	1.97 (1.49–2.60)	N/A

CI, confidence interval; I^2, heterogeneity statistic; k, number of studies; N, total number of participants; RR, risk ratio.

Table 6. Pooled serious adverse events (mirikizumab vs placebo)

Outcome	k	Mirikizumab (events/N)	Placebo (events/N)	RR (95% CI)	I^2
Serious adverse events (induction)	2	29/1020	19/384	0.56 (0.32–0.99)	0%
Serious adverse events (maintenance)	2	16/482	18/205	0.36 (0.19–0.70)	0%

CI, confidence interval; I^2, heterogeneity statistic; k, number of studies; N, total number of participants; RR, risk ratio.

tion-phase trials, extracted directly from the original trial publications (Sandborn et al.,[10] Table 1; D'Haens et al.,[11] Table 1), are summarized in Table 1. Corresponding baseline data for the two maintenance-phase re-randomizations (the Phase 2 responders re-randomized to placebo or mirikizumab and LUCENT-2) were not included because the baseline characteristics of these re-randomized subsets were not separately reported in an accessible peer-reviewed source.

Risk of bias

All four trial reports (arising from the two included RCT programs) were judged to have a low risk of bias for the randomization process, except LUCENT-2, which was rated as having "some concerns" because its maintenance population comprised only re-randomized induction responders rather than a treatment-naive randomized cohort. The trials were also judged to have a low risk of bias for deviations from intended interventions and measurement of the outcome, based on centrally read, blinded endoscopy and standardized Mayo/Geboes scoring. The main source of "some concerns" was missing outcome data related to the small placebo arm retained in the Phase 2 maintenance extension (n=13) and the ME2 China cohorts excluded from the confirmatory efficacy analysis in LUCENT-1/2. Domain-level judgments are summarized graphically in Figure 2 and in full in Table 3.

Induction outcomes

Mirikizumab significantly increased clinical remission, clinical response, endoscopic remission, and symptomatic remission relative to placebo at week 12 (Table 4, Figures 3–6). Heterogeneity was low for endoscopic remission (I^2=0%) but moderate to high for clinical remission, clinical response, and endoscopic improvement/response (Figure 7), reflecting the disproportionately large treatment effect observed in the small Phase 2 200-mg arm (e.g., clinical remission, 22.6% vs 4.8%; RR≈4.7) compared with the more precisely estimated effect in the LUCENT-1 300-mg arm (24.2% vs 13.3%; RR≈1.8). Histologic remission, reported only in LUCENT-1, was significantly higher with mirikizumab than with placebo (29.3% vs 15.6%; RR 1.87, 95% CI 1.41–2.49, Figure 8), consistent with independently reported histologic resolution data across the LUCENT program.

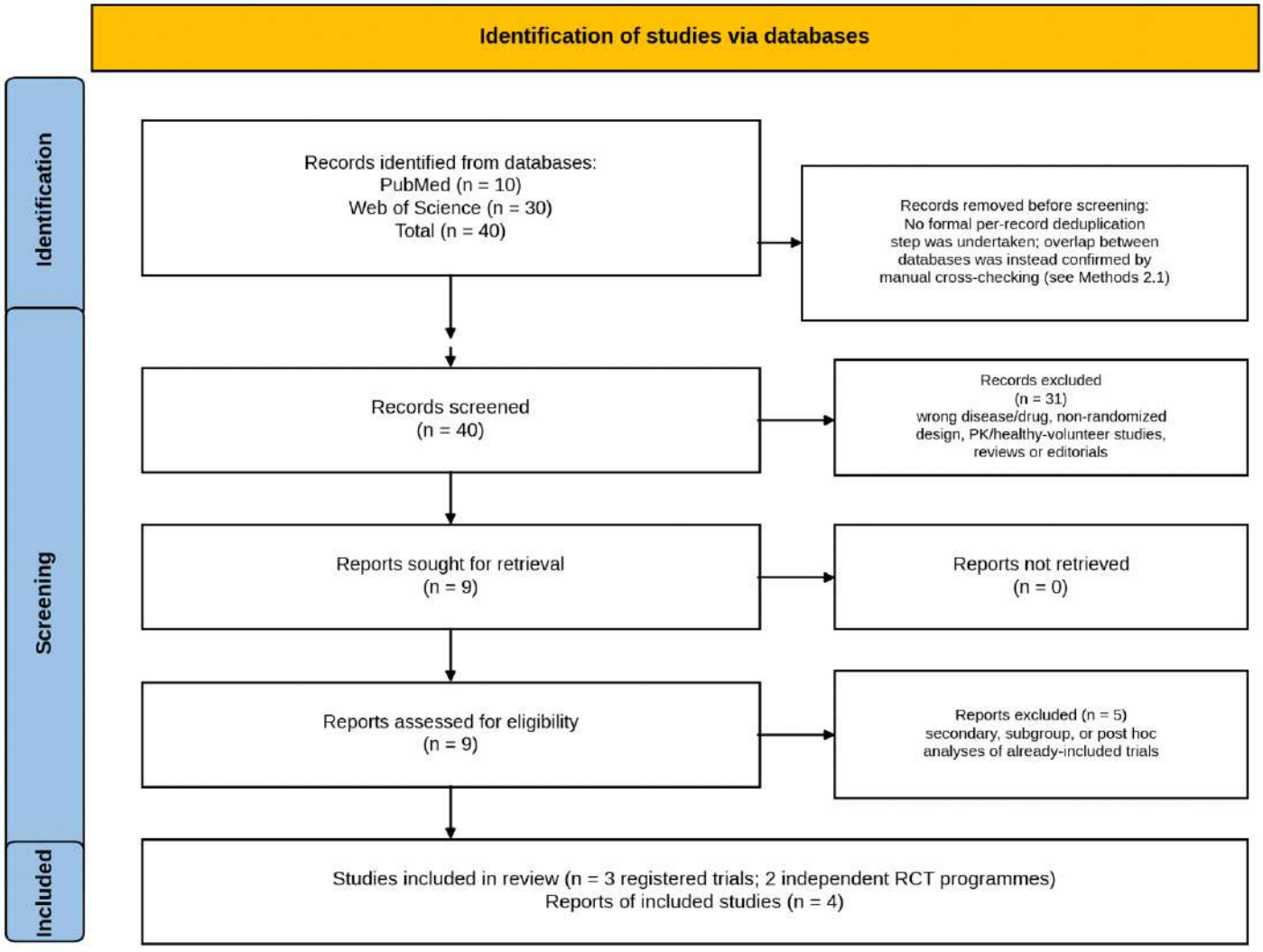

Figure 1. PRISMA 2020 flow diagram.

Maintenance outcomes

During the maintenance phase, mirikizumab was associated with approximately 1.6- to 2.0-fold higher rates of clinical remission, clinical response, endoscopic remission, endoscopic improvement/response, symptomatic remission, and histologic remission compared with placebo (Table 5, Figures 9-14).12 Heterogeneity was low when two trials contributed data (I^2=0–14%). Clinical remission and clinical response were reported only in LUCENT-2 because the Phase 2 maintenance extension did not reassess the Physician's Global Assessment component required for the full Mayo score definitions of clinical remission and response.

Safety

Serious adverse events were numerically less frequent with mirikizumab than with placebo during both induction (2.8% vs 5.3% pooled) and maintenance (3.3% vs 8.3% pooled), (Table 6, Figures 15-16) consistent with fewer disease-related complications (e.g., UC exacerbation, colectomy, hospitalization) among effectively treated patients rather than a direct drug-safety signal. No deaths were reported in any arm of any included trial. Discontinuation due to adverse events was numerically more frequent in the placebo arms of both LUCENT-1 (23/321 vs 15/958) and the Phase 2 induction trial.[13]

Certainty of evidence (GRADE)

Applying the GRADE criteria, certainty was downgraded for risk of bias when the Phase 2 maintenance re-randomization, with its very small placebo arm (n=13) and associated missing-outcome-data concerns, contributed to an outcome; for inconsistency when $I^2 \geq 50\%$; for indirectness when the composite "endoscopic improvement/response" outcome combined two nonidentically named endpoints; and for imprecision when a 95% CI approached or crossed the null or when only a single trial was available. Certainty ranged from "high" for induction endoscopic remission, which was homogeneous, based on ample events, and had a CI far from the null, to "very low" for induction endoscopic improvement/response, for which the pooled 95% CI crossed the null in the presence of substantial heterogeneity. Most efficacy outcomes were rated as having "low" or "moderate" certainty, chiefly reflecting the small number of contributing trials and, for maintenance outcomes, the very small placebo arm (n=13) in the Phase 2 maintenance re-randomization. The full GRADE Summary-of-Findings table, including domain-by-domain ratings and rationale, is provided in Supplementary Table S1.

DISCUSSION

This meta-analysis, based on arm-level data extracted directly from

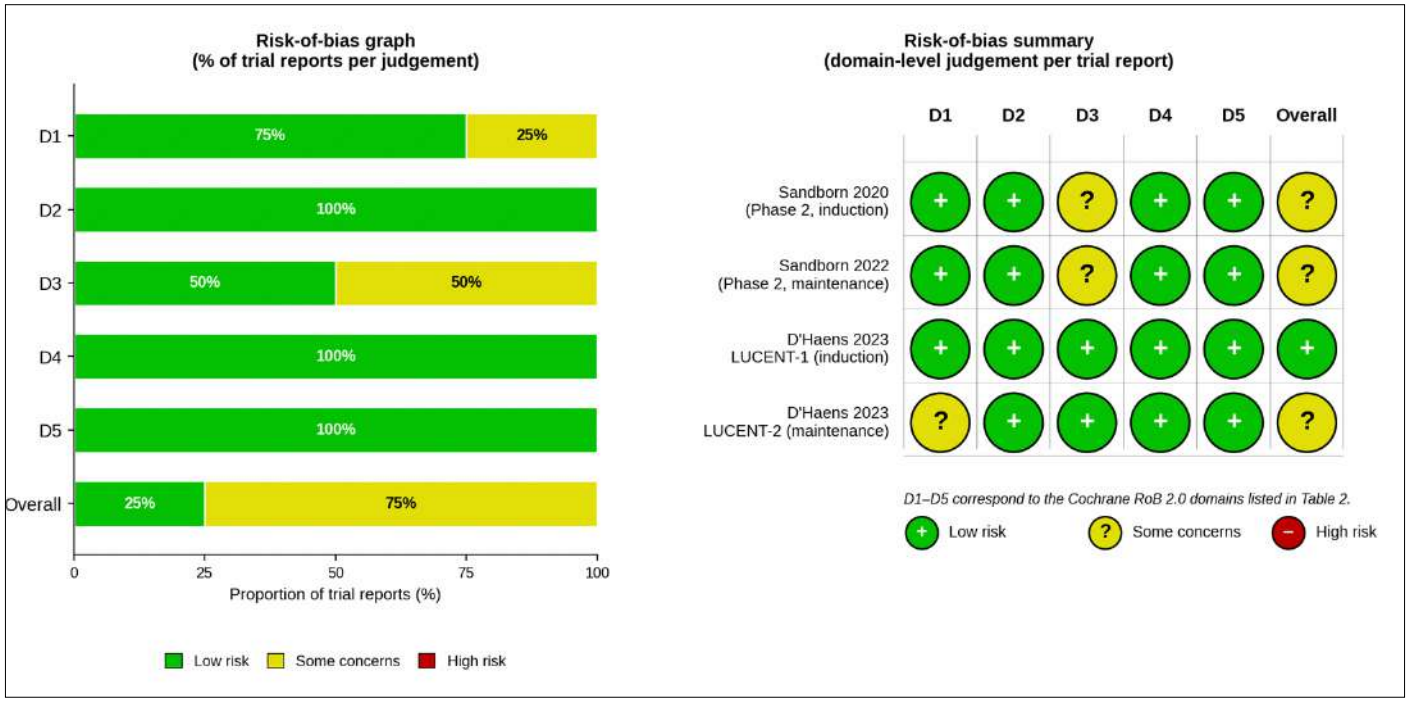

Figure 2. Risk-of-bias graph and summary (Cochrane Ro'B 2.0).

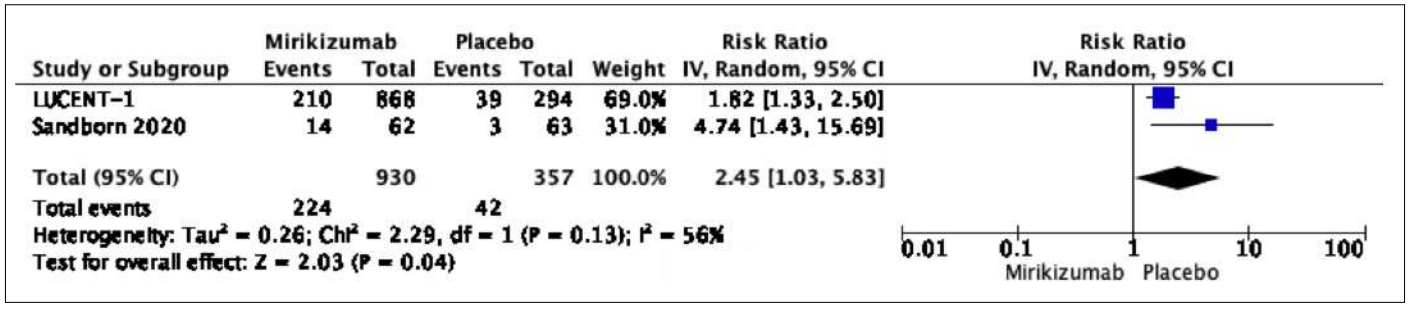

Figure 3. Forest plot of clinical remission during induction.

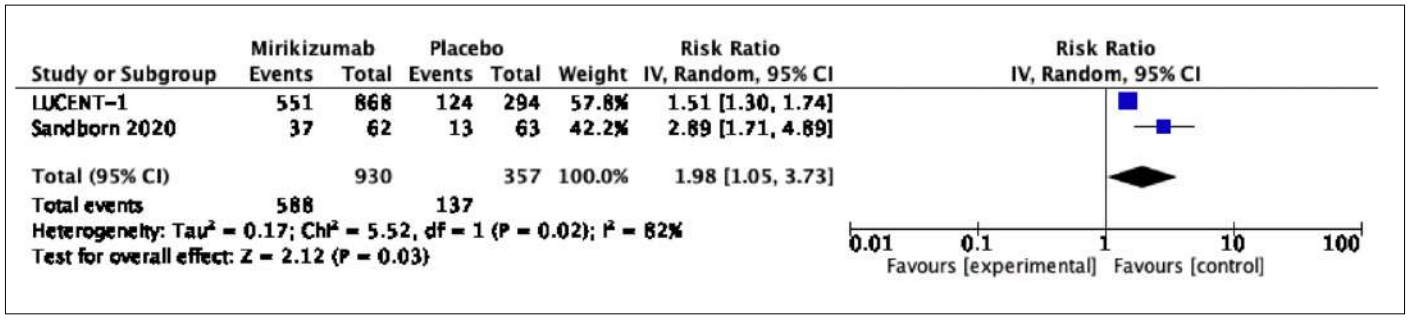

Figure 4. Forest plot of clinical response during induction.

primary trial registry records, confirms that mirikizumab significantly improves clinical, endoscopic, symptomatic, and histologic outcomes compared with placebo during both induction and maintenance treatment of moderately to severely active UC, with no signal of an increased risk of serious adverse events. However, for three induction outcomes—clinical remission (I^2=56%), clinical response (I^2=82%), and endoscopic improvement/response (I^2=79%)—this overall conclusion is based on moderately to highly heterogeneous pooled estimates and should therefore be interpreted as an average across a small, high-effect Phase 2 trial and a much larger, more conservative Phase 3

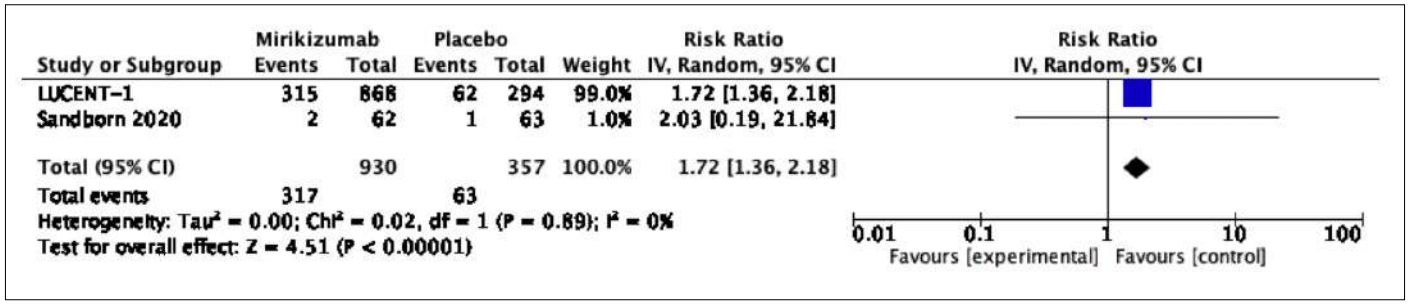

Figure 5. Forest plot of endoscopic remission during induction.

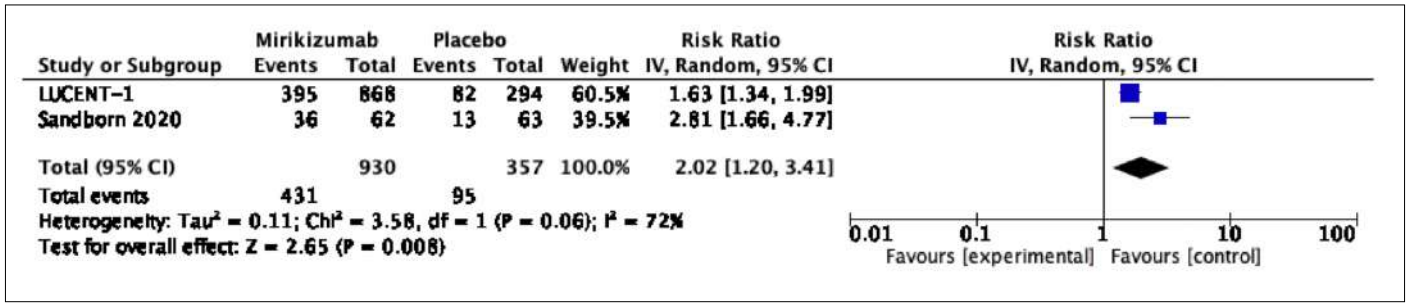

Figure 6. Forest plot of symptomatic remission during induction.

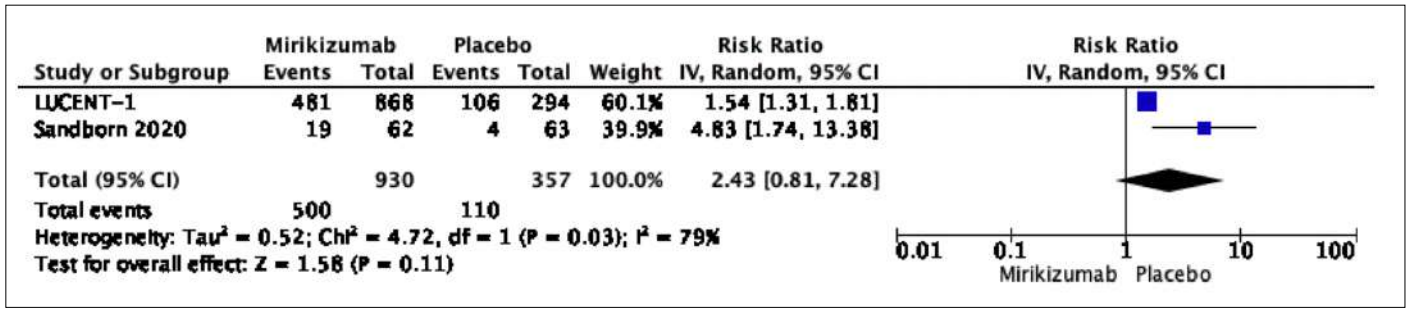

Figure 7. Forest plot of endoscopic improvement/response during induction. Endoscopic improvement/response combines two nonidentically named endpoints (Phase 2 "endoscopic improvement" vs LUCENT "endoscopic response"). Both are based on a reduction in the Mayo endoscopic subscore; however, this definitional difference is a source of indirectness.

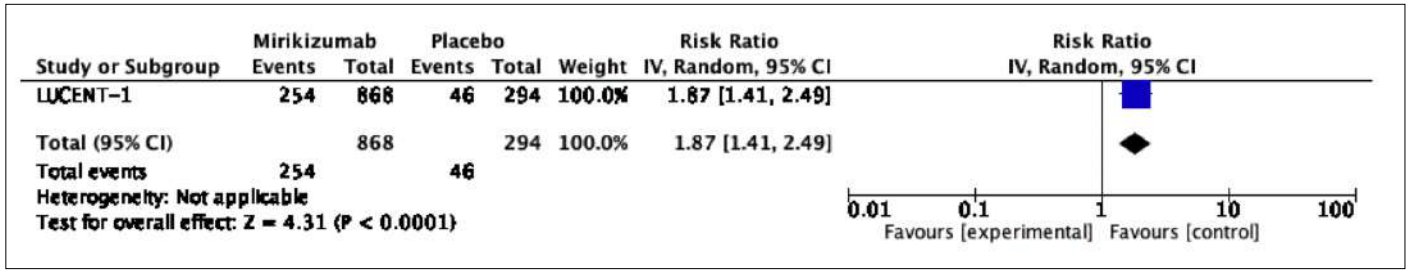

Figure 8. Forest plot of histologic remission during induction (single study, LUCENT-1).

trial rather than as a single homogeneous treatment effect (see Sections 3.4 and 4.2). Our pooled estimate for induction endoscopic remission (RR 1.72, 95% CI 1.36–2.18; I^2=0%) is numerically identical to that reported in the independent meta-analysis by Abu Elainein et al.[4] (RR 1.72, 95% CI 1.36–2.17; I^2=0%), despite the two analyses using different data-extraction sources (published article data vs ClinicalTrials.gov registry data).[4]

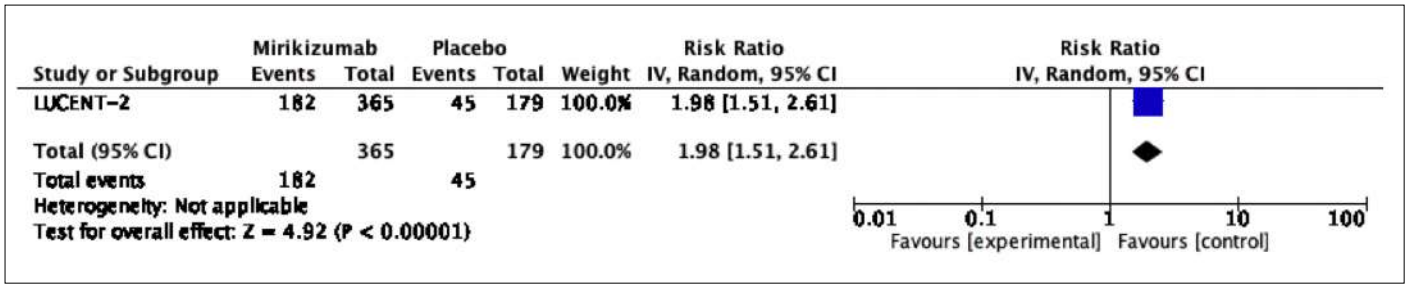

Figure 9. Forest plot of clinical remission during maintenance (single study, LUCENT-2).

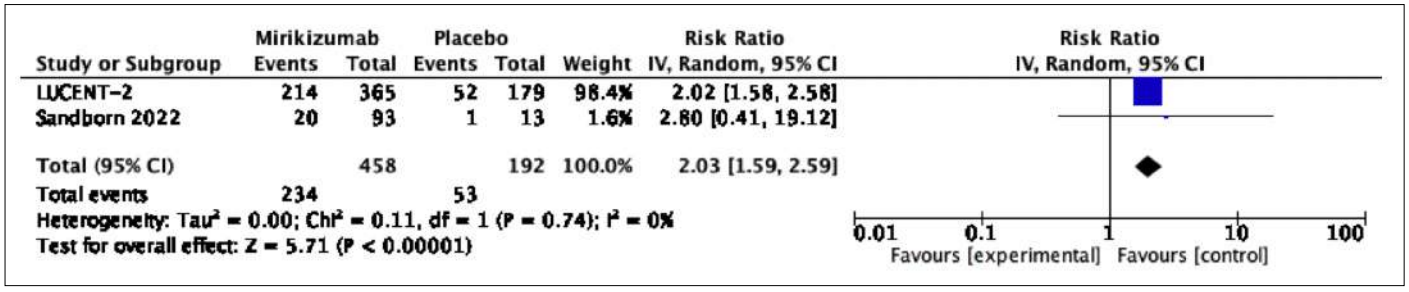

Figure 10. Forest plot of endoscopic remission during maintenance.

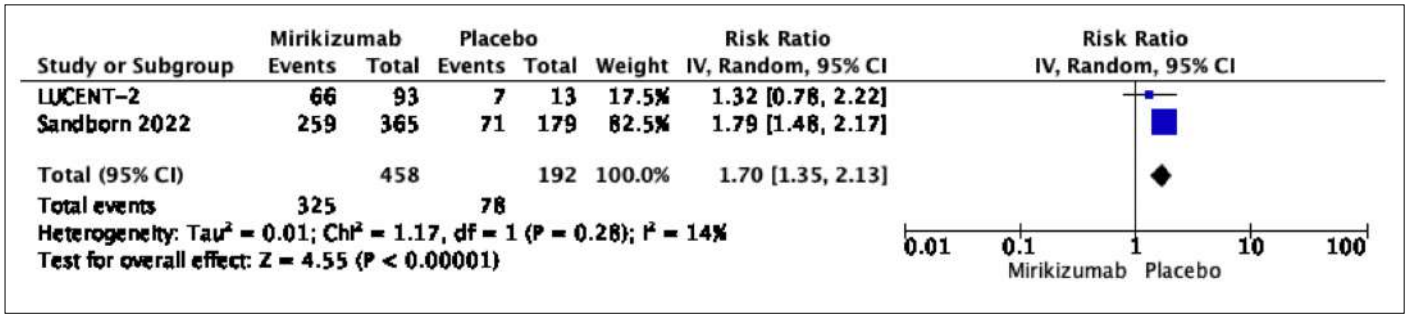

Figure 11. Forest plot of symptomatic remission during maintenance.

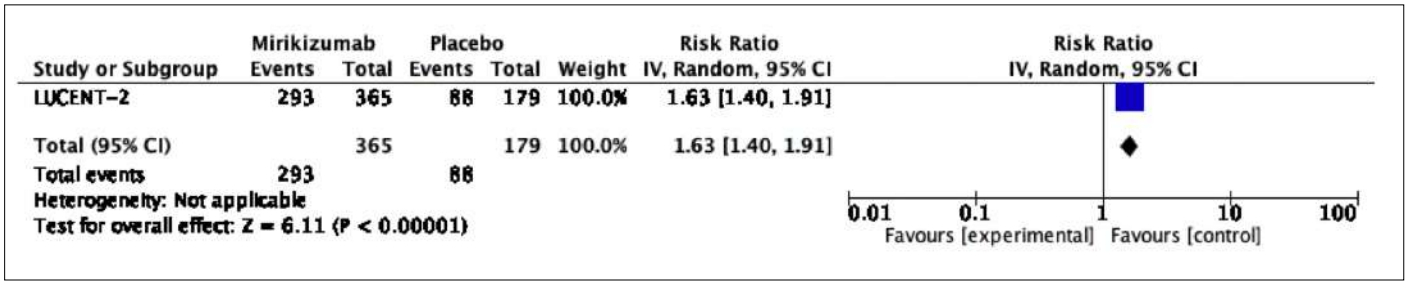

Figure 12. Forest plot of clinical response during maintenance (single study, LUCENT-2).'"

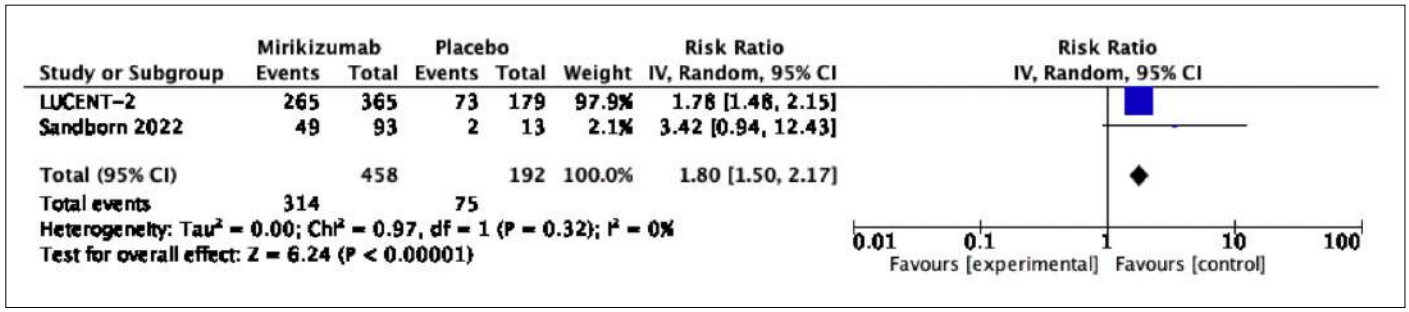

Figure 13. Forest plot of endoscopic improvement/response during maintenance. Endoscopic improvement/response combines two nonidentically named endpoints (Phase 2 "endoscopic improvement" vs LUCENT "endoscopic response"). Both are based on a reduction in the Mayo endoscopic subscore; however, this definitional difference is a source of indirectness.

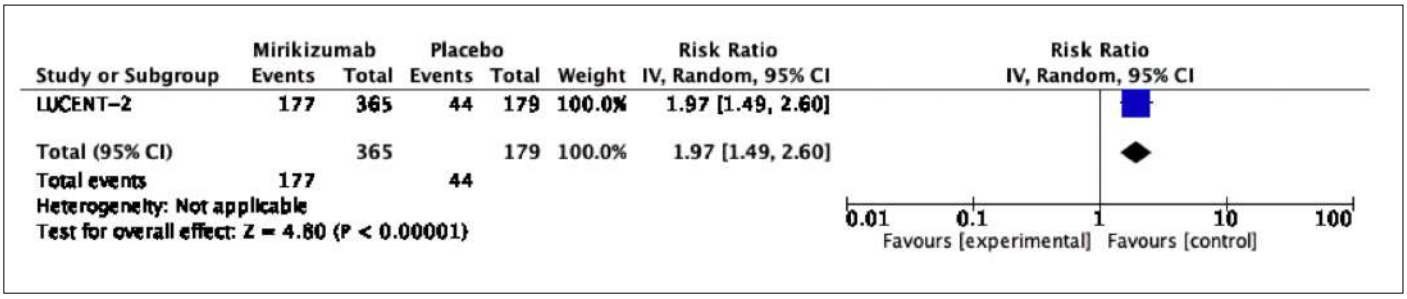

Figure 14. Forest plot of histologic remission during maintenance (single study, LUCENT-2).'

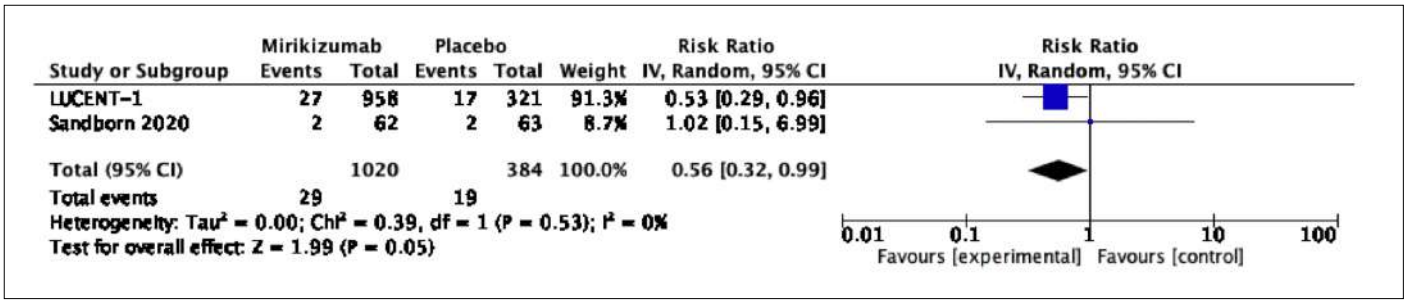

Figure 15. Forest plot of serious adverse events during induction.

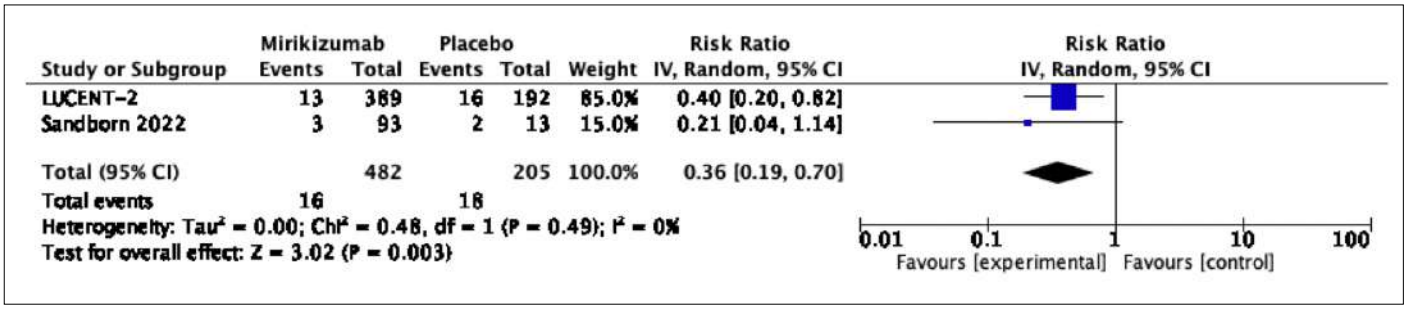

Figure 16. Forest plot of serious adverse events during maintenance.

Rather than simply reanalyzing the same data, our review provides a methodologically updated, GRADE-rated synthesis of the evidence, as detailed below. Our updated search (Section 2.1), conducted on August 22, 2026, postdates that of Abu Elainein et al.[4] by approximately 16 months and independently confirms that no additional eligible trial has since been published. This review necessarily draws on the same finite evidence base as Abu Elainein et al.,[4] currently comprising only two independent placebo-controlled RCT programs of mirikizumab in UC; our supplementary Cochrane Library search (Section 2.1) likewise confirmed that no additional eligible trial has become available. Some overlap in the underlying evidence base between contemporaneous systematic reviews addressing the same clinical question is expected and has been documented in the broader methodological literature.[14] The two analyses nonetheless differ methodologically in several respects that extend beyond simply reanalyzing the same trials: arm-level data were independently re-extracted directly from the primary ClinicalTrials.gov registry records rather than from published summary figures alone, yielding a fully transparent and reproducible extraction table (Table 1) across all tested dose groups, including doses not carried forward into Phase 3; risk of bias was assessed using the Cochrane RoB 2.0 tool rather than the older RoB1 tool; the approved clinical dosing regimen (300 mg IV induction/200 mg SC maintenance) was pooled as the primary comparison rather than combining all tested doses; a single prespecified random-effects model was applied throughout rather than switching between fixed- and random-effects models post hoc according to the observed I^2; and formal GRADE certainty-of-evidence ratings (Section 3.7) were assigned to every pooled outcome. Subgroup analysis according to prior biologic/JAK inhibitor exposure—a gap explicitly identified by Abu Elainein et al.4 as a priority for future research—was not undertaken in the present analysis and remains a direction for future work. Despite these methodological differences, both analyses reached the same overall conclusion that mirikizumab is superior to placebo.

The wider confidence intervals and greater heterogeneity observed for clinical remission, clinical response, and endoscopic improvement/response during induction are attributable to the small sample size and disproportionately large point estimate in the Phase 2 200-mg arm. Because random-effects pooling combines a small, high-variance early-phase trial with a much larger, more precise Phase 3 trial, the pooled

interval is appropriately wider. Clinicians should place greater weight on the LUCENT-1/2 (Phase 3, N>1,000) estimates when applying these results because these trials used the dose ultimately approved for clinical use (300 mg IV induction/200 mg SC maintenance) in a substantially larger and more representative population.

Limitations

This analysis has several limitations that warrant consideration. Only two independent RCT programs (four publications) were available for pooling; this reflects the current size of the evidence base for a relatively recently approved therapy rather than a limitation of the search strategy. The Phase 2 and Phase 3 trials used different mirikizumab doses/routes (200 mg vs 300 mg IV induction) and, in some instances, different clinical remission scoring conventions, introducing clinical heterogeneity that random-effects modeling only partially addresses. The Phase 2 maintenance placebo arm was very small (n=13), as it comprised only placebo-treated induction responders who were re-randomized, thereby limiting the precision of maintenance outcomes derived from that trial. Maintenance efficacy and safety should therefore be interpreted primarily in light of the LUCENT-2 results (placebo n=179 vs mirikizumab n=365), which provide a substantially larger and more precise basis for clinical inference. Long-term (>1 year) efficacy and safety data from the LUCENT-3 open-label extension were not pooled because that study lacked a placebo comparator beyond the initial randomized period. Study selection, data extraction, and GRADE certainty rating were divided between two authors (GD and AS), each following the prespecified eligibility, extraction, and rating rules described above, with the outputs reviewed by the other author before finalization. Because these steps were divided rather than independently duplicated, no formal disagreement-adjudication process was required; we acknowledge this as a deviation from best-practice duplicate review. The composite "endoscopic improvement/response" outcome combines two nonidentically named endpoints (Phase 2 "endoscopic improvement" vs LUCENT "endoscopic response"). Although both are based on a reduction in the Mayo endoscopic subscore, this definitional non-equivalence is a source of indirectness and likely contributes to the high heterogeneity and GRADE "very low"/"low" certainty ratings for this specific outcome (Section 3.7). Subgroup analysis according to prior biologic/JAK inhibitor exposure was not undertaken.

CONCLUSION

Mirikizumab is an effective and well-tolerated induction and maintenance therapy for moderately to severely active ulcerative colitis, with consistent benefits across clinical, endoscopic, symptomatic, and histologic domains. These conclusions are drawn from only two independent RCT programs; accordingly, the precision and generalizability of the pooled estimates are limited, and confirmatory evidence from additional independent trials and long-term real-world cohorts would strengthen confidence in these findings before they are considered definitive. Further head-to-head and longer-term randomized studies would help refine dose-specific effect estimates and clarify comparative efficacy against other advanced therapies.[15]

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Supplementary Table 1. GRADE Summary of Findings for all 14 pooled and single-study outcomes

Phase	Outcome	RR (95% CI)	I^2	k	Certainty	Rationale
Induction	Clinical remission	2.45 (1.03–5.83)	56.3%	2	Low	I^2=56% (moderate-to-high inconsistency); lower CI bound (1.03) close to the null; relatively few events (~272).
Induction	Clinical response	1.98 (1.05–3.73)	81.9%	2	Low	I^2=82% (high inconsistency); lower CI bound (1.05) close to the null.
Induction	Endoscopic remission	1.72 (1.36–2.18)	0%	2	High	Homogeneous (I^2=0%), with ample events and a CI far from the null, indicating robust evidence.
Induction	Symptomatic remission	2.02 (1.20–3.41)	72.1%	2	Moderate	I^2=72% (high inconsistency); however, the lower CI bound (1.20) is sufficiently far from the null.
Induction	Endoscopic improvement/ response (composite)	2.43 (0.81–7.28)	78.8%	2	Very low	The 95% CI crosses the null (not statistically significant); Phase 2 "endoscopic improvement" and LUCENT-1 "endoscopic response" are nonidentically named endpoints (indirectness); I^2=79% (high inconsistency).
Induction	Histologic remission (single study)	1.87 (1.41–2.49)	N/A	1	Moderate	Reported only in LUCENT-1 (single-study default imprecision downgrade).
Induction	Serious adverse events (SAEs)	0.56 (0.32–0.99)	0%	2	Moderate	Rare events (~48 total events); upper CI bound (0.99) close to the null.
Maintenance	Clinical remission (single study, LUCENT-2)	1.98 (1.51–2.61)	N/A	1	Moderate	Reported only in LUCENT-2 (single-study default imprecision downgrade); low risk of bias (double-blind RCT).
Maintenance	Endoscopic remission	2.03 (1.59–2.59)	0%	2	Moderate	Includes the Phase 2 maintenance re-randomization (RoB 2.0: "some concerns," driven by its small placebo arm [n=13] and risk of missing outcome data); otherwise homogeneous, with a CI far from the null.
Maintenance	Symptomatic remission	1.70 (1.35–2.13)	14.4%	2	Moderate	Includes the Phase 2 maintenance re-randomization (RoB 2.0: "some concerns," due to the small placebo arm [n=13] and risk of missing outcome data).
Maintenance	Clinical response (single study, LUCENT-2)	1.63 (1.40–1.91)	N/A	1	Moderate	Reported only in LUCENT-2 (single-study default imprecision downgrade).
Maintenance	Endoscopic improvement/ response (composite)	1.80 (1.50–2.17)	0%	2	Low	Includes the Phase 2 maintenance re-randomization (RoB 2.0: "some concerns," due to the small placebo arm [n=13] and risk of missing outcome data); Phase 2 and LUCENT use nonidentically named endpoints (indirectness), although the CI is narrow and far from the null.
Maintenance	Histologic remission	1.97 (1.49–2.60)	N/A	1	Moderate	Reported only in LUCENT-2 (single-study default imprecision downgrade).
Maintenance	Serious adverse events (SAEs)	0.36 (0.19–0.70)	0%	2	Low	Includes the Phase 2 maintenance re-randomization (RoB 2.0: "some concerns," due to the small placebo arm [n=13] and risk of missing outcome data); rare events (~34 total events).

CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; I^2, heterogeneity statistic; k, number of contributing trials; N/A, not applicable; RCT, randomized controlled trial; RoB, risk of bias; RR, risk ratio; SAE, serious adverse event. Certainty was rated down from "high" for risk of bias, inconsistency ($I^2 \geq 50\%$), indirectness, and imprecision according to the prespecified rules described in Sections 2.6 and 3.7.

Journal of Enterocolitis

Review

Transient Elastography for Liver Fibrosis and Steatosis in Inflammatory Bowel Disease: Current Evidence, Clinical Implications, and Future Directions

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Abstract

Inflammatory bowel disease (IBD) is frequently complicated by hepatobiliary conditions, including metabolic dysfunction-associated steatotic liver disease (MASLD), drug-induced liver injury, primary sclerosing cholangitis, and autoimmune liver disease. However, systematic liver assessment remains underused, and serum indices such as FIB-4 may be confounded by IBD-related thrombocytosis. Transient elastography (TE) quantifies liver stiffness measurement (LSM) for fibrosis and the controlled attenuation parameter (CAP) for steatosis through a rapid, noninvasive outpatient examination. This narrative review synthesizes evidence on the prevalence of fibrosis and steatosis, associated risk factors, the effects of IBD therapies, and the clinical utility of TE-based screening, drawing on original studies that used FibroScan®-based LSM and/or CAP in adult patients with IBD; studies using other elastography modalities were excluded. Across 13 studies involving more than 2,700 patients with IBD, the prevalence of significant fibrosis (F≥2) clustered around 4–12% (range, ~1–24%, depending on the threshold), while steatosis was detected in 29–46%. Anti-TNF therapy was associated with a lower prevalence of fibrosis, whereas cumulative corticosteroid exposure increased the risk of both fibrosis and steatosis. Two matched-control studies confirmed that IBD independently confers an increased hepatic risk: one reported steatosis in 42.0% versus 32.7% and advanced fibrosis in 9.5% versus 2.3% of controls (adjusted odds ratio [aOR] for steatosis, 1.99), while ELASTIBD reported significant fibrosis in 12.3% versus 4.2% (aOR, 3.31) and steatosis in 41.4% versus 28.3% (aOR, 2.51) compared with matched controls. TE therefore provides actionable information beyond standard liver function tests and should be integrated into IBD follow-up, particularly for patients with prolonged corticosteroid exposure, metabolic comorbidities, or longstanding disease, while standardization of cutoff values and longitudinal data remain research priorities.

Keywords: Controlled attenuation parameter, FibroScan, hepatic steatosis, inflammatory bowel disease, liver fibrosis, metabolic dysfunction-associated steatotic liver disease, transient elastography.

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, immune-mediated disorder of the gastrointestinal tract affecting an estimated 6.8 million individuals worldwide, with incidence rising particularly in newly industrialized regions.[1,2] Beyond intestinal inflammation, IBD is increasingly recognized as a systemic disease, with extraintestinal manifestations (EIMs) occurring in up to 50% of patients over the course of their illness.[3,4] Among these, hepatobiliary involvement is common and clinically underappreciated and includes metabolic dysfunction-associated steatotic liver disease (MASLD), primary sclerosing cholangitis (PSC), drug-induced liver injury (DILI), autoimmune hepatitis, and chronic viral hepatitis.[5]

The hepatic burden in IBD arises from several pathogenic pathways, including sustained systemic inflammation, gut microbiota dysbiosis driving aberrant gut-liver axis signaling, cumulative exposure to hepatotoxic drugs, and metabolic dysregulation that may paradoxically occur even in nutritionally compromised patients.[5,6] Despite this complexity, liver assessment in routine IBD care has historically relied on conventional liver function tests, which lack sensitivity for detecting early or subclinical fibrosis and steatosis.[7] Serum-based fibrosis indices such as FIB-4 and APRI are likewise unreliable in IBD because reactive thrombocytosis associated with chronic inflammation lowers their platelet-dependent scores and may mask significant fibrosis.[8] Liver biopsy, the reference standard for fibrosis staging, is invasive, subject to sampling error, and impractical for surveillance in an outpatient IBD population.[9]

Transient elastography, commercially implemented as FibroScan® (Echosens, Paris, France), addresses this diagnostic gap by providing simultaneous, noninvasive quantification of liver stiffness measurement (LSM) as a validated surrogate for fibrosis stage and the controlled attenuation parameter (CAP) as a quantitative index of hepatic steatosis.[10,11] The technique is rapid, reproducible, and well tolerated, making it particularly

suitable for integration into IBD outpatient workflows. Over the past decade, a growing body of evidence has evaluated transient elastography in IBD cohorts; however, important questions regarding optimal screening strategies, cutoff standardization, and the influence of IBD-specific therapies remain unresolved.

This narrative review synthesizes current evidence on the use of transient elastography in adult patients with IBD, examining the prevalence and determinants of liver fibrosis and steatosis, the impact of IBD therapies on hepatic outcomes, and the clinical scenarios in which TE-based assessment is most warranted. We also highlight key methodological limitations and priorities for future research.

Literature Search and Study Selection

This narrative review is based on a structured search of the PubMed/MEDLINE database from inception through 2025 using combinations of the terms "inflammatory bowel disease," "Crohn's disease," "ulcerative colitis," "transient elastography," "FibroScan," "vibration-controlled transient elastography," "liver stiffness," "controlled attenuation parameter," "liver fibrosis," and "hepatic steatosis." Original studies using FibroScan®-based LSM and/or CAP measurements in adult IBD populations were prioritized. Studies employing alternative elastography modalities, including acoustic radiation force impulse imaging, point or two-dimensional shear-wave elastography, and magnetic resonance elastography, were excluded to preserve methodological comparability. The reference lists of retrieved articles and relevant reviews were hand-searched to identify additional sources. Consistent with the narrative review design, no formal risk-of-bias assessment or quantitative meta-analysis was performed; the synthesis was qualitative and interpretive.

Burden Of Liver Disease In Inflammatory Bowel Disease

Hepatobiliary involvement is one of the most clinically significant extraintestinal manifestations of IBD. Although it has historically been estimated to affect approximately 5% of patients with IBD based on overt liver enzyme abnormalities or clinical presentation, this figure is widely considered an underestimate; subclinical hepatic involvement is considerably more prevalent when systematic noninvasive assessment is applied.[4,5] Liver enzyme elevations have been reported in up to 30% of patients with IBD at some point during their disease course; however, abnormal transaminase levels alone correlate poorly with the nature or severity of the underlying hepatic pathology.[7] The hepatobiliary complications of IBD vary widely, ranging from common and often silent conditions such as hepatic steatosis to rare but potentially fatal conditions such as cholangiocarcinoma arising from primary sclerosing cholangitis (PSC). These pathways converge on the liver through the mechanisms summarized in Figure 1.

Metabolic Dysfunction-Associated Steatotic Liver Disease

Hepatic steatosis, now classified under the umbrella of MASLD, is the most frequent hepatobiliary complication of IBD and accounts for the majority of abnormal liver findings in this population.[5,12] Reported prevalence rates vary considerably across studies, ranging from 1.5% to 55% in UC and from 1.5% to 39.5% in CD, owing to differences in diagnostic methods, population characteristics, and the extent of alcohol exclusion.[5] When quantitative noninvasive tools such as vibration-controlled transient elastography (VCTE) with the controlled attenuation parameter (CAP) are used, the prevalence of steatosis consistently ranges between 29% and 46%.[13–15]

The pathogenesis of MASLD in IBD is multifactorial and differs from that in the general population. In addition to conventional metabolic

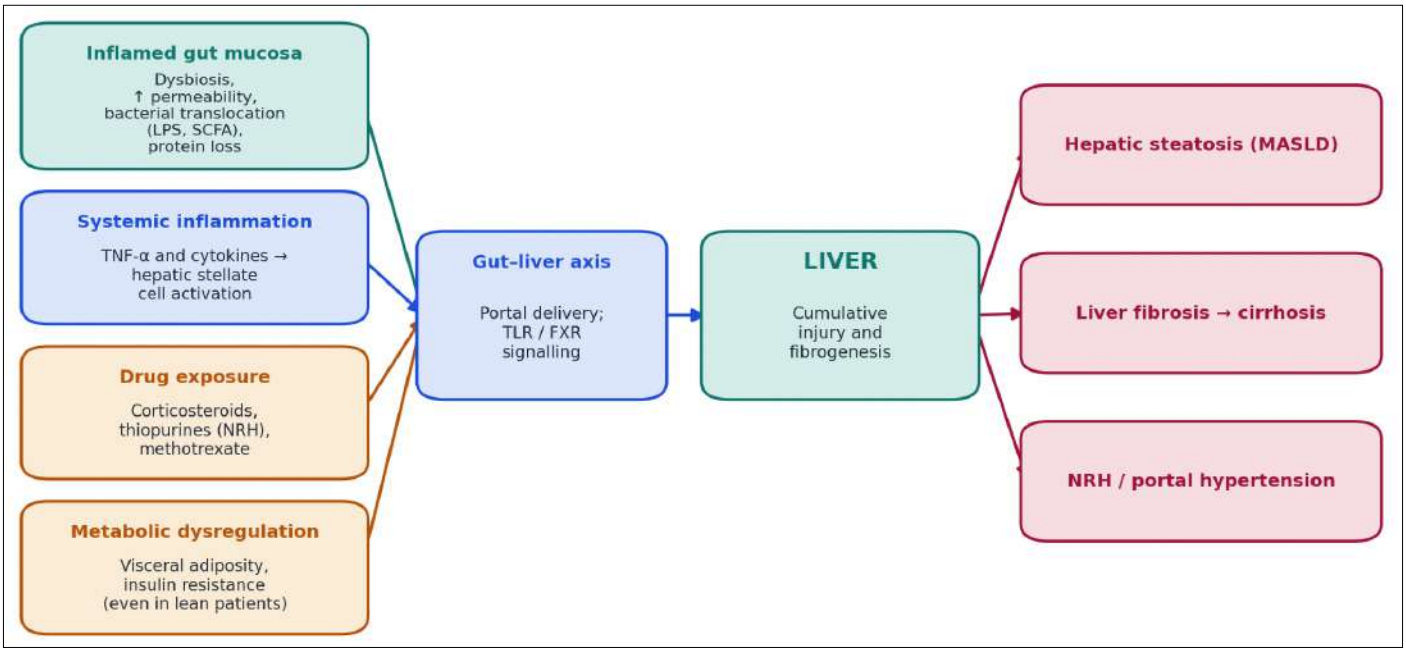

Figure 1. Pathogenesis of hepatic injury in inflammatory bowel disease. Intestinal, systemic inflammatory, iatrogenic, and metabolic pathways converge on the liver through the gut-liver axis, resulting in hepatic steatosis, fibrosis, and nodular regenerative hyperplasia/portal hypertension. FXR, farnesoid X receptor; LPS, lipopolysaccharide; MASLD, metabolic dysfunction-associated steatotic liver disease; NRH, nodular regenerative hyperplasia; SCFA, short-chain fatty acids; TLR, toll-like receptor; TNF, tumor necrosis factor.

risk factors, several IBD-specific contributors are well recognized, including sustained systemic inflammation, gut-liver axis dysregulation, malnutrition, and the metabolic effects of IBD therapies.[6,16] (Figure 1) These IBD-specific mechanisms, including the role of corticosteroids, are examined in detail in Metabolic Risk Factors: Shared and IBD-Specific.

Primary Sclerosing Cholangitis

PSC is the most IBD-specific hepatobiliary manifestation, occurring in approximately 4–5% of patients with IBD overall, with a marked predominance in UC.[17,18] Conversely, 70–80% of patients diagnosed with PSC have concurrent IBD, making IBD the strongest clinical association with this cholestatic disease.[17] PSC follows a progressive course characterized by biliary inflammation and fibrosis, ultimately leading to end-stage liver disease, and is associated with a substantially increased risk of cholangiocarcinoma and colorectal carcinoma.[19,20] Diagnosis is based on characteristic magnetic resonance cholangiopancreatography (MRCP) findings after exclusion of secondary causes; liver biopsy retains diagnostic utility primarily in small-duct PSC.[18] Although transient elastography is not a diagnostic modality for PSC, it has emerging value in monitoring fibrosis progression in patients with PSC-IBD and identifying those at risk of hepatic decompensation.[18]

Drug-Induced Liver Injury

IBD pharmacotherapy carries hepatotoxic potential and therefore warrants ongoing vigilance. Thiopurines, including azathioprine and 6-mercaptopurine, are associated with a range of hepatic adverse effects, including transaminase elevation, nodular regenerative hyperplasia (NRH), and noncirrhotic portal hypertension, which may remain clinically silent until esophageal varices develop because platelet counts are often preserved or even elevated in patients with IBD.[21] Methotrexate carries a cumulative dose-related risk of liver fibrosis, although this risk appears substantially lower in patients with IBD than in those with psoriasis or rheumatoid arthritis.[22,23] Repeated courses of corticosteroids promote visceral adiposity and hepatic fat accumulation, contributing to the burden of MASLD independently of disease activity.[13] In contrast, anti-TNF agents have been associated with a lower prevalence of fibrosis in multiple observational IBD cohorts, and experimental data suggest potential hepatoprotective effects through suppression of inflammatory cytokines implicated in hepatic stellate cell activation.[15,24]

Autoimmune Liver Diseases and Viral Hepatitis

Autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC) occur more frequently in patients with IBD than in the general population, and AIH–PSC overlap syndrome presents a particularly challenging diagnostic and therapeutic scenario.[7,25] Vigilance for HBV reactivation is essential in patients initiating immunosuppressive therapy; screening for HBsAg and anti-HBc before the initiation of biologics or immunomodulators, followed by antiviral prophylaxis when indicated, is mandated by current guidelines.[26] Chronic HCV coinfection, although less specifically associated with IBD, also influences hepatic outcomes and treatment decisions, particularly with respect to the risk of thiopurine- and methotrexate-related hepatotoxicity.

Taken together, this diverse and overlapping spectrum of hepatic pathology, occurring in a population characterized by chronic systemic inflammation, complex polypharmacy, and metabolic dysregulation, provides a strong rationale for systematic noninvasive liver assessment as an integral component of IBD care.

Principles of Transient Elastography

Technical Basis and Liver Stiffness Measurement

FibroScan® is an ultrasound-based technique that quantifies hepatic mechanical properties through the propagation of a low-frequency shear wave generated by a vibrating probe placed intercostally over the right hepatic lobe.[10] The velocity of shear wave propagation, which is directly proportional to tissue stiffness, is measured by pulse-echo ultrasound and converted into a liver stiffness measurement (LSM), expressed in kilopascals (kPa). Each examination requires a minimum of 10 valid acquisitions, with reliability defined by a success rate ≥60% and an interquartile range-to-median ratio (IQR/M) ≤30%.[27,28] The examination samples a hepatic volume approximately 100-fold greater than that of a conventional biopsy core, substantially reducing the sampling error inherent in histological staging.[9]

LSM correlates with the METAVIR fibrosis staging system, with manufacturer-recommended and widely adopted thresholds for significant fibrosis (F≥2) ranging from 7.0 to 8.0 kPa, advanced fibrosis (F≥3) at approximately 8.7–9.5 kPa, and cirrhosis (F4) at ≥12.5 kPa, depending on the underlying etiology and probe type (Table 1).[27,29] The M probe is recommended for patients with a skin-to-liver capsule distance ≤25 mm, whereas the XL probe is indicated for patients with obesity and yields LSM values approximately 1.0–1.5 kPa lower for equivalent fibrosis stages.[30]

Controlled Attenuation Parameter

The controlled attenuation parameter (CAP) is acquired simultaneously with LSM using the same ultrasonic signal and quantifies hepatic steatosis by measuring ultrasound attenuation caused by fat within the liver parenchyma, expressed in decibels per meter (dB/m).[11] The most widely applied CAP thresholds define steatosis grades as follows: S0 (no steatosis) below 248 dB/m, S1 (mild, >5% hepatocytes) at 248–267 dB/m, S2 (moderate, >33%) at 268–279 dB/m, and S3 (severe, >66%) at ≥280 dB/m.31 CAP is more sensitive than conventional B-mode ultrasonography for detecting mild steatosis, and because it is acquired simultaneously with LSM, it enables noninvasive assessment of both fibrosis and steatosis during a single outpatient visit.[28,32]

Spleen Stiffness Measurement

More recent generations of FibroScan® permit spleen stiffness measurement (SSM) using the same shear wave principle applied intercostally over the spleen. SSM correlates with portal pressure and has demonstrated value in predicting clinically significant portal hypertension and esophageal varices independently of LSM.[33,34] The Baveno VII consensus proposed SSM cutoffs of <21 kPa to rule out and >50 kPa to rule in clinically significant portal hypertension; however, these thresholds were derived primarily from patients with viral compensated advanced chronic liver disease, and their application to IBD remains an extrapolation pending dedicated validation.[35,36] In IBD, SSM is particularly relevant for detecting thiopurine-associated NRH and noncirrhotic portal hypertension, conditions in which liver architecture and LSM may remain entirely normal despite established portal hypertension; however, this association has so far been reported only in preliminary studies.[37]

Cutoff Heterogeneity and IBD-Specific Considerations

A major methodological challenge in interpreting transient elastography findings across IBD cohorts is the lack of consensus regarding LSM cutoff values, reflecting the absence of IBD-specific validation against liver biopsy as a reference standard in large, well-characterized

Table 1. Widely adopted transient elastography thresholds for fibrosis staging (LSM), steatosis grading (CAP), and portal hypertension assessment (SSM). Values reflect manufacturer-recommended and meta-analytic cutoffs for the M probe; XL-probe- and etiology-specific adjustments may apply. For MASLD-predominant disease, a pragmatic dual-cutoff approach is widely used: LSM <8 kPa rules out clinically significant fibrosis, LSM ≥12 kPa rules in advanced fibrosis, and values of 8–12 kPa are considered indeterminate and warrant confirmatory testing.38–40 SSM cutoffs (<21 kPa to rule out; >50 kPa to rule in) follow the Baveno VII consensus.[35,36]

Grade/stage	Cutoff value	Clinical interpretation
Liver stiffness measurement (LSM) – METAVIR fibrosis equivalents (M probe)		
Significant fibrosis (F≥2)	7.0–8.0 kPa	Threshold for hepatology referral and structured follow-up
Advanced fibrosis (F≥3)	8.7–9.5 kPa	Marked fibrosis; expedite etiologic work-up
Cirrhosis (F4)	≥12.5 kPa	Surveillance for portal hypertension and HCC is indicated
Controlled attenuation parameter (CAP) – steatosis grade		
S0 – no steatosis	<248 dB/m	Normal hepatic fat content
S1 – mild (>5%)	248–267 dB/m	Early steatosis; reinforce metabolic optimization
S2 – moderate (>33%)	268–279 dB/m	Moderate steatosis
S3 – severe (>66%)	≥280 dB/m	Severe steatosis; consider evaluation for steatohepatitis
Spleen stiffness measurement (SSM)		
Spleen stiffness (SSM)	>21 kPa (with LSM <7 kPa)	Disproportionate elevation suggests NRH/noncirrhotic portal hypertension, particularly in thiopurine-treated patients

CAP, controlled attenuation parameter; dB/m, decibels per meter; HCC, hepatocellular carcinoma; kPa, kilopascals; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; NRH, nodular regenerative hyperplasia; SSM, spleen stiffness measurement.

cohorts. For clinical decision-making, contemporary MASLD guidance favors a pragmatic dual-cutoff approach: an LSM below 8 kPa reliably excludes clinically significant fibrosis (rule-out), a value of 12 kPa or higher indicates a high probability of advanced fibrosis warranting hepatology referral (rule-in), and intermediate values of 8–12 kPa define an indeterminate zone requiring a second noninvasive test or, when needed, magnetic resonance elastography or liver biopsy.[38–40] Reported thresholds for significant fibrosis (F≥2) across IBD studies nevertheless range from 7.0 to 8.7 kPa for the M probe, and this heterogeneity directly limits cross-study comparisons and pooled prevalence estimates.[41,42] Because most IBD-associated liver disease is metabolic in origin, this framework provides a reasonable default for LSM interpretation in IBD pending IBD-specific validation.

Several IBD-specific physiological factors may confound LSM interpretation independently of fibrosis. Active intestinal inflammation with elevated CRP levels drives systemic inflammatory signaling that may transiently increase liver stiffness regardless of fibrosis stage.[43] Hepatic congestion associated with right-sided heart involvement, postprandial increases in hepatic blood flow, and cholestasis in patients with PSC can each elevate LSM without corresponding histological fibrosis.18 These confounders underscore the importance of performing TE in clinically stable, fasting patients and interpreting the results within the overall clinical context rather than in isolation. CAP values are similarly influenced by probe type, body mass index, and the presence of significant fibrosis, as higher fibrosis stages independently increase CAP readings, which is particularly relevant in patients with IBD and concurrent steatosis and fibrosis.[11,31]

Despite these limitations, transient elastography remains the most practical, reproducible, and evidence-supported noninvasive tool for the simultaneous assessment of hepatic fibrosis and steatosis in IBD outpatient settings.[8]

Evidence for Liver Fibrosis Assessment in IBD

Early Studies and the Pre-CAP Era

The systematic application of transient elastography in IBD populations began in the early 2010s, initially focusing on LSM as a surrogate for fibrosis without simultaneous quantification of steatosis. Barbero-Villares et al.[22] examined 46 methotrexate-treated patients with IBD and found that advanced fibrosis was uncommon despite cumulative exposure. Thin et al.[42] subsequently evaluated 110 patients with IBD alongside 55 non-IBD controls using an LSM threshold of ≥8 kPa for clinically significant liver disease, identifying elevated stiffness in only 6.4% of patients with IBD, with no significant difference from controls at the group level; within the IBD cohort, however, higher BMI and older age were independently associated with elevated LSM. Meijer et al.[41] contributed the first prospective two-center cohort, reporting significant fibrosis (F≥2) in 4% and severe fibrosis (F≥3) in <1% of 168 patients and noting that prior azathioprine exposure was associated with lower liver stiffness. The full body of included studies is summarized in Table 2.

The Landmark Cohort and CAP Integration

A major advance came from Saroli Palumbo et al.,[13] who screened 384 patients with IBD using VCTE with CAP as part of a routine outpatient program, representing the first large prospective cohort to quantify both fibrosis and steatosis. The reported prevalence of NAFLD (32.8%) and significant fibrosis (12.2%) was substantially higher than that observed in earlier TE-only studies, reflecting the greater sensitivity of CAP for detecting steatosis compared with clinical suspicion alone. Older age and higher BMI emerged as the primary independent predictors of both outcomes in logistic regression, establishing the metabolic phenotype as the dominant risk profile in IBD-associated liver disease. The study also linked NAFLD to extrahepatic comorbidities, including chronic kidney and cardiovascular disease, thereby broadening its clinical implications.

Table 2. Original studies of transient elastography in adult IBD populations included in this review (n=13), presented in chronological order

Study	Country	Design	N (IBD)	Steatosis	Fibrosis (F≥2)	Key finding
Barbero-Villares[22]	Spain	Prospective, multicenter	46	—[a]	23.9%	Advanced fibrosis was uncommon in MTX-treated patients with IBD
Thin[42]	Australia	Case-control	110	—[a]	6.4%	Higher BMI and older age were associated with increased LSM; no significant difference versus controls
Meijer[41]	Netherlands	Prospective, two-center	168	NR	4%	Prior azathioprine exposure was associated with lower LSM
Saroli Palumbo[13]	Canada	Prospective	384	32.8%	12.2%	First large CAP-based cohort; age and BMI were the main predictors
Arieira[44]	Portugal	Cross-sectional	161	16.8–45.3%[b]	NR	CAP reclassified steatosis compared with clinical indices
Yen[46]	Taiwan	Retrospective	81	29.6%	1.2%	Lower prevalence was observed in an Asian cohort
van Lingen[43]	Netherlands	Prospective, longitudinal	112	40%	20%[c]	Active IBD was associated with progression of steatosis and fibrosis
Trifan[14]	Romania	Prospective	82	46.3%	NR	Highest reported steatosis prevalence; associated with metabolic factors
Veltkamp[45]	Germany	Retrospective	132	30.3%	8%	Fibrosis occurred predominantly in patients with Crohn's disease
Hsiao[47]	Taiwan	Retrospective	120	29.2%	Low	MAFLD was assessed in patients in clinical remission
Rodriguez-Duque[48]	Spain	Matched case-control	831	42.0%[d]	9.5%[c]	IBD was an independent predictor of MAFLD (aOR, 1.99)
Ferraz-Amaro[8]	Spain	Cross-sectional	197	NR	NR	FIB-4 did not correlate with elastography-defined fibrosis
ELASTIBD[15]	Türkiye	Matched case-control	358	41.4%[d]	12.3%[d]	Anti-TNF therapy was associated with lower fibrosis risk; corticosteroid courses were associated with increased fibrosis risk

aOR, adjusted odds ratio; BMI, body mass index; CAP, controlled attenuation parameter; CD, Crohn's disease; FIB-4, Fibrosis-4 Index; FLI, Fatty Liver Index; HSI, Hepatic Steatosis Index; IBD, inflammatory bowel disease; LSM, liver stiffness measurement; MAFLD, metabolic dysfunction-associated fatty liver disease; MTX, methotrexate; NR, not reported; TNF, tumor necrosis factor. [a]Steatosis was not quantified because the study predated CAP. [b]Arieira et al.[44] reported hepatic steatosis as a range across noninvasive methods (HSI, FLI, and CAP) rather than as a single CAP-based prevalence. [c]Reported using higher liver stiffness thresholds (van Lingen, LSM ≥7.3 kPa; Rodriguez-Duque, advanced fibrosis ≥9.7 kPa); fibrosis cutoffs differed across studies, limiting direct comparisons. [d]Prevalence in patients with IBD versus matched controls. Steatosis: Rodriguez-Duque, 42.0% vs 32.7%; ELASTIBD, 41.4% vs 28.3%. ELASTIBD significant fibrosis: 12.3% vs 4.2%. Definitions of steatosis and fibrosis varied across studies; these figures should therefore be interpreted in light of this heterogeneity.

Confirmatory Cohorts and Geographic Variation

Subsequent studies across multiple healthcare settings reinforced and further refined these findings. Arieira et al.[44] demonstrated that TE with CAP identified hepatic steatosis in a substantial proportion of patients with IBD and reclassified cases compared with clinical steatosis indices such as the HSI and FLI, highlighting the value of quantitative CAP-based assessment. van Lingen et al.[43] contributed longitudinal data showing that active IBD at baseline, defined by elevated CRP and fecal calprotectin levels, was independently associated with both increased liver fat content and fibrosis progression at 6–12 months of follow-up, providing the first prospective evidence linking IBD disease activity to hepatic outcomes over time. Trifan et al.[14] reported the highest steatosis prevalence in the literature, at 46.3% among 82 Romanian patients, with steatosis associated with older age, higher BMI, longer disease duration, and adverse metabolic markers, possibly reflecting the cohort's metabolic profile. A German retrospective single-center cohort of 132 patients further demonstrated that, although steatosis was similarly distributed between CD and UC, liver fibrosis occurred predominantly in patients with CD, suggesting a disease-specific fibrogenic pathway potentially related to transmural inflammation, intestinal failure, or nutritional compromise.[45] Two Taiwanese series, reporting NAFLD/MAFLD prevalences of 29.6% and 29.2%, showed that IBD-associated MASLD is not confined to Western populations, although absolute fibrosis rates were lower, possibly reflecting differences in metabolic background and IBD phenotype in Asian populations.[46,47] The reported prevalences of steatosis and significant fibrosis across these cohorts are compared in Figure 2.

Case-Control Evidence and the Independent Role of IBD

Cohort-only designs cannot determine whether the elevated prevalence observed in IBD reflects disease-specific mechanisms or shared metabolic risk factors. Two matched case-control studies have directly addressed this question. Rodriguez-Duque et al.[48] enrolled 831 consecutive patients with IBD alongside general-population controls at two university hospitals and found a MAFLD prevalence of 42.0% in the IBD group versus 32.7% in controls and an advanced fibrosis prevalence of 9.5% versus 2.3%, with IBD remaining an independent predictor of both outcomes after adjustment for BMI, diabetes, and other conventional metabolic covariates. Liver biopsy in a subset of 40 patients confirmed the elastography-based staging; patients with IBD-MAFLD also had a lower BMI and a lower prevalence of type 2 diabetes than severity-matched non-IBD MAFLD controls, reinforcing the concept that inflammation-driven pathways operate independently of metabolic adiposity.

The ELASTIBD study[15] individually matched 358 adult patients with IBD to 358 controls according to age, sex, BMI, and diabetes status, thereby controlling for the principal metabolic confounders. Despite this matching, patients with IBD had a higher prevalence of significant

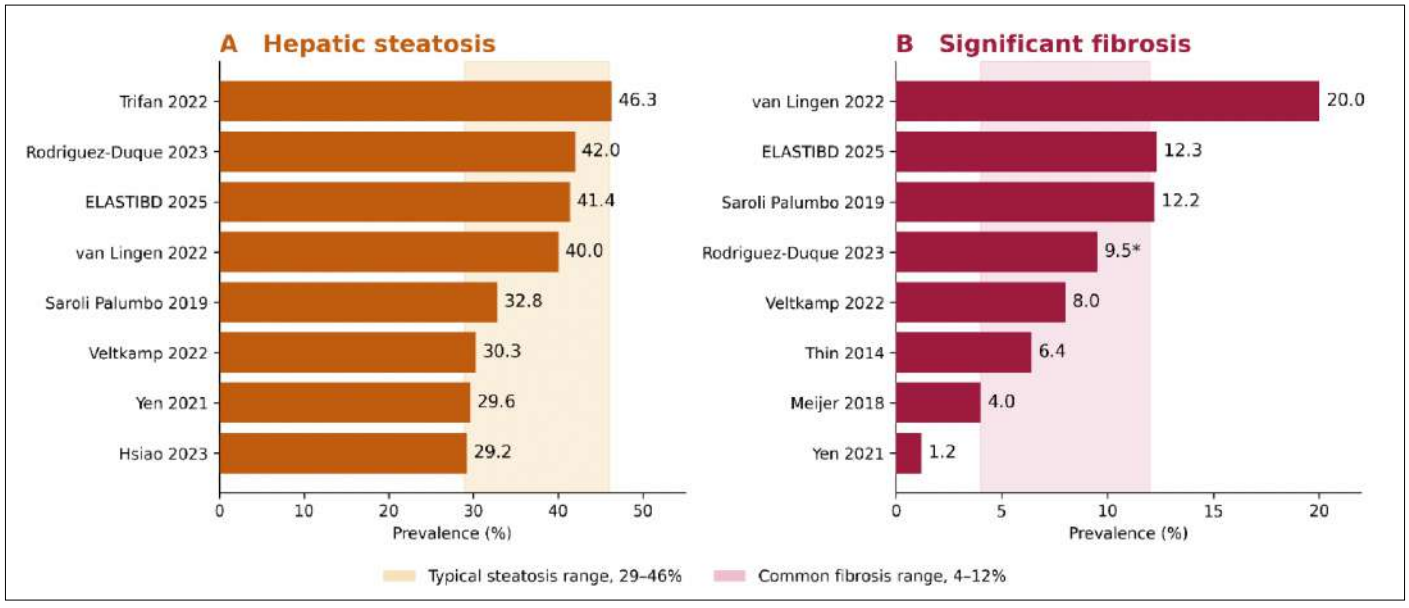

Figure 2. Reported prevalence of hepatic steatosis (panel A) and significant fibrosis (panel B) assessed by transient elastography across IBD cohorts. Shaded bands indicate the typical prevalence ranges referenced in the text (steatosis, 29–46%; fibrosis, 4–12%). Thresholds varied across studies (CAP cutoffs commonly 248–280 dB/m; LSM cutoffs for significant fibrosis, 7.0–8.0 kPa); the asterisk denotes advanced fibrosis (LSM ≥9.7 kPa) in the Rodriguez-Duque study.[48] Studies that did not report prevalence for a given parameter are omitted from the corresponding panel.

fibrosis (F≥2; 12.3% vs 4.2%) and hepatic steatosis (41.4% vs 28.3%) than controls. Because ELASTIBD excluded patients with other identifiable liver diseases, including PSC, viral hepatitis, autoimmune liver disease, and significant alcohol use, this excess could not be attributed to concurrent hepatic conditions and instead reflected an IBD-associated, predominantly metabolic and inflammatory hepatic burden, strengthening the inference of an independent IBD effect. Among patients with IBD, anti-TNF therapy was independently associated with 61% lower odds of fibrosis (aOR, 0.39; 95% CI, 0.16–0.95), whereas each corticosteroid course was associated with 41% higher odds of fibrosis (aOR, 1.41; 95% CI, 1.04–1.92). These findings provide the strongest available evidence that IBD itself, through mechanisms beyond conventional metabolic risk, contributes to hepatic fibrogenesis and that IBD-specific therapies may materially modify this risk.

Synthesis: Consistent Risk Factors Across the Literature

Despite methodological heterogeneity across studies, several risk factors for liver fibrosis and steatosis in IBD emerge consistently (Table 3). Older age and higher BMI are the most reproducibly identified predictors across virtually all cohorts.[13–15,45] Corticosteroid exposure, assessed as both cumulative dose and number of courses, is consistently associated with a higher risk of steatosis and fibrosis.[15,43] In contrast, anti-TNF therapy appears to be associated with a lower prevalence of fibrosis in multiple observational datasets.[15,24,48] Longer IBD duration correlates with steatosis in CD cohorts, whereas disease activity scores have shown an inverse association with steatosis.[15,45] Despite its validation in general MASLD populations, the FIB-4 index does not reliably correlate with elastography-defined fibrosis in patients with IBD, limiting its utility as a fibrosis-screening surrogate in this specific context.[8] A likely explanation is that both FIB-4 and APRI incorporate platelet count into their calculations; therefore, reactive thrombocytosis driven by chronic intestinal inflammation in IBD can spuriously lower these scores and mask significant fibrosis. The same inflammation-driven platelet elevation may also obscure the thrombocytopenia that would otherwise signal hypersplenism due to thiopurine-associated nodular regenerative hyperplasia and noncirrhotic portal hypertension, further favoring elastography, including spleen stiffness measurement, over platelet-based indices in this population.

Steatosis and MASLD in Inflammatory Bowel Disease

Evolving Nomenclature and Diagnostic Reclassification

The terminology for hepatic steatosis has changed considerably over the period covered by the IBD elastography literature. The transition from nonalcoholic fatty liver disease (NAFLD) to metabolic dysfunction-associated fatty liver disease (MAFLD) in 2020 and subsequently to MASLD in 2023 reflects a shift toward a positive, criteria-based diagnosis rather than one based on exclusion.[49,50] These nomenclature changes are not merely semantic: MAFLD and MASLD criteria allow concurrent alcohol use and secondary causes of steatosis to coexist with the diagnosis and reclassify patients based on the presence of at least one metabolic risk factor alongside hepatic steatosis. In IBD cohorts, this reclassification meaningfully affects prevalence estimates; not all TE-defined steatosis meets MASLD criteria, and not all patients meeting MASLD criteria have CAP-confirmed steatosis, creating important challenges when comparing studies published under different nomenclature frameworks.[50] Throughout this review, MASLD is used as the contemporary umbrella term, whereas the original terminology (NAFLD or MAFLD) is retained when reporting the findings of individual studies as originally defined by their authors.

CAP-Based Prevalence and Grade Distribution

Across IBD cohorts employing VCTE with CAP, the prevalence of hepatic steatosis ranges from 29% to 46%, with most affected patients exhibiting mild to moderate steatosis (S1–S2) rather than severe steatosis (S3).[13–15,44] The ELASTIBD study, which applied a CAP threshold of 248 dB/m in a matched-control design, found steatosis in 41.4%

Table 3. Determinants of hepatic fibrosis and steatosis in IBD and the directional effects of IBD-specific therapies. The aOR values shown for corticosteroid exposure and anti-TNF therapy are derived from the ELASTIBD matched-control cohort

Factor	Effect on hepatic outcomes	Evidence/mechanism
Older age	↑ fibrosis and steatosis	Most reproducible predictor across cohorts
Higher BMI	↑ fibrosis and steatosis	Dominant metabolic driver; effect persists after matching
Cumulative corticosteroid exposure	↑ fibrosis and steatosis	Visceral adiposity and insulin resistance; most modifiable factor (ELASTIBD aOR, 1.41 per course)
Anti-TNF therapy	↓ fibrosis	Suppression of TNF-α-driven hepatic stellate cell activation (ELASTIBD aOR, 0.39)
Thiopurines (azathioprine)	↑ NRH/portal hypertension; ↑ CAP at higher doses	Dose-related; may increase SSM despite normal LSM
Methotrexate	Minimal fibrosis risk in IBD	Lower risk than in psoriasis or rheumatoid arthritis
Longer disease duration	↑ steatosis, particularly in CD	Cumulative inflammatory burden mediated through the gut-liver axis
Active luminal disease (high activity)	Inverse association with steatosis	Nutritional depletion and lower visceral fat in active disease
Gut dysbiosis/increased permeability	↑ steatosis independent of adiposity	LPS and SCFA translocation; may contribute to lean MASLD

aOR, adjusted odds ratio; BMI, body mass index; CAP, controlled attenuation parameter; CD, Crohn's disease; IBD, inflammatory bowel disease; LPS, lipopolysaccharide; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; NRH, nodular regenerative hyperplasia; SCFA, short-chain fatty acids; SSM, spleen stiffness measurement; TNF, tumor necrosis factor.

of patients with IBD compared with 28.3% of individually matched controls, yielding an adjusted odds ratio of 2.51 (95% CI, 1.66–3.79) and confirming that IBD independently confers excess steatosis risk beyond shared metabolic determinants.[15] This finding is consistent with that of Rodriguez-Duque et al.,[48] who reported a higher prevalence of MAFLD in patients with IBD than in general-population controls after adjustment for metabolic factors. ELASTIBD also showed that steatosis and fibrosis frequently coexist in IBD, with elevated CAP scores independently associated with higher LSM values, suggesting that progressive steatohepatitis may be an underrecognized driver of fibrogenesis in this population.[15]

Metabolic Risk Factors: Shared and IBD-Specific

Conventional metabolic risk factors, including older age, higher BMI, increased waist circumference, type 2 diabetes, arterial hypertension, dyslipidemia, and elevated fasting glucose, are consistent predictors of steatosis in IBD across geographic regions and study designs.[13–15,44,45] However, these shared risk factors do not fully account for the excess burden of steatosis observed in patients with IBD compared with matched controls. IBD-specific contributors appear to operate through at least three partially overlapping mechanisms.

First, corticosteroid exposure promotes hepatic fat accumulation through visceral adiposity, hyperinsulinemia, and direct glucocorticoid receptor-mediated lipogenic signaling in hepatocytes.[16] The cumulative number of corticosteroid courses has been identified as an independent predictor of steatosis in multiple cohorts, and the temporal relationship between corticosteroid administration and CAP elevation is supported by longitudinal data showing that active IBD, which is often treated with corticosteroids, is associated with progression of steatosis during follow-up.[15,43]

Second, IBD disease activity exerts paradoxical, bidirectional effects on steatosis risk. In active Crohn's disease, high CDAI scores, reflecting nutritional depletion, weight loss, and negative energy balance, are inversely associated with steatosis prevalence because underweight patients with active luminal disease have less visceral fat.[15] Conversely, remission, by restoring nutritional status and promoting weight regain, sometimes accelerated by corticosteroid treatment, may increase the risk of MASLD. At the population level, however, longer disease duration and cumulative inflammatory burden appear to promote steatosis through systemic and gut-liver axis mechanisms independently of BMI.[14,45]

Third, gut microbiota dysbiosis and increased intestinal permeability, both characteristic of IBD, facilitate the translocation of bacterial products, including lipopolysaccharides and short-chain fatty acids, into the portal circulation, promoting hepatic inflammatory signaling, de novo lipogenesis, and impaired fatty acid oxidation through toll-like receptor and farnesoid X receptor pathways.[6,24] This gut-liver axis dysregulation operates independently of adiposity and may explain the occurrence of MASLD in lean patients with IBD, a subgroup in whom conventional metabolic risk factors are absent yet hepatic steatosis and even fibrosis may still be prevalent.[16,48]

IBD Therapy and Steatosis: Risk and Protection

The relationship between IBD pharmacotherapy and hepatic steatosis remains incompletely understood. Corticosteroids consistently emerge as risk factors for steatosis. Although azathioprine is primarily associated with fibrosis risk through NRH, some cohorts have also shown a positive correlation between higher azathioprine doses and CAP scores; however, whether azathioprine directly promotes steatosis or is preferentially used in patients with metabolic comorbidities remains uncertain.[15,21]

Anti-TNF therapy has attracted interest as a potential modifier of steatosis. Experimental models demonstrate that TNF-α inhibition reduces hepatic lipid accumulation and improves insulin sensitivity, while preliminary clinical data suggest a lower prevalence of MASLD among patients with IBD receiving anti-TNF agents.[24,48] Vedolizumab, a gut-selective anti-integrin agent, has shown a tentative inverse association with steatosis in observational data, possibly reflecting reduced intestinal mucosal inflammation and consequent attenuation of gut-liver axis dysregulation; however, the number of patients in available studies is insufficient to draw firm conclusions.[15] Whether biologic therapies with favorable metabolic or anti-inflammatory profiles can meaning-

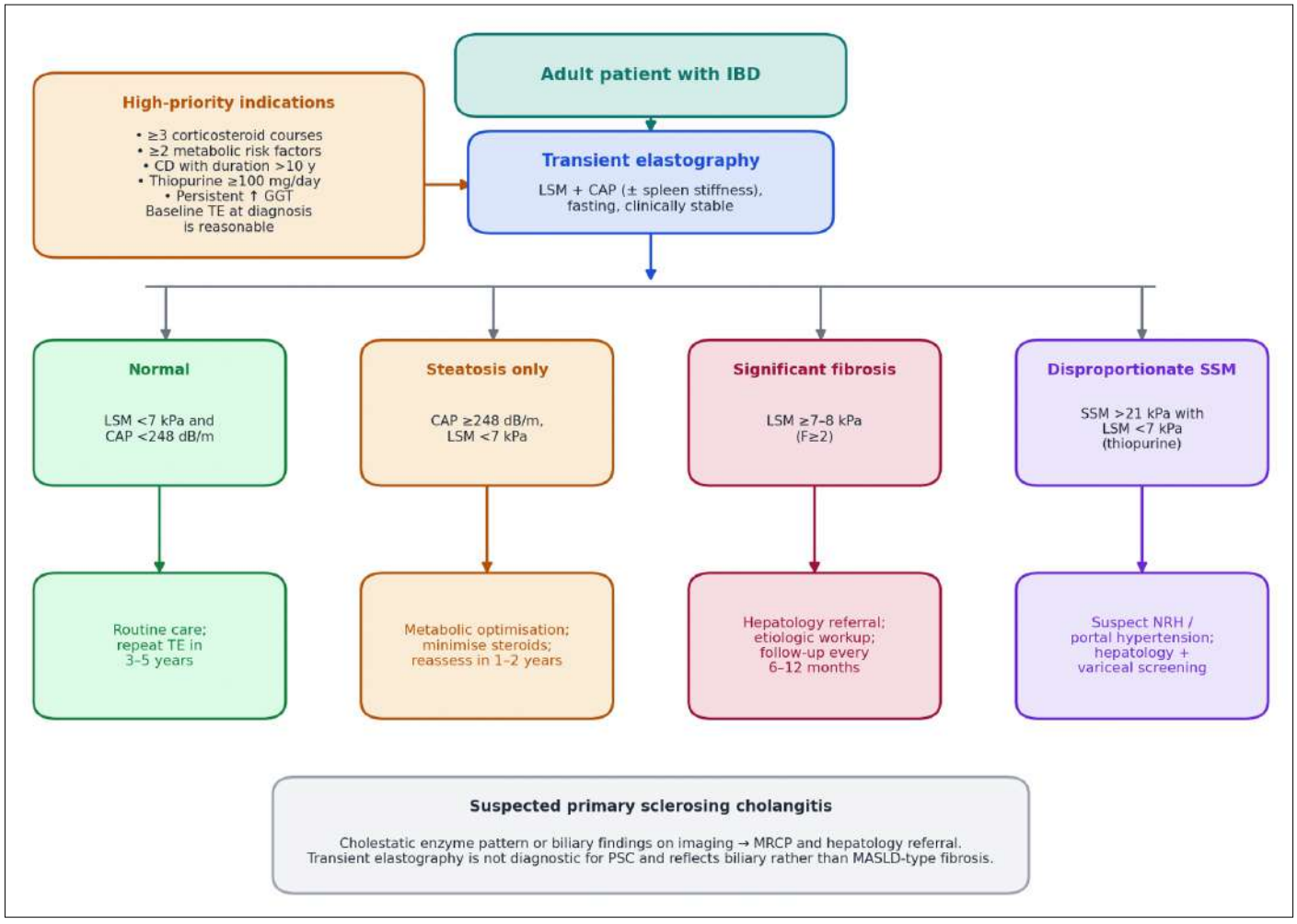

Figure 3. Proposed transient elastography screening and referral algorithm in IBD. After identification of high-priority indications, combined LSM and CAP (±SSM) assessment in a fasting, clinically stable patient stratifies management into four pathways. CAP, controlled attenuation parameter; CD, Crohn's disease; GGT, gamma-glutamyl transferase; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; MRCP, magnetic resonance cholangiopancreatography; NRH, nodular regenerative hyperplasia; SSM, spleen stiffness measurement.

fully reduce the burden of MASLD in IBD remains an important unanswered question.

Clinical Significance of Steatosis in IBD

Beyond its hepatic consequences, MASLD in IBD carries prognostic implications for cardiovascular risk, IBD disease behavior, and long-term outcomes. Hepatic steatosis and liver fibrosis in patients with IBD have been associated with increased atherosclerotic cardiovascular disease risk, with patients with steatosis having significantly higher calculated ASCVD risk scores than those without steatosis.[51] The coexistence of steatohepatitis and progressive fibrosis raises concern about accelerated progression to cirrhosis in a population already burdened by chronic systemic inflammation.[12] Detection of steatosis by CAP therefore provides actionable information beyond fibrosis staging alone and supports its routine inclusion in TE-based hepatic assessment protocols for patients with IBD.

Clinical Use Cases: Who, When, and How Often

Rationale for a Structured Screening Approach

Standard IBD follow-up protocols have historically prioritized monitoring of intestinal disease, including endoscopic mucosal healing, fecal calprotectin, and imaging of transmural inflammation, while hepatic surveillance has remained largely opportunistic and predominantly triggered by abnormal liver function tests. This reactive approach has an important limitation: significant fibrosis (F≥2) and clinically relevant steatosis frequently occur in patients with IBD who have normal transaminase levels.[13,15,42] A structured, proactive TE-based approach is therefore warranted, and the existing evidence base is sufficient to define risk-stratified indications (Table 4).

High-Priority Screening Indications

The following profiles carry the highest probability of significant fibrosis or steatosis and warrant priority TE assessment; these indications, together with the proposed referral pathway, are summarized in the screening algorithm (Figure 3).

Prolonged or recurrent corticosteroid exposure is the most consistently identified modifiable risk factor for both fibrosis and steatosis across IBD cohorts.[43] Patients who have received three or more corticosteroid courses or required corticosteroids for more than three cumulative

months within the preceding two years represent a priority group in whom hepatic assessment should be considered standard of care rather than optional.

Metabolic comorbidities, including obesity (BMI ≥30 kg/m²), type 2 diabetes, hypertension, and dyslipidemia, substantially amplify IBD-associated hepatic risk. Because IBD confers excess risk independently of these factors, their coexistence further compounds this risk.[13,14] All patients with IBD who have two or more metabolic risk factors should undergo baseline TE assessment at diagnosis or at the time the metabolic comorbidity is recognized.

Long disease duration, particularly exceeding 10 years in CD, has been associated with steatosis in multiple cohorts, likely reflecting cumulative inflammatory burden, nutritional compromise, and prolonged exposure to pharmacotherapy.[5,14] Patients with longstanding disease who have never undergone noninvasive hepatic assessment represent a clinically underserved group.

Thiopurine use at azathioprine doses ≥100 mg/day or an equivalent dose is also relevant, given the documented association between higher thiopurine doses and both increased spleen stiffness and NRH risk.[21,37] In this subgroup, SSM in addition to LSM may provide added value by identifying portal hypertension in the presence of otherwise normal hepatic parenchyma, a pattern characteristic of thiopurine-associated NRH.[37]

Persistently abnormal liver enzyme levels, particularly GGT elevation, which shows the strongest correlation with both fibrosis and steatosis in IBD, should prompt formal TE assessment to characterize the underlying hepatic pathology beyond the enzyme pattern alone.[13,15]

Baseline Assessment at IBD Diagnosis

A reasonable case can be made for offering TE assessment at the time of IBD diagnosis, independent of risk factors, for two reasons. First, the prevalence of clinically significant hepatic findings in newly diagnosed patients with IBD is not negligible, and early identification may allow timely hepatology referral and inform treatment decisions, such as consideration of corticosteroid-sparing strategies in patients with established steatohepatitis. Second, a baseline measurement provides an essential comparator for monitoring hepatic progression or regression in response to IBD treatment, an area in which data remain limited because existing studies are predominantly cross-sectional. Where universal screening is not feasible, a risk factor-guided approach targeting the high-priority indications outlined above provides a pragmatic alternative. No prospective outcome or cost-effectiveness data currently support universal baseline screening; this proposal is based on biological and clinical rationale rather than high-level evidence.

Follow-Up Intervals and Monitoring

Evidence regarding optimal follow-up intervals for TE-based hepatic monitoring in IBD is limited, as available longitudinal data are confined to a single study with a 6–12-month follow-up period.[43] Based on this evidence and extrapolation from MASLD monitoring recommendations in the general population, the following pragmatic framework is proposed (Table 4): in patients with IBD who have normal baseline LSM and CAP values and no high-risk features, repeat TE every three to five years; in patients with baseline steatosis (CAP ≥248 dB/m) but no significant fibrosis (LSM <8 kPa), annual or biennial reassessment is warranted alongside corticosteroid minimization and metabolic optimi-

Table 4. Proposed risk-stratified framework for transient elastography-based hepatic screening and monitoring in IBD

Clinical scenario	Recommended transient elastography action
≥3 corticosteroid courses or >3 cumulative months of corticosteroid therapy within 2 years	Perform baseline TE; consider this part of standard care
≥2 metabolic risk factors (obesity, T2DM, hypertension, or dyslipidemia)	Perform baseline TE at diagnosis or when metabolic comorbidity is recognized
Long-standing disease, particularly CD >10 years	Perform baseline TE if hepatic assessment has not been performed previously
Thiopurine ≥100 mg/day (azathioprine equivalent)	Perform TE with SSM to screen for NRH/portal hypertension
Persistently abnormal liver enzyme levels, particularly elevated GGT	Perform TE to characterize the underlying hepatic pathology
Normal LSM and CAP with no high-risk features	Repeat TE every 3–5 years
Steatosis (CAP ≥248 dB/m) without fibrosis (LSM <8 kPa)	Reassess annually or biennially; minimize corticosteroid exposure and optimize metabolic risk factors
Elevated LSM: 8–12 kPa (indeterminate) or ≥12 kPa (advanced fibrosis likely)	For LSM 8–12 kPa, perform confirmatory testing or seek hepatology consultation; for LSM ≥12 kPa, refer to hepatology and repeat TE every 6–12 months
Severe steatosis (CAP ≥280 dB/m) ± elevated liver enzyme levels	Provide metabolic counseling; refer to hepatology if steatohepatitis is suspected
SSM >21 kPa with LSM <7 kPa in a thiopurine-treated patient	Suspect NRH; refer to hepatology and perform endoscopic screening for varices
Suspected PSC based on a cholestatic pattern or biliary imaging findings	Perform MRCP and refer to hepatology regardless of the TE result
New or escalating corticosteroid therapy in a patient with known steatosis or borderline LSM	Reassess within 6 months after completion of the corticosteroid course

CAP, controlled attenuation parameter; CD, Crohn's disease; GGT, gamma-glutamyl transferase; IBD, inflammatory bowel disease; LSM, liver stiffness measurement; MRCP, magnetic resonance cholangiopancreatography; NRH, nodular regenerative hyperplasia; PSC, primary sclerosing cholangitis; SSM, spleen stiffness measurement; T2DM, type 2 diabetes mellitus; TE, transient elastography.

zation; and in patients with significant fibrosis (F≥2, LSM ≥7–8 kPa), prompt hepatology referral is indicated, with TE reassessment every six to twelve months to monitor progression. Any new or escalating corticosteroid exposure in a patient with known hepatic steatosis or borderline LSM values should prompt reassessment within six months after completion of the corticosteroid course.

When to Refer to Hepatology

Clear thresholds for hepatology referral can be derived from existing evidence. In a fasting, clinically stable patient with IBD without acute hepatic congestion or significant cholestasis, LSM is best interpreted using a pragmatic dual-cutoff approach: values below 8 kPa make clinically significant fibrosis unlikely, values of 8–12 kPa are indeterminate and warrant a confirmatory noninvasive test or hepatology consultation, and values of 12 kPa or higher indicate probable advanced fibrosis and should prompt hepatological evaluation regardless of liver enzyme status.[29,38,42] Isolated CAP elevation without fibrosis warrants structured metabolic counseling within the IBD multidisciplinary team, with hepatology involvement when steatosis is severe (CAP ≥280 dB/m) or accompanied by elevated liver enzyme levels suggestive of steatohepatitis.[31] Spleen stiffness values that are disproportionately elevated relative to LSM, particularly SSM >21 kPa with LSM <7 kPa in a thiopurine-treated patient, should raise suspicion for NRH and prompt dedicated hepatological assessment, including upper gastrointestinal endoscopy for variceal screening.[34,35,37] Suspected PSC based on a cholestatic enzyme pattern, IBD disease characteristics, or incidental biliary findings on cross-sectional imaging warrants hepatology referral independently of TE findings because LSM in PSC reflects biliary fibrosis rather than MASLD-type hepatic fibrosis and requires disease-specific interpretation.[18]

Limitations and Research Gaps

Cutoff Heterogeneity and the Absence of IBD-Specific Validation

The most pervasive limitation is the absence of IBD-specific LSM cutoffs validated against liver biopsy in a sufficiently powered, well-characterized cohort. All thresholds currently applied in IBD studies are derived from general chronic liver disease populations, predominantly patients with viral hepatitis or NAFLD, and their diagnostic performance in IBD has not been formally established.[27,29] IBD-specific confounders, including active intestinal inflammation, thiopurine-associated NRH, and PSC-related biliary fibrosis, can each distort the relationship between LSM and fibrosis in ways that general-population cutoffs cannot fully accommodate.[21,43] A prospective IBD cohort with paired liver biopsy and TE measurements, although ethically challenging to design in a population without primary hepatological indications for biopsy, remains necessary for evidence-based threshold calibration.

Predominance of Cross-Sectional Designs

With the sole exception of van Lingen et al.,[43] every original TE study in IBD identified in this review employed a cross-sectional design. This limitation has three important consequences. First, the directionality of observed associations cannot be established from prevalence data alone; for example, it remains unclear whether corticosteroid exposure causes fibrosis or whether patients with more severe disease receive more corticosteroids and independently have worse hepatic outcomes. Second, the natural history of IBD-associated liver disease remains largely unknown: whether steatosis progresses to fibrosis, whether remission reverses hepatic abnormalities, and what proportion of patients with F≥2 fibrosis progress to cirrhosis remain unanswered because of the lack of longitudinal TE data. Third, the impact of therapeutic escalation, including biologic initiation, corticosteroid withdrawal, or metabolic interventions, on hepatic outcomes cannot be assessed without repeated measurements over time. Prospective longitudinal cohort studies with TE reassessment at predefined intervals, ideally linked to therapeutic milestones, represent the most pressing methodological need in this field.

Paucity of Matched Control Data

Most IBD elastography studies lack a control group, precluding quantification of the excess hepatic risk attributable to IBD itself beyond shared metabolic determinants. Of the 13 studies reviewed, only three included a non-IBD comparator group, and only two, Rodriguez-Duque et al.[48] and ELASTIBD,[15] used individual matching for key metabolic confounders. This gap has created uncertainty regarding whether the observed prevalence reflects a disease-specific burden or merely the metabolic profile of a chronically ill, often overweight, and frequently corticosteroid-treated population. The matched-control evidence currently available consistently suggests that IBD confers an independent hepatic risk; however, this conclusion rests on a limited evidence base and requires corroboration in larger, multicenter, prospectively enrolled cohorts.

Small Sample Sizes and Population Heterogeneity

Several cohorts in the existing literature are underpowered for subgroup analyses, particularly disease-specific comparisons between CD and UC, which may have distinct hepatic risk profiles because of differences in inflammatory mechanisms, nutritional consequences, and pharmacotherapy patterns.[41,45] Sample sizes ranging from 46 to 384 patients in the pre-ELASTIBD literature limit the precision of prevalence estimates and the statistical power available for multivariable adjustment.[13,22] Cohorts also differ in IBD phenotype, disease activity, medication exposure, geographic and ethnic background, and the stringency of exclusion criteria for alcohol use and other concurrent liver diseases, including viral hepatitis, PSC, and autoimmune liver disease, all of which contribute to the wide prevalence ranges reported for both fibrosis and steatosis and complicate meta-analytic pooling. In particular, cohorts that did not exclude concurrent liver disease may overestimate fibrosis prevalence, for example through occult PSC-related biliary fibrosis or viral hepatitis, whereas MAFLD-based definitions explicitly permit coexisting etiologies, introducing an additional source of between-study variation.

Absence of Pediatric Data and Lean IBD Subgroups

The entire TE-based literature on hepatic involvement in IBD has focused on adult populations, leaving pediatric and adolescent patients with IBD essentially unstudied using objective noninvasive assessment, despite their potentially distinct hepatic risk trajectory related to cumulative corticosteroid exposure, impaired nutritional growth, and long disease duration beginning at an early age.[4,5] Similarly, lean patients with IBD (BMI <25 kg/m²) and MASLD remain undercharacterized in the TE literature. In this subgroup, conventional metabolic risk stratification may fail and clinical suspicion may be particularly low, despite emerging evidence that IBD-specific mechanisms can drive hepatic steatosis and fibrosis independently of adiposity.[48]

Spleen Stiffness and Emerging Parameters

SSM in IBD remains at an early investigative stage, with available data limited to preliminary, single-center observations.[37] The clinical utility of SSM for identifying thiopurine-associated NRH and noncirrhotic portal hypertension in patients with IBD and normal LSM has been demonstrated at the case level but lacks prospective cohort val-

idation. Future studies incorporating SSM alongside LSM and CAP in longitudinal IBD cohorts, particularly among thiopurine-treated patients undergoing dose escalation, would substantially advance the field. Similarly, newer elastography-derived parameters, including the FibroScan-AST (FAST) score for identifying at-risk steatohepatitis, have not been evaluated in dedicated IBD cohorts and represent an additional investigative opportunity.[52] More broadly, transient elastography is increasingly being applied beyond hepatic fibrosis and steatosis to other organs and systemic complications relevant to IBD; liver and transplanted-kidney stiffness measurements have recently been used to characterize organ involvement in AA amyloidosis, a systemic sequela of chronic inflammatory disease, illustrating the broader potential of this technique.[53]

CONCLUSION

Transient elastography has emerged as the most practical and evidence-supported noninvasive tool for hepatic assessment in inflammatory bowel disease, enabling the simultaneous quantification of liver fibrosis, hepatic steatosis, and portal hypertension through spleen stiffness measurement. The evidence reviewed here indicates that patients with IBD carry a hepatic burden exceeding that predicted by conventional metabolic risk factors alone. Matched-control data establish IBD itself as an independent determinant of both fibrosis and steatosis, with corticosteroid exposure emerging as the most consistently modifiable risk factor and anti-TNF therapy as potentially hepatoprotective.

Despite this accumulating evidence, hepatic assessment remains systematically underused in IBD clinical practice. Standard liver function tests are insufficient for detecting the subclinical fibrosis and steatosis that TE can reliably identify, and the absence of structured TE protocols in IBD guidelines represents a gap between evidence and practice. Integration of FibroScan® into IBD outpatient workflows, stratified by corticosteroid exposure, metabolic comorbidity burden, disease duration, and pharmacotherapy profile, is both feasible and clinically warranted based on existing data.

Key research priorities include the development of IBD-specific, biopsy-validated LSM cutoffs; longitudinal evaluation of the natural history of IBD-associated liver disease and its response to therapy; and extension of TE-based assessment to pediatric and lean IBD subgroups in whom conventional risk stratification may fail. The role of spleen stiffness measurement in monitoring thiopurine-associated portal hypertension and the potential utility of newer composite elastography parameters, such as the FAST score, for identifying at-risk steatohepatitis in IBD cohorts represent additional areas warranting prospective evaluation.

As IBD management increasingly targets deep remission and long-term organ preservation beyond the intestine, the liver should be recognized as a target organ requiring systematic surveillance. Transient elastography, which is noninvasive, reproducible, and supported by a growing body of controlled evidence, provides a practical clinical tool to meet this need.

Conflict of Interest: The author is an investigator of the ELASTIBD study.

Peer-review: Externally peer-reviewed.

Author Contribution: Concept – B.F.A.; Design – B.F.A.; Supervision – B.F.A.; Resource – B.F.A.; Materials – B.F.A.; Data Collection and/or Processing – B.F.A.; Analysis and/or Interpretation – B.F.A.; Literature Review – B.F.A.; Writing – B.F.A.; Critical Review – B.F.A.

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Journal of Enterocolitis

Case Report

Successful Treatment of Steroid-Refractory Immune Checkpoint Inhibitor–Related Colitis With Vedolizumab: A Case Report and Literature Review

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Abstract

A 72-year-old man with metastatic lung adenocarcinoma developed severe immune checkpoint inhibitor–related colitis after nivolumab therapy. The patient presented with frequent diarrhea and dehydration. Infectious causes were excluded, and colonoscopic findings were consistent with active colitis. Despite high-dose intravenous corticosteroid treatment, no clinical improvement was observed, and the condition was considered steroid-refractory. Vedolizumab was initiated as salvage therapy, resulting in a rapid clinical response, with a marked reduction in stool frequency and improvement in symptoms. Corticosteroids were successfully tapered, and no recurrence was observed during early follow-up.

Keywords: Immune checkpoint inhibitor, immune-related colitis, nivolumab, vedolizumab.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have significantly improved outcomes in advanced malignancies, including non–small cell lung cancer, by enhancing T-cell–mediated antitumor activity. However, immune activation may lead to immune-related adverse events (irAEs), among which colitis is one of the most common gastrointestinal toxicities.[1,2] Although most cases respond to corticosteroids, a subset of patients develop steroid-refractory disease requiring additional immunosuppressive therapy. Vedolizumab, a gut-selective anti-integrin agent, has emerged as a potential treatment option in such cases.[3,4] Here, we present the case of a patient with steroid-refractory nivolumab-associated colitis who was successfully treated with vedolizumab.

CASE PRESENTATION

A 72-year-old man was evaluated in August 2025 for dyspnea and cough. Thoracic computed tomography revealed a lobulated, centrally necrotic mass measuring 7 cm at its longest diameter in the middle lobe of the right lung. For staging, positron emission tomography-computed tomography demonstrated intense fluorodeoxyglucose uptake in the primary lung mass, as well as findings consistent with bone metastases in the right humerus and eighth rib. Core needle biopsy of the lung mass showed focal positivity for thyroid transcription factor-1 and negativity for p63 and p40, consistent with lung adenocarcinoma. The patient received first-line chemotherapy with carboplatin and paclitaxel at another institution. After three cycles of chemotherapy, radiological progression was observed, and second-line treatment with nivolumab was initiated in November 2025.

After the third cycle of nivolumab, the patient presented to the outpatient clinic with a 1-week history of diarrhea occurring approximately 20 times per day, containing blood and mucus, accompanied by deterioration in general condition and reduced oral intake. He was admitted to the oncology ward with a preliminary diagnosis of immune checkpoint inhibitor–related colitis. In 2003, he had undergone total laryngectomy for laryngeal carcinoma followed by adjuvant radiotherapy; he had not received chemotherapy and had remained in remission. The patient also had a history of coronary artery disease. Five months before the current admission, he had been hospitalized for non-ST-elevation myocardial infarction (NSTEMI), underwent coronary angiography, and received coronary stent implantation. His current medications included acetylsalicylic acid, clopidogrel, metoprolol, atorvastatin, levothyroxine, inhaled ipratropium bromide and salbutamol, and granisetron. On admission, he denied fever, chills, or abdominal pain. The patient had a tracheostomy. Physical examination revealed dry oral mucosa and decreased skin turgor, consistent with dehydration. Repeated stool studies performed over 3 consecutive days were negative for infectious pathogens, including Giardia antigen,

stool parasite cyst and trophozoite examination, Clostridioides difficile antigen, and stool culture. Stool microscopy revealed leukocytes and erythrocytes. The fecal calprotectin level was greater than 840 µg/g. Colonoscopy was performed up to the mid-descending colon; further advancement was not possible because of solid fecal material. In the examined segments, the colonic mucosa appeared hyperemic, edematous, and friable, with diffuse superficial ulcers covered by confluent white exudates. The normal mucosal and submucosal vascular pattern was absent (Figure 1A-B). Histopathological examination of biopsy specimens demonstrated marked mixed inflammatory cell infiltration, moderate cryptitis, surface epithelial injury, moderate crypt atrophy, moderate crypt architectural distortion, and lymphoid hyperplasia, consistent with active colitis. Cytomegalovirus immunohistochemistry was negative.

Based on these findings, the patient was diagnosed with nivolumab-related colitis, and treatment with intravenous methylprednisolone at a dose of 1 mg/kg/day was initiated. Despite 1 week of corticosteroid therapy, stool frequency did not decrease. After gastroenterology consultation, vedolizumab (300 mg IV) was initiated at weeks 0, 2, and 6, with maintenance dosing every 8 weeks. The patient received the first induction dose on February 6, 2026, and the second induction dose on February 20, 2026. After vedolizumab therapy, his clinical condition improved significantly, with stool frequency decreasing to 4 times per day and stool consistency normalizing. Nivolumab therapy was permanently discontinued, and treatment with pemetrexed was planned. The patient's clinical course, including oncologic treatment and the development of immune-related colitis, is summarized in Figure 2.

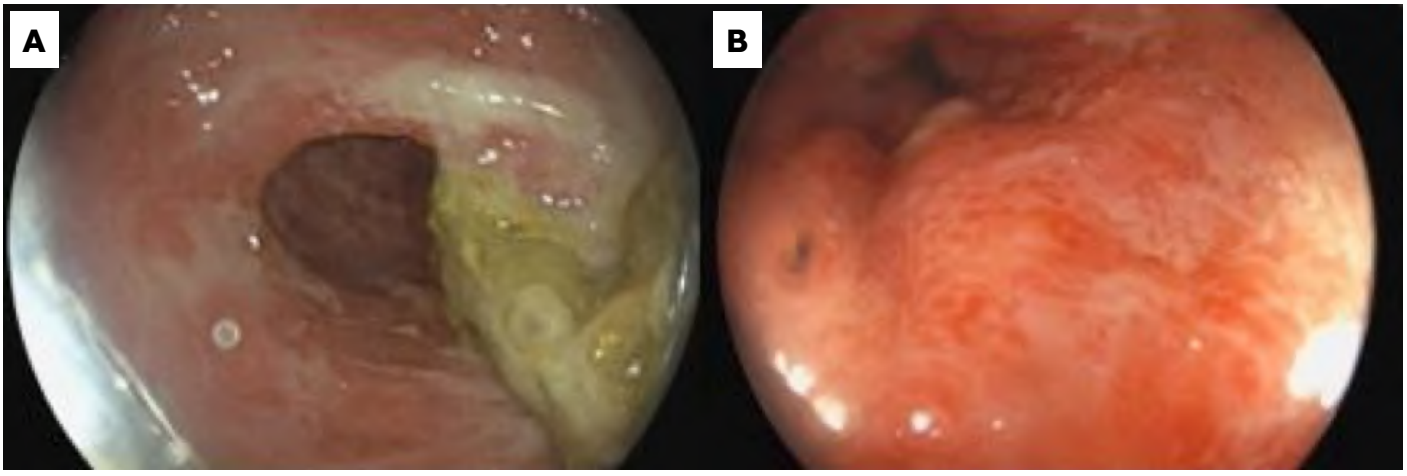

Figure 1. Colonoscopic findings of immune checkpoint inhibitor–associated colitis. **(a)** Diffuse hyperemia, mucosal edema, and friability with confluent superficial ulcerations covered by white exudates. The normal vascular pattern is absent. **(b)** Marked erythema and edema with loss of mucosal and submucosal vascular architecture, consistent with severe inflammatory activity.

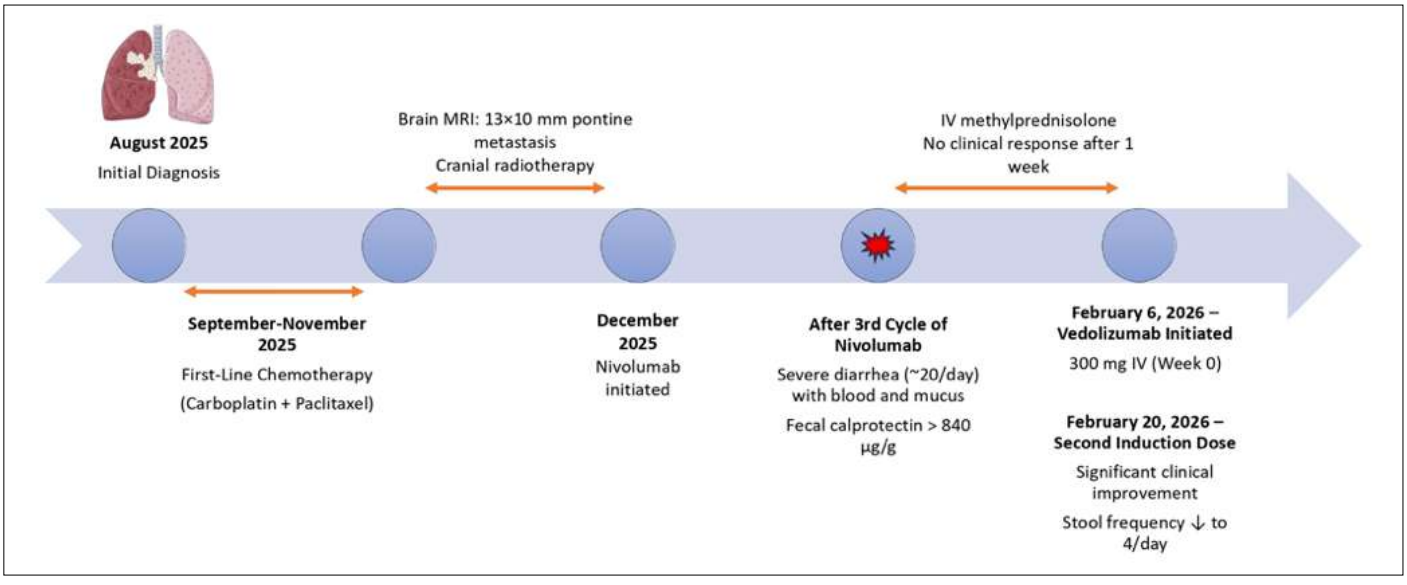

Figure 2. Clinical timeline of metastatic lung adenocarcinoma and the development of steroid-refractory nivolumab-associated colitis successfully treated with vedolizumab.

DISCUSSION

Immune checkpoint inhibitor–associated colitis is one of the most common and clinically significant immune-related adverse events in patients receiving PD-1 blockade. In the present case, severe steroid-refractory colitis developed after second-line nivolumab therapy and was successfully managed with vedolizumab.

Vedolizumab is a gut-selective monoclonal antibody directed against α4β7 integrin. It blocks lymphocyte trafficking to the gastrointestinal mucosa while minimizing systemic immunosuppression. In our case, vedolizumab was preferred for steroid-refractory immune checkpoint inhibitor–associated colitis, particularly because anti–tumor necrosis factor (anti-TNF) therapy was considered less suitable because of the patient's comorbidities.

To date, no randomized controlled trials have evaluated vedolizumab specifically for immune checkpoint inhibitor–associated colitis. Available evidence is largely derived from retrospective and multicenter observational studies, the largest of which demonstrated comparable clinical remission rates between vedolizumab and infliximab.5 In observational studies evaluating biologic therapies for immune-mediated colitis, vedolizumab has demonstrated efficacy comparable to that of infliximab. In a 2-center retrospective study of 184 patients conducted by Zou et al.,[6] clinical remission rates were similar between vedolizumab and infliximab (89% vs. 88%, p=0.79). Although the time to clinical response was longer in the vedolizumab group, patients treated with vedolizumab had shorter durations of corticosteroid exposure and reduced lengths of hospital stay. These findings suggest that vedolizumab is an effective alternative in steroid-refractory cases, particularly when minimizing systemic immunosuppression is clinically desirable. The gut-selective anti-integrin mechanism of vedolizumab provides a theoretical safety advantage over systemic tumor necrosis factor blockade. Compared with anti-TNF agents, vedolizumab has a lower impact on systemic immune function, which may translate into a reduced risk of systemic infectious complications.[7] In oncology patients, this consideration is particularly relevant because preserving systemic antitumor immunity remains a critical concern.

In addition, anti-TNF agents have been associated with adverse cardiac outcomes in patients with moderate-to-severe heart failure, with some studies reporting worsening cardiac function and increased hospitalization rates.[8] Consequently, multiple guidelines and regulatory product labels caution against the use of anti-TNF therapy in patients with advanced heart failure. In contrast, long-term safety analyses of vedolizumab in inflammatory bowel disease populations have not demonstrated an increased incidence of cardiovascular adverse events.[9,10] In our patient, who had a recent history of coronary artery disease, vedolizumab was therefore considered a more targeted and potentially safer therapeutic option than systemic tumor necrosis factor blockade. The rapid clinical improvement observed after induction therapy further supports its effectiveness in this setting.

Compared with classic inflammatory bowel disease, ICI-associated colitis may show a relatively rapid response to biologic therapies such as infliximab and vedolizumab. In many patients, clinical remission can be achieved after induction therapy alone, and prolonged maintenance biologic treatment may not always be necessary once immune checkpoint inhibitor therapy is discontinued. However, the optimal duration of biologic therapy in ICI-associated colitis remains uncertain, and long-term prospective data are still lacking.[3,4]

ICI-associated colitis is not only a significant acute toxicity but is also characterized by a substantial risk of recurrence. Reported relapse rates range up to 30% to 40%, particularly among patients with steroid-refractory disease, those requiring prolonged corticosteroid tapering, and those undergoing immunotherapy rechallenge. In a large cohort study by Abu-Sbeih et al.,[11] recurrence rates were notably higher in patients requiring biologic therapy or presenting with severe colitis. Similarly, in the multicenter retrospective analysis by Zou et al.,[6] although clinical remission rates were comparable between vedolizumab and infliximab, the importance of minimizing systemic immunosuppression for long-term disease control was emphasized. These findings highlight that therapeutic goals in ICI-associated colitis should extend beyond short-term symptomatic improvement and aim to achieve sustained control of mucosal inflammation. In steroid-refractory cases, gut-selective agents such as vedolizumab may provide a rational strategy by preserving systemic immune function while potentially reducing the risk of recurrent inflammatory activity.

In conclusion, vedolizumab is an effective salvage therapy for steroid-refractory immune checkpoint inhibitor–associated colitis, particularly in patients for whom minimizing systemic immunosuppression is desirable.

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Beyond Corticosteroids: The Case for Targeted Biologics in Lupus Colitis

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Dear Editor,

Lupus colitis, a rare but increasingly recognized gastrointestinal manifestation of systemic lupus erythematosus (SLE), presents a formidable clinical challenge. Characterized by mucosal inflammation and congestion, as depicted endoscopically in Figure 1, protein-losing enteropathy, and, in severe cases, intestinal pseudo-obstruction, it is associated with substantial morbidity.[1] Despite its impact, evidence-based therapeutic protocols remain limited, and most management strategies are extrapolated from the broader SLE literature. We advocate targeted investigation of three biologics with compelling mechanistic rationales: belimumab, voclosporin, and anifrolumab. The supporting evidence is currently mechanistic; direct gastrointestinal clinical trial data are lacking, and we identify this gap as a research priority.

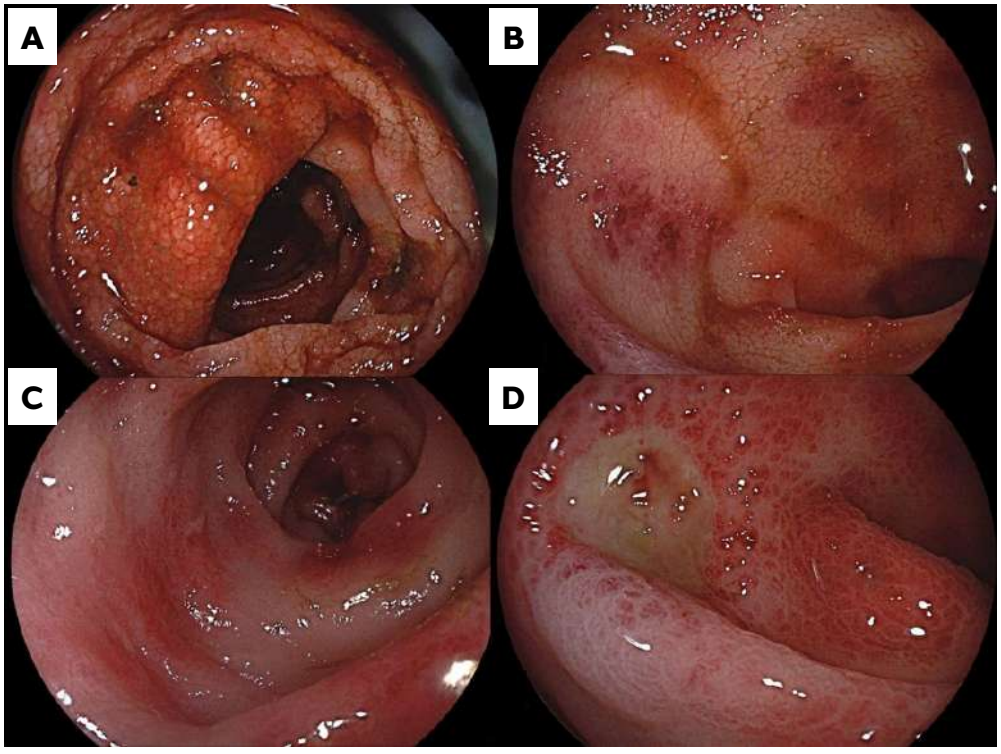

Figure 1. Endoscopic appearance of systemic lupus erythematosus-related colitis, showing congestive and granular mucosa. [1] Adapted from "Fatal Colitis Associated With Active Systemic Lupus Erythematosus Complicated by Cytomegalovirus Superinfection" © 2017, Elisa Gravito-Soares, licensed under CC BY-NC-ND 4.0. Available at: https://creativecommons.org/licenses/by-nc-nd/4.0/. Image obtained under a Creative Commons license.

Table 1. Mechanistic rationale and evidence basis for biologic agents in lupus colitis

Biologic	Mechanism	Evidence and Limitations	Proposed Investigation
Belimumab	BLyS inhibitor; reduces autoreactive B-cell survival and pathogenic autoantibody burden	Efficacy established in renal and mucocutaneous SLE.[2] Gastrointestinal endpoints are systematically underreported.	Prospective trial with bowel-specific endpoints
Voclosporin	Calcineurin inhibitor; suppresses T-cell activation and downstream cytokine release	Renal efficacy established in the AURORA trials.[3,4] No published data on intestinal disease.	Future trials including bowel-specific activity indices
Anifrolumab	Type I IFN receptor antagonist; attenuates IFN-alpha-driven SLE immunopathology	Elevated IFN signatures reported in intestinal SLE.[5] Direct colonic evidence is lacking; evidence is limited to a single case report of oral manifestations.[6]	Mucosal IFN activity studies before and after treatment

Belimumab, a B-lymphocyte stimulator (BLyS) inhibitor approved for active SLE, suppresses autoreactive B-cell survival and reduces the burden of pathogenic autoantibodies. Given that anti-C1q and anti-double-stranded DNA antibodies contribute to complement-mediated intestinal vasculitis in lupus colitis, belimumab's downstream attenuation of humoral autoimmunity is mechanistically persuasive.[2] Clinical series have demonstrated the efficacy of belimumab in renal and mucocutaneous SLE; however, gastrointestinal endpoints remain systematically underreported.[2] Dedicated prospective studies of belimumab in patients with active lupus colitis are urgently warranted.

Voclosporin, a next-generation calcineurin inhibitor approved for lupus nephritis, offers enhanced potency and a more predictable pharmacokinetic profile than cyclosporine, without the need for therapeutic drug monitoring.[3] Its inhibition of T-cell activation and downstream cytokine release makes it a rational candidate for lupus colitis, in which T-cell-driven mucosal inflammation is a recognized pathogenic contributor. The AURORA trials established its renal efficacy and tolerability.[4] However, intestinal disease was not an endpoint, and no published data currently address the effect of voclosporin on bowel inflammation. We urge investigators to include bowel-specific disease activity indices in future voclosporin trials.

Anifrolumab, a type I interferon receptor antagonist, represents a third therapeutic avenue. Interferon-alpha dysregulation is central to SLE immunopathology, and elevated interferon gene signatures have been documented in intestinal SLE.[5] Anifrolumab's approval for moderate-to-severe SLE and its established safety record provide a foundation for gastrointestinal investigation. Published evidence in this domain is currently limited to a single case report involving refractory oral manifestations.[6] Its applicability to colonic disease is plausible on mechanistic grounds but requires prospective validation, and this limitation must be acknowledged. Studies of mucosal interferon activity before and after anifrolumab treatment would meaningfully advance mechanistic understanding.

Before initiating any biologic therapy for lupus colitis, clinicians must exclude active infection. The case reported by Gravito-Soares et al.[1] illustrates the lethal potential of cytomegalovirus superinfection in the context of immunosuppression. Screening for cytomegalovirus, tuberculosis, hepatitis B, and hepatitis C should be standard practice before biologic initiation; infection risk must also inform treatment sequencing in steroid-refractory and escalation settings.

We call on the gastroenterology and rheumatology communities to act on three fronts. First, standardized reporting of lupus colitis must incorporate SLEDAI-2K alongside endoscopic and histopathological grading. It should be acknowledged that SLEDAI-2K does not include gastrointestinal subscores; therefore, a complementary bowel-specific activity index, such as a Mayo-adapted or radiologic scoring tool, is necessary to adequately capture the disease burden related to colitis. Second, dedicated registries for biologic use in gastrointestinal SLE should be integrated into existing lupus cohorts. Third, funding bodies must recognize lupus colitis as a distinct, underfunded entity that warrants targeted clinical trial infrastructure.

Patients with lupus colitis experience diagnostic delays, empirical corticosteroid exposure, and escalation to immunosuppressants without evidence to guide treatment sequencing. The biologic era offers real potential, but that potential requires clinical investigation before it can be translated into practice. We urge this journal to champion targeted research and support advocacy for the funding this patient population deserves.

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