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Evaluating spleen volume in inflammatory bowel disease

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Abstract

Crohn's disease (CD) and ulcerative colitis (UC), known as inflammatory bowel disease (IBD), are characterized by immune system dysregulation. The spleen holds a primary role in systemic inflammation and immune responses. Splenic involvement or splenomegaly in IBD patients may result from secondary causes, such as portal hypertension, myeloproliferative diseases, amyloidosis, splenic abscesses or granulomas. Current research on the direct association between IBD and spleen volume (SV) has expanded significantly. In CD, SV is predominantly increased, and is associated with worsen clinical outcomes. Successful treatment with infliximab often leads to a reduction in the elevated SV. Patients with UC often present spleens with invariant SV, or smaller spleens than those observed in CD, as UC typically affects a more limited part of the gastrointestinal tract compared to CD. However, reduction of SV in UC can also indicate relapsing pancolitis. Recent genetic data also suggest that an increased SV serves as a potential risk factor for the development of IBD, emphasizing the possible bidirectional causal relationship between IBD and SV. Shared pathogenic pathways, including intestinal immune activation, tumor necrosis factor-α activation, bowel toxin absorption and lymphatic tissue involvement, might explain the splenic and intestinal immune dysfunction. Thus, the measurement of SV and its adjustment for body mass index or weight, factors that affect the spleen size, may serve as a potential indicator for IBD monitoring, predicting disease-related flares and complications, and evaluating the response to current biologics. Nonetheless, further insights into the underlying pathogenic pathways linking SV and IBD are considered imperative.

Keywords Spleen volume, spleen, inflammatory bowel disease, ulcerative colitis, Crohn's disease

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Introduction

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), refers to a group of chronic, relapsing inflammatory diseases of the gastrointestinal tract [1]. CD can affect any part of the digestive system, from the mouth to the anus, whereas UC affects the colon [2,3]. Over the past 2 decades, the global incidence and prevalence of IBD have risen significantly, reflecting its growing impact on public health [4,5].

UC and CD are immune-mediated diseases that arise from a complex interplay of genetic, environmental, microbial and immunological factors [6-9]. Although the intestine remains the primary site of pathology, IBD is increasingly recognized as a systemic disease with a wide range of extraintestinal manifestations, highlighting the broader immune dysregulation that characterizes IBD [10,11]. Among the organs involved in immune function, the spleen holds a primary role in modulating systemic inflammation and

immune responses in various autoimmune diseases [12]. Secondary spleen involvement and/or splenomegaly in patients with IBD have been described in cases of portal hypertension, myeloproliferative diseases, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections, amyloidosis, splenic abscesses, and splenic granulomas [13-20].

However, data regarding the direct relationship between IBD and spleen volume (SV) remain scarce. Recent advances in imaging and immunological techniques have increased scientific interest in the spleen's role as an immune system modulator in IBD [21]. Changes in SV can may offer valuable insights into disease activity, severity, and response to current biologic therapies [20-23].

This present review aims to summarize the current evidence on splenic volumetric changes in IBD patients and explore potential associations with clinical outcomes, as outlined in the existing literature.

Materials and methods

We performed an in-depth review of the literature in ResearchGate, Google Scholar PubMed, EMBASE, Cochrane Library, Clinicaltrials.gov and Scopus up to March 2025. Keywords and phrases used included "spleen", "spleen volume", "splenic size", "spleen enlargement", "spleen features", "splenomegaly", "inflammatory bowel disease", "Crohn's disease" and "Ulcerative colitis". Inclusion criteria in the final review were: a) articles investigating the direct relationship between SV and IBD; and b) full articles, as well as articles in research letter form. Exclusion criteria were: a) articles that included animal models; and b) articles in abstract form.

Results

Nine studies met the inclusion criteria and were included in the final literature review [22-30]. Five studies were retrospective [22-26], while 2 studies were prospective [27,28]. It is important to note that 6 of the 7 aforementioned studies excluded patients with causes of SV alterations other than IBD [22-24,26-28]. Additionally, 2 studies included Mendelian randomization analyses [29,30]. The 9 included studies described various imaging techniques—such as computed tomography (CT) scans, abdominal ultrasound and magnetic resonance imaging—as well as genetic data from genome-wide association studies (GWAS) to assess the SV in correlation with IBD presence, activity, clinical outcomes and response to biologic treatment. Pereira *et al* conducted a prospective study involving 115 IBD patients undergoing laparotomy, where spleen size was measured during surgery [27]. They found no correlation between spleen size and disease site, extent or recurrence, but patients with CD were more likely to have enlarged spleens compared to those with UC. Smaller spleen sizes in both CD and UC were linked to more severe disease complications [27]. Muller *et al* also performed a prospective study using ultrasound in 50 IBD patients [28]. Although they did not define a specific cutoff for spleen size, they observed that patients with relapsing UC tended to have smaller spleens than those with controlled disease (P<0.01) [28]. Balaban *et al* conducted a retrospective study of 52 IBD patients, defining small spleens as less than 95 mm in length [24]. They found small spleens in 10% of CD patients and 21.9% of UC patients [24]. Kawashima *et al* carried out a single-center retrospective case–control study using CT scans [22]. They reported significantly larger SVs in CD patients (3.6±1.7 cm^3/kg) compared to controls (2.2±1.0 cm^3/kg; P=0.01), while no significant difference was seen in UC patients [22]. They also found a significant correlation between SV and CD disease activity (P<0.01) [22]. Khasper *et al* used CT imaging in a retrospective study of 90 CD patients [25]. While SV did not differ between active and inactive CD, the ratio of SV to body mass index (BMI) was significantly higher in active disease (15.26 vs. 11.69; P=0.004) [25]. Shi *et al* analyzed CT data from 49 CD patients treated with infliximab [23]. Responders showed significant reductions in SV (P<0.001) and SV/BMI ratio (P<0.001) [23]. In contrast, non-responders had increases in both SV and SV/BMI [23]. Additionally, SV/BMI was positively correlated with C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) levels [23]. Azam *et al* performed a retrospective study on 100 CD patients using CT scans [26]. They found that the SV/BMI ratio correlated with perianal disease severity (P=0.009) and disease duration (P=0.014) [26]. Elevated SV was also linked to worsen clinical outcomes, such as higher risk of bowel resection (odds ratio [OR] 1.184, P=0.03) and frequent flares (OR 1.089, P=0.05) [26]. Song *et al* conducted a 2-sample Mendelian randomization study using large GWAS datasets [29]. They found that a greater genetically predicted SV was associated with a higher risk of developing CD (OR 1.237, 95%CI 1.056-1.417; P=0.021 in the Integrative Epidemiology Unit dataset; OR 1.292, 95%CI 1.120-1.463; P=0.003 in the European Bioinformatics Institute dataset) [29]. They also showed that CD mildly increases SV (OR 1.009, 95%CI 1.000-1.018; P=0.047) [29]. Finally, Su *et al* performed a Mendelian randomization meta-analysis [30]. Their results indicated that increased SV is genetically associated with a higher risk of both UC and CD [30]. Each standard unit increase in SV raised the risk for UC by 11.5% (OR 1.115, 95%CI 1.014-1.227; P=0.025) and for CD by 27.2% (OR 1.272, 95%CI 1.133-1.428; P<0.001) [30]. Table 1 presents the characteristics of the observational (non-Mendelian) studies evaluating SV alterations in IBD patients, Table 2 displays the Mendelian randomization analyses exploring the bidirectional association between SV and IBD, and Table 3 presents studies that examined the correlation between SV disease activity in UC and CD.

Discussion

Splenic function and volume can be significantly altered in gastrointestinal diseases that have a strong immunological substrate, such as celiac disease and IBD [24,31]. Both CD and UC have been associated with hyposplenism, as

Table 1 Characteristics of observational (non-Mendelian) studies evaluating spleen volume alterations in patients with IBD

Author (year) [ref.]	Type of study	Number of patients (males)	Disease type	Spleen volume evaluation method	Definition criteria	Exclusion of patients with IBD who had spleen volume alterations due to causes unrelated to IBD (e.g., portal hypertension, myeloproliferative diseases)
Pereira *et al* (1987) [27]	Prospective study	115 (48)	UC=35 CD=80	Spleen size measured during laparotomy for inflammatory bowel disease	Small spleen if spleen length was <11 cm, normal if length was 11.5 to 15.5 cm and large if length was >16 cm	Yes
Muller *et al* (1993) [28]	Prospective study	50 (22)	UC=29 CD=21	Abdominal ultrasound	No specific numerical definition of "small spleen"	Yes
Balaban *et al* (2015) [24]	Retrospective study	52 (28)	UC=32 CD=20	Abdominal ultrasound	Small spleen defined as having a length of less than 95 mm along the longitudinal axis	Yes
Kawashima *et al* (2022) [22]	Single-center retrospective case–control study	44 (27)	UC=24 CD=40	CT	Cutoff value for spleen volume (adjusted for body weight) for both UC and CD was 2.5cm^3/kg	Yes
Khasper *et al* (2022) [25]	Retrospective cohort study	90 (58)	90 patients with CD	CT	Not applicable	Not specified
Shi *et al* (2023) [23]	Retrospective cohort study	49 (34)	49 patients with CD	CT	Not applicable	Yes
Azam *et al* (2023) [26]	Retrospective cohort study	100 (45)	100 patients with CD	CT	Not applicable	Yes

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; CT computed tomography

Table 2 Mendelian randomization analyses investigating the bidirectional association between spleen volume and IBD

Author (year) [ref.]	Type of study	Data	Techniques used for the evaluation of spleen volume	Outcomes
Song *et al* (2024) [29]	Two-sample Mendelian randomization study	Data from several large-scale GWAS	Not applicable	1. Predicted increased spleen volume may influence the risk of Crohn's disease: A) In the Integrative Epidemiology Unit (IEU) dataset, predicted increased spleen volume was associated with a higher risk of CD (OR 1.237, 95%CI 1.056-1.417; P=0.021) B) In the European Bioinformatics Institute (EBI) dataset, the same association was also statistically significant (OR 1.292, 95%CI 1.120-1.463; P=0.003) C) However, analyses using the UK Biobank and FinnGen datasets did not show a significant causal relationship 2. Crohn's disease mildly affects spleen volume: Analysis including all datasets indicated a mild but significant effect (OR 1.009, 95%CI 1.000-1.018; P=0.047)
Su *et al* (2025) [30]	Mendelian randomization meta-analysis	Data from several large-scale GWAS	MRI scans	1. UC: - Meta-analysis: OR 1.115 (95%CI 1.014-1.227; P=0.025) - Each standard unit increase in SV was associated with an 11.5% increased risk of developing UC 2. CD: - Meta-analysis: OR 1.272 (95%CI 1.133-1.428; P<0.001) - Each standard unit increase in SV was associated with a 27.2% increased risk of developing CD

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; GWAS, genome-wide association studies; MRI magnetic resonance imaging; OR, odds ratio; CI, confidence interval; SV, spleen volume

Table 3 Correlation between spleen volume and disease activity in CD and UC

Author (year) [ref.]	SV Correlation with disease activity	Associated outcomes
Pereira *et al* (1987) [27]	Patients with CD and UC with smaller spleens experienced the highest incidence of disease-related complications, including perforation, fistulae, abscess, bleeding, toxic megacolon	Smaller spleen size is potentially associated with severe complications in both CD and UC
Muller *et al* (1993) [28]	Smaller spleen size was detected in relapsed (5 of 6 patients) UC compared with quiescent or controlled UC (1 of 6 patients) (P<0.01)	Smaller spleen size is potentially associated with relapsing pancolitis in UC
Khasper *et al* (2022) [25]	- The average SV measured was 324±130.3 cm^3, with no significant difference observed between patients with active disease and those with non-active CD (339.2±118.4 cm^3 vs. 304.2±144.2 cm^3, P=0.21) - However, when adjusted for body mass index using the SV/BMI ratio, a significant difference emerged. Patients with active disease had a markedly higher SV/BMI index of 15.26±4.86 compared to 11.69±5.19 in the non-active group (P=0.004)	SV/BMI >14 was proposed as a functional marker of disease activity
Kawashima *et al* (2022) [22]	- In patients with CD, there was a strong and statistically significant correlation between disease activity and increased spleen volume adjusted for body weight (P<0.01) - SV was not correlated with CRP levels	Increased SV adjusted for body weight may reflect increased inflammatory activity in CD
Azam *et al* (2023) [26]	1. SV/BMI ratio correlated: A) with perianal disease severity according to MRI-based modified Van Assche index (r=0.280, P=0.009); B) with disease duration (r=0.257, P=0.014) 2. High SV independently predicted worse clinical outcomes in CD being significantly associated with an increased risk of bowel resections (OR=1.184, P=0.03) and a higher likelihood of experiencing multiple disease flares (OR=1.089, P=0.05) 3. However, SV/BMI ratio was not correlated with ESR and CRP levels	- SV/BMI may reflects inflammatory activity in CD - An increased SV/BMI ratio may be associated with more severe complications in CD, such as greater perianal disease severity, frequent disease flares, and a higher risk of bowel resection
Shi *et al* (2023) [23]	- In infliximab responders (41 patients): A) SV significantly decreased (from 248.4±101.7 cm^3 to 232.0±88.2 cm^3, P=0.00057); B) SV/BMI significantly decreased (from 13.5±5.8 to 11.5±4.7, P=9.11×10^{-7}); C) SV/weight significantly decreased (from 4.5±1.8 to 3.9±1.4, P=1.00×10^{-6}) - In infliximab non-responders (8 patients): A) SV significantly increased (from 186.6±57.3 cm^3 to 234.8±50.9 cm^3, P=0.0069); B) SV/BMI significantly increased (from 9.7±3.5 to 13.1±4.1, P=0.0032); C) SV/weight significantly increased (from 3.5±1.5 to 4.8±1.9, P=0.0039) - A positive correlation was found between SV/BMI and both CRP (r=0.32, P<0.05) and TNF-α levels (r=0.43, P<0.05), while SV/BMI ratio was not correlated with ESR levels	The decrease in the SV/BMI ratio may be associated with respond to infliximab therapy in patients with CD

CD, Crohn's disease; UC, ulcerative colitis; SV, spleen volume; BMI, body mass index; MRI magnetic resonance imaging; OR, odds ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

demonstrated by elevated pitted erythrocyte counts under differential interference contrast microscopy and reductions in immunoglobulin M levels [21,32,33]. Hyposplenism observed in IBD is reversible after successful treatment with biologics [21]. Splenic function impairment often corresponds with a reduction in spleen size [24,27,28]. Several pathogenic mechanisms have been proposed to explain splenic atrophy and dysfunction in IBD [27]. These include intense chronic immune activation—particularly in cases of pancolitis—as well as the systemic effects of absorbed bowel toxins [27]. In both CD and UC, small SV is associated with complications such as abscesses, fistulas, perforation, bleeding and toxic megacolon [27]. In CD, small spleens are further associated with a higher risk of perioperative and postoperative infections and complications [27]. In UC, smaller SVs are more frequently observed in patients with relapsing pancolitis, possibly due to circulating immune complexes that impair the function of the splenic reticuloendothelial system [28]. Given the increased susceptibility to infections in patients with reduced splenic function, it is reasonable that patients with IBD and small SV—possibly indicative of hyposplenism—should receive vaccinations and prophylactic antibiotics, following protocols similar to those accredited for post-splenectomy patients [28].

Interestingly, no significant correlation has been established between a small spleen size and the anatomical extent of CD [27,28]. This may be partly due to the fact that most studies investigating SV in CD have described splenomegaly rather than splenic atrophy [20,22,24-27,29]. Patients with CD present larger spleens than those with UC, as CD can affect a more extensive part of the gastrointestinal tract and deeper intestinal layers compared to UC [22,34]. It should be noted that studies addressing SV in UC predominantly report a reduction in spleen size [24,27,28]. In addition, there are data that indicate no substantial change in SV in UC patients compared to healthy controls [22]. Table 4 summarizes the studies that investigated differences in SV between CD and UC.

Table 4 Differences in spleen volume between Crohn's disease (CD) and ulcerative colitis (UC)

Author (year) [ref.]	Spleen volume in patients with CD	Spleen volume in patients with UC	Outcomes
Pereira *et al* (1987) [27]	Higher frequency of splenomegaly	Lower frequency of splenomegaly	Enlarged spleens were more common in CD patients compared to those with UC
Kawashima *et al* (2022) [22]	Significantly larger spleen volume compared to controls (3.6±1.7cm^3/kg vs 2.2±1.0cm^3/kg, P=0.01)	No significant difference in spleen volume compared to controls (2.0±1.0cm^3/kg vs. 2.2±1.0cm^3/kg, P=0.43)	CD patients exhibited larger spleen volumes than UC patients
Balaban *et al* (2015) [24]	Small spleen (<95mm) was detected in 10% of CD patients	Small spleen (<95mm) in 21.87% of patients with UC	CD patients exhibited larger spleen volumes than UC patients
Muller *et al* (1993) [28]	No significant difference in spleen size compared to controls	Patients with relapsed pancolitis had significantly smaller spleens compared to controls (P<0.02)	Patients with UC present smaller spleens than patients with CD

One major limitation in early studies by Pereira and Muller *et al*, is the lack of adjustment of SV for patients' body weight or BMI, both of which are important factors influencing spleen size [27,28,35]. The first study that adjusted SV for the body weight was reported by Kawashima *et al*, and revealed a positive correlation between SV and CD activity [22]. Nevertheless, the study's retrospective, single-center design and small sample size were major limitations [22]. Subsequently, Khasper *et al* introduced the SV/BMI ratio, proposing that values above 14 may serve as a potential marker of active CD [25]. In their study, the average SV did not differ significantly between patients with active and inactive CD (Table 3) [25]. This lack of statistical significance may be attributed to the small sample size, as well as the potential influence of non-cirrhotic portal hypertension, which affects up to 1% of patients with IBD and can contribute to spleen enlargement [25]. However, when SV was adjusted for BMI, a significant difference emerged: patients with active CD had a markedly higher SV/BMI ratio (15.26±4.86) compared to those with inactive disease (11.69±5.19, P=0.004) (Table 3) [25]. The recent work by Azam *et al* further correlated the elevated SV/BMI ratio with complicated phenotypes of CD, such as structuring and penetrating disease [26]. The utility of SV as a functional biomarker for monitoring CD activity and treatment response has been also investigated in a recent therapeutic study [23]. Treatment with infliximab, a TNF-α inhibitor, has been shown to significantly reduce SV/BMI and SV/weight ratios, with a parallel decrease in CRP and TNF-α levels, which are both established markers of CD activity [23,36,37]. Thus, according to Shi *et al*, a decrease in the baseline SV/BMI ratio may serve as a promising early indicator of therapeutic response to infliximab in CD patients [23].

It should be emphasized that splenomegaly in patients with CD is not linked to functional hypersplenism, as no decrease in platelet count is observed, a common laboratory finding in patients with splenomegaly and portal hypertension [22,38]. Additionally, in CD, the immune response can contribute to spleen enlargement and increased platelet counts, possibly due to splenic edema resulting in impaired splenic function—the exact underlying mechanism remains unclear [22,39]. However, in a study by Kawashima *et al*, despite the increased platelet counts seen in IBD patients, no correlation was found between platelet count and SV [22]. Furthermore, a study by Shi *et al* did not show a correlation between SV/BMI ratio and platelet count [23]. Therefore, splenomegaly in CD is probably driven by more complex immune processes, rather than simple hemodynamic changes [22]. The potential pathophysiology of splenomegaly in patients with CD is also thought to reflect the intense immune activation occurring in the intestinal mucosa, which disrupts the gut barrier and allows inflammatory cytokines such as TNF-α to enter the systemic circulation and affect the spleen [22,40,41]. Additionally, the presence of mesenteric lymphadenopathy in both UC and CD underscores the involvement of lymphatic tissue in IBD [42,43]. Given that splenomegaly can be observed in other autoimmune conditions, such as Felty's syndrome in patients with rheumatoid arthritis, further research into the underlying pathogenic mechanisms of spleen enlargement in CD is considered imperative [44,45].

New important insights into the causal relationship between SV and CD and UC have been established by recent Mendelian randomized studies [29,30]. These studies demonstrated a strong correlation between a genetically predicted increase in SV and the appearance of CD and UC [29,30]. Notably, a study conducted by Song *et al* reported that increased SV can be related with increased susceptibility to CD, while CD can also lead to spleen enlargement [29]. These observations suggest the existence of a potential bidirectional causal relation between increased spleen size and CD, which further highlights the complex interplay between immune system regulation and intestinal inflammation [29]. T-regulatory cells, which are trafficked between the spleen and the intestine, may play a crucial role in the shared pathogenic mechanisms underlying both the splenic and intestinal immune dysfunction [46,47]. This bidirectional movement of T-regulatory cells could represent a key component of the immune response in inflammatory diseases like IBD, where immune system dysregulation in one organ may influence and exacerbate dysfunction in the other [29,39]. The connection between splenic and intestinal immune dysfunction, facilitated by T-regulatory cells, emphasizes the need for further investigation into how immune regulation at these sites may influence disease progression and

Table 5 Pathogenetic mechanisms likely contributing to spleen size changes in patients with IBD

• TNF-α mediated spleen damage
• Systemic effects of absorbed bowel toxins
• Immune-mediated splenic edema
• Intestinal immune dysfunction facilitated by T-regulatory cells
• Lymphatic tissue involvement
• Splenic reticuloendothelial dysfunction due to circulating immune complexes
• Non-cirrhotic portal hypertension, which affects up to 1% of patients with IBD

IBD, inflammatory bowel disease; TNF-α, tumor necrosis factor-alpha

severity [29]. Thus, targeting spleen function and T-regulatory cells through anti-inflammatory therapies could present novel strategies for the management of IBD [30]. The pathogenetic mechanisms that may contribute to changes in spleen size in patients with IBD are summarized in Table 5.

Despite the advantages of Mendelian randomization in reducing confounding factors, compared to traditional observational studies, further research is needed to clarify the precise molecular pathways linking SV to IBD [29,30]. Additionally, future studies should include subgroup analyses based on age, sex and ethnicity, factors that may biologically influence SV, in order to provide a more comprehensive understanding of the complex relationship between spleen size and IBD [48-51]. Moreover, given the significant heterogeneity among existing studies evaluating the correlation between SV and IBD, future research should adopt standardized outcome measures, definitions and inclusion criteria, in order to reduce heterogeneity and enable meaningful comparisons and robust meta-analyses.

Concluding remarks

Secondary causes, such as portal hypertension, can lead to an increased SV in patients with IBD [38]. Research into the direct correlation between IBD and SV has expanded significantly [22-30]. Current evidence predominantly appears to associate CD with an increase in SV, which appears to decrease following treatment with infliximab, while spleens with small size in patients with CD are reported less frequently [22-26,29]. Patients with UC present spleens with either invariant SV, or smaller than those observed in CD, as UC typically affects a more limited part of the gastrointestinal tract compared to CD [22-24,27,28]. Recent genetic data also suggest that an increased SV potentially serves as a risk factor for the development of UC and CD, emphasizing the important immunological background of IBD, while there may be a bidirectional causal relationship between IBD and changes in SV [29,30]. The measurement of SV, easily performed through imaging techniques such as abdominal ultrasound, may serve as a promising indicator for disease monitoring, predicting IBD-related flares and complications, and evaluating the response to current biologics. However, future research into the underlying pathogenic pathways linking SV and IBD is considered imperative.

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