

Inflammatory bowel disease and cardiac function: a systematic review of literature with meta-analysis

Caroline Almeida Soares* , João Gouveia Fiúza* , Cláudio André Melo Rodrigues ,
Nuno Craveiro , Júlio Gil Pereira , Paula Cristina Ribeiro Fernandes Sousa ,
Diana Catarina Pinto Martins , Eugénia Maria Cancela and
Maria Paula Ministro dos Santos 

Ther Adv Gastroenterol

2024, Vol. 17: 1–19

DOI: 10.1177/
17562848241299534

© The Author(s), 2024.
Article reuse guidelines:
[sagepub.com/journals-](https://sagepub.com/journals-permissions)
permissions

Abstract

Background: Morphological and functional cardiac involvement is rarely described in patients with inflammatory bowel disease (IBD) but there is evidence that they have an increased risk of cardiovascular (CV) events despite the lower prevalence of traditional CV risk factors.

Objectives: Our systematic review and meta-analysis examined the relationship between IBD and cardiac function, namely the incidence of heart failure (HF) and subclinical echocardiographic changes.

Data sources and methods: Two medical databases, PubMed and Scopus, were systematically searched up to September 2022 to identify all studies reporting HF and/or echocardiographic changes in IBD patients.

Results: The qualitative analysis comprised a total of 18 studies (14 retrospective and 4 prospective studies) involving 59,838 patients. IBD was associated with subtle systolic and diastolic alterations, vascular dysfunction, increased risk for HF hospitalizations, and globally worse CV outcomes. Nine studies were included in the meta-analysis. In the IBD population, we found statistically significant reduced early to late diastolic transmitral flow (E/A), higher E to early diastolic mitral annular tissue velocity (E/e'), and decreased global longitudinal strain. Increased left atrial diameter and area were also present in IBD patients but no statistical significance was reached. Inter-atrial and right intra-atrial conduction delays were observed.

Conclusion: The IBD population has an increased risk for left ventricular and atrial dysfunction, vascular changes, arrhythmias, and HF hospitalization. Screening with sensitive imaging like speckle tracking echocardiography could identify early subclinical changes. IBD is in fact a CV risk factor and tight inflammation control may reduce CV risk.

Correspondence to:
Caroline Almeida Soares
Department of
Gastroenterology, Centro
Hospitalar Tondela-Viseu,
E.P.E., Av. Rei D. Duarte,
Viseu 3504-509, Portugal
carol.soares555@gmail.com

João Gouveia Fiúza
Nuno Craveiro
Júlio Gil Pereira
Cardiology Department,
Unidade Local de Saúde de
Viseu Dão Lafões, Viseu,
Portugal

Cláudio André Melo Rodrigues
Paula Cristina Ribeiro Fernandes Sousa
Diana Catarina Pinto Martins
Eugénia Maria Cancela
Maria Paula Ministro dos Santos
Gastroenterology
Department, Unidade
Local de Saúde de Viseu
Dão Lafões, Viseu,
Portugal

*Both authors contributed
equally as co-first authors

Plain language summary

Inflammatory bowel disease and cardiac function: What you need to know

Background and context: The risk of cardiovascular events is higher in patients with inflammatory bowel disease and has a multifactorial etiology.

New findings: Subclinical echocardiographic alterations are, to some extent, linked to the activity of the disease.

Limitations: Small sample size, observational nature and intra and inter study heterogeneity (which may exist due to differences between group characteristics and echocardiographic study protocols between centers, distinct techniques and modes).

Clinical research relevance: Echocardiographic evaluation may identify patients with inflammatory bowel disease at higher risk for cardiac events and determine those who might benefit from tighter inflammation control in order to achieve deeper levels of remission and decrease cardiovascular risk.

Basic research relevance: Our findings should motivate research toward a deeper understanding of the role of echocardiographic parameters as tools to evaluate systemic inflammation and its potential as new treatment targets. Indeed, improvement on these parameters may suggest deeper levels of remission.

Summary: IBD patients present subclinical cardiac alterations correlated with disease activity. Echocardiographic parameters may be used as inflammatory markers and identify those who might benefit from deeper remission levels.

Keywords: cardiovascular risk, inflammation, inflammatory bowel disease

Received: 11 May 2024; revised manuscript accepted: 18 October 2024.

Introduction

Inflammatory bowel disease (IBD) is a chronic immunomodulated disease of unknown etiology comprising Crohn's disease (CD) and ulcerative colitis (UC). It is characterized by chronic relapsing and remitting inflammation of the gastrointestinal tract. While some extra-intestinal manifestations are common (mainly osteoarticular, cutaneous, and ocular), others, such as cardiac involvement, are rarely seen.¹

IBD patients are mainly represented by young otherwise healthy patients, at least in the first years after the diagnosis. Nevertheless, the risk of CV events is higher in IBD patients.^{2,3} The pathogenesis of cardiac involvement in IBD patients is not clearly understood, but there are several potential mechanisms described.

First, chronic inflammation plays a central role in all phases of the atherosclerotic process through direct impact on endothelial dysfunction, hypercoagulability, and indirect disturbance of regular lipid metabolism.² Furthermore, an inflammatory environment leads to collagen deposition which can occur at cardiac extracellular matrix proteins and endocardial fibers changing the morphological structure of the myocardium, and therefore its appropriate function.⁴ On the other hand, the increased systemic immune response observed in these patients may cause myocarditis/pericarditis.⁵ In fact, mediators, such as tumor necrosis factor (TNF- α), interleukin-1 (IL-1), and IL-6, that are increased in IBD patients even in the remission phase, may cause cytotoxic damage in myocytes.⁶ Second, IBD patients are at higher risk of nutritional deficits in relation to chronic malabsorption which may compromise heart health.⁷

In addition, there is a major risk of drug-related cardiotoxicity. In fact, corticosteroids, TNF- α inhibitors, some Janus kinase (JAK) inhibitors, and selective sphingosine 1-phosphate receptor modulators have undesired cardiac effects which can accelerate the CV pathological process.⁸⁻¹⁴ It is important to notice that, regarding anti-TNF- α therapy, initial studies aimed to determine whether infliximab could yield positive effects in non-IBD patients with moderate-to-severe heart failure (HF). However, these studies not only failed to show any favorable effects but also revealed an elevated risk of worsening HF.¹⁵ In spite of that, recent studies have demonstrated a decreased risk of CV events in IBD patients exposed to anti-TNF- α therapy.¹⁶⁻²¹ Further research is required to determine whether this is linked to the management of disease activity or the underlying mechanism of the drug. As for ustekinumab, a monoclonal antibody targeting IL-12/23p40, 2-year follow-up data from CD and UC trials did not demonstrate an impact on CV events risk.^{22,23} Nevertheless, a recent epidemiological study reported a potential link between ustekinumab treatment and CV adverse events in patients with a high CV risk profile.²⁴ Further investigations are needed to clarify this association. In regard to anti-integrins, randomized controlled trials and real-world observational studies have not found an increase in CV events in IBD patients on vedolizumab.²⁵⁻²⁸ Despite this, data from long-term studies are lacking.

Furthermore, early cardiac death is increased in the IBD population, and the CV events go from myocarditis, pericarditis, cardiomyopathies, myocardial infarction, atrial fibrillation (AF), stroke, and HF.²⁹ The increased CV risk in these patients

might be fundamentally dependent on chronic systemic inflammation rather than traditional risk factors such as hyperlipidemia, hypertension, obesity, smoking, and alcohol use.²

Even though cardiac involvement and complications are rare, it is crucial to screen IBD patients to detect them early.³⁰ Previous studies suggested that some subclinical CV features such as abnormal echocardiographic parameters can predict and stratify patients who are at an increased risk of CV intercurrentence.^{8,31,32} Diastolic dysfunction represents a combination of impaired left ventricular (LV) relaxation, restoration forces, myocyte lengthening load, and atrial function which leads to increased LV filling pressures.^{33,34} Early to late diastolic transmitral flow (E/A) is used to assess diastolic function and E to early diastolic mitral annular tissue velocity (E/e') estimates LV filling pressures. To evaluate global LV function, left ventricular ejection fraction (LVEF) is the most widely used parameter. However, global longitudinal strain (GLS) is a more sensitive parameter, especially for detecting subclinical LV dysfunction when LVEF is within the normal range. GLS represents the percentage of myocardial fiber shortening in the longitudinal direction during systole, reflecting LV deformation, and more negative values are considered indicative of better systolic function.³⁵ Left atrial (LA) dimensions are correlated with systolic and diastolic function. Impaired LA function resulting in increased dimensions can be a marker of diastolic dysfunction when the left ventricle has decreased relaxing and filling properties.³⁶ Electrophysiological and electromechanical abnormalities originating from intra-atrial and inter-atrial conduction disturbances are associated with an increased risk of AF.³⁷ Moreover, an increase in atrial electromechanical delay (AEMD) duration was shown to be an independent variable for AF development. Supplemental Tables 1 and 2 present the most relevant echocardiographic parameters with the corresponding definition and interpretation.^{33–35,38–42}

In the literature, we found seven systematic reviews underlying the topic of CV impact and IBD disease.^{2,3,8,43–46} However, to our knowledge, there are currently no systematic reviews on echocardiographic changes in IBD patients. This review aims to summarize the latest evidence of the association between IBD and heart function and structural abnormalities that can lead to HF.

Our meta-analysis mainly adds up to the subclinical echocardiographic changes in patients with IBD. This work is the result of an ongoing collaboration between the gastroenterology and cardiology departments of our unit.

Materials and methods

Study design and data sources

We performed a systematic review and meta-analysis based on the guidelines dictated by PRISMA. Two medical databases, PubMed and Scopus, were systematically searched.

Search strategy

The article search was conducted independently by two authors until September 19, 2022. The following search queries were utilized in the “Advanced search” section of the PubMed and Scopus databases. From PubMed: (“heart failure”) and (“inflammatory bowel disease”), (“heart failure”) AND (“ulcerative colitis”), (“heart failure”) AND (“Crohn’s disease”), (“inflammatory bowel disease”) AND (“echocardiography” OR “echocardiogram”), (“ulcerative colitis”) AND (“echocardiography” OR “echocardiogram”), and (“Crohn’s disease”) AND (“echocardiography” OR “echocardiogram”). From Scopus: (ABS (“HEART FAILURE”)) AND (ABS (“INFLAMMATORY BOWEL DISEASE”)), (ABS (“HEART FAILURE”) AND ABS (“CROHN’S DISEASE”)), (ABS (“HEART FAILURE”) AND ABS (“ULCERATIVE COLITIS”)), (ABS (“inflammatory bowel disease”) AND (“echocardiography” OR “echocardiogram”)), (ABS (“ulcerative colitis”) AND (“echocardiography” OR “echocardiogram”)), and (ABS (“Crohn’s disease”) AND (“echocardiography” OR “echocardiogram”)).

Eligibility criteria

We included randomized controlled trials, observational studies, case-control studies, and cohort studies comparing HF, and/or echocardiographic changes between IBD patients (UC and CD; age ≥ 16 years old) and healthy individuals, with sufficient data to extract the effect estimates. Studies that evaluated electrocardiographic changes and other cardiac imaging modalities were also eligible. There were no restrictions regarding patients’

past medical history or the treatment approach employed for managing their disease. Only articles published in English were included. Case reports, as well as those detailing laboratory, in vitro, or animal studies, were excluded.

Outcomes

The main outcome of interest in our systematic review was the association between IBD and the heart's functional and structural abnormalities that can lead to HF. Other outcomes included the impact of disease activity, duration, and treatment (mainly corticosteroids and TNF-alpha inhibitors) on cardiac health.

In the meta-analysis, the main focus resided on quantifying subclinical echocardiographic changes in IBD patients compared to healthy individuals. The cardiac changes were divided into their structural and electrical components, and echocardiographic parameters were selected by their clinical and practical relevance.

Data extraction

Two independent reviewers performed the data selection and extraction process using the pre-established form. The information extracted from each eligible study included the following: author(s), year of publication, study design, sample size, participant characteristics (age, sex, type of IBD), details of the IBD treatment approach used, echocardiographic, electrocardiographic, and other cardiac imaging parameters, main outcomes, and key findings.

Any discrepancies between the two reviewers were resolved through discussion and, when necessary, consultation with a third reviewer. It is important to note that not all variables outlined in the data extraction process were covered in each study included in our review. Missing data were objectively reported through the number of studies that provided information on specific variables. This was considered in the section "Discussion," and the potential impact on overall findings is acknowledged.

Quality assessment

The methodological quality of each study was assessed using the validated CASP for cohort studies. This tool consists of three sections ("Are

the results of the study valid?"—Section A; "What are the results?"—Section B; "Will the results help locally?"—Section C) and each question is answered based on "yes," "no," and "can't tell." Then an overall appreciation is obtained.⁴⁷

Statistical analysis

Data analysis was conducted using the Cochrane Review Manager Software (Review Manager (RevMan). Version 5.4. The Cochrane Collaboration, 2020). For individual measures of interest, a meta-analysis was performed if studies reported continuous variables as means and standard deviations. Data were then meta-analyzed using a random-effects model for overall effect size and assessed through standardized mean difference at a 95% level of confidence. Statistical significance was evaluated at $p < 0.05$. Heterogeneity was assessed using *I*-square test (I^2). An I^2 above 50% was defined as the cutoff for moderate heterogeneity, and low heterogeneity was determined above 25%. High heterogeneity was defined by I^2 above 75%.⁴⁸

A sensitivity analysis for each meta-analysis with at least three studies was conducted. Within each meta-analysis, each study was taken out one at a time and recalculated the pooled effect size and I^2 to assess the influence of each study.

Funnel plot was the method used to assess the potential of publication bias.

Results

Search results

The total number of records identified through our search was 1287. We proceeded to duplicate elimination using the Rayyan online tool, obtaining a total of 658 articles. Subsequently, the remaining studies were screened by manually reviewing their titles and abstracts, and at this phase, 562 articles were excluded. In all, 96 full-text articles were assessed for eligibility. A total of 18 were considered eligible for qualitative synthesis. From the selected studies, nine were included for meta-analysis. Figure 1 shows the PRISMA flowchart depicting the search and selection process (Supplemental Table 3). The exclusion explanation step by step is presented as Supplemental Material (Supplemental Table 4).

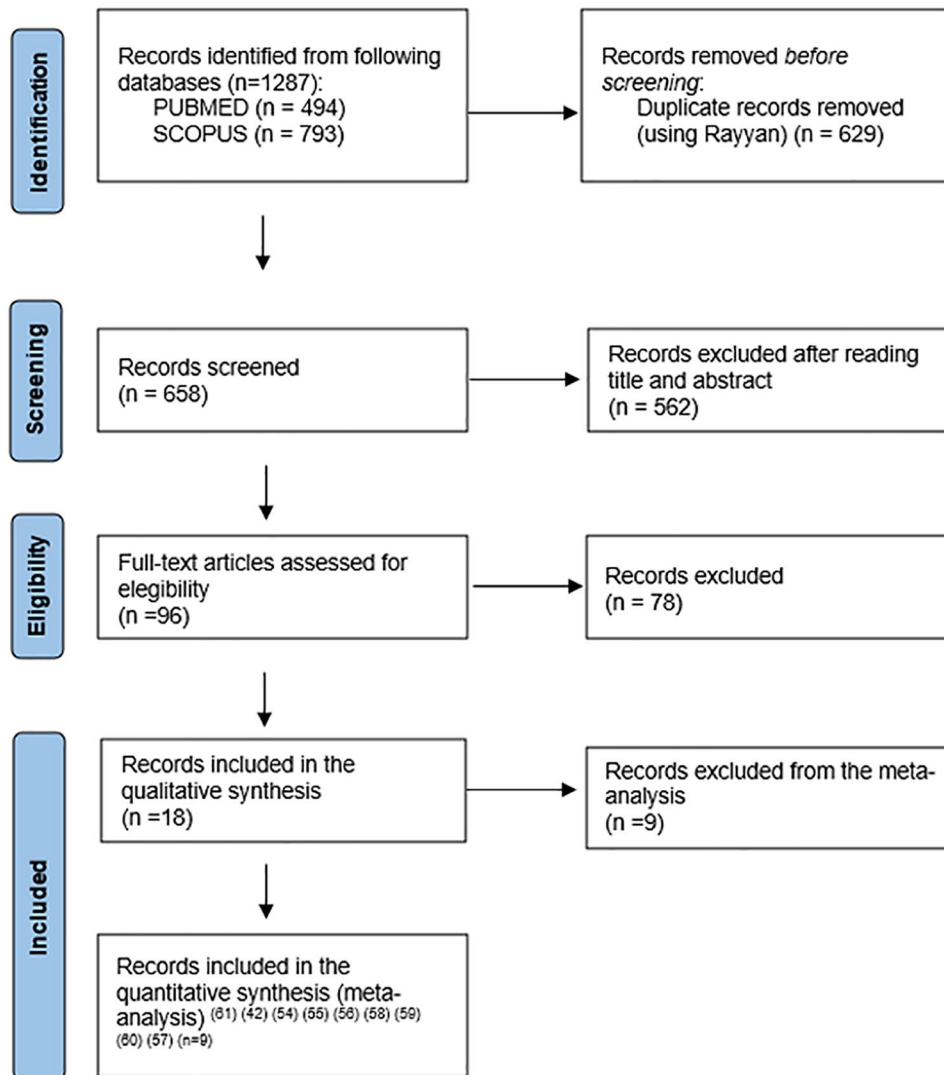


Figure 1. PRISMA flowchart depicting the search and selection process.

Quality assessment

The evaluation obtained through CASP Checklists showed that all included studies clearly stated the issue evaluated (Supplemental Table 5). On the other hand, most of them addressed the most relevant confounding factors.

Characteristics of included studies

All included studies were cohorts, and the majority were retrospective. Nine studies included both CD and UC patients, four

included only CD patients and three UC patients only. The detailed characteristics and outcomes of the eligible studies are presented in Table 1. A total of 59,838 patients with IBD from the 18 studies were included in this review. Two articles included IBD patients without specified subtypes. Six studies analyzed IBD patients according to disease activity. Age, disease duration, disease activity, localization, and/or behavior were considered in 10. The impact of medical therapy was descriptively analyzed in 11 studies.

Table 1. Individual study characteristics and the outcomes analyzed in each study.

Author/country/time period/design	Sample size (IBD patients/controls)	CD/UC patients (active/remission, if applicable)	Study objective	Characteristics (correspondent to IBD patients)	Methods	Main findings
Aniwan et al. (2018) ⁴⁹ Minnesota, 1980–2010 Retrospective observational cohort study	2208 (736/1472)	339/397 (NA)	Examine the risk of AMI/HF in patients with IBD	Median age at index date, years (IQR) 34, 1 (24.0–47.8) Median duration of follow-up, years (IQR) 14.3 (8.3–22.3)	Medical records revision. MI was defined using the third universal definition and HF by the Framingham Heart Study criteria. A multivariate analysis was performed to adjust to multiple known CV risk factors. A subgroup analysis included previous medical and surgical interventions and IBD location and behavior.	IBD is independently associated with an increased risk of AMI (aHR, 2.82; 95% CI, 1.98–4.04) and HF (aHR, 2.03; 95% CI, 1.36–3.03). The relative risk of HF was significantly increased among patients with UC (aHR, 2.06; 95% CI, 1.18–3.65) but not CD. The relative risk of HF was increased among users of systemic corticosteroids (aHR, 2.51; 95% CI, 1.93–4.57) but not non-users.
Aslan et al. (2016) ⁵⁰ Turkey, December 2013–October 2014 Retrospective observational cohort study	122 (72/50)	16/56 (0/72)	Assess the relation between aortic stiffness (AS) and the left ventricle function in IBD patients	Age (years) 41.6 ± 11.7 The mean disease duration was 68.2 ± 18.7 months (mini to max: 1–240 months) All IBD patients were in remission. 84% (n = 60) were treated with salicylates only, whereas the remaining 16% (n = 12) were treated with salicylates and steroids or immunosuppressors	Echocardiographic measurements were performed by conventional and TDI.	E/E' ratio in IBD 0.09 ± 0.01 vs controls 0.06 ± 0.01. Lower S', E', A', and E'/A' in IBD patients. AS is significantly correlated with LV systolic and diastolic dysfunction in patients with IBD vs controls: Aortic strain (%) 7.38 ± 2.6 vs 15.1 ± 4.5, p < 0.001 Aortic distensibility (10–3 cm ² × dyn ⁻¹) 3.3 ± 1.4 vs 6.9 ± 2.2, p < 0.001
Bragagni et al. (2007) ⁵¹ Italy Retrospective observational cohort study	128 (68/60)	68/0 (NA)	Evaluate possible morphofunctional cardiac alterations in patients with CD using ECHO	Mean age 41.75 ± 14.8 years	Evaluation with transthoracic echocardiogram with Doppler study.	Significantly more mitral valve prolapse, and pericardial effusion in CD patients. More “morphologically altered” echocardiographic parameters in CD patients. No correlation with age, sex, duration, therapy, or localization of disease was found.
Caliskan et al. (2015) ⁵² Turkey Retrospective observational cohort study	108 (72/36)	36/36 (NA)	To investigate whether CFR and LV diastolic function were altered in IBD patients	Mean age 39.7 ± 12.1 years Mean CD duration 3.5 ± 1.9 years Mean UC duration 6.5 ± 6.9 years Mean CDAI 63.7 ± 21.4 and TWAS score 3.52 ± 0.69	Measure of CFR through transthoracic Doppler ECHO.	There was a significant impairment in CFR in IBD patients. hs-CRP (mg/L), ESR (mm/h), disease duration, and TWAS score were negatively correlated with CFR.
Can et al. (2021) ⁵³ April 2019–October 2019 Retrospective observational cohort study	149 (79/70)	28/51 (NA)	Assess atrial conduction times in IBD patients	Mean age 37.7 ± 11.0 years 46 (58.2%) male Median disease duration 4 (1–20) years All IBD patients were in remission.	Simultaneous surface recording ECG with transthoracic ECHO and TDI methods.	Significantly increased atrial conduction durations in all IBD patients.

(Continued)

Table 1. (Continued)

Author/country/time period/design	Sample size (IBD patients/controls)	CD/UC patients (active/remission, if applicable)	Study objective	Characteristics (correspondent to IBD patients)	Methods	Main findings
Cincin et al. (2014) ⁵⁴ Turkey Retrospective observational cohort study	135 (45/90)	NA/45 (NA)	To evaluate the LV function of UC patients	Mean age 36.65 ± 13.81 years Female sex (n) 18 Corticosteroids (n, %) 10, 22% Anti-TNF/AZA (n, %) 11, 24% Mayo 2.16 ± 2.13 Mean disease duration 2.77 years	Evaluation with conventional ECHO, TDI, and 2D-STE.	In UC patients, mean GLS and GLSR were significantly lower when compared to healthy individuals (-21.16 ± 2.71 vs -23.36 ± 3.34; p=0.001 and -1.33 ± 0.24 vs -1.43 ± 0.24; p=0.037, respectively).
Curtis et al. (2013) ⁵⁵ USA, January 1998–December 2002 Retrospective observational cohort study	4018 (CD and RA)	1897/NA (INA)	To investigate the association between TNF-α antagonist use and incident HF	569 infliximab exposed and 1328 bio-naïve	Based on abstracted medical records of suspected HF cases.	The relative risk of HF among TNF-α antagonist-treated CD patients was 1.2 (p=NS).
Efe et al. (2016) ⁴² Turkey, April– October 2015 Retrospective observational cohort study	78 (52/26)	22/30 (25/27)	Assess the relation between atrial electromechanical properties and IBD	25 IBD patients in active period and 27 in remission with a disease duration of 69.0 ± 44.1 and 55.9 ± 45.4 months, respectively 16.7% of active patients were on TNF-α inhibitors and 37.5% on glucocorticoids	Measures were performed by transthoracic ECHO and TDI with simultaneous surface ECG recording.	IAEMD (ms) was longer between patients with active IBD: 40.0 ± 9.0 (active), 31.4 ± 9.1 (remission), 22.25 ± 5 (controls), p=0.001. No difference between patients with CD and UC. No significant differences in LVEF, wall dimension, deceleration time, E/E', E wave, and A wave.
Hasbey et al. (2022) ⁵⁶ Ireland, June 2018–June 2019 Prospective observational cohort study	40 (20/20)	20/0 (NA)	Investigate cardiac MRI findings in CD compared with healthy controls	Mean age 40.5 ± 7.7 years 10 men No access to the supplementary document.	Cardiac MRI.	Increased T2-relaxation time was correlated with higher CRP. In patients with CD, there was significantly mildly decreased right ventricular ejection fraction (47 ± 5.8 vs 56.4 ± 7.9, p < 0.01) and no differences in left ventricle assessment.
Kahyaoglu et al. (2019) ⁵⁷ Turkey, July 2018–December 2018 Retrospective observational cohort study	103 (51/52)	0/51 (0/51)	Evaluate LA function by STE and correlate with disease extent	Mean age 40.2 ± 11.2 years 57% male 20 pancolitis, 26 left-sided colitis, and 5 had proctitis. Mean disease duration 6.6 ± 4.8 years	Measures performed by STE.	Lower peak atrial longitudinal strain (%) (32.6 ± 9.3 vs 36.8 ± 10.9, p=0.026) and LV GLS (%) (-20.9 ± 2.7 vs -22.1 ± 1.8, p=0.012) in UC patients than in controls. In pancolitis, the PALS was also significantly lower. Higher E/Em (8.6 ± 1.8 vs 7.1 ± 1.3, p < 0.001), LA volume (36.3 ± 9.3 vs 26.1 ± 6.8, p < 0.001), and LA stiffness index (0.29 ± 0.09 vs 0.19 ± 0.06) in UC vs controls. The difference was also significant between the pancolitis and non-pancolitis groups.

(Continued)

Table 1. (Continued)

Author/country/time period/design	Sample size (IBD patients/controls)	CD/UC patients (active/remission, if applicable)	Study objective	Characteristics (correspondent to IBD patients)	Methods	Main findings
Kivrak et al. (2016) ⁵⁸ Turkey Retrospective observational cohort study	100 (50/50)	50/0 (NA)	To explore the LV functions with 2D-STE in patients with CD	Mean age 41.0 ± 13.9 years 24 male Mean disease duration 3.3 ± 2.4 years Mean Crohn's Disease Activity Index score of 111.6 ± 109.7 Ileal involvement in 18 patients (36%), ileocolonic in 22 patients (44%), and colonic in 10 patients (20%) Half of the patients were treated with anti-TNF drugs and 9 patients underwent surgery due to intestinal complication	Evaluation with 2D-STE.	GLS was significantly lower in CD patients (19.6 ± 3.3 vs 21.2 ± 2.9, <i>p</i> = 0.014). Crohn's Disease Activity Index is inversely correlated with LV GLS (<i>r</i> = -0.703, <i>p</i> < 0.001).
Kristensen et al. (2014) ⁵⁹ Denmark, January 1997–December 2011 Prospective observational cohort study	5,436,647 (23,681/5,412,966)	6322/17,359 (70,581/46,718)	Assess the time to first hospitalization for HF in patients with IBD	Mean age (SD) 38.3 (18.3) years Mean follow-up time 6.4 years 50,221 (42.8%) were in a flare, 20,360 (17.4%) had persistent activity, and 46,718 (39.8%) were in remission	Information collected from existing registries.	In active stages, IBD patients had a 2.5-fold increased risk of first HF hospitalization.
Nar et al. (2016) ⁶⁰ Turkey, October 2014–May 2015 Retrospective observational cohort study	91 (45/46)	0/45 (NA)	To evaluate AEMD using ECHO in patients diagnosed with UC, comparing to healthy controls	Mean age 46.8 ± 13.1 years Disease duration 5.55 ± 4.40 years 31 patients were in acute flare Mean Rchmilewitz Endoscopic Activity Index 3.9 ± 3.5 Mean Mayo Clinical Activity Index 1.6 ± 0.8	Assessment made by using M-mode, 2D, continuous-wave Doppler, pulsed-wave Doppler, and tissue Doppler methods according to the American Society of Echocardiography.	Diastolic parameters: A wave (0.64 ± 0.18 vs 0.56 ± 0.06 m/s, <i>p</i> 0.017), E/A ratio (1.1 ± 0.4 vs 1.3 ± 0.7, <i>p</i> 0.013), E' wave (0.7 ± 0.2 vs 0.8 ± 0.2, <i>p</i> 0.008) IAEMD was prolonged in IBD patients: 26.9 ± 8.3 vs 21.6 ± 7.1 ms, <i>p</i> 0.002 Significant correlation between AEMD and age and duration of illness. No differences in left ventricle systolic parameters.
Prasada et al. (2020) ⁶¹ USA, January 2000–January 2019 Retrospective observational cohort study	37,636 (5078/19,358)	5078 (IBD subtype not mentioned) (NA)	Compare incident HF among several chronic inflammatory diseases, of which IBD and determine risks by severity	Mean age 44.55 years Median follow-up period of 3.6 year	An electronic health records database from a large urban medical system analysis.	There was no significant increase in incident HF in patients with IBD.
Pujades-Rodriguez et al. (2020) ⁶² United Kingdom, 1998–2017 Retrospective observational cohort study	87,794	27,739 (IBD subtype not mentioned) (NA)	To estimate oral glucocorticoid dose and cardiovascular disease risk in people with inflammatory conditions	Median age (IQR) 41.00 (31.00, 55.00) Mean follow-up time (SD) 6.4 years (5.0) Prescribed oral glucocorticoids in last year, <i>n</i> (%) 4583 (16.5)	Assessment of medical records.	There was an increase in hazard of all-cause cardiovascular disease per 5 mg increase of daily dose.

(Continued)

Table 1. (Continued)

Author/country/time period/design	Sample size (IBD patients/controls)	CD/UC patients (active/remission, if applicable)	Study objective	Characteristics (correspondent to IBD patients)	Methods	Main findings
Sari et al. (2020) ⁴³ Turkey, December 2015–October 2018 Prospective observational cohort study	165 (72/93)	27/45 (26/46)	To study the subclinical involvement of cardiac functions in IBD patients according to disease activity using 2D speckle-tracking	Mean age 40.4 ± 13.1 years 48.6% female sex Mean disease duration 8.62 ± 3.58 years Usage of anti-TNF- α /AZA: 15.3% in active patients and 13.04 in remission Usage of steroids: 23.07% vs 10.8%	Conventional and 2D-STE assessment.	IBD patients had lower GLS: -15.47 ± 6.87% vs -19.48 ± 2.16%, $p < 0.001$, with preserved circumferential contractile functions. Signs of LV diastolic dysfunction in IBD patients (E/E' ratio 9.5 ± 2.5 vs 7.2 ± 1.4).
Tomáš et al. (2013) ⁴⁴ Slovakia, January 2007–December 2009 Prospective observational cohort study	31 (21/0)	7/14 (21/0)	To examine the acute and long-term effect of infliximab on the heart morphology and function in patients with chronic inflammatory disorders (RA, AS, CD, and UC).	Mean age of 37.5 ± 9.7 years The mean duration of the disease was 7.1 ± 6.2 years	Assessment of N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP) and 2D and Doppler echocardiogram parameters.	Acute effect of infliximab on NT-proBNP (pg/mL), before and after administration: 81.74 ± 23.14 vs 84.86 ± 20.45, $p = 0.012$ after 6 months and 56.83 ± 17.77 vs 60.48 ± 17.80, $p = 0.0344$ after 12 months Long-term effects of infliximab on NT-proBNP (pg/mL): 88.40 ± 14.09 vs 81.74 ± 23.14 vs 56.83 ± 17.77 at the beginning, 6, and 12 months, respectively No significant changes in the parameters of the left ventricle.
Triantafyllou et al. (2021) ⁴⁵ Greece Prospective observational cohort study	60	45/15 (NA)	To examine and identify the vascular and cardiac impact of local (surgical) and systemic anti-inflammatory treatment	Mean age 40 ± 13 years 47% female sex 4-month follow-up	Laboratory tests, transthoracic ECHO exams, and non-invasive evaluation of the vascular endothelial function.	IBD patients presented with LV diastolic dysfunction and decreased LV deformation index. Anti-inflammatory treatment improves the LV deformation index. Surgical resection had a comparable effect to anti-TNF- α treatment.

AEMD, atrial electromechanical delay; aHR, adjusted hazard ratio; AMI, acute myocardial infarction; AS, ankylosing spondylitis; AZA, azathioprine; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CFR, coronary flow reserve; CI, confidence interval; CV, cardiovascular; 2D-STE, two-dimensional speckle tracking echocardiography; E/A, early to late diastolic transmitral flow; ECG, electrocardiography; ECHO, echocardiography; ESR, erythrocyte sedimentation rate; GLS, global longitudinal strain; GLSR, global longitudinal strain rate; HF, heart failure; IBD, inflammatory bowel disease; IQR, interquartile range; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable; PALS, peak atrial longitudinal strain; RA, rheumatoid arthritis; TDI, tissue Doppler imaging; TNF- α , tumor necrosis factor-alpha; TWAS: Truelove and Witts Severity; UC, ulcerative colitis.

HF was the main direct outcome in four studies^{49,55,59,61}; myocardial infarction in one⁴⁹; mitral valve prolapse in one⁵¹; and pericardial effusion in one.⁵¹

Twelve studies reported echocardiographic evaluation results, one reported cardiac MRI analysis, and one described non-invasive evaluation of the vascular endothelial function.

Four studies met the criteria to analyze E/A^{50,52,53,63} and two for E/e',^{50,63} including in 295 and 144 IBD patients, respectively. Four studies, with a total of 218 IBD patients, were included to evaluate GLS.^{54,57,58,63} LA diameter was analyzed in six studies (340 IBD patients),^{42,50,52,58,60,63} and LA area in two (95 IBD patients).^{54,58}

Electrocardiography was analyzed in three, but only the two that presented results as means and standard deviations were considered for meta-analysis, englobing 97 IBD patients.^{42,60} Five studies reported outcomes based only on medical records revision.^{49,55,59,61,62}

Outcomes from a systematic review

Female patients with IBD have a higher risk of atherosclerotic cardiovascular (CV) disease compared to males and the risk is more pronounced in younger patients, despite the prevalence of traditional CV risk factors being lower.⁴⁹ After adjusting for age, sex, familial coronary disease, diabetes mellitus, hyperlipidemia, and hypertension, IBD (all subtypes) is associated with an increased risk of acute myocardial infarction (adjusted hazard ratio, aHR, 2.82; 95% confidence interval (CI), 1.98–4.04).⁴⁹ Furthermore, in a group of 68 patients with CD and 60 healthy subjects, CD patients had a statistically significant higher prevalence of mitral valvular prolapse and pericardial effusion, the last associated with high disease activity.⁵¹ Vascular dysfunction was also objectified in patients with IBD, which presented with higher aortic stiffness and associated LV systolic and diastolic dysfunction, without known CV risk factors.⁵⁰ Furthermore, a significant impairment in coronary microvascular function in IBD patients was demonstrated which was correlated to disease activity and duration.⁵²

Regarding HF, a study involving 736 IBD patients (339 CD, 397 UC) compared to 1472 matched controls presented a twofold increased incidence of HF in IBD patients after adjusting for

traditional CV risk factors (HR, 2.03; 95% CI, 1.36–3.03), and this risk was higher among UC, females, those with diagnosis after 40 years old, more extensive disease, and systemic steroids users.^{49,62} Besides that, these patients had a higher risk of first HF hospitalization, increasing to 2.5-fold risk in active stages.⁵⁹

In a small study involving 7 patients with CD, and 14 with UC, evaluating the acute and long-term effects of infliximab, there were no significant cardiac changes in 12 months follow-up. Despite that, plasma NT-proBNP mildly but significantly increased immediately after infliximab infusion.⁶⁴ Another study concluded that CD patients on anti-TNF therapy had a relative risk of HF of 1.2, but no statistical significance was reached.⁵⁵

Despite this, conflicting results are present in the literature as in an observation study involving electronic health records of 5078 IBD patients (subtype not mentioned) and there was no significant increase in incident HF in patients with IBD.⁶¹

Echocardiographic parameters evaluating LV global function, such as GLS, show a significantly impaired function in UC and CD patients.^{54,57,58,63} This association was stronger in pancolitis patients and positively correlated to CDAI score.^{57,58} Diastolic dysfunction was consistently reported.^{50,60,63,65} Specific data on systolic parameters are not so widely discussed and Nar et al.,⁶⁰ even outline no differences in these parameters between IBD and healthy patients. Cardiac MRI evaluations also demonstrated a reduction in right ventricular ejection fraction but no differences in LV assessment.⁵⁶

Electrical disturbances were also shown by increased AEMD duration which was correlated with disease duration and severity.^{42,53,60}

Outcomes from meta-analysis

Effect of IBD on echocardiography and electrophysiological parameters

Functional and structural parameters. IBD and LV diastolic dysfunction parameters. There is a significant difference between controls and IBD patients showing a significant reduction in E/A ratio values for the IBD population (Std. MD -0.51, 95% CI -1.00 to -0.02; $I^2 = 87%$), with an overall test effect of $Z = 2.05$ at $p = 0.04$ (Figure 2).

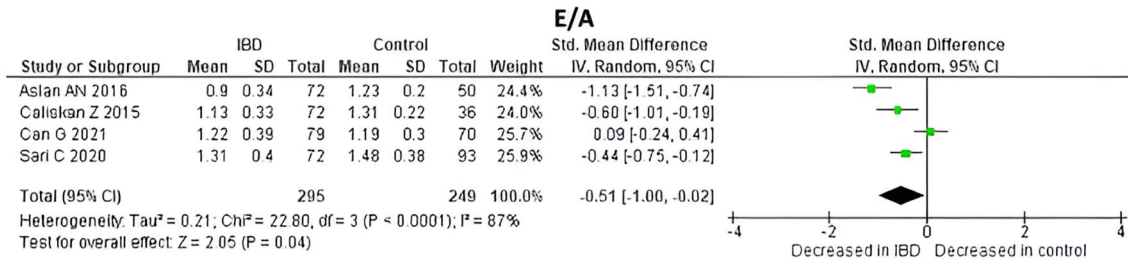


Figure 2. E/A values at IBD patients and controls.
 E/A, early to late diastolic transmitral flow; IBD, inflammatory bowel disease.

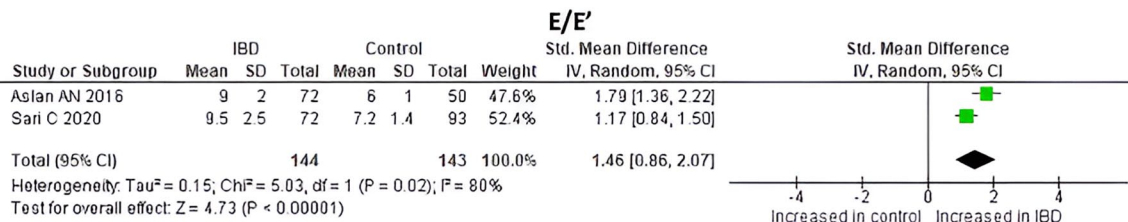


Figure 3. E/E' values at IBD patients and controls.
 IBD, inflammatory bowel disease.

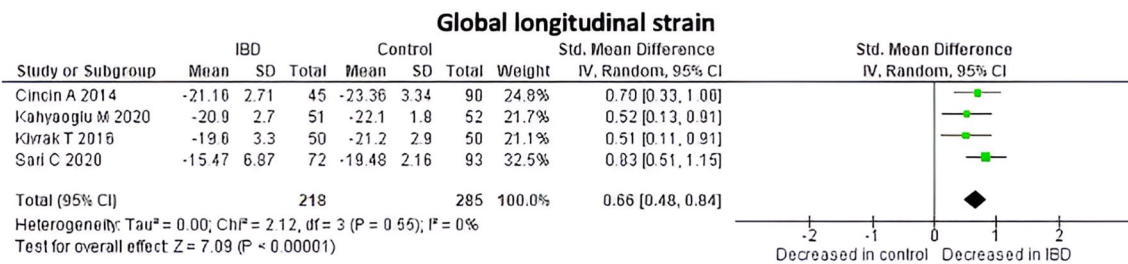


Figure 4. GLS values at IBD patients and controls.
 GLS, global longitudinal strain; IBD, inflammatory bowel disease.

Patients with IBD had significantly higher values of E/e' ratios (Std. MD 1.46, 95% CI 0.86–2.07; $P = 80\%$), with an overall test effect of $Z = 4.73$ at $p < 0.00001$ (Figure 3).

IBD and LV global function. Overall IBD patients had a significant decrease in GLS absolute values (Std. MD 0.66, 95% CI 0.48–0.84; $P = 0\%$), with an overall test effect of $Z = 7.09$ at $p < 0.00001$ (Figure 4) indicating worse GLS values.

IBD and LA dimensions. Overall IBD patients seem to have increased LA diameter, in millimeters (Std. MD 0.06, 95% CI -0.12 to 0.24; $P = 20\%$), with an overall test effect of $Z = 0.68$ at $p = 0.50$. IBD patients had a numerically higher LA area when

compared to healthy controls, but without a statistically significant difference (Std. MD 0.03, 95% CI -0.24 to 0.29; $P = 0\%$; overall test effect of $Z = 0.19$ at $p = 0.85$) (Figures 5 and 6).

Electrical parameters. Inter-atrial electromechanical delay. A significant increase in inter-atrial electromechanical delay (IAEMD) was observed in IBD patients (Std. MD 0.88, 95% CI 0.45–1.31; $P = 42\%$), with an overall test effect of $Z = 4.02$ at $p < 0.0001$ (Figure 7).

Intra-right and left AEMD (IAEMD). IBD patients had prolonged IAEMD either at right or left conduction systems. Std. MD for intra-right AEMD was 0.9, 95% CI 0.57–1.22 with an $P = 0\%$ and

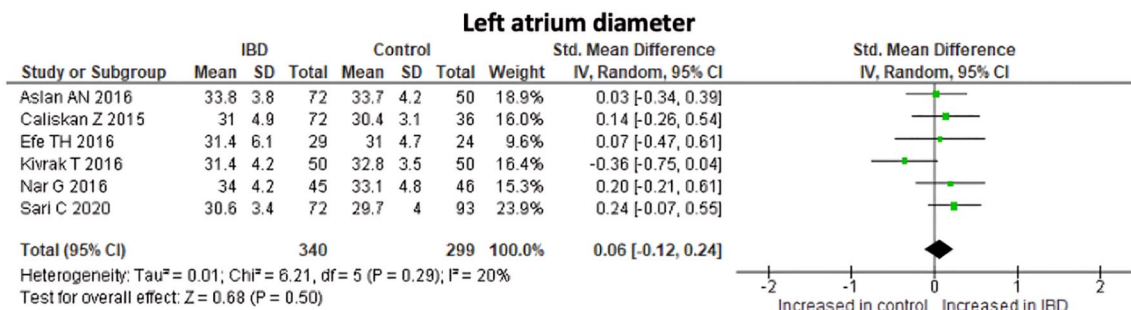


Figure 5. Left atrium diameter at IBD patients and controls. IBD, inflammatory bowel disease.

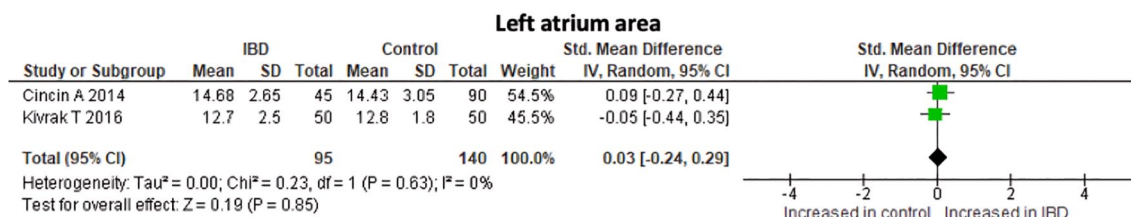


Figure 6. Left atrium area at IBD patients and controls. IBD, inflammatory bowel disease.

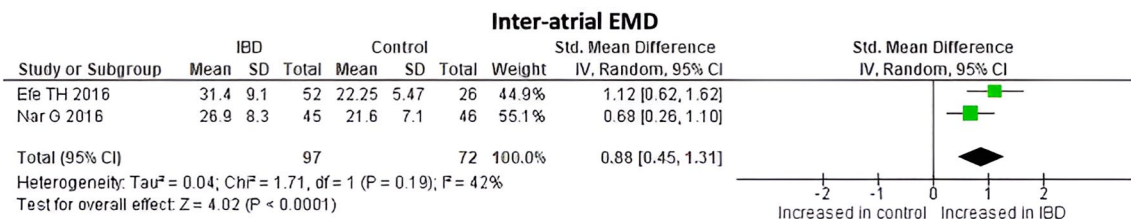


Figure 7. Inter-atrial EMD values at IBD patients and controls. EMD, electromechanical delay; IBD, inflammatory bowel disease.

an overall test effect of $Z=5.42$ at $p<0.00001$ (Figure 8).

A prolonged intra-left AEMD was observed in IBD patients compared to healthy controls but without statistically significant differences (Std. MD 0.33, 95% CI -0.08 to 0.74 ; $I^2=41\%$; with an overall test effect of $Z=1.57$ at $p=0.12$) (Figure 9).

Discussion

This systematic review and meta-analysis examined the relationship between IBD and cardiac function, namely the incidence of HF and echocardiographic changes. The cumulative evidence derived from our study reveals a pattern

of subtle, yet significant, cardiac changes among patients with IBD. We included studies with patients above 16 years to ensure the relevance of our findings to a primarily adult population. Besides that, we did not place any restrictions on the past medical history of the patients involved in these studies as we aimed to include a wide range of patients with diverse health backgrounds, which, in turn, would increase the generalizability of our findings.

Evaluating LV diastolic function and estimation of LV filling pressure is complex, and no single parameter can be utilized to determine such impairment. The most used parameters in clinical practice are E and A wave velocities, E/A ratio, e' velocity, E/e' ratio, E wave deceleration time,

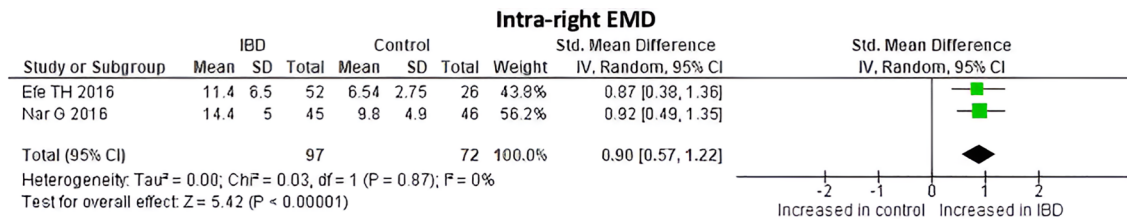


Figure 8. Intra-right EMD values at IBD patients and controls.
EMD, electromechanical delay; IBD, inflammatory bowel disease.

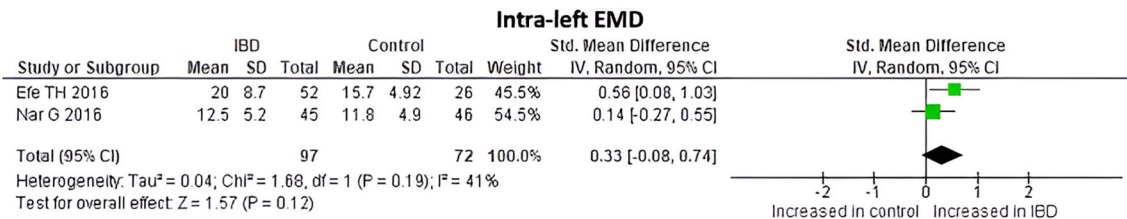


Figure 9. Intra-left EMD values at IBD patients and controls.
EMD, electromechanical delay; IBD, inflammatory bowel disease.

isovolumetric relaxation time (IVRT), left atrium volume, tricuspid regurgitation maximum velocity, and pulmonary venous flow patterns. In our meta-analysis, we included E/A and E/e' ratio parameters due to the availability of the data in the included studies. In a normal heart, ventricular filling occurs in two main stages, the passive LV filling (E wave) and the atrial contraction phase (A wave). The passive LV filling phase represents the major contributor to LV filling, with atrial contraction representing an important but proportionally smaller contribution. This means that in the healthy population, the E wave is larger than the A wave, resulting in an E/A ratio greater than 1. In the elderly, the E wave tends to be smaller than the A wave, and so the E/A ratio tends to be less than 1. The E/e' ratio is an echocardiographic parameter that reflects the relationship between early diastolic filling (E) and myocardial relaxation velocity (e') and is widely used to estimate LV filling pressures in conjunction with the abovementioned parameters. Normal diastolic function is characterized by an E/A ratio >0.8 and a normal E/e' ratio. Impaired relaxation shows an E/A ratio <0.8 and normal E/e'. A pseudonormal pattern occurs when the E/A ratio appears normal but E/e' is elevated, due to a decrease in e' which represents impaired myocardial relaxation and consequently abnormal diastolic function. This represents an intermediate stage of diastolic dysfunction. In included

studies, we observed a trend toward a lower E/A ratio in the IBD population, meeting statistical significance ($p=0.04$). We also observed a trend toward higher values of E/e' ratios ($p<0.00001$), with values in the IBD population of 9.5⁵⁰ and 9.5.⁶³ A significant decrease in the E/A ratio in IBD patients likely reflects early-stage diastolic dysfunction (impaired relaxation). A significant increase in the E/e' ratio in the studied IBD population may indicate impaired relaxation of the left ventricle. Of note, the larger the E wave and the higher the E/e' ratio, the higher LV pressures and worse diastolic function. In the statistical analysis, we obtained high heterogeneity (87% for E/A and 80% for E/e' analysis). This could be explained by differences in the study protocol, population characteristics, or other possible factors that can also influence the results and their interpretation.

Multiple studies demonstrated changes in LV diastolic function in IBD patients compared to healthy non-IBD patients, even in young patients and those without traditional CV risk factors. This was shown through echocardiographic parameters such as reduced E/A ratio, prolonged IVRT and deceleration time (DT), and increased E/e' indicating impaired relaxation and increased filling pressures.^{50,52,57,65} Some evidence of subtle systolic dysfunction in IBD patients was also found when measured by

more sensitive echocardiographic techniques like 2D speckle tracking strain imaging.^{54,57,58,63} Reduced GLS was commonly reported and correlated with disease activity scores in some studies.^{54,58} Though LV dysfunction was subclinical in most patients, even small changes in parameters like GLS are associated with worse outcomes like HF and mortality.^{65,66,67} Although statistically significant differences were observed between groups in these parameters, the data should be interpreted with consideration of multiple parameters. Most of the differences remained within the normal range.

Left atrium dimensions (diameter and area) were not statistically significantly different between the included studies in our meta-analysis. Of note, all mean values were within the normal range. Increased LA dimensions are associated with chronic elevated LV filling pressures and serve as a marker for diastolic dysfunction and atrial remodeling. Nowadays, the most accurate LA dimension parameter measured by echocardiogram is LA volume, acquired by disk summation algorithm. LA volume has a stronger association with CV outcomes. This measurement is also included in diastolic function algorithms. We may hypothesize that LA dilatation could be associated with chronic exposure to inflammation and uncontrolled IBD burden and so may be mitigated by appropriate disease activity control.

In the included studies in the systematic review, we have also explored the impact of vascular changes in IBD patients and its CV consequences. We observed that increased aortic stiffness was demonstrated to be associated with LV diastolic dysfunction, worse CV outcomes, and mortality.⁶⁸ Coronary microvascular dysfunction obtained by echocardiography measures of coronary flow reserve was validated over 30 years ago and is associated with a worse prognosis even in patients with non-obstructive coronary disease.⁶⁹⁻⁷¹ Reduced coronary flow contributes to LV dysfunction and was positively associated with inflammation markers in some studies. These vascular changes may be due to endothelial dysfunction and low-grade inflammation from IBD. This may likely increase the risk for atherogenesis and coronary disease in the long term.⁷²

A few studies demonstrated increased AEMD in IBD patients, indicating impaired atrial conduction and this was also associated with

inflammation.⁴² Given this impaired conduction (prolonged intra- and inter-AEMD), it may indicate underlying electromechanical atrial dysfunction, a known risk factor for AF. Some studies propose that IBD may increase AF risk through inflammatory and structural atrial changes. One study found that IBD-associated inflammation had a stronger effect on AF development, even in younger patients and those without CV risk factors.⁷³

Large cohort studies consistently showed an increased risk of hospitalization for HF in IBD populations compared to the general population. The risk was higher during periods of active inflammation. In some studies, the overall HF risk was higher in UC patients compared to CD. Younger onset IBD and extensive colitis also had higher risks. The studies propose that uncontrolled inflammation is one factor contributing to a higher risk of HF. However, surveillance bias may also play a role.

One intriguing finding from our review was the transient rise in NT-proBNP levels following the administration of infliximab. This could suggest a possible acute deleterious effect of infliximab on cardiac function. Potential explanations range from the drug's cytotoxic effects to induced volume overload. However, this study also found that long-term treatment with TNF-alpha blockers, including infliximab, did not seem to induce a lasting deterioration of cardiac function, hinting at a possible short-term impact rather than a prolonged adverse CV effect. This study, however, had a small sample size. Larger longitudinal studies are needed to clarify the relationship between IBD disease activity, inflammation levels, myocardial stress, and NT-proBNP kinetics. Despite this, anti-TNF therapy was not clearly linked with increased HF risk.

A few studies found that corticosteroid use increased the risk of HF in IBD patients, possibly due to effects on recovery from cardiac injury. Furthermore, some small interventional studies showed improvements in LV function or strain after treating inflammation with immunosuppression, suggesting a beneficial cardiac effect. The use of systemic corticotherapy, due to its mechanism of action, contributes to water and sodium retention, especially when in high doses, which can precipitate HF decompensation in susceptible individuals.^{3,74} Corticosteroid use is also

associated with increased incidence of hypertension and dyslipidemia which are known risk factors for CV disease and specifically HF.^{75,76}

These associations might be explained through the cumulative effect of inflammation, fibrosis, collagen deposition, endothelial dysfunction, toxicity from drug therapy, and malnutrition. There is a potential effect of vitamin deficit, mainly selenium, on cardiac health.

Importantly, these changes are detectable even in the absence of overt cardiac disease, implying that routine cardiac monitoring might be beneficial in this patient population, particularly those with long-standing or severe disease.

Limitations and strengths of the study

Some limitations of our study are the small sample size and observational nature of the studies which can introduce some selection biases. The lack of longitudinal follow-up in some of the included studies limits the ability to draw firm conclusions about the direction of causality and long-term outcomes. Heterogeneity was particularly high in the analysis of E/A and E/e' measurements. The high heterogeneity in E/A meta-analysis ($I^2=87\%$) was not reduced by sensitivity analysis. The ability to thoroughly explore this degree of heterogeneity was limited by the small number of studies included in the pooled analysis. It could be attributed to intra- and inter-study heterogeneity, resulting from differences between patient groups' characteristics. In addition, differences may exist in echocardiographic study protocols between centers as also as distinct echocardiography techniques and modes might have been used. These limitations may reduce the validity of the data. Furthermore, the absence of blinding in certain studies introduces the possibility of measurement bias.

Future studies should aim to investigate whether IBD contributes independently to cardiac dysfunction or acts through interactions with other CV risk factors.

The strengths of our article are the rigorous systematic review methodology, the evaluation of included articles bias using standardized tools, the evaluation of multiple topics on the relation between IBD and cardiac disease, and the

inclusion of several studies with diverse patient populations.

In summary, from the findings of our systematic review and meta-analysis, there is significant evidence to conclude that the IBD population has an increased risk for mostly subclinical LV and atrial dysfunction, vascular changes, arrhythmias, and HF hospitalization. Screening with sensitive imaging like speckle tracking echocardiography could identify early subclinical changes. IBD is in fact a CV risk factor and tight inflammation control may reduce the risk.

Declarations

Ethics approval and consent to participate

This study was a systematic review with meta-analysis in which no human subject or animal was employed.

Consent for publication

Not applicable.

Author contributions

Caroline Almeida Soares: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Visualization; Writing – original draft; Writing – review & editing.

João Gouveia Fiuza: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Visualization; Writing – original draft; Writing – review & editing.

Cláudio André Melo Rodrigues: Methodology; Writing – review & editing.

Nuno Craveiro: Investigation; Writing – review & editing.

Júlio Gil Pereira: Investigation; Writing – review & editing.

Paula Cristina Ribeiro Fernandes Sousa: Methodology; Visualization; Writing – review & editing.

Diana Catarina Pinto Martins: Methodology; Writing – review & editing.

Eugénia Maria Cancela: Methodology; Writing – review & editing.

Maria Paula Ministro dos Santos: Conceptualization; Methodology; Project administration; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Acknowledgements

None.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

M.P.M.d.S. has the following conflicts of interest: Abbvie, Yansen, Pfizer, Tillots, Falk, and Takeda. P.C.R.F.S. served as speaker for Janssen and received Congress support from Janssen, Abbvie, Dr Falk, Norgine, and Pfizer. D.C.P.M. received Congress support from Ferring, Abbvie, Tillots Pharma, Takeda, Pfizer, and Dr Falk. E.M.C. received Congress support from Ferring, Janssen, Tillots Pharma, and Endotécnica. J.G.P. received Congress support from Medtronic and Biotronik. N.C. has the following conflict of interest: Novartis. Received Congress support from Bial. Other authors have nothing to declare.


Availability of data and materials


The original contributions presented in the study are included in the article/Supplemental Material, further inquiries can be directed to the corresponding authors.

ORCID iDs


Caroline Almeida Soares  <https://orcid.org/0009-0005-2994-9054>


João Gouveia Fiuza  <https://orcid.org/0000-0002-8769-4863>


Cláudio André Melo Rodrigues  <https://orcid.org/0000-0002-7997-4638>

Nuno Craveiro  <https://orcid.org/0000-0003-1265-8152>

Júlio Gil Pereira  <https://orcid.org/0000-0003-0277-4512>

Paula Cristina Ribeiro Fernandes Sousa  <https://orcid.org/0000-0002-9009-9635>

Diana Catarina Pinto Martins  <https://orcid.org/0000-0002-9462-1662>

Maria Paula Ministro dos Santos  <https://orcid.org/0000-0003-2439-9522>

Supplemental material

Supplemental material for this article is available online.

References

1. Bunu DM, Timofte CE, Ciocoiu M, et al. Cardiovascular manifestations of inflammatory bowel disease: pathogenesis, diagnosis, and preventive strategies. *Gastroenterol Res Pract* 2019; 2019: 3012509.
2. Chen B, Collen LV, Mowat C, et al. Inflammatory bowel disease and cardiovascular diseases. *Am J Med* 2022; 135(12): 1453–1460.
3. Wu H, Hu T, Hao H, et al. Inflammatory bowel disease and cardiovascular diseases: a concise review. *Eur Heart J Open* 2021; 2(1): oeab029.
4. Kjeldsen J, Rasmussen M, Schaffalitzky de Muckadell OB, et al. Collagen metabolites in the peripheral and splanchnic circulation of patients with Crohn disease. *Scand J Gastroenterol* 2001; 36(11): 1193–1197.
5. Patel RS, Rohit Reddy S, Llukmani A, et al. Cardiovascular manifestations in inflammatory bowel disease: a systematic review of the pathogenesis and management of pericarditis. *Cureus* 2021; 13(3): e14010.
6. Bracamonte-Baran W and Čiháková D. Cardiac autoimmunity: myocarditis. *Adv Exp Med Biol* 2017; 1003: 187–221.
7. Geerling B, Badart-Smook A, Stockbru Ègger R, et al. Comprehensive nutritional status in recently diagnosed patients with inflammatory bowel disease compared with population controls. *Eur J Clin Nutr* 2000; 54(6): 514–521.
8. Sinh P and Cross R. Cardiovascular risk assessment and impact of medications on cardiovascular disease in inflammatory bowel disease. *Inflamm Bowel Dis* 2021; 27(7): 1107–1115.
9. Souverein PC, Berard A, Van Staa TP, et al. Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population based case-control study. *Heart* 2004; 90(8): 859–865.
10. Chung ES, Packer M, Lo KH, et al. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor- α , in patients with moderate-to-severe heart failure: results of the anti-TNF therapy against congestive

- heart failure (ATTACH) trial. *Circulation* 2003; 107(25): 3133–3140.
11. Yang V, Kragstrup TW, McMaster C, et al. Managing cardiovascular and cancer risk associated with JAK inhibitors. *Drug Saf* 2023; 46(11): 1049–1071.
 12. Sandborn WJ, Vermeire S, Peyrin-Biroulet L, et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies. *Lancet* 2023; 401(10383): 1159–1171.
 13. Vermeire S, Chiorean M, Panés J, et al. Long-term safety and efficacy of etrasimod for ulcerative colitis: results from the open-label extension of the OASIS study. *J Crohns Colitis* 2021; 15(6): 950–959.
 14. Schreiber S, Rubin DT, Ng SC, et al. Major adverse cardiovascular events by baseline cardiovascular risk in patients with ulcerative colitis treated with tofacitinib: data from the OCTAVE clinical programme. *J Crohns Colitis* 2023; 17(11): 1761–1770.
 15. Coletta AP, Clark AL, Banarjee P, et al. Clinical trials update: RENEWAL (RENAISSANCE and RECOVER) and ATTACH. *Eur J Heart Fail* 2002; 4(4): 559–561.
 16. Rungoe C, Basit S, Ranthe MF, et al. Risk of ischaemic heart disease in patients with inflammatory bowel disease: a nationwide Danish cohort study. *Gut* 2013; 62(5): 689–694.
 17. DeFonseka AM, Tuskey A, Conaway MR, et al. Antitumor necrosis factor—a therapy is associated with reduced risk of thromboembolic events in hospitalized patients with inflammatory bowel disease. *J Clin Gastroenterol* 2016; 50(7): 578–583.
 18. Kirchgessner J, Nyboe Andersen N, Carrat F, et al. Risk of acute arterial events associated with treatment of inflammatory bowel diseases: nationwide French cohort study. *Gut* 2020; 69(5): 852–858.
 19. Lewis JD, Scott FI, Brensinger CM, et al. Increased mortality rates with prolonged corticosteroid therapy when compared with antitumor necrosis factor- α -directed therapy for inflammatory bowel disease. *Am J Gastroenterol* 2018; 113(3): 405–417.
 20. Tripodi A, Spina L, Pisani LF, et al. Anti-TNF- α treatment reduces the baseline procoagulant imbalance of patients with inflammatory bowel diseases. *Inflamm Bowel Dis* 2021; 27(12): 1901–1908.
 21. Singh S, Iversen AT, Allin KH, et al. Comparative outcomes and safety of vedolizumab vs tumor necrosis factor antagonists for older adults with inflammatory bowel diseases. *JAMA Netw Open* 2022; 5(9): e2234200.
 22. Sandborn WJ, Rutgeerts P, Gasink C, et al. Long-term efficacy and safety of ustekinumab for Crohn's disease through the second year of therapy. *Aliment Pharmacol Ther* 2018; 48(1): 65–77.
 23. Adedokun OJ, Xu Z, Marano C, et al. Ustekinumab pharmacokinetics and exposure response in a phase 3 randomized trial of patients with ulcerative colitis. *Clin Gastroenterol Hepatol* 2020; 18(10): 2244–2255.e9.
 24. Poizeau F, Nowak E, Kerbrat S, et al. Association between early severe cardiovascular events and the initiation of treatment with the anti-interleukin 12/23p40 antibody ustekinumab. *JAMA Dermatol* 2020; 156(11): 1208–1215.
 25. Narula N, Peerani F, Meserve J, et al. Vedolizumab for ulcerative colitis: treatment outcomes from the VICTORY consortium. *Am J Gastroenterol* 2018; 113(9): 1345.
 26. Loftus EV, Feagan BG, Panaccione R, et al. Long-term safety of vedolizumab for inflammatory bowel disease. *Aliment Pharmacol Ther* 2020; 52(8): 1353–1365.
 27. Meserve J, Aniwan S, Koliiani-Pace JL, et al. Retrospective analysis of safety of vedolizumab in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2019; 17(8): 1533–1540.e2.
 28. Dahiya DS, Chandan S, Bapaye J, et al. Safety and effectiveness of vedolizumab in elderly patients with inflammatory bowel disease: a systematic review and meta-analysis. *J Clin Gastroenterol* 2024; 58(4): 378–388.
 29. Mitchell NE, Harrison N, Junga Z, et al. Heart under attack: cardiac manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 2018; 24(11): 2322–2326.
 30. Sleutjes JAM, van der Woude CJ, Verploegh PJP, et al. Cardiovascular risk profiles in patients with inflammatory bowel disease differ from matched controls from the general population. *Eur J Prev Cardiol* 2023; 30(15): 1615–1622.
 31. Kozakova M and Palombo C. Imaging subclinical atherosclerosis in cardiovascular risk stratification. *Eur J Prev Cardiol* 2021; 28(3): 247–249.
 32. Akiya A, Takahashi K, Akimoto S, et al. Novel findings of early cardiac dysfunction in patients with childhood-onset inflammatory bowel disease

- using layer-specific strain analysis. *Inflamm Bowel Dis* 2023; 29(10): 1546–1554.
33. Nagueh SF. Left ventricular diastolic function: understanding pathophysiology, diagnosis, and prognosis with echocardiography. *JACC Cardiovasc Imaging* 2020; 13(1 Pt 2): 228–244.
 34. Henein MY and Lindqvist P. Diastolic function assessment by echocardiography: a practical manual for clinical use and future applications. *Echocardiography* 2020; 37(11): 1908–1918.
 35. Diaz-Navarro RA and Kerkhof PLM. Left ventricular global function index and the impact of its companion metric. *Front Cardiovasc Med* 2021; 8: 695883.
 36. Braunauer K, Dungen HD, Belyavskiy E, et al. Potential usefulness and clinical relevance of a novel left atrial filling index to estimate left ventricular filling pressures in patients with preserved left ventricular ejection fraction. *Eur Heart J Cardiovasc Imaging* 2020; 21(3): 260–269.
 37. Akamatsu K, Ito T, Miyamura M, et al. Usefulness of tissue Doppler-derived atrial electromechanical delay for identifying patients with paroxysmal atrial fibrillation. *Cardiovasc Ultrasound* 2020; 18(1): 22.
 38. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28(1): 1–39.e14.
 39. Deniz A, Sahiner L, Aytemir K, et al. Tissue Doppler echocardiography can be a useful technique to evaluate atrial conduction time. *Cardiol J* 2012; 19(5): 487–493.
 40. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2016; 29(4): 277–314.
 41. Klæboe LG and Edvardsen T. Echocardiographic assessment of left ventricular systolic function. *J Echocardiogr* 2019; 17(1): 10–16.
 42. Efe TH, Cimen T, Ertem AG, et al. Atrial electromechanical properties in inflammatory bowel disease. *Echocardiography* 2016; 33(9): 1309–1316.
 43. Bigeh A, Sanchez A, Maestas C, et al. Inflammatory bowel disease and the risk for cardiovascular disease: does all inflammation lead to heart disease? *Trends Cardiovasc Med* 2020; 30(8): 463–469.
 44. D’Ascenzo F, Bruno F, Iannaccone M, et al. Patients with inflammatory bowel disease are at increased risk of atherothrombotic disease: a systematic review with meta-analysis. *Int J Cardiol* 2023; 378: 96–104.
 45. Sun HH and Tian F. Inflammatory bowel disease and cardiovascular disease incidence and mortality: a meta-analysis. *Eur J Prev Cardiol* 2018; 25(15): 1623–1631.
 46. Shehab M, Alrashed F, Alkazemi A, et al. Impact of biologic therapies and small molecules on the risk of major adverse cardiovascular events in patients with inflammatory bowel diseases: systematic review and meta-analysis of randomized controlled trials. *Expert Rev Gastroenterol Hepatol* 2023; 17(5): 469–477.
 47. Critical Appraisal Skills Programme. CASP Cohort Study Checklist. 2018, <https://casp-uk.net/casp-tools-checklists/> (accessed 7 April 2024).
 48. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327(7414): 557–560.
 49. Aniwan S, Pardi DS, Tremaine WJ, et al. Increased risk of acute myocardial infarction and heart failure in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2018; 16(10): 1607–1615.e1.
 50. Aslan AN, Sari C, Sari SÖ, et al. Association between aortic stiffness and left ventricular function in inflammatory bowel disease. *Cardiol J* 2016; 23(2): 202–210.
 51. Bragagni G, Brogna R, Franceschetti P, et al. Cardiac involvement in Crohn’s disease: echocardiographic study. *J Gastroenterol Hepatol* 2007; 22(1): 18–22.
 52. Caliskan Z, Gokturk HS, Caliskan M, et al. Impaired coronary microvascular and left ventricular diastolic function in patients with inflammatory bowel disease. *Microvasc Res* 2015; 97: 25–30.
 53. Can G, Ekmen N, Can H, et al. Is there any link between atrial arrhythmias and inflammatory bowel disease? *Saudi J Gastroenterol* 2021; 27(5): 289–295.
 54. Cincin A, Sunbul M, Kivrak T, et al. Evaluation of cardiac function by two-dimensional speckle tracking echocardiography in ulcerative colitis patients. *Dig Dis Sci* 2014; 59(12): 3004–3011.
 55. Curtis JR, Kramer JM, Martin C, et al. Heart failure among younger rheumatoid arthritis

- and Crohn's patients exposed to TNF-alpha antagonists. *Rheumatology (Oxford)* 2007; 46(11): 1688–1693.
56. Hasbey I, Ufuk F, Kaya F, et al. Cardiac MRI findings in patients with Crohn's disease. *Ir J Med Sci* 2022; 191(3): 1161–1169.
 57. Kahyaoglu M, Gunay N, Bayam E, et al. Atrial peak longitudinal strain may be predictive of pancolitis in patients with ulcerative colitis. *J Clin Ultrasound* 2020; 48(2): 102–107.
 58. Kivrak T, Sunbul M, Cincin A, et al. Two-dimensional speckle tracking echocardiography is useful in early detection of left ventricular impairment in patients with Crohn's disease. *Eur Rev Med Pharmacol Sci* 2016; 20(15): 3249–3254.
 59. Kristensen SL, Ahlehoff O, Lindhardsen J, et al. Inflammatory bowel disease is associated with an increased risk of hospitalization for heart failure a Danish nationwide cohort study. *Circ Heart Fail* 2014; 7(5): 717–722.
 60. Nar G, Ergul B, Aksan G, et al. Assessment of atrial electromechanical delay and left atrial mechanical functions in patients with ulcerative colitis. *Echocardiography* 2016; 33(7): 970–976.
 61. Prasada S, Rivera A, Nishtala A, et al. Differential associations of chronic inflammatory diseases with incident heart failure. *JACC Heart Fail* 2020; 8(6): 489–498.
 62. Pujades-Rodriguez M, Morgan AW, Cubbon RM, et al. Dose-dependent oral glucocorticoid cardiovascular risks in people with immunemediated inflammatory diseases: a population-based cohort study. *PLoS Med* 2020; 17(12): e1003432.
 63. Sari C, Özer Sari S, Duran Karaduman B, et al. Assessment of left ventricular contractile functions in inflammatory bowel disease according to disease activity. *J Dig Dis* 2020; 21(11): 629–638.
 64. Tomáš L, Lazúrová I, Pundová L, et al. Acute and long-term effect of infliximab on humoral and echocardiographic parameters in patients with chronic inflammatory diseases. *Clin Rheumatol* 2013; 32(1): 61–66.
 65. Triantafyllou C, Nikolaou M, Ikonomidis I, et al. Effects of anti-inflammatory treatment and surgical intervention on endothelial glycocalyx, peripheral and coronary microcirculatory function and myocardial deformation in inflammatory bowel disease patients: a two-arms two-stage clinical trial. *Diagnostics* 2021; 11(6): 993.
 66. Biering-Sørensen T, Biering-Sørensen SR, Olsen FJ, et al. Global longitudinal strain by echocardiography predicts long-term risk of cardiovascular morbidity and mortality in a low-risk general population: The Copenhagen City Heart Study. *Circ Cardiovasc Imaging* 2017; 10(3): e005521.
 67. Chimed S, Stassen J, Galloo X, et al. Prognostic relevance of left ventricular global longitudinal strain in patients with heart failure and reduced ejection fraction. *Am J Cardiol* 2023; 202: 30–40.
 68. Cardoso CRL and Salles GF. Prognostic value of changes in aortic stiffness for cardiovascular outcomes and mortality in resistant hypertension: a cohort study. *Hypertension* 2022; 79(2): 447–456.
 69. Iliceto S, Marangelli V, Memmola C, et al. Transesophageal Doppler echocardiography evaluation of coronary blood flow velocity in baseline conditions and during dipyridamole-induced coronary vasodilation. *Circulation* 1991; 83(1): 61–69.
 70. Civieri G, Montisci R, Kerkhof PLM, et al. Coronary flow velocity reserve by echocardiography: beyond atherosclerotic disease. *Diagnostics (Basel)* 2023; 13(2): 193.
 71. Brainin P, Frestad D and Prescott E. The prognostic value of coronary endothelial and microvascular dysfunction in subjects with normal or non-obstructive coronary artery disease: a systematic review and meta-analysis. *Int J Cardiol* 2018; 254: 1–9.
 72. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol* 2019; 74(10): e177–e232.
 73. Choi YJ, Choi EK, Han K-D, et al. Increased risk of atrial fibrillation in patients with inflammatory bowel disease: a nationwide population-based study. *World J Gastroenterol* 2019; 25(22): 2788–2798.
 74. Pérez-Belmonte LM, Sanz-Cánovas J, Salinas A, et al. Corticosteroid therapy in patients with heart failure hospitalized for COVID-19: a multicenter retrospective study. *Intern Emerg Med* 2021; 16(8): 2301–2305.
 75. Sholter DE and Armstrong PW. Adverse effects of corticosteroids on the cardiovascular system. *Can J Cardiol* 2000; 16(4): 505–511.
 76. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; 42(36): 3599–3726.