Cardiovascular Manifestation of Inflammatory Bowel Disease Patient (Tissue Doppler Echocardiography and Cardiac MRI)

Running Title: Tissue Doppler Echocardiography versus Cardiac MRI in IBD

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Abstract

Background: Inflammatory Bowel Disease (IBD) is distinguished by primarily affecting the gastrointestinal system. Nevertheless, recent findings indicate a substantial correlation between IBD and cardiovascular disease. This study aimed to provide early detection of cardiac manifestations in IBD patients utilizing advanced imaging modalities like cardiac magnetic resonance imaging (CMR)and echocardiography.

Methods: This single-center prospective cross-sectional research was performed on 100 patients diagnosed with IBD with disease flare between December 2021 and December 2022. All enrolled patients were subjected to Doppler echocardiography and CMR with Gadolinium enhancement.

Results: Our patients' mean Ejection Fraction (EF) by echocardiography was 58.66 ± 3.11, while by CMR, it was 52.45 ± 3.45, and the P-value was 0.01. Two patients presented with recent symptoms of acute heart failure. Their echocardiographic and CMR findings displayed dilated Left Ventricular(LV) dimensions with a significantly reduced LV EF of 35%. Four additional patients were presented with recurrent chest pain and dyspnea suggestive of possible myocardial ischemia. Their echocardiogram revealed a slight impairment in left ventricular systolic function, with an average ejection fraction of 51%. Nevertheless, according to CMR, the average EF of the four previous patients was 48%. Two out of the four patients had coronary stenosis, while the other two had either disease-induced or drug-induced systolic dysfunction.

Conclusion: Cardiac MRI may play a role in patients with IBD assessing cardiac affection's etiology, presence, and extent.

Keywords: IBD, Doppler Echocardiograghy, Cardiac MRI.

Introduction:

IBD is well-defined for its predominant gastrointestinal symptoms. Nevertheless, emerging data indicates a significant correlation between IBD and cardiovascular complications (1). While it has been recognized that IBD can lead to venous thrombosis, its contribution to ischemic heart disease, arterial atherosclerosis, and risk of
acute myocardial infarction is just starting to be acknowledged and is now being explored (2).

Cardiac magnetic resonance imaging is mostly utilized to identify considerably reduced ejection fractions (EFs) and abnormalities in wall motion. Contrast enhancement (CE) cardiac MRI is a very sensitive technique that may identify regions of myocardial injury in individuals with acute myocarditis (3). The study aimed to assess cardiovascular alterations in participants with IBD using Doppler echocardiography and cardiac MRI. Additionally, the study attempted to determine the occurrence of myocardial damage in IBD patients experiencing a disease flare. To assess the sensitivity and specificity of echocardiography in detecting heart damage in IBD patients, compared to cardiac MRI.

Methods

This study was conducted in the IBD Outpatient Clinics at Al-Rajhi University Hospital as a cross-sectional study. The study was completed during the timeframe spanning from December 2021 to December 2022. This study adhered to the guidelines of Assiut University's Ethical Committee (IRB No: 17101232). The clinical protocol has been recorded on ClinicalTrials.gov, and the registration number is NCT04656015. Every participant in this study provided written informed consent. We recruited 100 patients, ranging in age from 18 to 65 years, who were diagnosed with inflammatory bowel disease based on comprehensive evaluation including clinical, laboratory, radiographic, endoscopic, and/or histological data (4) and presented with markedly disease flare. Patients with known previous cardiac diseases such as ischemic, valvular, or congenital heart diseases, hemodynamic instability, atrial fibrillation, second-or third-degree heart block, and patients with other general contraindications to magnetic resonance imaging, such as implanted devices such as cardiac pacemaker, automatic implanted cardiac defibrillator were excluded from the study. In addition, cases contraindicated for administering contrast material involving known allergy and kidney impairment (serum creatinine more than 1.5 mg/dl) were also excluded.

All enrolled patients were subjected to Transthoracic Doppler echocardiography and CMR image. Using Simpson's method, Doppler echocardiography was conducted using a Philips HD 11 machine to evaluate left ventricular volumes and ejection fraction (LVEF). Pulsed tissue Doppler was done over the mitral annulus to estimate LV relaxation and diastolic function. Right ventricular dimensions and function were evaluated by Tricuspid annulus plane systolic excursion (TAPSE) and systolic wave velocity of anterior tricuspid annulus (Ś) by pulsed tissue Doppler.

A contrast-enhanced CMR imaging procedure was conducted utilizing a 1.5-Tesla MR system at the MRI Unit of the Radiology Department of Assiut University Hospitals by Philips 1.5 Tesla system Achieva, Medical Systems, The Netherlands). Localizer sequences were captured in three perpendicular planes, followed by typical cardiac 2-, 3-, and 4-chamber views and short axis (SA) cine images using steady-state free precession. Ac 2-, 3-, and 4-chamber views and short axis (SA) cine images in steady state free precession (SSFP).

The images were obtained utilizing an 8-element phased-array cardiac coil (receive only) manufactured by Philips. The acquisition was performed during single breath-holds lasting approximately 9-13 seconds at the end of expiration, with ECG gating. The acquisition parameters for functional Cine pictures were as follows: a repetition time of 2.9 milliseconds, an echo time of 1.4 milliseconds, a flip angle of 60 degrees, a slice thickness of 8 millimeters, a slice number ranging from 9 to 11, a field of view (FOV) of 320 square millimeters, and a matrix size of 160 by 256.

A dose of approximately 0.2 mmol/kg of body weight of a contrast agent was given. Five slices were acquired using a free-breathing technique to obtain real-time

retrospective gated dynamic cine short-axis views. Subsequently, late gadolinium enhancement (LGE) pictures were acquired ten minutes following administering the contrast material utilizing an inversion recovery (IR) sequence (phase-sensitive inversion recovery is the greatest dependable sequence).

Images analysis was done using a specialized cardiac software named extended workspace "EWS"; Nederland BV Best, Netherlands (Philips Medical Systems).

The endo- and epicardial contours of the left ventricle were demarcated at end-diastole and end-systole to measure the dimensions and volumes of the LV, thereby measuring LV systolic function and EF. Utilizing the 17-segment model of the American Heart Association (AHA), segmental functional analysis was also qualitatively evaluated (categorized as normal, hypokinetic, akinetic, or dyskinetic).

Visual evaluation of delayed enhancement segments was employed to distinguish between ischemia and non-ischemic cardiomyopathy. Assessment of Myocardial edema at T2 WI with fat suppression.

Patients with less than 52% left ventricular EF are considered abnormal (5).

Statistical Analysis

The SPSS version 20 software was utilized to analyze the recorded data. The mean ± Standard Deviation (SD) was used to represent quantitative data. The P-value was considered significant if it was less than 0.05, as the confidence level was maintained at 95%.

Results

Baseline information of studied patients (Table 1):

The patients in the study had a mean age of 39.27 years, ranging from 25 to 45 years old. Of the cases examined, 75 (75%) were men. The mean duration of the disease was 4.55 years. The majority (90%) of the patients had ulcerative colitis.

Baseline laboratory data within the examined group (Table 2):

The baseline data of the studied group are summarized in Table 4. Based on colonoscopy, most (88%) patients had mild disease activity, and 12 (12%) had severe active disease.

Comparison between CMR and Doppler echocardiography tissue patients (Table 3):

The mean EF of our patients by echocardiography was 58.66 ± 3.11, while by CMR was 52.45 ± 3.45, and P-value was 0.01. Two patients presented with symptoms of acute heart failure; their echocardiographic findings CMR findings displayed dilated left LV dimensions with a significantly reduced LV EF of 35%. Four additional patients were presented with recurrent chest pain and dyspnea suggestive of possible myocardial ischemia. Their echocardiogram revealed a slight impairment in left ventricular systolic function, with an average ejection fraction of 51%. Nevertheless, according to CMR, the average EF of the four previous patients was 48%. Two out of the four patients had coronary stenosis, while the other two had either disease-induced or drug-induced systolic dysfunction.

Two patients exhibited impaired cardiac relaxation (i.e., diastolic dysfunction grade I) with E/A ratio < 1 and È by pulsed tissue Doppler < 8cm over medial mitral annulus by echocardiography, while CMR diagnosed eight patients. Right ventricular dimensions and function were normal in all patients assessed by echo through TAPSE, Ś by pulsed tissue Doppler, and CMR.

Other data was comparable between both techniques ($p > 0.05$).

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Table 1: Demographic data and clinical characteristics of patients among the studied groups

	N= 100
Age (years)	39.27 ± 6.83
Range	25-45 years
Body mass index (kg/m^2)	26.04 ± 3.96
Sex	
Male	75 (75%)
Female	25 (25%)
Residence	
Rural	70 (70%)
Urban	30 (30%)
Duration (years)	4.55 ± 1.59
Range	2-6
Type of Disease	
Ulcerative colitis	90 (90%)
Crohn's disease	10 (10%)
Therapy	
5-amino salicylates	35 (35%)
Steroid	65 (65%)
Azathioprine	25 (25%)
Biological agents	10 (10%)
Clinical manifestations	
Bloody diarrhea	75 (75%)
Abdominal pain	40 (40%)
Vomiting	25 (25%)
Abdominal distention	20 (20%)
Severe colitis	13 (13%)
Extra intestinal manifestations	
Fatigue	23 (23%)
Arthralgia	17 (17%)
Skin manifestations	10 (10%)
Sclerosing cholangitis	2 (2%)

Data expressed as mean (SD), frequency (percentage)

Table 2:Baseline laboratory data and disease activity in the studied group

	N= 100
Hemoglobin (gm/dl)	11.11 ± 2.34
Mean corpuscular volume (fl)	83.45 ± 12.11
Mean corpuscular hemoglobin (pg)	31.23 ± 7.01
Red cell distribution width (%)	14.44 ± 4.12
Leucocytes (10^3/ul)	8.01 ± 2.11
Platelets (10^3/ul)	312.34 ± 59.98
Urea (mg/dl)	12.45 ± 2.34
Creatinine (mmol/l)	90.44 ± 35.75
Total proteins (mg/dl)	73.43 ± 9.27
Albumin (mg/dl)	32.33 ± 6.61
Alanine transaminase (u/L)	23.34 ± 10.55
Aspartate transaminase (u/L)	25.55 ± 6.78
Bilirubin (mmol/l)	10.10 ± 3.53
1st h erythrocytes sedimentation rate (ml/h)	55.55 ± 5.98
2nd h erythrocytes sedimentation rate (ml/h)	90.34 ± 12.32
C-reactive protein (mg/dl)	26.78 ± 2.11
Disease activity based on colonoscopy.	
Mild activity	12 (12%)
Severe activity	88 (88%)

Data expressed as mean (SD), frequency (percentage)

Table 3:Doppler echocardiography tissue and CMR among the studied patients

	Doppler echocardiography	**CMR**	***P-value***
Ejection fraction (%)	58.66 ± 3.11	52.45 ± 3.45	**0.01**
LVEDD (mm)	4.91 ± 0.73	5.1 ± 0.03	0.45
LVESD (mm)	3.5 ± 0.76	3.80 ± 0.11	0.11
Stroke volume (ml)	51.55 ± 12.45	50.11 ± 2.88	0.34
E-wave/A-wave	1.4 ± 0.20	1.33 ± 0.12	0.17
Mitral deceleration time (s)	0.17 ± 0.05	0.16 ± 0.01	0.56

	Doppler echocardiography	**CMR**	***P-value***
PASP (mmHg)	29.34 ± 2.22	29.01 ± 1.89	0.18
Cardiac output (l/minute)	3.4 ± 0.44	3.0 ± 0.89	0.09
Left ventricle diastolic dysfunction	2 (1%)	7 (7%)	0.07
Segmental wall motion abnormalities	6 (6%)	6 (6%)	---

Data expressed as mean (SD) frequency (percentage). SWMA: segmental wall motion abnormality; PASP: pulmonary artery systolic pressure; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter

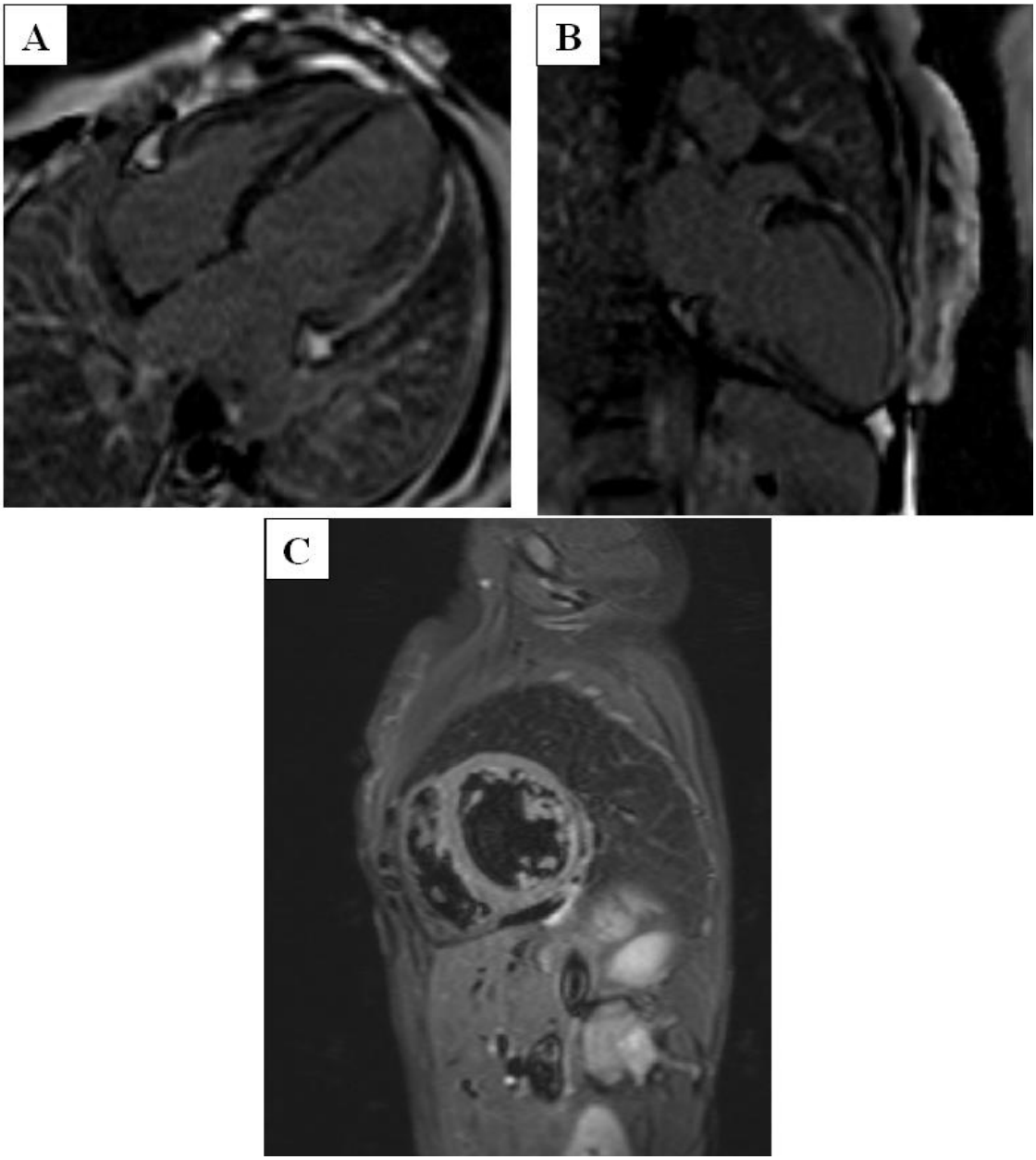

Fig 1: conventional CMR findings in acute myocarditis. (a & b) Four chamber & Two chamber views of late gadolinium enhancement (LGE) revealed epi-myocardial distribution along the lateral wall

(c) short axis view of T2-weighted imaging enables visualization of areas of myocardial oedema in the lateral wall that are concordant with regional late gadolinium enhancement

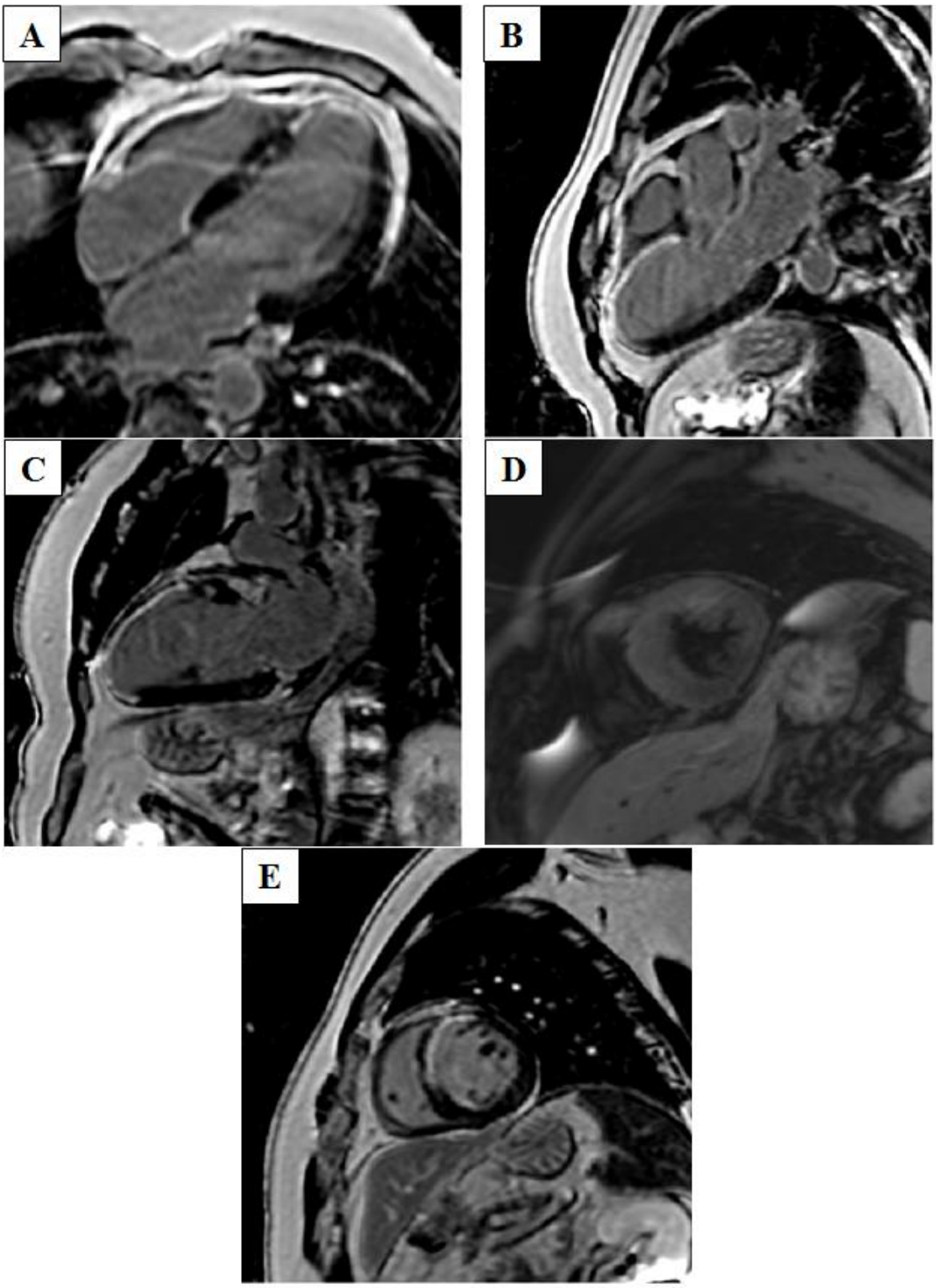

Fig 2: conventional CMR findings in acute ischaemic changes in case of inflammatory bowel disease. (a) Four chambers, (b) Three chambers, (c) Two chambers, (e) short axis views of late gadolinium enhancement (LGE) revealed subendocardial enhancement of anterior &anterio-septal myocardial wall at mid & apical levels as well as an apex. (d) A short axis view of T2-weighted imaging enables visualization of areas of myocardial oedema that denote recent insults.

Discussion

The pathogenesis of cardiovascular diseases has been linked to many pathways that are consistently activated in IBD patients. These factors encompass GIT and systemic inflammation, abnormalities in the gut flora, thrombosis, endothelial dysfunction, dyslipidemia, and the adverse impacts of irritable bowel syndrome medications, mainly corticosteroids and5-aminosalicylic acid(6). The previous report reported a 26% rise in IHD risk in irritable bowel syndrome cases than non-IBD participants (7).

Based on this documented risk of CVD in cases with irritable bowel syndrome, it is recommended for early detection of these cardiovascular abnormalities that allow prompt management. In the recent research, we purposed to evaluate the risk of cardiovascular disease in patients with IBD by echocardiography versus CMR.

In addition, this article discusses the academic debate over the use of CMR and its comparison to echocardiography in identifying cardiac involvement in cases with irritable bowel syndrome. The research reveals interesting data, showing that a considerable proportion of those with IBD may have had subtle cardiac affection despite having normal echocardiography. This phenomenon demands a more profound comprehension of cardiac well-being and its complicated interaction with IBD.

According to our research, CMR was superior to echocardiography in evaluating this. It can precisely estimate the ejection fraction while also detecting diastolic dysfunction in individuals at an early stage. We have found that the mean EF by CMR was statistically significantly lower than that by echocardiography; the P-value was 0.01.

During their hospitalization for treatment of UC flare, two patients exhibited symptoms of acute heart failure. Echocardiographic and CMR examinations revealed dilated left ventricular dimensions and a severely reduced LV EF of 35%. The patients had taken 5-aminosalicylic acid (5 ASA) within the past two weeks. The abrupt cardiac failure is primarily attributed to the consumption of 5 ASA (8) or the emergence of extra-intestinal complications of IBD. Distinguishing between them is challenging and requires an endomyocardial biopsy.

Four additional patients who had been receiving corticosteroid and mesalazine treatment for a lengthy period for their IBD experienced a disease flare, recurring chest pain, and dyspnea. The presence of severe anemia was excluded, and their electrocardiogram (ECG) results were normal. Their echocardiography results indicated a mild decrease in the LV systolic function, with an average ejection fraction of 51%. However, as per CMR, the mean EF of the four preceding patients was 48%. Two of them exhibited substantial multi-vessel coronary stenosis, while the other two displayed either disease-induced or drug-induced systolic dysfunction. Fang et al. concluded a raised risk of premature ischemic heart disease in irritable bowel syndrome cases after performing an updated meta-analysis of multiple cohort studies. Furthermore, many published studies described variable cardiac affection due to IBD, such as pericarditis, myocarditis, heart failure, Takayasu vasculitis, and arrhythmias(9-11). The main pathogenesis of cardiac disease is either drug-related or immune-mediated myocarditis due to being exposed to autoantigens (9).

Souverein et al. revealed that corticosteroids, especially when administered in high dosages, elevate the susceptibility to cardiovascular disease (CVD) in cases with irritable bowel syndrome. Utilizing any oral steroids, whether currently or previously, was linked to a 25% higher likelihood of developing heart failure and cardiovascular disease (CVD), but not stroke. Corticosteroids also exert a substantial impact on conventional CVD risk factors such as hyperlipidemia, hyperglycemia, and hypertension (12).

Two patients in our study experienced impaired cardiac relaxation (i.e., diastolic

dysfunction grade I), as evidenced by an E/A ratio of less than one and a È measurement of less than eight cm/s over the medial mitral annulus using pulsed tissue Doppler echocardiography. In contrast, eight patients were diagnosed with CMR. According to a prior study, it was observed that the E/E' ratio was considerably higher in cases with IBD compared to healthy individuals. This indicates the presence of early diastolic dysfunction (13). Two investigations conducted in 2015 and 2016 have confirmed the presence of decreased coronary microvascular and left ventricular diastolic performance in individuals with IBD (14, 15).

Although individuals with IBD are more prone to developing atherosclerosis due to chronic inflammation and have a higher prevalence of risk factors like overweight and obesity, research on their cardiovascular risk has yielded inconsistent findings. Two retrospective cohort studies, encompassing around 17,000 and 25,000 persons, respectively, have demonstrated that the incidence of myocardial infarction in cases with IBD is comparable to that of the control group(16, 17).

CIMT evaluation is a noninvasive imaging test that has been extensively utilized as a reliable predictor of major cardiovascular events, like stroke, myocardial infarction, or CV death. It is utilized to diagnose subclinical atherosclerosis. Overall, Previous research indicates that patients with IBDs are at an elevated risk of cardiovascular disease (18). Consequently, it is essential to implement strict monitoring of cardiovascular risk factors and subclinical atherosclerosis warning signs. This correlates with previous research that has indicated an elevated risk of major cardiovascular events in patients with inflammatory bowel disease (IBD) (19, 20)

A case report of a patient who experienced recurrent, extensive UC flares; he manifested severe chest pain, increased TnI levels, and MRI changes that were indicative of myocarditis on two separate occasions that were separated by a period of more than one year. Steroid treatment resulted in a faster resolution. The initial episode manifested through a severe pancolitis exacerbation that was initially managed with MSZ. MSZ was discontinued due to its association with myocarditis (21).

A recent study evaluated 20 CD patients and 20 healthy controls with CMR. The authors found decreased ejection fraction among patients with CD. The authors recommended the role of CMR in early detection of chronic systemic inflammation-induced unnoticeable myocardial association with Crohn's disease patients(22).

Even though CMR is superior to echocardiography in evaluating subtle cardiac affection in IBD patients, it may have some disadvantages, including cost, the need for radiologist expertise for good interpretation, and the possibility of inter-observer variability. In addition, it is specific contraindications, such as the presence of metallic implants. So, we could recommend CMR evaluation in only those patients with risk factors for cardiac toxicity, including old age, those with early diagnosis of IBD, and longer duration on aminoacylates. Also, it could be done as complementary to echocardiography to confirm the findings. So, customizing imaging techniques to suit the specific requirements of each patient is of utmost importance. Factors such as patient comfort, contraindications, and specific clinical inquiries influence the selection between cardiac MRI and echocardiography.

The current research has several restrictions, including a relatively small sample size and a lack of long-term patient follow-up. Additionally, the research was performed in a single tertiary center, which may limit the generalizability of the results to the broader population of individuals with IBD who may be treated in other centers. In addition, we included patients experiencing disease exacerbation and patients using medications that may hurt the heart to identify and describe any cardiac involvement in cases with IBD. Our study

did not include a control group of healthy participants to evaluate the differences between cases with IBD and the control participants.

This study was regarded as our region's premiere examination of this particular topic. In addition, all patients in the present study underwent echocardiography and cardiac magnetic resonance imaging.

Conclusion: Cardiac MRI may play a role in patients with IBD to assess the presence, extent, and etiology of cardiac affection, especially in those patients who are suspected to have non-ischemic cardiomyopathy.

References:

1. Bernstein CN, Benchimol EI, Bitton A, et al. The impact of inflammatory bowel disease in Canada 2018: extra-intestinal diseases in IBD. J Can Assoc Gastroenterol. 2019;2(Suppl 1)
2. Zanoli L, Rastelli S, Inserra G, Castellino P. Arterial structure and function in inflammatory bowel disease. World J Gastroenterol. 2015;21(40):11304.
3. Caforio ALP, Malipiero G, Marcolongo R, Iliceto S. Myocarditis: a clinical overview. Curr Cardiol Rep. 2017;19:1-12.
4. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390(10114):2769-78.
5. 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. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-71.
6. Kayahan H, Sari I, Cullu N, et al. Evaluation of early atherosclerosis in patients with inflammatory bowel disease. Dig Dis Sci. 2012;57:2137-43.
7. Bernstein CN, Blanchard JF, Houston DS, et al. The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. Thromb Haemost. 2001;85(3):430-4.
8. Chen J, Duan T, Fang W, et al. Analysis of clinical characteristics of mesalazine-induced cardiotoxicity. Front Pharmacol. 2022;13:970597.
9. 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.
10. Bhardwaj A, Singh A, Midha V, Sood A, Wander GS, Mohan B, Batta A. Cardiovascular implications of inflammatory bowel disease: an updated review. World J Cardiol. 2023;15(11):553.
11. Reddy Meda AK, Fredrick FC, Rathod U, Shah P, Jain R. Cardiovascular Manifestations in Inflammatory Bowel Disease. Curr Cardiol Rev. 2024;20(1):15-20.
12. 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):859-65.
13. Hensel KO, Abellan Schneyder FE, Wilke L, Heusch A, Wirth S, Jenke AC. Speckle tracking stress echocardiography uncovers early subclinical cardiac involvement in pediatric patients with inflammatory bowel diseases. Sci Rep. 2017;7:2966.
14. 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.

15. 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):202-10.
16. Osterman MT, Yang YX, Brensinger C, Forde KA, Lichtenstein GR, Lewis JD. No increased risk of myocardial infarction among patients with ulcerative colitis or Crohn's disease. Clin Gastroenterol Hepatol. 2011;9(10):875-80.
17. Ha C, Magowan S, Accortt NA, Chen J, Stone CD. Risk of arterial thrombotic events in inflammatory bowel disease. Am J Gastroenterol. 2009;104(6):1445-51.
18. Wu GC, Leng RX, Lu Q, Fan YG, Wang DG, Ye DQ. Subclinical atherosclerosis in patients with inflammatory bowel diseases: a systematic review and meta-analysis. Angiology. 2017;68(5):447-61.
19. Singh S, Singh H, Loftus EV Jr, Pardi DS. Risk of cerebrovascular accidents and ischemic heart disease in patients with inflammatory bowel disease: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2014;12(3):382-93.
20. Xiao Z, Pei Z, Yuan M, Li X, Chen S, Xu L. Risk of stroke in patients with inflammatory bowel disease: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis. 2015;24(12):2774-80.
21. Caio G, Lungaro L, Caputo F, et al. Recurrent myocarditis in a patient with active ulcerative colitis: a case report and review of the literature. BMJ Open Gastroenterol. 2021;8(1)
22. Hasbey I, Ufuk F, Kaya F, Celik M. Cardiac MRI findings in patients with Crohn's disease. Ir J Med Sci. 2021;190:833-9.