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Prevalence and independent predictors of Iron deficiency in Yemeni patients with congestive heart failure: a retrospective cross-sectional study

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Heart failure (HF) constitutes a substantial burden on healthcare systems worldwide, contributing to elevated rates of mortality and morbidity. Iron deficiency (ID), both with and without concurrent anemia, has been identified in up to half of all patients with CHF and is associated with an increased risk of HF exacerbations, higher rates of hospitalization, and diminished quality of life. However, data from resource-limited settings remain limited. In this study, we reviewed 108 adult Yemeni patients with HF who also had concomitant ID, defined as serum ferritin concentrations of < 100 ng/mL or 100–299 ng/mL with transferrin saturation < 20%. The prevalence of ID among HF patients was determined, and independent predictors of ID were assessed using univariate and multivariate regression analyses. Anemia was present in 64 (59.3%), ID was observed in 65 (60.2%), and both anemia and ID were concurrently present in 44 (40.7%) patients. The mean ejection fraction among the study cohort was 34.2 ± 6.3%. Multivariate regression analysis identified New York Heart Association class III (OR: 4.46; 95% CI: 1.65–12.90, $p = 0.004$), presence of anemia (OR: 3.95; 95% CI: 1.51–11.23, $p = 0.007$), and an EF < 30% (OR: 9.42; 95% CI: 1.97–54.64, $p = 0.007$) as independent predictors of ID. These findings highlight the potential under-recognition of ID in patients with congestive HF, suggesting the need for routine assessment of iron status in this patient population.

Keywords Heart failure, Ejection Fraction, Iron Deficiency; predictive factors

Heart failure (HF), which affects 1–2% of the general population, is a leading cause of death, morbidity, and poor quality of life[1]. The overall prevalence of HF is estimated to grow drastically on a global level, placing a tremendous burden on patients, their families, and healthcare systems[2]. In addition to increased mortality, HF patients are prone to recurrent hospitalizations, worse functional performance, and poor quality of life[3]. Iron deficiency (ID), with or without concomitant anemia, has been reported extensively in HF patients, affecting up to 50% of stable patients, with a higher prevalence reaching 80% for decompensated patients[4,5]. Notably, ID has been associated with poor functional capacity, increased length of hospitalization, and increased mortality in HF patients[6–8].

The pathogenesis of ID in HF appears to be multifactorial, involving a persistent inflammatory state that leads to iron sequestration and impaired mobilization, along with reduced bowel absorption in advanced stages of HF[9,10]. The critical cellular role of iron in aerobic respiration, particularly in energy-demanding cardiac myocytes, highlights the clinical significance of ID in HF patients[11]. Furthermore, ID has been associated with adverse cardiac remodeling, which is particularly detrimental in cases of iron deficiency anemia (IDA), leading to impaired cardiac function and a worsening of clinical status[12–14].

The European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) recommend baseline anemia evaluations for HF patients in outpatient settings, as well as pre-discharge assessments of iron stores for patients hospitalized due to HF exacerbations[15,16]. The prevalence of ID anemia has been reported to exceed 80% among children and pregnant women in Yemen[17]. However,

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there is limited knowledge regarding the incidence of ID among HF patients in Yemen. The present study aims to evaluate the prevalence and independent predictors of ID in Yemeni patients with HF in a resource-limited setting.

Result
Basic characteristics
The patient demographic characteristics are mentioned in Table 1. The mean age was 60.4 ± 14.9 years (range 25–100 years), and 34 (31.5%) were older than 70. Most patients were male ($n = 77$, 71.3%). Anemia was represented in 64 (59.3%) cases, and ID was represented in 65 (60.2%) cases, while both anemia and ID were seen in 44 (40.7%) cases. The mean EF was $34.2 \pm 6.3\%$, and EF was between 30% and 40% in 62 (57.4%) cases. Current smoking and Khat chewing were seen in 51 (47.2%) and 88 (81.5%) cases, respectively. The comorbidities were hypertension in 63 (58.3%), diabetes in 30 (27.8%), coronary artery disease in 55 (50.9%), chronic renal failure in 15 (13.9%), and liver disease in 4 (370%) of cases. History of cardiac intervention includes PCI in 29 (26.9%) and CABG in 4 (3.7%) cases. New York Heart Association (NYHA) class 3 was represented in 76 (70.4%), while NYHA-2 was represented in 32 (29.6%). Previous blood transfusion was reported in 11 (10.2%) cases.

Variables	Subgroups	Total (108)	Without ID (43)	With ID (65)	OR (95%CI)	p-value
Age (year)	Mean ± SD	60.4 ± 14.9	60.7 ± 13.7	60.3 ± 15.7	1.00 (0.97–1.02)	0.893
Age group	≤ 70 years	74 (68.5)	32 (74.4)	42 (64.6)	References group	0.389
	> 70 years	34 (31.5)	11 (25.6)	23 (35.4)	1.59 (0.69–3.84)	
Gender	Female	31 (28.7)	11 (25.6)	20 (30.8)	References group	0.714
	Male	77 (71.3)	32 (74.4)	45 (69.2)	0.77 (0.32–1.81)	
Current smoking	No	57 (52.8)	21 (48.8)	36 (55.4)	References group	0.638
	Yes	51 (47.2)	22 (51.2)	29 (44.6)	0.77 (0.35–1.67)	
Khat (Catha edulis) chewing	No	20 (18.5)	5 (11.6)	15 (23.1)	References group	0.213
	Yes	88 (81.5)	38 (88.4)	50 (76.9)	0.44 (0.13–1.24)	
Hypertension	No	45 (41.7)	15 (34.9)	30 (46.2)	References group	0.335
	Yes	63 (58.3)	28 (65.1)	35 (53.8)	0.63 (0.28–1.37)	
Diabetes mellitus	No	78 (72.2)	33 (76.7)	45 (69.2)	References group	0.526
	Yes	30 (27.8)	10 (23.3)	20 (30.8)	1.47 (0.62–3.65)	
Coronary artery disease	No	53 (49.1)	18 (41.9)	35 (53.8)	References group	0.306
	Yes	55 (50.9)	25 (58.1)	30 (46.2)	0.62 (0.28–1.34)	
Chronic kidney disease	No	93 (86.1)	39 (90.7)	54 (83.1)	References group	0.403
	Yes	15 (13.9)	4 (9.3)	11 (16.9)	1.99 (0.63–7.59)	
Chronic liver disease	No	104 (96.3)	42 (97.7)	62 (95.4)	References group	0.923
	Yes	4 (3.7)	1 (2.3)	3 (4.6)	2.03 (0.25–41.84)	
Previous blood transfusion	No	97 (89.8)	35 (81.4)	62 (95.4)	References group	**0.043**
	Yes	11 (10.2)	8 (18.6)	3 (4.6)	0.21 (0.04–0.78)	
Cardiac intervention	No	75 (69.4)	25 (58.1)	50 (76.9)	References group	0.114
	PCI	29 (26.9)	16 (37.2)	13 (20.0)	0.41 (0.17–0.97)	
	CABG	4 (3.7)	2 (4.7)	2 (3.1)	0.50 (0.06–4.37)	
Ejection fraction (%)	> 40	23 (21.3)	16 (37.2)	7 (10.8)	References group	**0.001**
	40 − 30	62 (57.4)	23 (53.5)	39 (60.0)	3.88 (1.43–11.42)	
	< 30	23 (21.3)	4 (9.3)	19 (29.2)	10.86 (2.91–49.43)	
Anemia	No	44 (40.7)	23 (53.5)	21 (32.3)	References group	**0.046**
	Yes	64 (59.3)	20 (46.5)	44 (67.7)	2.41 (1.10–5.39)	
NHYA Class	Class2	32 (29.6)	21 (48.8)	11 (16.9)	References group	**0.001**
	Class 3	76 (70.4)	22 (51.2)	54 (83.1)	4.69 (1.98–11.66)	
Duration of illness (months)	< 6 m	33 (30.6)	13 (30.2)	20 (30.8)	References group	1.000
	> 6 m	75 (69.4)	30 (69.8)	45 (69.2)	0.98 (0.42–2.24)	
Previous hospitalization	No	74 (68.5)	29 (67.4)	45 (69.2)	References group	1.000
	Yes	34 (31.5)	14 (32.6)	20 (30.8)	0.92 (0.40–2.13)	

Table 1. Characteristics and factors associated with Iron deficiency in heart failure patients in univariate analysis. ID: Iron deficiency, NYHA: New York Heart Association, PCI: Percutaneous coronary intervention, CABG: coronary artery bypass grafting. Boldface indicates a statistically significant result (P< 0.05).

Variables	N (%)
Hb (g/dL), Mean ± SD	11.9 ± 2.6 (Range 6.7–18.0)
RBC (10^6/μl), Mean ± SD	4.7 ± 1.0 (Range 2.6–9.2)
WBC, Mean ± SD	168.0 ± 1599.2 (Range 2.8–16000.0)
MCV (fL), Mean ± SD	81.3 ± 7.6 (Range 55.7–95.6)
MCH (pg), Mean ± SD	26.5 ± 4.0 (Range 2.2–33.1)
MCHC (g/dl), Mean ± SD	32.7 ± 2.5 (Range 26.6–42.9)
Cholesterol (mg/dl), Mean ± SD	182.0 ± 46.5 (Range 94.0–310.0)
Iron (μg/L), Mean ± SD	78.2 ± 44.1 (Range 2.7–297.0)
Ferritin (μg/L), Mean ± SD	128.5 ± 133.3 (Range 8.8–925.0)
Transferrin saturation, mean (%)	23.7 (Range 17.8–30.9)

Table 2. Laboratory findings of admitted heart failure patients (n = 108). RBC: Red Blood Cell count, Hb: Hemoglobin, Hct: Hematocrit, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration.

Variables	OR (95% CI)	p-value
Previous blood transfusion (No vs. Yes)	0.20 (0.04–0.92)	0.046
Anemia (No vs. Yes)	3.95 (1.51–11.23)	**0.007**
NYHA class (II vs. III)	4.46 (1.65–12.90)	**0.004**
EF (%) (40 − 30% vs. > 40%)	2.88 (0.91–9.74)	0.077
EF (%) (< 30% vs. > 40%)	9.42 (1.97–54.64)	**0.007**

Table 3. Factors associated with Iron deficiency in heart failure patients in regression analysis. EF: Ejection fraction, OR: Odds ratio, CI: Confidence Interval, NYHA: New York Heart Association. Boldface indicates a statistically significant result (P < 0.05).

Laboratory findings

The mean hemoglobulin level was 11.9 ± 2.6 g/dL (Range 6.7–18.0 g/dL). The mean iron level was 78.2 ± 44.1 μg/L (Range 2.7–297 μg/L). The mean ferritin level was 128.5 ± 133.3 μg/L (8.8–925 μg/L). The main laboratory findings are mentioned in Table 2.

Independent predictors of iron deficiency

In univariate analysis, factors including previous blood transfusion ($p = 0.043$), low Ejection fraction (%) ($p = 0.001$), anemia ($p = 0.046$), and NYHA class ($p = 0.001$) were associated with ID and were statistically significant (Table 1). However, in regression analysis, only NYHA class 3 (OR: 4.46; 95% CI: 1.65–12.90, $p = 0.004$), anemia (OR: 3.95; 95 CI%: 1.51–11.23, $p = 0.007$), and EF < 30% (OR: 9.42; 95% CI: 1.97–54.64, $p = 0.007$) were independent predictors of ID and statistically significant (Table 3).

Discussion

The pathogenesis of iron deficiency in HF is complex, involving several cellular alterations that lead to structural changes and functional dysfunction[18]. The poor nutritional status of HF patients, which tends to worsen as HF progresses, along with reduced iron absorption due to gut congestion, contributes to this deficiency[19]. Additionally, HF represents an inflammatory state characterized by elevated levels of proinflammatory cytokines, which can result in iron trapping within the reticuloendothelial system. This has been linked to decreased myocardial iron stores and impaired mitochondrial function in HF patients. Iron deficiency is also associated with reduced exercise endurance, poor quality of life, and increased morbidity and mortality, even without anemia[20,21].

The mean age of our patients was 60.4 ± 14.9 years. While males were disproportionately presented (71.3%), females had a relatively higher prevalence of ID (64.5%) compared to males (58.4%). The difference was not statistically significant; however, it is consistent with prior reports that identified female gender as an independent predictor of ID among HF patients[1,22,23]. This is consistent with national and international reports that highlighted the higher incidence of ID among females in the settings of menstruation, pregnancy, and breastfeeding[5,24]. More evidence suggests different hepcidin expressions, which might influence iron storage and transport[25]. This study found anemia in 64 patients (59.3%), while anemia and ID were present in 44 (40.7%). Similar to our result, Sharma et al. found that 76% of HF patients had ID, with anemia present in 51.3%, and a large percentage of patients (24.7%) had ID without anemia[1]. These findings highlight the possibility of ID even with normal hemoglobin levels and the need for comprehensive iron level assessment[8]. In support of the prior findings, Yeo et al. emphasized assessing functional ID, which correlates with HF symptoms independent of EF[26].

A sub-analysis of our patient cohort demonstrated a higher prevalence of ID among those without concurrent anemia (60.2%). Previous studies have reported varying prevalence rates, ranging from 37 to 75.3%, with lower rates, ranging from 30 to 50%, observed in developed countries[22,27]. Conversely, higher rates have been documented in India. Singh et al. reported that, among 204 HF patients, the prevalence of absolute ID was 83.3%, functional ID 5.3%, and total ID 88.7%.[22] This variation may be attributable to differences in dietary patterns, healthcare access, and treatment practices. Nonetheless, the retrospective design of these studies limits their generalizability and suggests that differences in baseline patient characteristics and comorbid conditions may contribute to these findings.

In this study, worse functional status, as indicated by NYHA $\geq$ class 3, and an EF < 30% were observed in 76 (70.4%) and 23 (21.3%) HF patients with ID, respectively. Furthermore, these factors emerged as independent predictors of ID in HF patients, with statistically significant associations observed in the regression analysis. Our findings align with previous studies, such as those by Yeo et al., who also reported a correlation between worse functional status, low EF, and ID in HF patients[26]. Despite these observations, ID remains prevalent even among patients with HF with preserved EF (21.3%). Unlike individuals with HF and reduced EF, those with preserved EF have not been shown to exhibit downregulation of the myocardial transferrin receptor. In cases of functional ID, activation of the cardiac transferrin receptor in patients with preserved EF suggests the persistence of compensatory mechanisms[28].

Although comorbidities did not differ substantially across the groups we studied, individuals with ID had a higher prevalence of hypertension (35% vs. 28%) and diabetes (20% vs. 10%) compared to those without ID. Both hypertension and diabetes were shown to be independently associated with cardiovascular disease, contributing to microvascular and macrovascular complications through mechanisms involving oxidative stress, inflammation, and endothelial dysfunction[29]. These conditions are also linked to impaired renal function, which can exacerbate anemia and lead to iron sequestration[30]. These factors may also worsen cardiac elasticity and stiffness[28,31]. However, in the absence of anemia, we could not establish a significant role for ID in contributing to left ventricular stiffness. This could be attributed, in part, to the relatively younger patient population and the small sample size in our study.

Few studies have identified ID as an independent predictor of outcomes in HF, and the current evidence remains inconsistent. Observational studies have demonstrated unfavorable outcomes associated with ID, independent of anemia[5,32,33]. However, a recent observational study by Parikh et al. found no association between ID and all-cause or cardiovascular mortality. However, this study did not exclude heart failure with preserved ejection fraction[34]. Data from prospective clinical trials have also failed to demonstrate mortality benefits. For example, the administration of intravenous ferric carboxymaltose showed no cardiovascular mortality benefit[35].

Similarly, the IRONMAN trial reported inconclusive findings regarding the role of iron in improving the quality of life for HF patients, and no benefit was observed in terms of hospitalization reduction[36]. While these studies were conducted among hospitalized patients, who are generally sicker, data from the HEART-FID trial, conducted among ambulatory HF patients, also failed to show a mortality benefit or reduced hospitalization rates[37]. In contrast, a meta-analysis by Ponikowski et al. found that ferric carboxymaltose was associated with reduced hospitalization rates[38]. European guidelines currently recommend frequent assessment of iron status and replenishment therapy to improve the quality of life in HF patients[39,40].

The causes of anemia in HF patients present a clinical challenge. In addition to ID, other potential causes of anemia include chronic inflammation, elevated erythropoietin levels, increased renin-angiotensin-aldosterone system activity, sodium and water retention due to RAAS activation, and the use of medications such as beta-blockers and digoxin. Therefore, heart failure patients with low hemoglobin but without ID should be investigated with the same urgency as those with confirmed ID anemia[41]. In this study, anemia without ID was presented in 20 patients (18.5%). However, due to the study's retrospective nature, data on the primary causes of anemia without ID were not collected, which is attributed to limited documentation or incomplete work-up for such patients. Future prospective studies are needed to explore the underlying causes of anemia without ID.

Clinical implication of iron deficiency

Low iron levels in HF patients lead to diminished exercise tolerance, reduced peak oxygen consumption, and increased ventilatory response. Aerobic capacity and ventilatory response are correlated with TSAT and ferritin. ID, despite its role in reducing exercise capacity and quality of life, has been linked to increased hospitalization and mortality rates, regardless of anemia. Thus, all HF patients should be screened for ID and receive promoted treatment[20,21,41,42]. Other effective measures include mass iron food fortification, targeted iron supplementation programs/interventions, hookworm and malaria management, and public education regarding iron-rich plant and animal-based meals[20].

Study limitation

This single-center study is limited by its reliance on secondary data, which introduces potential variability in data quality due to inconsistencies in documentation, data integrity, and record-keeping practices. Additionally, the retrospective design may introduce inherent biases, and excluding records with incomplete data could lead to selection bias. Furthermore, the relatively small sample size limits the scope for robust statistical analysis. Moreover, the mortality rate, the effects of iron supplementation, and the impact of ID on mortality were not evaluated due to a lack of available data. There were also technical limitations related to the methods used for defining ID and ejection fraction (EF). Left ventricular (LV) systolic dysfunction was assessed using the Teichholtz formula, which has inherent limitations in sensitivity, as the calculation of LV volumes and EF is based on LV dimensions in end-diastole and end-systole, relying on assumptions that may not be reliable in cases of distorted LV geometry. Despite these limitations, this study represents the first report on the prevalence

and impact of ID in heart failure patients in Yemen. Our findings highlight the need for further research to understand better the unique challenges and opportunities for treatment in resource-constrained settings.

Conclusion

Our results found that ID is standard in HF patients, with ejection fraction < 30%, anemia, and NYHA class 3 being independent predictors of ID. Routine assessment of iron status in chronic HF patients and those hospitalized with worsening HF is crucial—even in patients with normal hemoglobin levels. Further studies are warranted to evaluate this population's potential long-term benefits of iron supplementation.

Materials and methods

Study design

A retrospective cross-sectional study consisted of 108 Adult Yemeni patients with heart failure (HF) who had been admitted from Jun 2021 to Sept 2022 to Al-Thorah General Hospital (Ibb University-affiliated Hospital).

Inclusion criteria

Adult patients who were ≥ 18 years of age, clinically diagnosed with HF, and recently admitted for HF progressive symptoms in our hospital were included. Diagnosis of HF was established based on validated clinical criteria from the European Society of Cardiology (ESC), the ESC guidelines for the diagnosis of HF with preserved ejection fraction (HFPEF), and the Framingham criteria[43–45].

Exclusion criteria

Patients with comorbid noncardiac conditions causing ID or anemia, including upper or lower gastrointestinal bleeding, malignancy, end-stage renal failure [estimated glomerular filtration rate (eGFR) < 15 ml/ min)], patients with congenital heart disease, or who would be expected to have a different natural history than a 'typical' HF patient were excluded.

Sample size

The sample size was calculated using G Power version 3 software and selected by setting a 95% confidence interval, 80% power, and 5% alpha error based on a previously reported prevalence and spectrum of ID in HF patients in South Rajasthan by Sharma et al[1].. The sample size was determined to be 90 patients in the first stage. Taking into account 15% attrition, in the end, at least 100 samples were required in this study.

Data collection

Patient demographic characteristics include age (categorized as ≤ 70 years and > 70 years), gender, history of Khat chewing, and current smoking status. Comorbidities include a history of diabetes mellitus, hypertension, chronic renal failure, coronary artery disease, chronic liver disease, duration of illness (categorized as < six months and > six months), previous blood transfusion, New York Heart Association (NYHA) functional class, and history of cardiac intervention such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). The laboratory findings include Red Blood Cell count (RBC), Hemoglobin (HB), Hematocrit (Hct), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Ferritin level, Iron level, triglyceride, and cholesterol levels and transthoracic echocardiography findings (Fig. 1).Ejection Fraction (EF) was obtained via echocardiography, and patients were categorized as > 40%, between 40 and 30%, and < 30%.[22]Iron deficiency was defined as ferritin levels of < 100 µg/L or 100–299 µg/L with transferrin saturation (TSAT) of < 20%. Anemia was defined by the World Health Organization (WHO) as hemoglobin of < 13 g/dL in males and < 12 g/dL in females[33]. Renal dysfunction was diagnosed with a GFR of less than 60 ml/min/1.73 m^2. Diabetes mellitus was defined as glycosylated hemoglobin (A1c) > 6.4% if the patient is actively taking anti-hypoglycemic agent(s) or is on insulin therapy. In addition, the patients' charts were reviewed for any previous diagnosis or treatment for hypertension, chronic obstructive pulmonary disease (COPD), or liver diseases. Functional status was classified according to the NYHA functional classification system (Class I-IV). Data were collected through independent chart reviews. The collected data were thoroughly assessed for accuracy, completeness, and consistency. In cases where contradictory or missing information was identified, the charts were reviewed and reevaluated to ensure data quality.

Study outcome

The primary outcome was to report the prevalence of iron deficiency, and the secondary outcome was to find the independent predictors of ID among admitted patients with heart failure.

Statistical analysis

Before statistical analysis, the normality of the data was assessed using the Shapiro-Wilk test. We utilized mean ± SD representations for numerical data, and for categorical ones, we opted for frequency (percentage) portrayals. We determined statistical variances for numeric data via an independent t-test, and to discern significant associations between qualitative variables, we implemented the chi-square test. In instances where the expected frequency was restricted, Fisher's exact test was deemed appropriate. Logistic regression was performed with variables for any association to obtain odds ratios (OR) and 95% confidence intervals (CI). The logistic regression models included variables with $P \leq 0.05$ in univariable models. Statistical significance was considered with a P-value under 0.05. The data was processed using the software SPSS (IBM SPSS, version 22, Armonk, New York: IBM Corp).
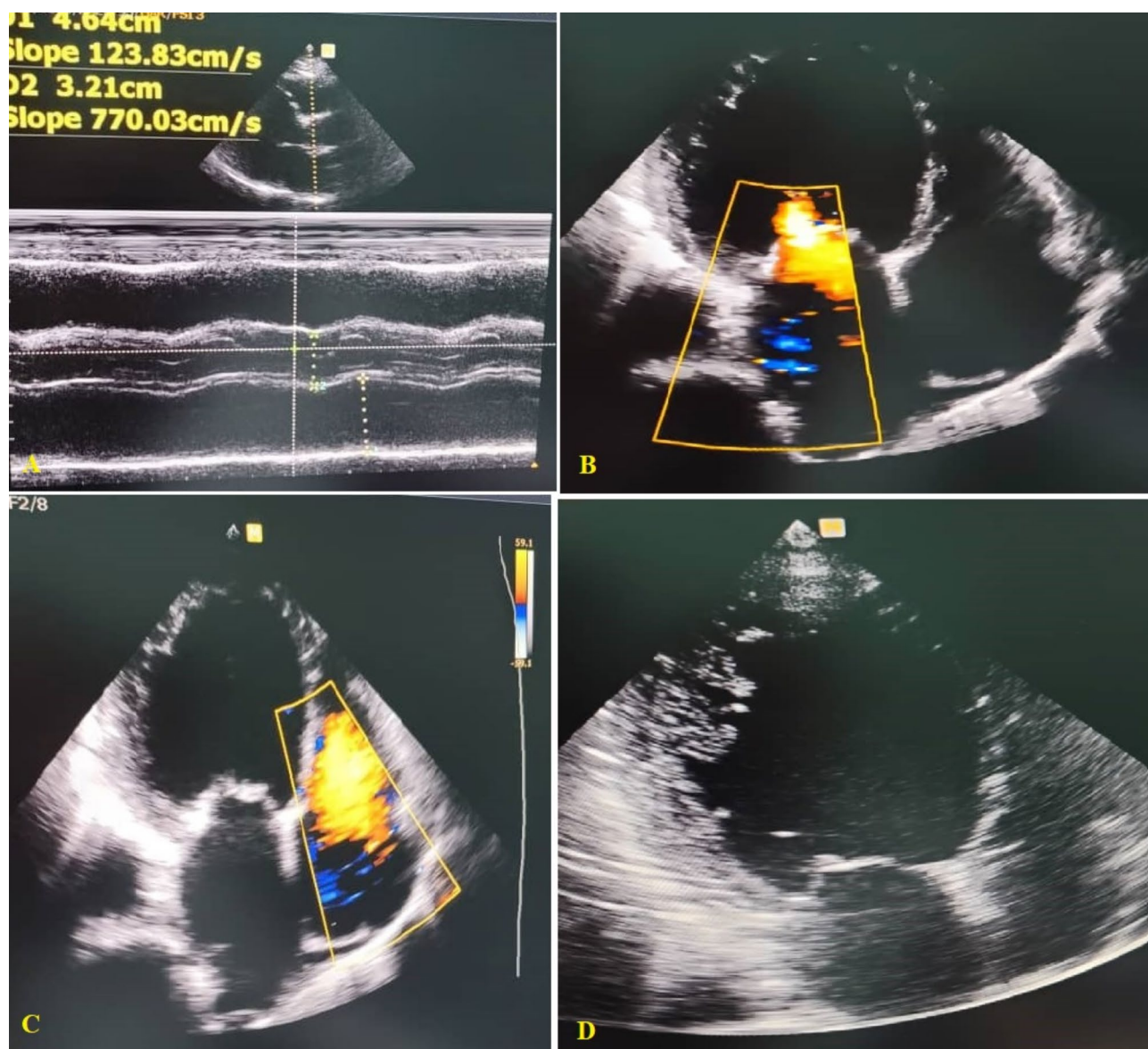
Fig. 1. Echocardiographic aspects of dilated cardiomyopathy. (**A**): Parasternal long-axis view: dilated left atrium and left ventricle in diastole. (**B**): Apical 4 chamber view: dilated left ventricle, dilated left atrium, significant secondary mitral regurgitation flow with Coanda effect. (**C**): Apical 4 chamber view: dilated cardiomyopathy with tricuspid regurgitation flow. (**D**): Apical 4 chamber view: global hypokinesia suggesting ischemic dilated cardiomyopathy.

Ethics statement

Data availability

References

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M.A. and B.A. conceived and wrote the first draft of the manuscript; F.A., K.A., N.A., and M.B. conducted the data analysis; F.A., M.A., B.A., and K.A. provided insights into the study's conceptualization and extensively reviewed all manuscript drafts. All the authors read and provided significant inputs into all manuscript drafts, agreed to be accountable for all aspects of the work, and approved the final version of this manuscript for publication.

Declarations

Competing interests
The authors declare no competing interests.

Ethics declarations
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by Ibb University's Ethics Committee (Code number: IBBUNI.AC.YEM.2023.117).

Consent to participate/Consent to publish
All patients provided written informed consent to be involved in this study.

Additional information
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