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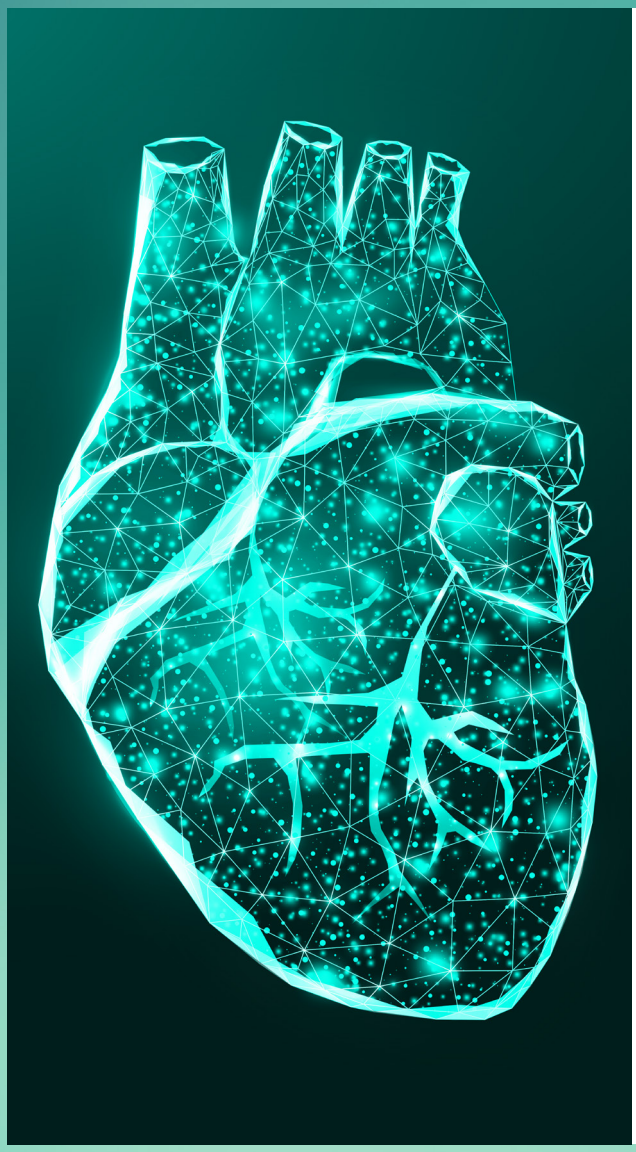

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EDITORIAL COMMENT

DOI: 10.4274/ijca.2025.54227
Int J Cardiovasc Acad 2025;11(2):38-40

Artificial Intelligence and Coronary Artery Calcium Scoring: Enhancing Cardiovascular Risk Assessment

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Coronary artery disease remains one of the leading causes of illness and death worldwide, this highlights the importance of for effective prevention and treatment. Coronary artery calcium (CAC) scoring, obtained through non-contrast computed tomography, measures the amount of calcified plaques in the coronary arteries. The Agatston score is commonly used to quantify this calcification. Higher CAC scores are strongly associated with a greater likelihood of future cardiovascular events. When combined with traditional risk assessment tools such as the Framingham Risk Score, CAC scoring improves the ability to personalize risk predictions.[1,2] However, traditional methods have limitations, including their static nature and potential biases across different ethnic groups.

Recent technological progress has enabled the use of artificial intelligence (AI) to improve CAC scoring. AI algorithms can analyze complex imaging data along with clinical, genetic, and proteomic information to refine cardiovascular risk estimates. Studies have shown that AI-enhanced models outperform conventional scoring methods, offering higher accuracy in predicting major adverse cardiovascular events (Table 1). For example, a 2024 study by the Global CAC Consortium found that incorporating AI increased the model's discrimination ability, with the area under the curve rising from 0.81 to 0.92. AI systems can also identify microcalcifications that may be missed by traditional techniques; these microcalcific foci calcifications are linked to increased plaque vulnerability and

higher risk of adverse outcomes. Importantly, AI maintains consistent accuracy across diverse populations, helping to address disparities in risk assessment.[3,4]

Beyond imaging, AI's capabilities extend to integrating genetic risk scores, proteomic biomarkers, and electronic health records. Polygenic risk scores, which combine multiple genetic

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Table 1: Comparison of traditional and AI-enhanced CAC scoring

Feature	Traditional CAC scoring	AI-enhanced CAC scoring
Data type	CT imaging	CT + Clinical + Genetic + Proteomic data
Analytical method	Static, human interpretation	Dynamic, machine learning algorithms
Scoring method	Agatston score	Deep learning risk algorithms
Predictive accuracy (AUC)	~0.81 (as per text)	~0.92 (as per text)
Microcalcification detection	Limited	Enhanced detection capabilities
Bias across populations	Potential for variability	Demonstrated consistency
Sensitivity in ethnic diversity	Limited	High
Multimodal integration	Primarily imaging-based	Seamless integration with omics and EHR data
Temporal sensitivity	Snapshot in time	Potential for real-time monitoring

AI: Artificial intelligence, CAC: Coronary artery calcium, AUC: Area under the curve, EHR: Electronic health record, CT: Computed tomography

Table 2: Applications and benefits of AI in coronary artery calcium scoring

Application area	Description	Benefits
Automated CAC detection	AI algorithms automatically identify and quantify coronary calcifications	Reduces human error, saves time, ensures reproducibility
Risk reclassification	Reclassifies patients into more accurate risk categories based on integrated data	Improves decision-making, reduces under-/over-treatment
Microcalcification analysis	Detects tiny calcifications often missed by human readers	Enables early detection of high-risk plaque
Personalized risk prediction	Combines imaging, genetic, and clinical data for individualized risk scores	Enhances precision medicine and tailored interventions
Workflow integration	Embeds AI tools in radiology and cardiology software platforms	Improves efficiency, supports point-of-care decisions
Population health management	Assists in identifying high-risk individuals across large datasets	Optimizes screening strategies, reduces healthcare disparities

AI: Artificial intelligence

variants, provide insights into inherited susceptibility to cardiovascular disease. When used alongside CAC data, they can improve prediction accuracy, especially in younger or genetically predisposed individuals.[5] Proteomic markers such as interleukin-6 and GDF-15, associated with inflammation and cardiovascular risk, can also be incorporated into AI-driven models to enhance prognostic precision and guide targeted therapies.[6]

Despite these advances, challenges remain. Ethical issues such as transparency of algorithms, mitigation of biases, and equitable access are critical considerations. It is essential to validate AI tools across diverse populations to prevent the widening of healthcare disparities and to ensure clinical acceptability and user confidence through transparent algorithm design and equitable implementation strategies. Additionally, integrating AI into clinical workflows requires careful planning regarding the timing and frequency of testing, as well as patient selection. Currently, CAC screening is most beneficial for individuals at intermediate risk, but AI's capabilities suggest potential benefits in earlier detection among high-risk groups, such as those with familial hypercholesterolemia, and in reducing unnecessary testing in low-risk populations.

Optimal use of AI-enhanced CAC scoring involves strategic timing typically rescreening every 5 to 7 years for individuals with an initial zero CAC score, and every 3 to 5 years for those with higher scores, unless clinical circumstances change. This approach aims to monitor disease progression effectively while minimizing radiation exposure and healthcare costs. Evidence indicates that AI-based risk assessments can improve clinical decision-making, leading to more personalized interventions such as targeted statin therapy and lifestyle modifications. For instance, AI-generated risk scores have been shown to motivate patients to adhere to healthier behaviors, thereby improving health outcomes beyond traditional risk assessments.[7-9]

Looking ahead, integrating AI-driven CAC scoring with data from wearable devices and real-time biometric monitoring could enable continuous risk assessment and early intervention. Large-scale, longitudinal studies are necessary to validate these approaches and determine their impact on clinical outcomes (Table 2). As AI tools become more embedded in clinical guidelines, their role in reducing healthcare disparities, optimizing preventive strategies, and personalizing patient care will likely expand-provided that ethical and logistical challenges are adequately addressed.[10]

In summary, combining AI with CAC scoring represents a significant advancement in cardiovascular risk assessment. This integration moves beyond traditional static models, offering more accurate, equitable, and personalized approaches to prevention. To realize this potential, rigorous validation, transparent algorithms, and efforts to ensure equal access are essential. As these technologies develop, they hold the promise to enable clinicians to identify at-risk individuals earlier and more precisely, ultimately improving cardiovascular health outcomes worldwide.

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RESEARCH ARTICLE

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The Naples Prognostic Score as a Predictive Tool for Saphenous Vein Graft Disease in Post-coronary Artery Bypass Grafting Patients

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Abstract

Background and Aim: Coronary artery bypass grafting (CABG) remains the gold standard for managing complex coronary artery disease. However, saphenous vein graft disease (SVGD) significantly undermines long-term graft patency, with up to 50% of grafts failing within 10 years. Chronic inflammation, oxidative stress, and nutritional deficiencies are central to SVGD pathophysiology, underscoring the need for comprehensive predictive tools. This study evaluates the Naples Prognostic Score (NPS), a composite index of inflammatory and nutritional markers, as a predictor of SVGD.

Materials and Methods: A retrospective analysis was conducted on 514 patients who underwent CABG and follow-up angiography between 2019 and 2022. Patients were categorized into SVGD (n=252) and the control (n=197) groups based on significant stenosis (≥50%) in at least one saphenous vein graft. NPS was calculated using albumin levels, lymphocyte-monocyte ratio, neutrophil-lymphocyte ratio, and cholesterol parameters. Logistic regression and receiver operating characteristic (ROC) curve analyses were performed to evaluate NPS as an independent predictor of SVGD.

Results: The SVGD group demonstrated significantly higher rates of diabetes (59.4% vs. 49.2%, p=0.033), smoking (41.2% vs. 29.3%, p=0.011), and chronic kidney disease (27% vs. 17.8%, p=0.021). NPS stratification revealed a higher prevalence of high-risk patients (NPS Group 3: 42.5% vs. 29.6%; p=0.052) in the SVGD cohort. Multivariate regression identified smoking [Odds ratios (OR)=3.02; p=0.001], graft age (OR=1.07; p=0.011), albumin levels (OR=0.91; p<0.001), and NPS (OR=1.27; p=0.023) as independent predictors of SVGD. ROC analysis demonstrated strong predictive accuracy for NPS, supporting its clinical applicability.

Conclusion: NPS is a robust, independent predictor of SVGD, integrating systemic inflammatory and nutritional parameters to enhance risk stratification. Its adoption in clinical workflows may guide targeted therapeutic interventions and improve graft patency outcomes. Further prospective studies are warranted to validate its utility across diverse populations and optimize long-term CABG success.

Keywords: Coronary artery bypass grafting (CABG), saphenous vein graft disease (SVGD), Naples prognostic score (NPS), inflammation

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INTRODUCTION

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality worldwide. Coronary artery bypass grafting (CABG) is the gold standard for the management of complex CAD, particularly in patients with multivessel disease or left main coronary artery stenosis. Despite the success of CABG, saphenous vein grafts (SVGs), which are commonly used as conduits, demonstrate high rates of disease and failure over time. Studies indicate that SVG patency decreases by 3-12% in the first postoperative months and up to 50% within 10 years due to severe stenosis or occlusion.[1]

The pathophysiology of saphenous vein graft disease (SVGD) is multifactorial, encompassing thrombotic occlusion, intimal hyperplasia, and accelerated atherosclerosis.[2] Early failure, often within the first month, is primarily attributed to thrombosis, while intermediate failure results from intimal hyperplasia compromising luminal flow dynamics. Long-term occlusion is frequently driven by progressive atherosclerosis within the graft. Chronic inflammation is a key contributor to these processes, with endothelial dysfunction, oxidative stress, and the release of pro-inflammatory cytokines exacerbating graft deterioration.[2,3]

Established risk factors for SVGD include smoking, diabetes mellitus, hypertension, and dyslipidemia.[2,4] These factors enhance inflammation and oxidative stress, further impairing endothelial function and accelerating disease progression. Efforts to mitigate SVGD involve both surgical and medical strategies, including optimal conduit selection, surgical technique improvements, anti-thrombotic therapy, and statin use. Lifestyle modifications, such as smoking cessation and dietary changes, also play a critical role.[2,5]

In this study, we evaluate the Naples Prognostic Score (NPS) as a potential tool for predicting SVGD. NPS integrates inflammatory and nutritional status markers, offering a holistic view of the underlying pathophysiology. This study explores whether NPS could be an effective predictor of SVGD and a practical tool in clinical decision-making.

METHODS

This retrospective study analyzed data from 514 patients who underwent CABG and subsequent coronary angiography at two centers between 2019 and 2022. Patients were categorized into two groups: those with significant stenosis (≥50%) in at least one SVG beyond the anastomotic site (SVGD group) and those without significant stenosis (control group).

Ethics approval for the study was granted by Health Sciences University Türkiye, Hamidiye Scientific Research Ethics Board on February 24, 2023, ethics approval no.: 2023/4-4/5.

Patients with a minimum of one year of follow-up post-CABG were included. Patients with acute coronary syndrome, active cancer, decompensated heart failure, rheumatological diseases, or a history of pulmonary embolism were excluded from the study.

Demographic data, medical history, and laboratory parameters were retrieved from hospital records. NPS was calculated using parameters outlined in Table 1, including albumin levels, lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR), and cholesterol levels.

Statistical Analysis

Were performed using SPSS version 27.0. Normality was assessed using histograms and the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR) based on distribution. Group comparisons employed independent t-tests or Mann-Whitney U tests for continuous data and chi-square tests for categorical variables. Receiver operating characteristic curves determined the sensitivity and specificity of predictors. Variables with $p<0.2$ in univariate analyses were included in multivariate logistic regression, with results expressed as Odds ratio (OR) and 95% confidence intervals. Statistical significance was defined as $p<0.05$.

RESULTS

A total of 514 patients were included in this study, providing a robust dataset for analysis. The demographic and clinical data are summarized comprehensively in Table 2. Of the study population, the SVGD group comprised 252 patients, while the control group included 197 individuals without significant SVGD.

Key differences between the groups were observed in the prevalence of comorbidities and lifestyle factors. Diabetes mellitus was significantly more prevalent in the SVGD group (59.4%) compared to the control group (49.2%; $p=0.033$).

Table 1. Calculation of Naples prognostic score

Variables	Cut-off value	Points	NPS group
Serum albumin (mg/dL)	≥4	0	Group 1: 0 point
	<4	1	Group 2: 1 or 2 points
Total cholesterol (mg/dL)	>180	0	Group 3: 3 or 4 points
	≤180	1	
NLR	≤2.96	0	
	>2.96	1	
LMR	>4.44	0	
	≤4.44	1	

LMR: Lymphocyte monocyte ratio, NLR: Neutrophil lymphocyte ratio, NPS: Naples prognostic score

Smoking rates were also notably higher in the SVGD group at 41.2% compared to 29.3% in the control group (p=0.011). Chronic kidney disease was present in 27% of SVGD patients, compared to 17.8% in the control group (p=0.021). There were no significant differences between groups in terms of hypertension, peripheral arterial disease, or cerebrovascular accident prevalence.

Analysis of medication usage revealed distinct patterns. Statin therapy was more common among SVGD patients (67.1%) compared to the control group (55.8%; p=0.015). Similarly, spironolactone use was higher in the SVGD group (19.4%) versus the control group (10.2%, p=0.007). Angiotensin converting enzyme inhibitors were used by 66.3% of the SVGD group compared to 53.3% in the control group (p=0.005). The use of beta blockers, calcium channel blockers, and diuretics showed varying degrees of statistical difference, with diuretic use significantly higher in the SVGD group (21% vs. 13.7%; p=0.044).

Laboratory markers provided additional distinctions. Table 3 summarizes the laboratory findings of the groups. The LMR was significantly lower in the SVGD group (median: 0.8286; p=0.002). However, no significant differences were noted for the NLR between the groups (p=0.737). Total cholesterol, high density lipoprotein, low density lipoprotein, and triglyceride levels showed no statistically significant differences, suggesting lipid profiles were similar across groups.

The median age of SVGs was higher in the SVGD group (8 years; IQR: 4-13) compared to the control group (5 years; IQR: 4-10; p=0.005). The number of grafts was also greater in the SVGD group, with a median of 2 grafts (IQR: 2-3) compared to the control group, which had a median of 2 grafts (IQR: 1-2) (p<0.001).

Table 4 demonstrates the number of grafts to each coronary artery. The patients without a SVG implant to the left anterior descending artery had left internal mammary artery anastomoses instead. Table 4 also demonstrates the diseased grafts and the coronary arteries to which they are anastomosed.

When stratified by NPS, the distribution differed significantly. The SVGD group had a higher proportion of patients in Naples group 3 (42.5%) compared to the control group (29.6%; p=0.052).

Results of the regression analyses were listed in Table 5. Univariate regression analysis identified several predictors of

Table 2. Demographic and clinical data of the study population

	SVGD (252)	Control group[a] (197)	*P*-value
Male gender, n (%)	213 (84.5%)	167 (84.8%)	0.942
Age, years (mean ± SD)*	68 (62-75)	68 (62-75)	0.228
Hypertension, n (%)	218 (86.5%)	162 (82.2%)	0.213
Diabetes mellitus, n (%)	149 (59.4%)	97 (49.2%)	0.033
Hyperlipidemia, n (%)	174 (69.3%)	125 (63.5%)	0.190
Previous percutaneous treatment of coronary atherosclerotic disease	36 (14.2%)	26 (13.1%)	0.740
Peripheral arterial disease, n (%)	45 (17.9%)	27 (13.7%)	0.234
Chronic kidney disease, n (%)	68 (27%)	35 (17.8%)	0.021
Cerebrovascular accident, n (%)	24 (9.5%)	14 (7.1%)	0.361
Smoking, n (%)	96 (41.2%)	55 (29.3%)	0.011
Medical treatment, n (%)			
Anti-aggregant	232 (92.1%)	182 (92.4%)	0.899
Anti-coagulant	33 (13.1%)	20 (10.2%)	0.338
Beta blocker	203 (80.6%)	152 (77.2%)	0.380
ACE/ARB	167 (66.3%)	105 (53.3%)	0.005
Spironolactone	49 (19.4%)	20 (10.2%)	0.007
Statin	169 (67.1%)	110 (55.8%)	0.015
Calcium channel blocker	61 (24.2%)	43 (21.8%)	0.553
Alpha blocker	12 (4.8%)	9 (4.6%)	0.923
Diuretics	53 (21%)	27 (13.7%)	0.044

*Chi-square test was used for parameters with parametric distribution and Mann-Whitney U test was used for parameters non-parametric distributions

[a]Patients with patent saphenous vein grafts without disease.

ACE/ARB: Angiotensin converting enzyme/angiotensin receptor blocker, SVGD: Saphenous vein graft disease, SD: Standard deviation

Table 3. Laboratory parameters and inflammatory indices			
	SVGD (252)	**Control group (197)**	***P*-value**
Age of saphenous vein graft (median, IQR)	8 (4-13)	5 (4-10)	**0.005**
Saphenous graft (median, IQR)	2 (2-3)	2 (1-2)	**<0.001**
Hemoglobin, mg/dL (median, IQR)	13 (11.5-14.7)	13.6 (12-14.9)	0.077
WBC, x 1000 µL (median, IQR)	7.8 (6.6-9.5)	7.6 (6.3-9)	0.805
Platelet, x 1000 µL (median, IQR)	217 (176-265)	218 (179-253)	0.675
Total cholesterol, mg/dL (median, IQR)	165 (140-199)	176 (140-202)	0.382
LDL, mg/dL (median, IQR)	94 (75-120)	101 (75-127)	0.536
HDL, mg/dL (median, IQR)	42 (35-49)	42 (37-50)	0.440
Triglyceride mg/dL (median, IQR)	132 (92-198)	136 (96-175)	0.984
Albumin g/L (median, IQR)	40.8 (37-44)	41 (35-44)	0.264
Lymphocyte-monocyte ratio (median, IQR)	3.4 (2.26-4.6)	3.87 (2.77-5.2)	**0.006**
Neutrophil-lymphocyte ratio (median, IQR)	2.42 (1.9-3.5)	2.4 (1.8-3.3)	0.737
Triglyceride/HDL (median, IQR)	3.1 (2.1-5)	3.3 (2-4.7)	0.789
SII index (median, IQR)	524 (355-765)	492 (365-764)	0.452
Naples group, n (%)			0.052
Group 1	28 (19.2%)	27 (23.5%)	
Group 2	56 (38.4%)	54 (47%)	
Group 3	62 (42.5%)	34 (29.6%)	
Naples score, n (%)	2 (1-3)	2 (1-3)	**0.020**

HDL: High density lipoprotein, LDL: Low density lipoprotein, SII: Systemic inflammation index, SVGD: Saphenous vein disease, WBC: White blood cell, IQR: Interquartile range

Table 4. Distribution of saphenous grafts		
Distribution of saphenous grafts	**SVGD (n=252)**	**Control (n=197)**
LAD	121 (48.4%)	109 (55.3%)
CX	103 (40.8%)	127 (64.4%)
RCA	105 (41.6%)	104 (52.7%)
SVGD distribution		
LAD	113 (44.8%)	
CX	87 (34.5%)	
RCA	95 (37.6%)	

LAD: Left anterior descending artery, CX: Left circumflex artery, RCA: Right coronary artery, SVGD: Saphenous vein graft disease

SVGD, including diabetes mellitus [OR=1.5060; p=0.0329], chronic kidney disease (OR=1.7106; p=0.0219), and smoking (OR=1.6945; p=0.0114). In multivariate regression, key independent predictors were identified: Smoking (OR=3.0163; p=0.0013), Age of the saphenous vein graft (OR=1.0656; p=0.0111), albumin levels (OR=0.9143; p<0.0001) NPS (OR=1.2733; p=0.0228)

DISCUSSION

This study highlights the NPS as a robust independent predictor of SVGD, showcasing its relevance in clinical settings where long-term graft patency is critical. NPS, through its unique integration of inflammatory and nutritional biomarkers, offers a nuanced understanding of the systemic factors that drive graft failure. By combining parameters such as albumin levels, LMR, NLR, and cholesterol levels, the score provides a holistic snapshot of a patient's physiological state, which is directly relevant to graft health.[6,7]

The inclusion of inflammation as a cornerstone in NPS's design reflects the critical role of systemic inflammatory processes in the pathophysiology of SVGD.[2,4] Inflammation contributes to endothelial dysfunction, intimal hyperplasia, and accelerated atherosclerosis, all of which compromise graft integrity.[2,5] Moreover, the nutritional markers embedded within the NPS framework, such as albumin levels, underscore the interplay between systemic health and localized vascular responses.

This comprehensive approach makes NPS an invaluable tool in the identification of patients at higher risk for SVGD. The ability of NPS to stratify patients based on both inflammatory burden and nutritional deficits allows clinicians to tailor postoperative management strategies. For example, patients with elevated NPS values may benefit from more aggressive anti-inflammatory therapies, nutritional supplementation, or intensified monitoring protocols. Beyond its predictive capacity, NPS serves as a potential guide for optimizing therapeutic interventions and improving clinical outcomes.

The versatility of NPS is further demonstrated by its applicability across diverse patient populations. While this study primarily

Table 5. Regression analyses

	Univariate regression			Multivariate regression		
	OR	**%95 CI**	**P-value**	**OR**	**%95 CI**	***P*-value**
Diabetes mellitus	1.5060	1.0339-2.1936	**0.0329**			
Chronic kidney disease	1.7106	1.0807-2.7074	**0.0219**			
Smoking	1.6945	1.1264-2.5492	**0.0114**	3.0163	1.5385-5.9135	**0.0013**
ACE/ARB	1.7215	1.1739-2.5243	**0.0054**			
Spironolactone	2.1362	1.2229-3.7315	**0.0076**			
Statin	1.6104	1.0960-2.3663	**0.0152**			
Age of saphenous vein graft (mean ± SD)	1.0454	1.0139-1.0778	**0.0044**	1.0656	1.0146-1.1191	**0.0111**
Saphenous graft (mean ± SD)	1.5343	1.322-2.3643	**0.0122**			
Albumin g/L (median, IQR)	0.9239	0.9041-0.9441	**<0.0001**	0.9143	0.8913-0.9379	**<0.0001**
Lymphocyte-monocyte ratio (median, IQR)	0.8286	0.7356-0.9333	**0.0020**			
Naples group, n (%)	1.2925	0.9389-1.7792	**0.1156**	0.3604	0.1396-0.9303	**0.0349**
Naples score, n (%)	1.2733	1.0342-1.5677	**0.0228**			

CI: Confidence interval, OR: Odds ratio, ACE/ARB: Angiotensin converting enzyme/angiotensin receptor blocker, SD: Standard deviation, LMR: Lymphocyte-monocyte ratio

evaluates its role in SVGD, the broader implications of NPS in cardiovascular and systemic disease management suggest that it could be integrated into routine clinical workflows. The predictive power of NPS, validated in this and other studies, supports its use not only as a risk stratification tool but also as a marker for treatment efficacy in managing graft health.

Inflammatory processes play a pivotal role in graft disease, particularly through mechanisms such as intimal hyperplasia and atherosclerosis. Low albumin levels, a component of NPS, are associated with heightened inflammatory states and poor clinical outcomes. Our findings align with prior research demonstrating the negative prognostic implications of hypoalbuminemia in cardiovascular disease.[7,8]

Reduced LMR in the SVGD group reflects an imbalance between anti-inflammatory lymphocytes and pro-inflammatory monocytes,[9] underscoring the systemic inflammatory milieu associated with graft failure. Similar trends have been observed in other cardiovascular and vascular pathologies, suggesting LMR's utility as a prognostic marker.[10]

Smoking emerged as a strong independent predictor of SVGD, consistent with its established role in endothelial dysfunction, oxidative stress, and systemic inflammation. Smoking cessation remains a critical component of postoperative management to improve graft patency.

Graft age was another significant determinant, with older grafts showing increased vulnerability to intimal hyperplasia and atherosclerosis. This finding underscores the importance of optimizing graft selection and surgical techniques to enhance long-term outcomes. Arterial grafts, known for superior patency rates, should be prioritized where feasible.

Diabetes mellitus and chronic kidney disease further exacerbate SVGD risk by promoting systemic inflammation and endothelial dysfunction. Enhanced surveillance and targeted interventions for these high-risk populations are imperative.

NPS offers a novel approach to risk stratification, combining multiple inflammatory and nutritional markers.[11,12] Its predictive value in SVGD aligns with prior evidence supporting its utility in various clinical settings. Future studies should explore its application in larger, diverse populations and compare its performance to other prognostic tools.

Beyond confirming the predictive validity of NPS, prospective studies should investigate its role in guiding therapeutic strategies. For instance, higher-risk individuals identified via NPS may benefit from intensified medical therapy or closer surveillance. Additionally, the integration of advanced biomarkers with NPS could enhance the discriminatory power of NPS.

Study Limitations

Several limitations of this study warrant consideration. First, its retrospective design may introduce selection bias and limit the ability to establish causality. Despite efforts to retrieve comprehensive data from medical records, the potential for incomplete or missing documentation remains. Second, the study population was drawn from two centers, which may affect the generalizability of the findings to broader or more diverse patient groups. Third, although we included patients with a minimum of one year of postoperative follow-up, the duration of follow-up varied among participants, potentially influencing graft outcome assessments. Moreover, changes in medical therapy or lifestyle factors over time could not be

thoroughly captured in a retrospective framework, potentially impacting the progression of SVGD.

An important limitation of our study is the lack of echocardiographic data as it was not commonly recorded in the database we acquired our data from. A higher NPS is associated with a worse left ventricular function[12]; and this should be kept in mind when interpreting NPS results.

Additionally, while the NPS was shown to be a useful predictor, the cross-sectional measurement of its components (e.g., albumin levels, LMR) does not fully account for longitudinal fluctuations in nutritional or inflammatory status. Further, we did not include other emerging biomarkers of inflammation and oxidative stress, which might yield deeper insights into SVGD pathophysiology. Finally, as this study focused solely on angiographically evident SVG stenosis, noninvasive imaging or functional assessments were not performed, and could provide valuable complementary information in future research.

Higher NPS is associated with an increased risk of vein graft occlusion due to persistent inflammation and endothelial dysfunction. Patients with high NPS may benefit from aggressive lipid-lowering therapy (statins), anti-inflammatory strategies, and close follow-up after CABG.

These limitations highlight the need for prospective, multicenter studies with standardized follow-up protocols and more extensive biomarker profiling to validate and refine the prognostic utility of NPS for SVGD.

CONCLUSION

This study demonstrates that the NPS is an independent and robust predictor of SVGD, reflecting the interplay between systemic inflammation and nutritional status. Smoking and graft age also emerged as notable contributors to graft failure risk. These findings emphasize the potential value of incorporating NPS into clinical risk stratification and targeted therapeutic strategies, although further prospective research is warranted to confirm its utility and optimize long-term patient outcomes.

Ethics

Ethics Committee Approval: This study was approved by the Health Sciences University Hamidiye Scientific Research Ethics Board on February 24, 2023, ethics approval no.: 2023/4-4/5.

Informed Consent: As this was a retrospective study, informed consent was waived.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ş.K., S.A., M.Ş., S. Dil, S.D., D.M., A.L.O., Concept: Ş.K., S.A., A.T., S.D., Design: S.A., A.T., M.Ş., A.L.O., Data Collection or Processing: Ş.K., M.Ş., S. Dil, S.Y., D.M., Analysis or Interpretation: Ş.K., S.A., M.Ş., S.Y., Literature Search: Ş.K., S.A., S. Dil, S.Y., A.L.O., Writing: Ş.K., S.A., A.L.O.

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RESEARCH ARTICLE

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Biomarkers in the Pathogenesis of Heart Failure with Preserved as Well as Reduced Ejection Fraction: A Cross-sectional Study

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Abstract

Background and Aim: Heart failure (HF) is a multifaceted cardiovascular condition characterized by various pathophysiological mechanisms that lead to impaired ventricular structure or function. Diagnosing HF with preserved ejection fraction (HFpEF) and reduced EF (HFrEF) presents significant challenges due to overlapping symptoms and distinct underlying causes. This study aimed to investigate metabolic and inflammatory markers in patients with HFrEF and HFpEF.

Materials and Methods: The study included 80 HF patients, comprising HFpEF (n=40) and HFrEF (n=40), aged 30-90 years, of both genders. Participants were recruited from the department of cardiology at a tertiary care hospital. Blood samples were collected to analyze biomarker levels and statistical analysis was conducted considering a *P*-value of ≤0.05 as statistically significant.

Results: Patients with HFpEF had lower levels of total cholesterol, plasma glucose, glycated hemoglobin, N-terminal pro brain natriuretic peptide (NT-proBNP), and high sensitivity C-reactive protein (hsCRP), compared to those with HFrEF. There were significant differences in echocardiography variables when compared among the groups. hsCRP showed a cut-off value of 3.15 mg/L, whereas NT-proBNP showed 437.8 pg/mL.

Conclusion: The study identified notable differences in metabolic and inflammatory marker profiles between HFpEF and HFrEF patients. HFpEF was associated with less severe dyslipidemia and inflammation, as indicated by lipid profiles, NT-proBNP and hsCRP levels, compared to HFrEF. Understanding these biomarker variations may aid in developing personalized treatment strategies and enhancing patient care.

Keywords: Heart failure, reduced ejection fraction, preserved ejection fraction, biomarkers, inflammation

INTRODUCTION

Heart failure (HF) is a multifaceted cardiovascular disorder in which there is impairment of blood supply to various organs of the body, leading to multiorgan dysfunction. It is a major global health concern, affecting millions of individuals and contributing to rising morbidity, mortality, and healthcare costs associated with its diagnosis and treatment.[1,2] In 2017, it was found that 64.3 million are suffering from HF globally.[3] In Asia, the prevalence of HF is 1.3-6.7%. In China, the prevalence is 1.3%, which amounts to 4.2 million.[4] Other Asian countries also report varying prevalence rates: Hong Kong (2-3%), the Philippines (1-2%), Indonesia (5%), Taiwan (6%), South Korea (0.6%), Japan (1%), and Thailand (0.4%). In Southeast Asia, approximately nine million people are affected, with prevalence rates of 6.7% in Malaysia and 4.5% in Singapore.[5]

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India has reported a significant increase in HF prevalence, affecting between eight and ten million people. Unlike Western countries, where HF primarily affects the elderly, in India, it tends to impact younger individuals. States such as Punjab, Tamil Nadu, and Haryana report the highest HF cases. Since 1990, India's HF burden has increased by 104%, contributing to 17.8% of deaths in 2016.[6,7] In rural areas, HF prevalence is estimated at 1.2 cases per 1,000 people, with cardiovascular diseases (CVD) being less common compared to urban regions.[8]

HF is grouped into HF with preserved ejection fraction (HFpEF) and HF with reduced EF (HFrEF), and they have distinct pathophysiology, comorbidities, and treatment responses. In HFrEF, EF is less than 49% and is often linked to ischemic heart disease, leading to systolic dysfunction. Symptoms include reduced cardiac output, fatigue, shortness of breath, and fluid retention. Effective management includes various medications involving the renin-angiotensin-aldosterone system, beta-blockers, and diuretics.[8-10]

HFpEF, on the other hand, is defined by an EF of more than 50%, indicating normal heart contraction but impaired left ventricular relaxation and increased stiffness. This form of HF is primarily associated with dysfunction in left ventricular filling and with obesity, diabetes, hypertension, and dyslipidemia, among others In addition, high-sensitivity C-reactive protein (hsCRP), a general inflammatory marker, plays a significant role in CVDs. hsCRP plays a major role in the adverse prognosis of HF, altered endothelial function, arrhythmias, cardiorenal syndrome and increased morbidity and mortality.[11] hsCRP levels of more than 2 mg/L are found to predict an increased risk of HF with preserved EF and a worse prognosis and poor cardiovascular outcomes.[12] N-terminal pro brain natriuretic peptide (NT-proBNP) levels and echocardiography (ECHO) are the guideline diagnostic indicators of HF. There is a significant association between NT-proBNP and diastolic dysfunction.[13]

Managing HFpEF poses a greater challenge than HFrEF, as conventional HF medications often fail to provide the same therapeutic benefits.[14,15] The distinct pathophysiology and treatment approaches for these HF subtypes highlight the importance of understanding their metabolic and inflammatory differences. This study was conducted to investigate metabolic and inflammatory markers in HFrEF and HFpEF patients.

METHODS

HF patients were enrolled from the Department of Cardiology, and further analyses were carried out in the Department of Biochemistry at Sri Ramachandra Institute. This study was carried out on a subsample of a larger study. Part of the larger study which- to be removed has been previously published.[16] Approval was obtained from the ethics committee was obtained from Sri Ramachandra Institute of Higher Education and Research (approval number: IEC-NI/19/FEB/68/09, date: 10.11.2020). The participants provided voluntary written informed consent at the time of induction into the study.

The study was carried out during the coronavirus disease-2019 (COVID-19) pandemic. Only patients with HF were seeking medical advice at the hospital. Apparently healthy individuals who could serve as controls were not attending the hospital. Hence, the study did not consist of a control group.

Based on the study "DuBrock HM, AbouEzzeddine OF, Redfield MM (2018) hsCRP in HF with preserved EF. PLOS One 13(8): e0201836", sample size was calculated.

$\alpha = 0.05$

Power = 80%

$\sigma = 2.0$

$\Delta = 1.5$

The calculated sample size was 28, which was increased to 80.

Study Design

Cross-sectional study.

Study Participants

Patients with HFpEF (EF ≥50%) (n=40)

Patients with HFrEF (EF ≤49%) (n=40)

Inclusion Criteria

Individuals aged 30 to 90 years of both genders, diagnosed with HF based on the Framingham Heart Failure Diagnostic Criteria.

Exclusion Criteria

Patients with a history of acute HF in the past three months or acute myocardial infarction within the last six weeks.

Individuals with thyroid, lung, renal, or liver disorders, cancer, systemic infectious diseases, or connective tissue disorders.

Participants currently taking anticancer medications, steroids, anabolic steroids, or oral contraceptive pills.

Sample Collection and Biomarker Analysis

The study participants were subjected to transthoracic 2D Doppler ECHO. Venous samples were collected from the individuals, and the separated serum was aliquoted and stored at -80 °C for testing. The following biomarkers were measured using specific methods: total cholesterol (TC) was analyzed by cholesterol oxidase-peroxidase, triglyceride (TGL) by glycerol phosphate oxidase-peroxidase, high density lipoprotein (HDL) by polymer-polyanion, low density lipoprotein cholesterol (LDL) by direct enzymatic method, blood urea nitrogen (BUN) by ultraviolet/

urease-glutamate dehydrogenase, creatinine by Jaffe's method, glucose by hexokinase, and glycated hemoglobin (HbA1c) by ion-exchange chromatography. hsCRP and NT-proBNP were measured by the enzyme-linked immunosorbent assay method.

Statistical Analysis

Statistical analysis was performed in SPSS software version 16. The Kolmogorov-Smirnov test was performed to assess the normality of data distribution. Results were expressed as means and standard deviations. The Student's t-test and Mann-Whitney U test were used to compare the continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test. The variables were subjected to correlation analysis using either Pearson's or the Spearman correlation test. Additionally, the receiver operating characteristic (ROC) curve was conducted to determine the cut-off value, area under the curve (AUC), 95% confidence interval, *P*-value, sensitivity, and specificity for hsCRP and NT-proBNP. A *P*-value of ≤0.05 was considered statistically significant.

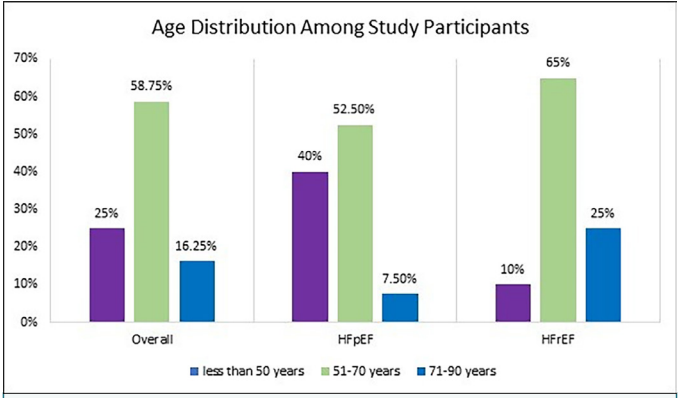

Figure 1: Bar diagram shows the age distribution among HFpEF and HFrEF patients

HFpEF: Heart failure with preserved ejection fraction, HFrEF: Heart failure with reduced ejection fraction

Results

Table 1 illustrates the age distribution among HFpEF and HFrEF patients. Of the 80 participants, 25% were under 50 years old, with a higher proportion in the HFpEF group (40%) while the HFrEF group had 10%. In the 51-70 age range, which comprised 58.75% of the total study population, HFrEF patients were more prevalent (65%) than HFpEF patients (52.5%). Among those aged 71-90 years (16.25% of participants), 7.5% were HFpEF patients, whereas 25% were HFrEF patients.

Chi-square test analysis revealed a significant difference in age distribution between the two groups ($P = 0.01$), indicating that age is a key distinguishing factor between HFpEF and HFrEF. The age distribution of study participants is also represented in a bar diagram (Figure 1).

Of the 80 patients, 35% were female, with 32.5% in the HFpEF group and 37.5% in the HFrEF group. In contrast, 65% of the

Table 1: Demographic details of the participants

Variables	Total (n=80)	HFpEF (n=40)	HFrEF (n=40)	*P*-value
Age (years)	58.93 (12.29)	53.17 (11.25)	64.68 (10.57)	<0.001**
Age distribution among participants (n/%)@				
<50	20 (25%)	16 (40%)	4 (10%)	0.003**
51-70	47 (58.75%)	21 (52.5%)	26 (65%)	
71-90	13 (16.25%)	3 (7.5%)	10 (25%)	
Gender distribution among participants (n/%)@				
Female	28 (35%)	13 (32.5%)	15 (37.5%)	0.007**
Male	52 (65%)	27 (67.5%)	25 (62.5%)	
Height (m)	1.60 (0.06)	1.59 (0.06)	1.60 (0.06)	0.45
Weight (kg)	65.99 (9.40)	66.23 (8.99)	65.75 (9.90)	0.82
BMI (kg/m²)	25.95 (3.79)	26.08 (3.64)	25.8 (4.0)	0.74
Waist (in)	36.46 (5.52)	37.47 (5.33)	35.45 (5.6)	0.1
Hip (in)	38.81 (5.13)	39.42 (5.25)	38.20 (5.00)	0.29
WHR	0.95 (0.04)	0.95 (0.03)	0.94 (0.05)	0.28
NYHAFC (n)#	I-38, II-2, III-17, IV-23	I-38, II-2	III-17, IV-23	<0.001**

P-value: *: Significant, **: Highly significant

Classification expressed as mean and SD. @Expressed frequency and percentage. #Epressed as frequency Student's t-test was used. @Chi-square test was used. #Fisher's exact test used.

HFpEF: Heart failure with preserved ejection fraction, HFrEF: Heart failure with reduced ejection fraction, BMI: Body mass index, WHR: Waist hip ratio, NYHAFC: New York Heart Association Functional Classification, SD: Standard deviation

total participants were male, comprising 67.5% of HFpEF patients, and 62.5% of HFrEF patients. Statistical analysis using the chi-square test revealed a significant difference in gender distribution between the two groups ($P = 0.01$). The gender distribution of study participants is also illustrated in a bar diagram (Figure 2). Among patients with HFpEF, 38 belonged to class I, while 2 belonged to class II. Among HFrEF patients, 17 were in class III and 23 were in class IV according to New York Heart Association Functional Classification (NYHAFC).

ECHO showed measurements at the level of the left ventricle (LV) and the aortic valve to assess aortic root diameter, left atrial (LA) diameter, LA volume, fractional shortening (FS%), LV internal diameter at end diastole (LVIDd) and LVIDs cavity diameters, LV posterior wall diameter in diastole (LVPWd) and LVPW thickness in systole (LVPWs) diameters, diastolic IV septum diameter (IVSd), IV septum diameter systolic (IVSs), LV mass, LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), EF, and stroke volume (SV). Among the ECHO variables, EF, LVIDs, LVIDd, IVSs, IVSd, LVPWs, LVPWd, LVESV, LVEDV, SV, FS, LA, LV early diastole filling (E-wave), left ventricular late diastole caused by atrial contraction (A-wave) and E/A ratio were statistically significant between the groups (Table 2).

Table 3 presents the levels of metabolic and inflammatory biomarkers in HFpEF and HFrEF patients. TC levels were significantly lower in HFpEF patients compared to those with HFrEF ($P = 0.01$). Similarly, fasting plasma glucose (FPG), postprandial PG (PPPG), HbA1c, BUN, creatinine, hsCRP, and NT-proBNP showed significant differences between the groups. HFpEF patients exhibited lower levels of FPG, PPPG, HbA1c, BUN, creatinine, hsCRP, and NT-proBNP compared to HFrEF patients statistically significant *P*-values. In contrast, hemoglobin (Hb) levels were higher in HFpEF patients than in HFrEF patients, which was also statistically significant.

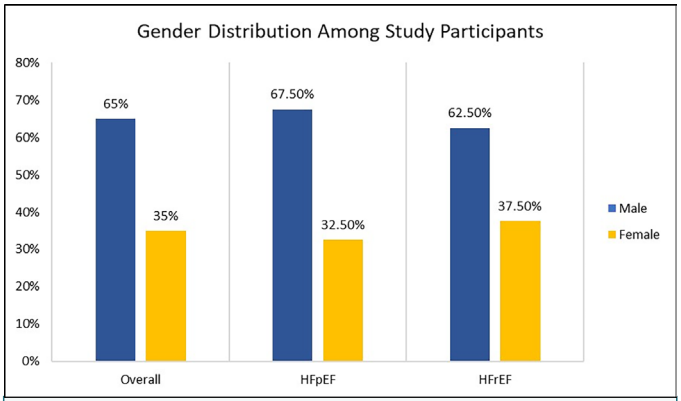

Figure 2: Gender distribution among HFpEF and HFrEF patients

HFpEF: Heart failure with preserved ejection fraction, HFrEF: Heart failure with reduced ejection fraction

Table 2: Echocardiography findings in the study participants

Variables	Total (n=80)	HFpEF (n=40)	HFrEF (n=40)	*P*-value
EF (%)	47.98 (15.27)	61.80 (2.40)	34.15 (8.63)	<0.001**
LVIDs (cm)	38.10 (6.39)	34.33 (3.31)	41.88 (6.52)	<0.001**
LVIDd (cm)	48.89 (5.97)	45.13 (2.17)	52.65 (6.19)	<0.001**
IVSs (cm)	10.43 (3.03)	11.80 (2.95)	9.05 (2.43)	<0.001**
IVSd (cm)	11.55 (2.88)	12.8 (2.84)	10.3 (2.35)	<0.001**
LVPWs (cm)	11.33 (2.78)	12.6 (2.62)	10.05 (2.34)	<0.001**
LVPWd (cm)	12.39 (2.71)	13.63 (2.63)	11.15 (2.19)	<0.001**
LVESV (mL)	58.56 (28.06)	34.65 (3.42)	82.48 (20.25)	<0.001**
LVEDV (mL)	109.19 (25.99)	88.20 (7.88)	130.2 (20.06)	<0.001**
SV (mL)	49.64 (8.06)	53.25 (3.3)	46.02 (9.68)	<0.001**
FS (%)	24.50 (7.71)	31.08 (1.83)	17.92 (5.31)	<0.001**
AO (mm)	29.08 (1.53)	28.93 (0.86)	29.22 (1.99)	0.4
LA (mL)	35.83 (5.97)	33.18 (3.88)	38.47 (6.53)	<0.001**
E-wave velocity (m/s)#	0.7 (0.6-0.9)	0.7 (0.6-0.8)	0.8 (0.65-0.9)	0.04*
A-wave velocity (m/s)#	0.7 (0.5-0.85)	0.8 (0.6-0.9)	0.6 (0.4-0.8)	0.006**
E/A ratio#	1.13 (0.75-1.5)	0.88 (0.73-1.26)	1.33 (0.81-2.12)	0.01*

P-value: *: Significant, **: Highly significant

Expressed as mean and SD. #Expressed as median and interquartile range Student's t-test was used. #Mann-Whitney U test used.

EF: Ejection fraction, LVIDs: Left ventricular internal diameter at end systole, LVIDd: Left ventricular internal diameter at end diastole, IVSs: Interventricular septum thickness in systole, IVSd: Interventricular septum thickness in diastole, LVPWs: Left ventricular posterior wall in systole, LVPWd: Left ventricular posterior wall in diastole, LVESV: Left ventricular end-systolic volume, LVEDV: Left ventricular end diastolic volume, SV: Stroke volume, FS: Fractional shortening, AO: Aortic annulus, LA: Left atrial volume, E-wave: left ventricular early diastole filling, A-wave: left ventricular late diastole caused by atrial contraction

DISCUSSION

HF is a multiorgan debilitating disorder, precipitated by the inability of the heart to cope with the routine functioning, both at rest and during physical activity. Common clinical features include dyspnea, fatigue, and pulmonary edema.[17] HF arises from various cardiac and non-cardiac conditions that impair heart structure and function resulting in cardiac dysfunction. Common cardiac causes include acute myocardial infarction, myocarditis, aortic stenosis, hypertension, valvular regurgitation, and genetic cardiomyopathy.[18]

According to the World Health Organization, India significantly contributes to global CVD-related deaths, accounting for one-fifth of worldwide fatalities, particularly among younger individuals. The Global Burden of Disease study reports that India's mortality rate due to CVD stands at 272 per 100,000 individuals, exceeding the global average of 235 per 100,000. Furthermore, mortality from coronary artery disease (CAD) among Asians is 20-50% higher than other demographic groups.[19]

The age distribution of study participants revealed distinct trends in HFpEF and HFrEF prevalence. Most of the participants were in the 51-70 years age group (58.75%), followed by those under 50 years (25%) and those aged 71-90 years (16.25%). Among individuals aged 51-70 years, 52.5% of HFpEF cases and 65% of HFrEF cases were observed, suggesting that HF predominantly affects individuals between 50 and 75 years. (Table 1, Figure 1). Although clinical symptoms may manifest earlier, they tend to significantly impact daily life as age advances. The lower prevalence of HF in individuals over 75 years may be attributed to increased mortality or a reluctance to seek medical care.

There was a statistically significant difference in age distribution between HFpEF and HFrEF patients (P = 0.01), emphasizing that both conditions are more prevalent among older adults, particularly those aged 51-70 years. Notably, 40% of HFpEF patients were under 50 years old, whereas only 10% of HFrEF patients belonged to this younger age group, suggesting that HFpEF may have an earlier onset compared to HFrEF. In contrast, among the oldest age group (71-90 years), HFrEF was more prevalent (25%) compared to HFpEF (7.5%), indicating that reduced EF becomes more common in the elderly. These findings indicate that age is an important determinant in the diagnostic workup and further treatment of HF.

The significant differences in HFpEF and HFrEF prevalence across age groups suggest that age-specific management strategies may be necessary, particularly for middle-aged and older adults, who make-up the majority of HF patients. Additionally, the earlier onset of HFpEF in younger individuals underscores the importance of early intervention and preventive measures in high-risk populations to slow disease progression. The increasing prevalence of HF with age is attributed to prolonged exposure to deleterious effects of metabolic and inflammatory insults. Consequently, older individuals tend to have greater impairment in cardiac reserve and an elevated risk of HF due to the cumulative effects of these risk factors.[20]

In India, HF manifests at a younger age compared to Western populations. For instance, HF patients in the Thai Heart Failure Registry (THFR) and International Congestive HF (Indian subset) studies had a median age of 61.2 years and 56 years, respectively. The male-to-female gender distribution (70:30, according to the THFR) also differs from that in the USA and

Table 3: Metabolic and inflammatory biomarkers levels in HFpEF and HFrEF patients

Variables	Total (n=80)	HFpEF (n=40)	HFrEF (n=40)	*P*-value
TC (mg/dL)	203.37 (47.38)	190.08 (38.99)	216.67 (51.61)	0.005**
TGL (mg/dL)	152.76 (62.68)	144.20 (60.16)	161.32 (64.72)	0.112
HDL (mg/dL)	43.33 (11.44)	42.68 (8.50)	44 (13.86)	0.303
LDL (mg/dL)	128.7 (39.75)	124.85 (32.72)	132.55 (45.82)	0.194
FPG (mg/dL)	116.26 (44.99)	107.34 (14.87)	140.5 (80.29)	0.008**
PPPG (mg/dL)	158.01 (73.99)	116.29 (25.11)	188.36 (82.89)	<0.001**
HbA1c (%)	6.95 (2.11)	5.80 (0.53)	8.11 (2.46)	<0.001**
BUN (mg/dL)	12.8 (6.98)	10.43 (2.88)	15.17 (8.88)	<0.001**
Creatinine (mg/dL)	0.95 (0.38)	0.88 (0.26)	1.03 (0.46)	0.03*
Hb (g/dL)	12.79 (2.07)	13.30 (1.87)	12.29 (2.15)	0.01*
hsCRP (mg/L)	3.50 (1.59)	2.28 (1.07)	4.72 (0.97)	<0.001**
NT-proBNP (pg/mL)	394.02 (134.25)	287.27 (103.18)	500.80 (49.91)	<0.001**

Expressed in mean and SD. Student's t-test was used. P-value: *: Significant; **: Highly significant

TC: Total cholesterol, TGL: Triglycerides, HDL: High density lipoprotein, LDL: Low density lipoprotein, FPG: Fasting plasma glucose, PPPG: Postprandial plasma glucose, HbA1c: Glycated hemoglobin, BUN: Blood urea nitrogen, Hb: Hemoglobin, hsCRP: High sensitivity C-reactive protein, NT-proBNP: N-terminal-pro brain natriuretic peptide

Africa (approximately 50:50). This discrepancy may be partly explained by the fact that, unlike in Western countries, men in India are more likely to seek healthcare compared to women. Additionally, risk factor prevalence varies between India and the West, with diabetes mellitus being significantly more common among Indians, as reported in the THFR data.[21-23]

In the present study, gender distribution indicated that 65% of HF patients were males, and 35% were women. When comparing HF subtypes, females accounted for 32.5% of the HFpEF group and 37.5% of the HFrEF group, while males comprised 67.5% and 62.5% of these groups, respectively ($P = 0.01$) (Table 1, Figure 2). Traditionally, HF has been more prevalent in men due to their higher risk of CAD; however, women tend to develop HF more frequently at an advanced age. In this study, the proportion of patients in the HFrEF group comprised women; women in general have a longer survival rate and a lower risk of sudden death compared to men.

The underlying causes of HF also vary by gender. In men, CAD is the underlying etiology, whereas in women, uncontrolled diabetes and hypertension play more significant roles. Notably, type 2 diabetes mellitus increases the risk for women with HFpEF compared to men.[24] Women also tend to have stiffer and smaller LVs with higher EFs than men. This increased stiffness may result from greater fibrosis, particularly as they age. Estrogen has an effect on collagen synthesis; in women, there is decreased formation. On the contrary, there is increased collagen production and further damaging effects on the heart. Furthermore, under stressful conditions, energy metabolism is maintained in women's hearts more effectively compared to male hearts, thus contributing to sex-based differences in HF progression and outcomes.[25]

When the study participants were classified according to the NYHAFC, among HFpEF, 38 patients belonged to class I, while 2 belonged to class II. Seventeen participants among those with HFrEF were in class III, while 23 were in class IV. NYHAFC is used to assess the functional capacity of HF patients (Table 1). NYHAFC came into existence in 1921, and has undergone remarkable change from an assessment of symptoms during activity to being used as a benchmark inclusion criterion in contemporary HF clinical trials. Thus, the treatment recommendations are mainly based on the NYHAFC.[26]

Among the ECHO variables EF, LVIDs, LVIDd, IVSs, IVSd, LVPWs, LVPWd, LVESV, LVEDV, SV, FS, LA, E-wave, A-wave and E/A ratio were statistically significant between the groups (Table 2). ECHO is a fundamental diagnostic tool used to detect early cardiac dysfunction and offers vital support and management for cardiovascular patients.[27] Two-dimensional assessments of LV cavity diameter, wall thickness, and mass are performed according to the criteria of the American Society of ECHO and the European Association of Cardiovascular Imaging.[28] Thus, there were structural and functional alterations in ECHO parameters.

The variations in biomarker levels observed in this study highlight the distinct pathophysiological mechanisms underlying HFpEF and HFrEF, which have important implications for diagnosis, treatment, and prognosis. A significant difference in TC levels was observed, with HFrEF patients exhibiting higher levels than HFpEF patients ($P = 0.01$) (Table 3). This finding suggests that dyslipidemia may be more pronounced in HFrEF, potentially accelerating the progression of CAD, a major contributor to HFrEF. Although TGL and LDL levels were also higher in the HFrEF group, these differences were not statistically significant. HDL levels were nearly identical in both groups. Dyslipidemia is a well-recognized modifiable risk factor for CVD, with elevated LDL and reduced HDL levels being associated with impaired cardiac function. Inflammation linked to dyslipidemia further exacerbates HF progression.[29]

HFrEF patients exhibited significantly higher levels of FPG ($P = 0.01$), PPPG ($P = 0.001$), and HbA1c ($P = 0.001$) compared to HFpEF patients (Table 3). This suggests that poor glycemic control is more prevalent among HFrEF patients, reinforcing the strong link between diabetes and HFrEF. These findings emphasize the importance of blood glucose management in HFrEF patients to potentially slow HF progression. In diabetes mellitus, lipid accumulation, including TGL, ceramides, and diacylglycerols, within the myocardium contributes to cardiac dysfunction.[30] Diabetes also impairs cellular glucose uptake, increases serum glucose concentrations, and disrupts mitochondrial oxidative phosphorylation, resulting in a toxic environment that damages myocardial cells and alters cardiac relaxation patterns, which are characteristic of HFpEF.[31,32]

Additionally, BUN ($P = 0.001$) and creatinine ($P = 0.03$) levels were significantly higher in HFrEF patients compared to HFpEF patients (Table 3), indicating more severe renal impairment in HFrEF. Renal dysfunction is a well-established predictor of poor HF outcomes, highlighting the need for vigilant renal function monitoring in HFrEF patients. BUN, which reflects renal perfusion changes, serves as a more accurate marker of HF progression than creatinine. Notably, for every 10 mg/dL increase in BUN, HF mortality risk rises by 21%.[33] HFrEF patients also had significantly lower Hb levels than HFpEF patients ($P = 0.01$), indicating a higher prevalence of anemia in HFrEF. Anemia is a common comorbidity in HF and is linked to worse clinical outcomes. Its precise etiology in HF remains unclear, but is considered multifactorial, with iron deficiency anemia and inflammation playing major roles.[34]

hsCRP, a key inflammatory biomarker, was significantly elevated in HFrEF patients compared to HFpEF patients ($P =$

0.001) (Table 3). CRP is synthesized in the liver in response to inflammation via IL-1/IL-6 pathway activation; it is a commonly used clinical marker. HF patients frequently exhibit increased hsCRP levels, particularly during acute exacerbations, reflecting systemic inflammation.[35] Chronic inflammation contributes to endothelial dysfunction, activation of the renin-angiotensin and sympathetic nervous systems, reduced myocardial contractility, and interstitial fibrosis, all of which promote HF progression. While hsCRP levels typically decline following HF stabilization, they remain elevated compared to the general population, underscoring the chronic inflammatory nature of HF.[36] Figure 3 and Table 4 illustrate the ROC curve for hsCRP, showing a strong predictive value with an AUC of 0.946 (95% confidence interval: 0.890-0.994). The optimal cut-off value for hsCRP was determined to be 3.157 mg/L, with a sensitivity of 100% and specificity of 85% ($P < 0.001$). Patients with hsCRP ≥2 mg/L experience frequent HF hospitalizations, poorer health-related quality of life, and increased mortality risk.[12] Elevated hsCRP at the time of risk assessment correlates with a worse prognosis in HF patients.[35] Rather than being a static marker, hsCRP fluctuates over time, acting as a dynamic risk indicator. Recent studies suggest that cumulative hsCRP burden is a stronger predictor of new-onset HF than a single baseline measurement.[37]

The mean NT-proBNP levels in HFpEF and HFrEF were 287.27 and 500.80 pg/mL, which was statistically significant ($P < 0.001$). (Table 2) The cut-off level of NT-proBNP was 437.8 pg/mL with an AUC) of 0.995; sensitivity and specificity were 100% and 97%, respectively (Figure 3, Table 4). HFpEF is a common condition due to its prevalence in an ageing western population. HFpEF is associated with significant morbidity and mortality and has outcomes similar to HFrEF. NT-proBNP levels and ECHO are used as the guidelines diagnostic indicators of HF. The National Institute for Health and Care Excellence and European guidelines recommend a single NT-proBNP threshold of >400 ng/L and >125 ng/L, respectively, to use ECHO assessment of HF in the outpatient setting. A significant relationship between NT-proBNP levels and diastolic dysfunction has been established. NT-proBNP has a high negative predictive value, which increases its use in clinical medicine.[13]

EF, LVID, IVS, LVPW, EDV, ESV, FS, and LA showed correlation with other ECHO parameters in both groups (Table 5). hsCRP showed correlation with NT-proBNP and ECHO parameters such as EF, LVID, IVS, LVPW, EDV, FS and E-wave, which were statistically significant. Even though NT-proBNP is a gold standard marker of HF, it showed correlation only with a few ECHO parameters, such as LVID, EDV, ESV, FS and LA (Table 6). Even though NT-proBNP performed well in the ROC curve, the correlation of hsCRP with ECHO variables was better than that of NT-proBNP. ECHO combined with NT-pro BNP had higher accuracy in NYHAFC class and prognostic assessment of Diastolic HF than the separate applications of ECHO and NT-proBNP.[38] High hsCRP during hospital admission may help identify patients with a higher morbidity risk in the long-term follow-up. In many studies, an elevated hsCRP (>2 mg/L) is one the key inclusion criteria. Thus, hsCRP may aid in risk stratification in HF and identify patients with an inflammatory phenotype who may benefit from specific anti-inflammatory therapies.[39]

These biochemical variations between HFpEF and HFrEF emphasize the need for a distinct management approach for each HF subtype. The elevated levels of glucose, lipids, renal markers, and inflammatory biomarkers in HFrEF patients indicate a more advanced disease state that may necessitate aggressive treatment strategies. In contrast, HFpEF management should prioritize controlling comorbid conditions such as hypertension and preserving renal function.

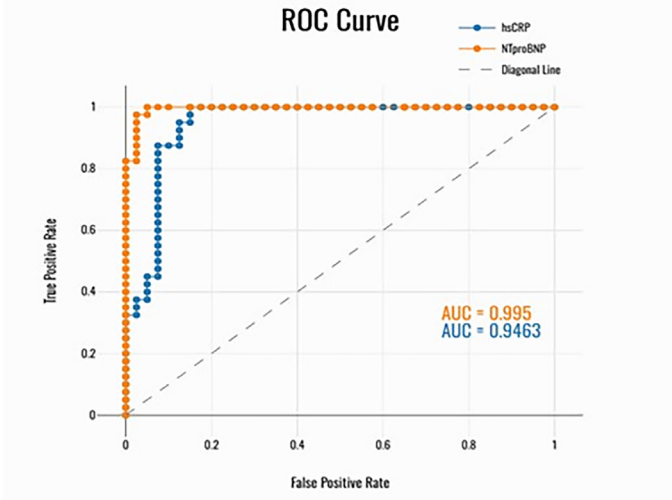

Figure 3: ROC curve of hsCRP and NT-proBNP in heart failure patients

ROC: Receiver operating characteristic, hsCRP: High sensitivity C-reactive protein, NT-proBNP: N-terminal pro brain natriuretic peptide

Table 4: ROC curves of hsCRP and NT-proBNP in heart failure patients

Variable	AUC	95% CI	Cut-off	Sensitivity	Specificity	*P*-value
hsCRP (mg/L)	0.946	0.890-0.994	3.157	100%	85%	<0.001
NT-proBNP (pg/mL)	0.995	0.899-0.999	437.8	100%	97%	<0.001

ROC: Receiver operating characteristic, hsCRP: High sensitivity C-reactive protein, NT-proBNP: N-terminal pro brain natriuretic peptide

Table 5: Comparisons among ECHO parameters of study participants

		EF	LVIDd	LVIDs	IVSs	IVSd	LVPWs	LVPWd	EDV	ESV	SV	FS	AO	LA	E	A
LVIDd	*R*-value	**-0.77**	**1**													
	P-value	**<0.001**	**1**													
LVIDs	*R*-value	**-0.75**	**0.91**	**1**												
	P-value	**<0.001**	**<0.001**	**1**												
IVSs	*R*-value	**0.48**	**-0.53**	**-0.63**	**1**											
	P-value	**0.009**	**0.003**	**<0.001**	**1**											
IVSd	*R*-value	**0.47**	**-0.51**	**-0.6**	**0.99**	**1**										
	P-value	**0.01**	**0.004**	**0.001**	**<0.001**	**1**										
LVPWs	*R*-value	**0.44**	**-0.49**	**-0.55**	**0.96**	**0.96**	**1**									
	P-value	**0.01**	**0.007**	**0.002**	**<0.001**	**<0.001**	**1**									
LVPWd	*R*-value	**0.42**	**-0.46**	**-0.53**	**0.96**	**0.97**	**0.99**	**1**								
	P-value	**0.02**	**0.01**	**0.003**	**<0.001**	**<0.001**	**<0.001**	**1**								
EDV	*R*-value	**-0.96**	**0.67**	**0.63**	**-0.45**	**-0.43**	**-0.41**	**-0.39**	**1**							
	P-value	**<0.001**	**<0.001**	**<0.001**	**0.01**	**0.01**	**0.02**	**0.03**	**1**							
ESV	*R*-value	**-0.95**	**0.61**	**0.62**	**-0.41**	**-0.41**	**-0.38**	**-0.37**	**0.93**	**1**						
	P-value	**<0.001**	**<0.001**	**<0.001**	**0.02**	**0.02**	**0.04**	**0.05**	**<0.001**	**1**						
SV	*R*-value	0.03	0.05	0.01	-0.12	-0.13	-0.19	-0.19	-0.07	-0.1	1					
	P-value	0.87	0.81	0.98	0.53	0.51	0.33	0.32	0.72	0.60	1					
FS	*R*-value	**0.92**	**-0.81**	**-0.75**	**0.45**	**0.46**	**0.41**	**0.39**	**-0.84**	**-0.82**	0.12	**1**				
	P-value	**<0.001**	**<0.001**	**<0.001**	**0.01**	**0.01**	**0.02**	**0.03**	**<0.001**	**<0.001**	0.52	**1**				
AO	*R*-value	-0.19	0.31	0.15	-0.05	-0.03	-0.09	-0.04	0.25	0.24	-0.07	-0.27	1			
	P-value	0.31	0.10	0.43	0.79	0.87	0.63	0.85	0.18	0.21	0.71	0.15	1			
LA	*R*-value	**-0.82**	**0.83**	**0.78**	**-0.52**	**-0.51**	**-0.49**	**-0.47**	**0.7**	**0.78**	0.03	**-0.79**	0.28	**1**		
	P-value	**<0.001**	**<0.001**	**<0.001**	**0.004**	**0.004**	**0.007**	**0.01**	**<0.001**	**<0.001**	0.85	<0.001	0.14	**1**		
E	*R*-value	-0.11	0.25	0.17	-0.15	-0.18	-0.14	-0.13	0.04	0.12	0.25	-0.04	0.09	0.27	**1**	
	P-value	0.57	0.19	0.36	0.42	0.35	0.47	0.49	0.81	0.54	0.19	0.81	0.65	0.15	**1**	
A	*R*-value	0.35	-0.18	-0.23	0.29	0.3	0.35	0.35	-0.32	**-0.43**	-0.11	0.24	-0.16	**-0.39**	-0.12	**1**
	P-value	0.06	0.36	0.23	0.13	0.11	0.06	0.06	0.09	**0.01**	0.55	0.20	0.40	**0.03**	0.55	**1**
E/A	*R*-value	**-0.38**	0.35	**0.37**	-0.31	-0.33	-0.35	-0.35	0.28	**0.44**	0.28	-0.24	0.07	**0.54**	**0.68**	**-0.74**
	P-value	**0.03**	0.06	**0.04**	0.09	0.07	0.06	0.06	0.13	**0.01**	0.14	0.21	0.73	**0.003**	**<0.001**	**<0.001**

LVIDd: Left ventricular internal diameter at end diastole, LVIDs: Left ventricular internal diameter at end systole, IVSs: Interventricular septum thickness in systole, IVSd: Interventricular septum thickness in diastole, LVPWs: Left ventricular posterior wall in systole, LVPWd: Left ventricular posterior wall in diastole, LVEDV: Left ventricular end diastolic volume, LVESV: Left ventricular end systolic volume

Table 6: Comparisons among ECHO parameters of study participants

		TC	TGL	HDL	LDL	FPG	PPPG	HbA1c	hsCRP	NT-proBNP
TGL	*R*-value	**0.36**	1							
	P-value	**0.05**	1							
HDL	*R*-value	0.3	0.05	1						
	P-value	0.11	0.80	1						
LDL	*R*-value	**0.83**	0.3	0.1	1					
	P-value	**0.001**	0.06	0.61	1					
FPG	*R*-value	0.24	0.06	-0.18	0.34	1				
	P-value	0.20	0.73	0.34	0.07	1				
PPPG	*R*-value	0.32	0.12	-0.11	0.35	**0.96**	1			
	P-value	0.09	0.54	0.58	0.06	**<0.001**	1			
HbA1c	*R*-value	0.11	0.19	-0.26	0.2	**0.89**	**0.84**	1		
	P-value	0.55	0.31	0.18	0.29	**<0.001**	**<0.001**	1		
hsCRP	*R*-value	0.01	-0.08	-0.15	-0.11	0.26	0.27	0.26	1	
	P-value	0.99	0.68	0.44	0.56	0.17	0.15	0.17	1	
NTpoBNP	*R*-value	-0.13	0.08	-0.16	-0.26	0.31	**0.36**	0.35	0.33	1
	P-value	0.49	0.66	0.39	0.16	0.10	**0.05**	0.06	0.07	1
EF	*R*-value	-0.27	-0.27	0.07	0.03	**-0.39**	**-0.47**	**-0.48**	**-0.49**	**-0.59**
	P-value	0.15	0.16	0.72	0.86	**0.03**	**0.01**	**0.009**	**0.007**	**0.001**
LVIDd	*R*-value	0.09	0.22	0.04	-0.15	0.12	0.19	**0.37**	**0.39**	**0.42**
	P-value	0.65	0.26	0.81	0.44	0.52	0.31	**0.04**	**0.03**	**0.02**
LVIDs	*R*-value	0.09	0.24	0.03	-0.09	0.16	0.2	**0.4**	**0.4**	0.3
	P-value	0.64	0.21	0.88	0.63	0.39	0.29	**0.03**	**0.03**	0.11
IVSs	*R*-value	-0.27	0.02	0.09	-0.14	-0.26	-0.24	-0.27	**-0.41**	0.15
	P-value	0.15	0.93	0.65	0.46	0.16	0.21	0.15	**0.02**	0.42
IVSd	*R* value	-0.34	0.01	0.04	-0.21	-0.25	-0.24	-0.24	**-0.4**	0.16
	P-value	0.07	0.98	0.85	0.28	0.18	0.21	0.21	**0.03**	0.40
LVPWs	*R*-value	-0.3	-0.11	0.1	-0.2	-0.28	-0.26	-0.3	**-0.38**	0.18
	P-value	0.11	0.55	0.59	0.30	0.14	0.17	0.12	**0.04**	0.33
LVPWd	*R*-value	-0.33	-0.1	0.07	-0.24	-0.26	-0.24	-0.25	**-0.36**	0.19
	P-value	0.08	0.62	0.71	0.21	0.17	0.20	0.2	**0.05**	0.31
EDV	*R*-value	0.26	0.18	-0.16	-0.08	**0.45**	**0.52**	**0.51**	**0.54**	**0.59**
	P-value	0.17	0.34	0.40	0.67	**0.01**	**0.004**	**0.005**	**0.002**	**0.001**
ESV	*R*-value	0.34	0.28	-0.07	0.03	0.29	**0.38**	0.31	**0.55**	**0.58**
	P-value	0.07	0.14	0.70	0.99	0.13	**0.04**	0.10	**0.002**	**0.001**
SV	R-value	0.31	0.34	0.06	**0.37**	0.01	-0.03	0.1	-0.35	-0.32
	P-value	0.10	0.07	0.75	**0.04**	0.95	0.88	0.61	0.06	0.09
FS	*R*-value	-0.29	-0.18	-0.03	-0.03	**-0.45**	**-0.57**	**-0.5**	**-0.41**	**-0.61**
	P-value	0.13	0.35	0.87	0.88	**0.01**	**0.001**	**0.005**	**0.02**	**<0.001**
AO	*R*-value	0.15	0.3	-0.14	-0.03	0.02	0.15	0.1	0.25	0.22
	P-value	0.44	0.11	0.45	0.89	0.91	0.42	0.59	0.19	0.26

Table 6: Continued

		TC	TGL	HDL	LDL	FPG	PPPG	HbA1c	hsCRP	NT-proBNP
LA	*R*-value	0.23	0.26	0.1	-0.1	-0.05	0.07	0.09	0.35	**0.4**
	P-value	0.23	0.16	0.61	0.61	0.80	0.70	0.64	0.06	**0.03**
E	*R*-value	0.03	0.21	0.18	-0.1	**-0.44**	**-0.41**	**-0.37**	0.16	-0.13
	P-value	0.89	0.27	0.35	0.59	**0.01**	**0.03**	**0.05**	0.40	0.49
A	*R*-value	-0.13	-0.34	0.23	-0.05	-0.02	-0.04	-0.09	-0.34	-0.13
	P-value	0.50	0.06	0.23	0.79	0.90	0.84	0.65	0.07	0.50
E/A	*R*-value	0.11	**0.41**	-0.03	0.01	-0.27	-0.24	-0.15	**0.36**	0.05
	P-value	0.58	**0.02**	0.86	0.98	0.16	0.21	0.44	**0.05**	0.79

TGL: Triglycerides, HDL: High density lipoprotein, LDL: Low density lipoprotein, FPG: Fasting plasma glucose, PPPG: Postprandial plasma glucose, HbA1c: Glycated hemoglobin, hsCRP: High sensitivity C-reactive protein, NTpoBNP: High sensitivity C-reactive protein, EF: Ejection fraction, LVIDd: Left ventricular internal diameter at end diastole, IVSs: Interventricular septum thickness in systole, IVSd: Interventricular septum thickness in diastole, LVPWs: Left ventricular posterior wall in systole, LVPWd: Left ventricular posterior wall in diastole, EDV: End-diastolic volume, ESV: End-systolic volume, SV: Stroke volume, FS: Fractional shortening, AO: Aortic annulus, LA: Left atrial volume

Study Limitations

The study was carried out during the COVID-19 pandemic. Only patients with HF were seeking medical advice from the hospital. Apparently healthy individuals who could serve as controls were not attending hospital. Hence the study did not consist of a control group. The cross-sectional design had limitations in assessing the outcomes. Further studies could be conducted as case-control or cohort studies, which could help identify better outcomes. Since this was a single centre study with a small sample size, and due to the study design, the findings are not generalizable. Other inflammatory markers, such as interleukin-6, tumor necrosis factor-alpha, total white blood cell count and differential count, could have provided further insights. A further study could be carried out as a multicentric study to increase validity, reliability, and generalizability.

CONCLUSION

In summary, the significant biochemical and metabolic differences between HFpEF and HFrEF patients highlight distinct underlying pathophysiological mechanisms. hsCRP and NT-proBNP were higher in HFrEF compared to HFpEF. Even though NT-proBNP performed well in ROC curve, correlation of hsCRP with ECHO variables with hsCRP was better than NT-proBNP. Recognizing these differences is crucial for enhancing diagnosis, treatment strategies, and prognosis in HF management. These findings underscore the necessity for personalized therapeutic interventions and the refinement of treatment protocols, ultimately aiming to improve patient outcomes.

Ethics

Ethics Committee Approval: Approval was obtained from the Ethics Committee of Sri Ramachandra Institute of Higher Education and Research (approval number: IEC-NI/19/FEB/68/09, date: 10.11.2020).

Informed Consent: Written informed consent was obtained from all the study participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.T., J.C.A., K.R., S.S., Concept: S.T., J.C.A., K.R., S.S., Design: S.T., J.C.A., K.R., S.S., Data Collection or Processing: S.T., J.C.A., K.R.,S.S., Analysis or Interpretation: S.T., J.C.A., K.J., S.S., Literature Search: S.T., J.C.A., K.R., S.S., Writing: S.T., J.C.A., K.R., S.S.

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RESEARCH ARTICLE

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Serum Osmolality as a Predictor of Coronary Slow Flow Phenomenon

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Abstract

Background and Aim: Coronary slow flow (CSF) phenomenon is defined as a delay in the filling of epicardial coronary arteries in the absence of obstructive disease. Primary CSF phenomenon (PCSFP) is a noteworthy angiographic observation that should be regarded as a distinct clinical condition, although its precise pathophysiology is not yet fully understood. This study aims to investigate the correlation between serum osmolality and PCSFP in patients subjected to coronary angiography.

Materials and Methods: This is a case-control study that included one hundred and twenty patients who presented to Ain Shams University. They were divided into two equal groups. Group A: patients who had PCSFP and Group B: patients with normal coronary flow.

Results: Among PCSFP patients, the mean age was recorded as 54.53±11.6 years. Male sex was significantly associated with PCSFP, with an [odds ratio (95% confidence interval) of 2.582 (1.16-5.75)] and a *P*-value of 0.019. Among the traditional risk factors, smoking was markedly higher, contributing to 66.7% of the slow flow group of patients compared to 40% of the control group, with *P*-value = 0.003. PCSFP patients had increased hemoglobin and triglyceride levels, and both were strongly associated with PCSFP following multivariate analysis. A significant increase in serum osmolality was observed in PCSFP patients in comparison to control subjects. The calculated serum osmolality values were 295.08±6.77 mOsmol/kg in the PCSF group and 284.64±4.74 mOsmol/kg in the control group (*P*-value ≤ 0.001).

Conclusion: PCSFP predominantly affects males with a history of smoking. Furthermore, hypertriglyceridemia, higher hemoglobin levels, and greater serum osmolality have been identified as independent predictors of its development.

Keywords: Osmolality, primary coronary slow flow, thrombolysis in myocardial infarction frame count

INTRODUCTION

Coronary slow flow (CSF) phenomenon refers to an angiographically observed delay in the advancement of injected contrast within the coronary arteries, resulting in prolonged opacification of the epicardial vessels despite no evident obstructive coronary pathology.[1]

It is a frequently unrecognized risk factor in patients experiencing chest pain and abnormal non-invasive ischemia, despite having non-obstructive coronary arteries.[2] This condition has been documented in 1% to 7% of cases among patients subjected to coronary angiography due to clinical suspicion of coronary artery disease (CAD).[3]

Primary CSF phenomenon (PCSFP) is a noteworthy angiographic finding commonly identified in patients presenting with acute coronary syndrome (ACS), particularly those with unstable angina. It warrants recognition as a distinct clinical entity characterized by unique pathophysiological attributes, well-

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defined diagnostic parameters, and specific underlying mechanisms.[4]

The precise pathophysiology of the CSF phenomenon is not fully understood. Multiple mechanisms have been proposed in the pathophysiology of this condition, encompassing endothelial dysfunction, microvascular disturbances, undetected atherosclerosis, and inflammatory cascades.[5]

This phenomenon must be clearly differentiated from the contrast delay seen in coronary reperfusion strategies, including percutaneous interventions for acute myocardial infarction, as well as from secondary causes such as coronary stenosis, arterial ectasia, or transient vasospasm.[6]

Serum osmolality, a key indicator of solute particle concentration within bodily fluids, is determined by the levels of several biochemical markers, including sodium (Na), blood urea nitrogen (BUN), chloride, proteins, and glucose. The normal range for serum osmolality is typically between 275 and 295 mOsmol/kg.[7]

Serum osmolality estimates the body's hydration balance, so we thought of correlating it with this phenomenon of dehydration, as dehydration has been linked previously to PCSFP.[8]

Multiple formulas have been devised for the estimation of serum osmolality. In 1976, Smithline and Gardner proposed a widely recognized equation, expressed as [2(Na) + glucose/18 + BUN/2.8], to facilitate this calculation.[9] Worthley et al.[10] highlighted the Smithline-Gardner formula as the superior method for serum osmolality estimation, citing its precision and reliability.

Previous studies have investigated the association of PCSF with different clinical risk factors such as diabetes, dyslipidemia, and smoking, and various hematological and biochemical parameters such as hematocrit, platelet count, uric acid, glycosylated hemoglobin A1c (HbA1c), and serum triglycerides.[3,4,6]

This study to assess the potential correlation between serum osmolality and the development of PCSFP.

METHODS

In the period between January and July 2024, 120 patients presenting to the Cardiology Department at Ain Shams University were recruited for this case-control study. This time frame was selected to ensure alignment with our institutional review board (IRB) and the availability of clinical and research staff during this period. Our study employed a matched case-control design. Matching was performed on a 1:1 ratio based on key demographic and clinical characteristics, including age, sex, and the presence of major comorbidities. The participants were allocated to two groups: 60 patients with PCSFP confirmed by coronary angiography and 60 individuals in the control group with normal coronary flow.

The inclusion criteria were: patients above 18 years of age presenting either by ST segment elevation myocardial infarction (STEMI), non-ST ACS or chronic coronary syndrome (CCS), the exclusion criteria included the presence of CAD (including plaque, spasm, ectasia, or obstructive lesion), presence of a myocardial bridge, patients who underwent previous percutaneous coronary intervention in the vessel showing slow flow, and patients with history of coronary artery bypass grafting.

Prior to participation, all patients were given a detailed explanation of the procedure, and written informed consent was duly acquired. The study adhered to the ethical principles outlined by the IRB, Ain Shams University Faculty of Medicine Research Ethics Committee (approval number: FWA000017585, date: 14.02.2024).

Participants Were Subjected to

History and clinical examination

- A full history was taken from all patients regarding age, gender, detailed risk profile including smoking status, hypertension, history of CAD, drug history, previous coronary intervention, family history of premature ischemic heart disease (IHD) and dyslipidemia. The examination included vital data, and a full cardiac examination.

- A standard 12-lead surface electrocardiogram (ECG) was done for all participants.

- In line with the American Society of Echocardiography guidelines, a complete transthoracic echocardiographic evaluation was conducted for each patient using the General Electric (GE) Vivid E95 cardiac ultrasound device with a 3.5 MHz transducer.

- Laboratory investigations: Blood samples were collected from all the participants, including: complete blood picture, random blood sugar, kidney function tests, serum electrolytes, lipid profile, and HbA1C. Smithline and Gardner formulae were used to calculate serum osmolality: Serum Osmolality = 2(Na+) + glucose/18 + BUN/2.8.

- Coronary angiography: the procedure was performed by expert interventional cardiologists. All patients underwent coronary angiography using cine angiographic equipment, Philips Allura Xper Flat Detector 10 and GE Innova 2100 Angio Systems, with cineframes at 15 fps. A scaling factor of 2 was implemented to convert frame rate values from 15 frames per second to match the 30 frames per second acquisition speed

used in the initial cine angiographic studies. Sterilization and local infiltration with 2% lidocaine, followed by femoral or radial artery puncture, were performed using the Seldinger technique. To visualize coronary arteries, selective angiography was performed with multi-angulated projections-including right, left, cranial, and caudal views-utilizing 6Fr Judkins catheters and Iohexol (Omnipaque 350 mg/mL) as the contrast medium.

Angiographic interpretation was performed by experienced clinicians who were blinded to the clinical characteristics and outcomes of the patients. To minimize potential diagnostic bias and ensure an objective evaluation of coronary flow, with normal coronary flow is defined as the absence of any significant obstruction or irregularity in the coronary vessels, achieving thrombolysis in myocardial infarction (TIMI) III flow. The definition of normal flow was further corroborated by consensus between two independent reviewers to ensure consistency in the assessment.

As per the description by Gibson et al.[11], PCSFP was diagnosed through the TIMI frame count technique. This technique quantifies the number of cine frames required for contrast dye to reach specific distal landmarks within the coronary arteries. Using the cine viewer frame counter, we recorded number of frames needed for contrast to reach standard distal reference points in the left circumflex (LCX) artery, left anterior descending (LAD) artery, and right coronary artery (RCA). The initial frame corresponded to the instant when contrast fully occupied the artery, with the dye reaching both sides at its origin and progressing antegradely. The last frame was noted at the moment the contrast medium arrived at key distal reference points: the "whale's tail" structure at the LAD apex, the bifurcation of the primary obtuse marginal branch for the LCX, and the initial branch extending from the posterior lateral RCA beyond the posterior descending artery's origin.

To obtain the corrected TIMI frame count (CTFC), the final TIMI frame count for the LAD artery was adjusted by dividing the count by 1.7.

CSF was defined as a CTFC greater than 27, a threshold exceeding the normal reference range of 21±3 by more than two standard deviations.[11]

Statistical Analysis

The dataset was collected, meticulously reviewed, systematically coded, and subsequently entered into IBM SPSS 23 for analysis. Categorical variables were represented as frequencies and corresponding percentages, whereas continuous data were summarized using means with standard deviation and ranges for normally distributed variables and medians with interquartile ranges (IQR) for those following a non-parametric distribution after applying the Kolmogorov-Smirnov test for normality.

To assess disparities in categorical data between groups, the chi-square test was employed. For non-parametric distributions, the Mann-Whitney U tests was conducted, while an independent t-test was used to assess parametric quantitative data. The receiver operating characteristic curve was used to assess the best cut-off point for serum osmolality to differentiate between patients with and without slow flow with its sensitivity, specificity, positive, negative predictive values, and area under the curve. Univariate and multivariate logistic regression analysis (Backward-Wald model), assess the most important factors associated with slow flow among the studied patients. Also, variance inflation factors were used to assess the multicollinearity, and we used the Hosmer-Lemeshow test to assess the fit of the logistic regression model. A 95% confidence interval was applied with a 5% margin of error, and a statistical significance level was set at $P < 0.05$.

RESULTS

Throughout this study, the mean age of patients affected by PCSFP was 54.53±11.6 years. Males constituted a notably greater percentage of the slow flow group (78.3%) than control group (58.3%), with a *P*-value of 0.019.

As presented in Table 1, smoking emerged as a notable traditional risk factor, accounting for 66.7% of patients in slow-flow group compared to 40% in control group ($P = 0.003$).

The most common presentation of the slow flow group was unstable angina followed by non-STEMI (NSTEMI). Figure 1 demonstrates the clinical presentation of the two groups.

Table 2 shows that hemoglobin level was significantly higher, with a mean value of 14±1.92 in the study group, compared to 13.17±1.78 in the control group, with a *P*-value of *P*-value = 0.015. Also, serum creatinine was found significantly higher, at a mean value, of 1.02± 0.42 in the CSF group compared to 0.88±0.28 in the control group with *P*-value = 0.044. In addition, serum triglycerides (TGs) were found greater in the CSF group with a median (IQR) of 142.5 (103.5-200) as compared to 112 (85-155) in the control group, with *P*-value = 0.016. A notable increase in serum osmolality and its determinants (BUN, Na, and glucose) was observed in CSF patients. The mean serum osmolality was 295.08±6.77 mOsmol/kg in the slow flow group, compared to 284.64±4.74 mOsmol/kg in the control group ($P<$ 0.001).

The receiver operating characteristic curve, illustrated in Figure 2, identified >290.28 mOsmol/kg as the optimal cut-off value for serum osmolality in distinguishing patients with and without CSF. The established threshold attained a sensitivity of 91.67%, a specificity of 88.33%, and an area under the curve of 0.953, denoting superior diagnostic precision.

Table 1: Comparison between both groups regarding demographic data and risk factors

		Slow flow group	Control group	Test value	*P*-value	Sig.
		No:60	No:60			
Age (years)	Mean ± SD	54.53±11.6	54.48±12.39	0.023•	0.982	NS
	Range	21-76	27-78	0.023•	0.982	NS
Gender	Female	13 (21.7%)	25 (41.7%)	5.546*	0.019	S
	Male	47 (78.3%)	35 (58.3%)	5.546*	0.019	S
Smoking		40 (66.7%)	24 (40.0%)	8.571*	0.003	HS
Hypertension		24 (40.0%)	33 (55.0%)	2.707*	0.100	NS
Diabetes mellitus		19 (31.7%)	15 (25.0%)	0.657*	0.418	NS
Dyslipidemia		17 (28.3%)	14 (23.3%)	0.391*	0.532	NS
Ischemic heart disease		6 (10.0%)	1 (1.7%)	3.793*	0.051	NS
Chronic kidney disease		3 (5.0%)	1 (1.7%)	1.034*	0.309	NS
Atrial fibrillation		2 (3.3%)	3 (5.0%)	0.209*	0.647	NS
Hypothyroidism		1 (1.7%)	4 (6.7%)	1.878*	0.170	NS

P-value < 0.05: Significant; •: Independent t-test, *: Chi-square test, SD: Standard deviation, Sig.: Significance, No: Number, NS: Not significant, HS: Highly significant

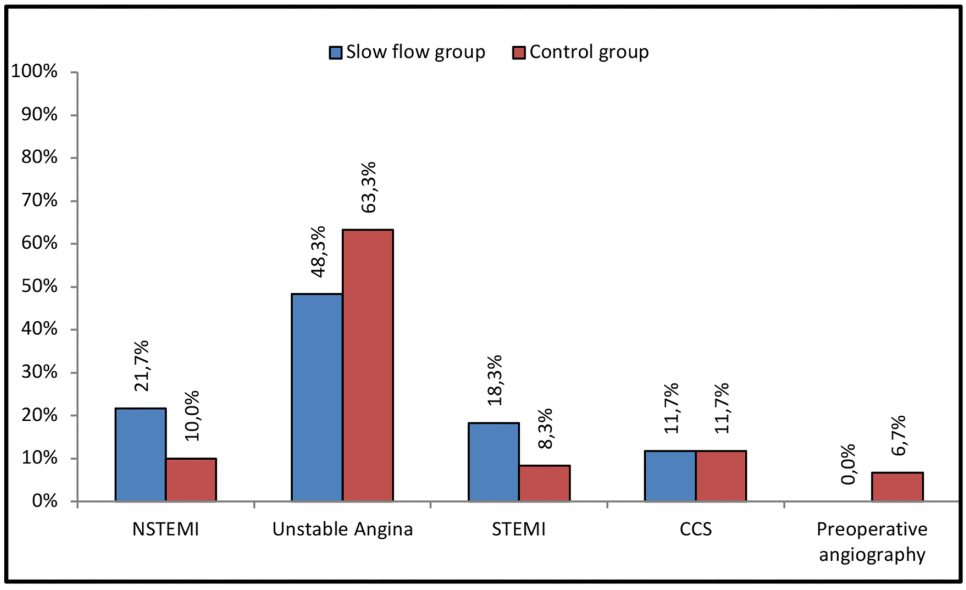


Figure 1: Comparison between patients with slow flow and control group regarding clinical presentation. The most common presentation of the slow flow group was an unstable angina followed by NSTEMI, and the patients undergoing preoperative coronary angiography were more prevalent in the control group

NSTEMI: Non-ST segment elevation myocardial infarction, STEMI: ST segment elevation myocardial infarction, CCS: Chronic coronary syndrome

As shown in Table 3, univariate logistic regression analysis revealed a significant association between all assessed parameters and CSF phenomenon. Furthermore, multivariate logistic regression identified serum osmolality > 290.26 mOsm/kg as the strongest predictor, with an [odds ratio (OR) (95% confidence interval (CI)] of 83.119 (4.488-1539.245) and a *P*-value of 0.003. This was followed by serum glucose > 127 mg/dL (OR = 20.291, 95% CI: 2.611–157.687, *P* = 0.004), smoking (OR = 15.366, 95% CI: 1.458–161.956, *P* = 0.023), BUN > 14 mg/dL (OR = 12.057, 95% CI: 1.827–79.566, *P* = 0.010), and TGs > 127 mg/dL (OR = 7.729, 95% CI: 1.251–47.738, *P* = 0.028).

DISCUSSION

We aimed to investigate in our study the correlation of serum osmolality with the PCSFP among Egyptian people. To assess

Table 2: Comparison between the two groups regarding laboratory parameters

		Slow flow group No: 60	Control group No: 60	Test value	*P*-value	Sig.	Cohen's d
Hemoglobin (g/dL)	Mean ± SD	14±1.92	13.17±1.78	2.465•	0.015	S	0.45
	Range	9.4-19.8	9-17				
Total leukocyte count (x10^3/uL)	Mean ± SD	8.86±3.48	8.84±2.98	0.025•	0.980	NS	0.006
	Range	2.8-19.8	3.3-19.4				
Platelets (x10^3/uL)	Mean ± SD	260.67±81.02	260.62±81.74	0.003•	0.997	NS	0.0006
	Range	84-557	121-532				
Creatinine (mg/dL)	Mean ± SD	1.02±0.42	0.88±0.28	2.033•	0.044	S	0.39
	Range	0.5-2.88	0.33-2.08				
Potassium (mmol/L)	Mean ± SD	4.17±0.43	4.1±0.46	0.901•	0.369	NS	0.16
	Range	3.4-5	2.5-5				
HbA1c (%)	Mean ± SD	6.33±1.34	6.02±1.11	1.371•	0.173	NS	0.25
	Range	4.9-10.3	4.8-9.8				
Total cholesterol (mg/dL)	Mean ± SD	170.48±47.92	183.48±53.91	-1.396•	0.165	NS	0.25
	Range	76-312	83-300				
Triglycerides (mg/dL)	Median (IQR)	142.5(103.5-200)	112(85-155)	-2.412≠	0.016	S	0.45
	Range	49-474	47-397				
Low density lipoprotein (mg/dL)	Mean ± SD	102.23±39.51	113.32±44.04	-1.451•	0.149	NS	0.27
	Range	12-194	38-230				
High density lipoprotein (mg/dL)	Mean ± SD	38.77±13.18	41.78±11.96	-1.313•	0.192	NS	0.24
	Range	14-108	25-75				
Sodium (mmol/L)	Mean ± SD	139.28±2.71	136.3±2.79	5.941•	0.000	HS	1.08
	Range	132-149	127-142				
Random blood glucose (mg/dL)	Mean ± SD	165.87±56.28	125.43±50.09	4.157•	0.000	HS	0.76
	Range	90-370	81-400				
Blood Urea Nitrogen (mg/dL)	Median (IQR)	18(15 – 20)	14(11 – 16)	-4.944≠	0.000	HS	1.01
	Range	9 – 107	6 – 27				
Serum Osmolality (mOsm/kg)	Mean ± SD	295.08 ± 6.77	284.64 ± 4.74	9.790•	0.000	HS	1.79
	Range	284.64 – 330.49	267.15 – 293.13				

P-value < 0.05: Significant, •: Independent t-test; ≠: Mann-Whitney test, IQR: Inter quantile range, SD: Standard deviation, Sig.: Significance, No: Number, NS: Not significant, HS: Highly significant

Cohen's d Interpretation: Neglected: < 0.2, Small: > 0.2, Medium: > 0.5, Large: ≥0.8

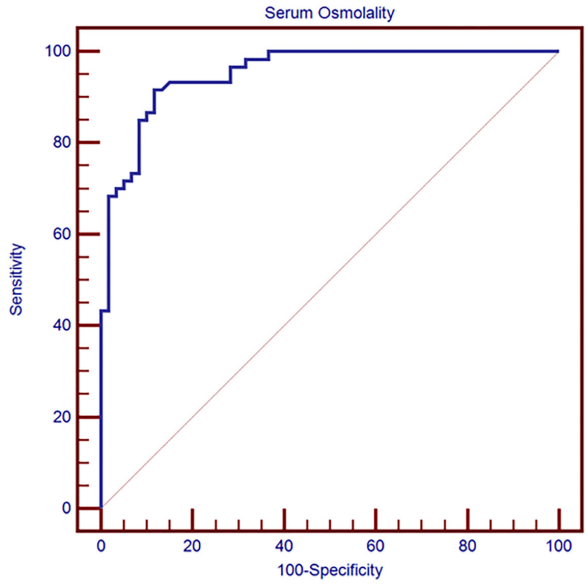
coronary flow, the TIMI frame counting method was used as it is a quantitative and relatively objective method.[11]

In our study, the mean age was 54.53±11.6 years. This is consistent with previous studies that found individuals with PCSFP are generally younger compared to those with obstructive CAD.[4]

In a cohort study involving 213 patients with CSF, Mikaeilvand et al.[12] reported a mean patient age of 53.81±11.91 years.

Seventy-eight-point three percent of PCSFP patients were males, indicating that PCSFP is more often encountered in males. Male gender was statistically significant in PCSFP with OR (95% CI) of 2.582 (1.16-5.75) and with *P*-value = 0.02. Male sex was independently associated with PCSFP in multivariable regression analysis. This finding may be explained by the greater incidence of smoking in men and the cardioprotective influence of female hormones against atherosclerosis.[13] This is consistent with other studies as Hawkins et al.[14] and Sanghvi et al.[15] where they found that male sex was significant in PCSFP than in normal coronary flow. Hawkins et al.'s [14] study revealed that male sex independently predicted the presence of CSFP with OR (95% CI) of 3.36 (1.17-8.61) and a *P*-value = 0.02.

Smoking was notably associated with PCSFP in our study, with 66.7% of patients in the PCSFP group being smokers. A notable variation was observed, and multivariate regression analysis confirmed smoking as an independent predictor of PCSFP (OR = 15.366, 95% CI: 1.458-161.956, *P* = 0.023).



Cut-off point	AUC 95% (CI)	Cross validated AUC (CI)	Sensitivity 95% (CI)	Specificity 95% (CI)	PPV 95% (CI)	NPV 95% (CI)
> 290.28	0.953 (0.898-0.983)	0.870 (0.79–0.95)	91.67 (77.4 - 95.2)	88.33 (81.6 - 97.2)	88.7 (81.0 - 97.1)	91.4 (78.1- 95.3)

Figure 2: ROC curve for serum osmolality level to differentiate between patients with and without slow flow

ROC: Receiver operating characteristic, AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value

Table 3: Univariate and Multivariate logistic regression analysis for predictors of slow flow group

	Univariate				Multivariate			
	P-value	OR	95% CI for OR		*P*-value	OR	95% CI for OR	
			Lower	Upper			Lower	Upper
Male gender	0.020	2.582	1.160	5.750	0.796	1.348	0.140	12.967
Smoking	0.004	3.000	1.424	6.319	0.023	15.366	1.458	161.956
Dilated LA	0.034	0.381	0.156	0.930	0.411	0.388	0.041	3.700
Hemoglobin	0.034	2.347	1.067	5.162	0.905	1.131	0.149	8.576
Creatinine	0.026	2.366	1.111	5.040	0.337	2.261	0.428	11.952
Triglycerides	0.011	2.600	1.243	5.439	0.028	7.729	1.251	47.738
Sodium	0.000	10.789	4.520	25.753	0.570	2.272	0.134	38.627
Serum glucose	0.000	12.000	5.072	28.391	0.004	20.291	2.611	157.687
Blood urea nitrogen	0.000	7.410	3.094	17.748	0.010	12.057	1.827	79.566
Serum osmolality	0.000	68.143	21.482	216.157	0.003	83.119	4.488	1539.245

OR: Odds ratio, CI: Confidence interval

This might be attributed to the injurious effect of smoking on vascular endothelium and its contribution to subclinical atherosclerosis. Also, smokers generally have higher hemoglobin and hematocrit levels, which have been linked to the pathogenesis of this phenomenon.[16] These results harmonize with the evidence presented by Kalayci et al.[17] and disagree with Güneş et al.[18], in which smokers represented only 30% of the cases; this might be due to their small study population, which was only 30 patients.

Our study did not establish a meaningful association between PCSFP and either diabetes mellitus or hypertension. Our results concur with those reported by Sanghvi et al.[15] ; however, they diverge from the study by Sanati et al.[19] on an Iranian population, which demonstrated a substantial prevalence of

hypertension in the CSF group than in the control group (52% vs. 31%, $P = 0.008$).

According to the clinical presentation, the PCSFP presentation varied from STEMI, NSTEMI, unstable angina, and CCS. In our study, unstable angina was the most common mode of presentation (48.3%). This disagrees with the study by Kumar and Garre[20] where the common clinical presentation was CCS (56%).

Regarding the ECG, Mohammad Muthiullah's prospective cross-sectional study stated that 67% of patients with PCSFP had an abnormal resting ECG[21]; this matches the results of our study as most patients in our study presented with an abnormal resting ECG (56.7%).

All the echocardiographic parameters were statistically non-significant between the 2 study groups except dilated left atrium and presence of significant valvular lesions which were more found in the control group. This is due to higher representation of patients undergoing preoperative coronary angiography for valvular heart disease in the control group.

Based on the vessel affected in PCSFP, slow flow affecting the three vessels was the most common angiographic finding (60%). This supports the theory that the phenomenon is a systemic condition.

LAD was the most common artery involved. LAD, LCX, and RCA were involved in 88.3%, 81.7%, and 73.3% of cases, respectively. Our results resonate with those of Sanghvi et al.[15], who documented the highest incidence of involvement in the LAD artery (82.5%), followed by the LCX artery (67.5%) and the RCA (60%).

As part of the investigation into PCSFP, commonly available laboratory markers, including platelet count, hemoglobin levels, and white blood cells (WBCs) count, were assessed. Our findings revealed no correlation between PCSFP and WBCs or platelet counts, and no notable difference was detected between the PCSFP and control groups. This is consistent with the study by Ghaffari et al.[22], which found no link between PCSFP and WBCs, unlike platelet count, which was elevated in PCSFP relative to normal coronary flow in their study.

The hemoglobin level of patients in the PCSFP group was higher than in the control group, demonstrating a substantial variation between groups, with a mean value of 14 ± 1.92 in the study group relative to 13.17 ± 1.78 in the control group, with a P-value = 0.015. In addition, a strong association between hemoglobin level and PCSFP was found following multivariate analysis. It can be hypothesized that a rise in erythrocyte concentration could lead to a reduction in coronary blood flow by increasing blood viscosity.[23] This agrees with Ghaffari et al.[22] and with Nough et al.[24], who found that the hemoglobin level of patients in the PCSFP group was higher than in the normal coronary flow group.

Regarding lipid profile, there was a statistically significant variation in the TGs level between both groups. TAG level was elevated in the PCSFP group, relative to the control group, with median (IQR) of 142.5 (103.5-200) and 112 (85-155), respectively. TAG levels were determined to be independent predictors of PCSFP through multivariable analysis, yielding an OR (95% CI) of 7.729 (1.251-47.738) with a P-value of 0.028. In contrast, no notable variations were detected in total cholesterol, low-density lipoprotein (LDL), or high-density lipoprotein levels between the groups. This is in agreement with Kalayci et al.[17] regarding TAG level, it disagrees regarding the rest of the lipid profile, where there was a notable correlation between the PCSFP phenomenon and higher TAG, cholesterol, and LDL levels. Reflecting our results, Sezgin et al.[25] also reported that high TAG levels might cause endothelial dysfunction in PCSFP patients.

According to HbA1c levels, the two groups did not differ substantially the two groups. This is consistent with the study by Kalayci et al.[17]

PCSFP patients were found to have markedly greater serum osmolality levels than the control group, as demonstrated in this study. Calculated serum osmolality values were 295.08 ± 6.77 mOsmol/kg in the PCSF group and 284.64 ± 4.74 mOsmol/kg in the control group (P-value ≤ 0.001).

Also, the multivariate logistic regression analysis showed that serum osmolality was a strong predictor of CSF phenomenon, with serum osmolality > 290.26 mOsm/kg, OR of 83.119 (95% CI, 4.488-1539.245) and P-value = 0.003.

This observation corresponds with the study by Kargin et al.[8], which found that dehydration was significantly more pronounced in CSFP patients than in the control group.

Serum osmolality and Na act as essential biomarkers for assessing the body's hydration balance.[26] The pathophysiological link between hyperosmolality and CSF may involve increased blood viscosity and resultant endothelial dysfunction. Elevated osmolality can promote hemoconcentration and oxidative stress, both of which have been implicated in microvascular dysfunction. Moreover, hyperosmolar conditions may impair nitric oxide availability and contribute to inflammatory responses, affecting the vascular endothelial factors known to underlie PCSFP.[27]

Furthermore, as serum osmolality reflects hydration status and given that hydration was not directly measured in our study, the potential influence of dehydration on osmolality,

and indirectly on coronary flow, cannot be excluded. Previous studies have emphasized that markers like Na and osmolality may partly reflect intravascular volume depletion, especially in the absence of direct fluid status monitoring.[26,27]

Study Limitation

Certain limitations should be considered in this study. First, the single-center nature of the study may limit the generalizability of our findings. Additionally, the observational and cross-sectional design raises the concern of reverse causation, as PCSFP, could potentially lead to elevated serum osmolality through a stress response (e.g., catecholamine release). Also, the relatively small sample size due to the rarity of the disease may limit the statistical power. The lack of extended follow-up in our study population also prevents us from assessing long-term outcomes and the temporal stability of the observed associations. Finally, while we adjusted for several key confounders, residual confounding from unmeasured factors such as hydration status, subclinical inflammation, or neurohormonal activation remains a possibility.

CONCLUSION

Primary coronary phenomenon is more common in males. Smoking, hypertriglyceridemia, elevated hemoglobin levels, and serum osmolality can be considered independent predictors of this phenomenon.

Thus, while our findings support a strong association between hyperosmolality and PCSFP, further studies are warranted to clarify the causal relationship and elucidate whether correcting hydration imbalances could modify the risk or severity of PCSFP.

Ethics

Ethics Committee Approval: This study was approved by the Ain Shams University Faculty of Medicine Research Ethics Committee (approval number: FWA000017585, date: 14.02.2024).

Informed Consent: Prior to participation, all patients were given a detailed explanation of the procedure, and written informed consent was duly acquired.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.R.E., M.M.A.I., Concept: R.R.E., I.I.E., Design: R.R.E., M.M.N.A., Data Collection or Processing: R.R.E., M.M.N.A., I.I.E., M.M.A.I., Analysis or Interpretation: M.M.N.A., I.I.E., M.M.A.I., Literature Search: R.R.E., M.M.A.I., Writing: R.R.E., M.M.A.I.

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RESEARCH ARTICLE

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Left Atrial Remodeling After Anterior STEMI: A Randomized Trial of Continuous High-Intensity Versus Moderate-Intensity Aerobic Training in Post-PCI Cardiac Rehabilitation

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Abstract

Background and Aim: Myocardial infarction (MI) triggers adverse structural and functional cardiac remodeling. While moderate-intensity exercise-based cardiac rehabilitation (CR) improves recovery, emerging evidence suggests higher-intensity regimens may yield greater benefits. Although high-intensity interval training has demonstrated safety and efficacy in cardiac populations, the impact of high-intensity continuous aerobic training (HICT) on left atrial (LA) mechanics post-primary percutaneous coronary intervention (PCI) for anterior wall ST-segment elevation MI (STEMI) remains underexplored. This study aims to investigate the impact of HICT versus moderate-intensity continuous training (MICT) on LA mechanics in patients post-primary PCI for anterior STEMI.

Materials and Methods: In a single-center randomized controlled trial at Aim Shams University Hospital, 60 adults 1-month post-primary PCI for anterior STEMI were randomized to 6 weeks of CR involving either high-intensity continuous training [HICT; 80-90% peak heart rate (HR)] or (MICT; 50-70% peak HR). Participants completed 18 treadmill sessions (3/week). Diastolic function and LA mechanics (reservoir, conduit, contractile strains) were assessed via two-dimensional speckle-tracking echocardiography pre- and post-intervention.

Results: This study examined patients with a mean age of 51.82 years, predominantly male (91.7%). Both the HICT group and the comparator group exhibited improvements in LA mechanics and diastolic function, though intergroup differences were statistically non-significant. HICT group demonstrated numerically greater gains in LA reservoir strain (5.67±4.39% vs. 3.80±3.32%, $P = 0.115$) and LA contractile strain (-2.93±4.27% vs.-1.33±3.74%, $P = 0.110$). Similarly, reductions in diastolic indices were comparable between groups: E/A (0.14±0.12 vs. -0.14±0.14, $P = 0.927$) and E/E' (-0.25±0.16 vs. -0.30±0.34, $P = 0.568$). While trends favored HICT, no outcome reached statistical significance, suggesting comparable efficacy between interventions.

Conclusion: HICT and MICT show comparable safety and efficacy in enhancing cardiac function, suggesting exercise intensity may be tailored to patient preference or tolerance.

Keywords: High-intensity exercise, left atrial strain, cardiac rehabilitation, primary PCI, anterior STEMI.

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INTRODUCTION

Myocardial infarction (MI) induces substantial structural alterations in the heart, affecting both systolic and diastolic functions. Advances in diagnostic and therapeutic strategies have significantly reduced mortality rates from acute MI; however, rehabilitating acute MI (AMI) survivors remains a pressing public health concern.[1] For patients with ST-segment elevation MI (STEMI) who undergo primary percutaneous coronary intervention (PCI), moderate-intensity exercise is commonly recommended during cardiac rehabilitation (CR) to enhance cardiac function.[2] Emerging evidence, however, suggests that high-intensity exercise may provide superior benefits compared to moderate-intensity regimens in improving cardiovascular outcomes.[3]

CR programs traditionally include aerobic, resistance, and endurance exercises, with aerobic exercise categorized into low, moderate, and high intensities. Initially, low-intensity aerobic exercise was favored due to fears of triggering cardiac events.[4] However, research later confirmed the safety and effectiveness of moderate-intensity exercise in enhancing cardiovascular fitness and reducing risks. More recently, high-intensity interval training (HIIT) has gained recognition for significantly improving cardiovascular health, endothelial function, and patient prognosis. Despite early concerns, studies indicate that sustained high-intensity exercise when kept below the myocardial ischemic threshold is not only safe but may also boost myocardial blood flow and heart function. This evolution reflects a shift toward incorporating higher-intensity regimens as evidence of their benefits and safety grows.[3,5] Compared to HIIT, high-intensity continuous aerobic training (HICT) may be psychologically more acceptable to some cardiac patients, especially those in the early phase of rehabilitation. The structured nature of HIIT can promote confidence, reduce exercise-related anxiety, and improve adherence to long-term rehabilitation programs.

High-intensity continuous exercise is linked to reduced all-cause mortality and a lower risk of heart disease, independent of workout duration, and it is more effective than moderate-intensity exercise in improving cardiovascular risk factors, particularly through enhancing VO_2 peak. Biologically, high-intensity exercise triggers heightened calcium release, adenosin trifosfat turnover, and carbohydrate utilization, leading to metabolite, ion, and free radical accumulation. This accumulation is key to the activation of Ca+/calmodulin-dependent protein kinase II and AMP-activated protein kinase, which collectively stimulate the gene expression for peroxisome proliferator-activated receptor gamma coactivator 1-alpha. This cascade increases mitochondrial protein synthesis rates, resulting in greater mitochondrial content compared to moderate-intensity exercise, thereby enhancing metabolic and endurance adaptations.[2,6]

After a MI, the heart often undergoes adverse remodeling, leading to increased stiffness, impaired function, and collagen buildup. Exercise counteracts these effects by reducing fibrosis, promoting angiogenesis, and improving heart contraction and mitochondrial efficiency. These benefits arise through the modulation of hormonal systems (renin-angiotensin-aldosterone), the regulation of enzymes (matrix metalloproteinases), and the reduction of oxidative stress.[7] Speckle tracking echocardiography (STE) is highlighted as a sensitive imaging tool to assess heart deformation and strain, surpassing traditional metrics like ejection fraction. Left atrial (LA) strain analysis via STE has emerged as a sensitive tool to assess LA mechanics, which are critical for ventricular filling and cardiac output. In patients with anterior STEMI treated with primary PCI, LA dysfunction often precedes structural remodeling and heart failure.[8]

This study investigates whether HICT is safe and effective for improving LA strain in patients recovering from anterior wall STEMI after primary PCI. While HIIT is known to be safe and effective, there is limited evidence on HICT in cardiac populations. The researchers hypothesize that HICT will lead to greater improvements in LA strain compared to moderate-intensity continuous training (MICT); aiming to address this evidence gap and evaluate HICT's potential benefits in cardiac rehabilitation.

METHODS

Study Design and Population

This six-month randomized controlled trial (February-August 2024) enrolled 60 adult patients at Aim Shams University Hospital's Cardiac Rehabilitation Unit. Participants had undergone successful primary PCI for anterior STEMI at least three weeks prior and achieved complete revascularization. They were randomized via a computer-generated method between March and May 2024. Ethical (approval number: MS 215/2024, date: 13.03.2025) was secured, and written informed consent was obtained, with confidentiality and privacy assured for all participants.

Patients were excluded if they had significant cardiac conditions [e.g., severe left ventricular (LV) dysfunction, decompensated heart failure, hemodynamic instability, severe valvular disease, uncontrolled arrhythmias, angina at low workloads], physical or musculoskeletal limitations, incomplete revascularization, major comorbidities (severe hepatic/renal impairment, chronic obstructive pulmonary disease, morbid obesity, clinical depression), or high-risk features identified during symptom-limited modified Bruce protocol stress testing [e.g., symptoms below 5 metabolic equivalents (METS), silent ischemia with ≥2 mm ST-segment depression].

This randomized controlled trial assigned patients to two groups: Group A received HICT, while Group B (the control group) underwent MICT as part of cardiac rehabilitation. Both groups were monitored over a six-week follow-up period.

Initial Risk Stratification and Exercise Prescription

Prior to the CR program, patients underwent a comprehensive evaluation. This included recording demographic data (age, gender, occupation, smoking history), assessing cardiovascular risk factors and comorbidities, performing general and systematic physical examinations, and screening for musculoskeletal limitations that could affect exercise capacity.

Before starting rehabilitation, patients underwent laboratory testing (complete blood count, urea, creatinine, electrolytes, hemoglobin A1c, cardiac biomarkers) and a 12-lead electrocardiogram (ECG). Risk stratification was performed via a symptom-limited treadmill stress test (modified Bruce protocol) to determine maximal heart rate (HR_{max}) and HR reserve (HRR). High-risk criteria included symptoms at <5 METS, ventricular arrhythmias, abnormal hemodynamics, or silent ischemia (ST-segment depression ≥2 mm). Exercise intensity was tailored using the Karvonen formula, with high-intensity training targeting ≥60% HRR (≥80% HR_{max}) and moderate-intensity training set at 40-60% HRR (60-80% HR_{max}).[9]

Exercise Training Protocol

Patients completed an 18-session supervised treadmill exercise program over six weeks (3 sessions/week). Each 40-minute session included:

1. Warm-up: Ten minutes.

2. Main training phase: Twenty minutes at prescribed intensity (treadmill speed/incline adjusted to achieve target heart rate).

3. Cool-down: Ten minutes.

Continuous ECG monitoring was used during sessions, and patients were instructed to report symptoms (e.g., chest pain, dizziness). Participants who missing three consecutive sessions were excluded.

Echocardiographic Assessment

Echocardiographic evaluations were performed by experienced echocardiographers before and after the rehabilitation program. Echocardiographers were blinded to the study groups. LA strain was assessed using two-dimensional STE in apical four-chamber and two-chamber views, following American Society of Echocardiography/European Association of Cardiovascular Imaging guidelines. The LA endocardium was traced to define the region of interest, which was adjusted for thinner atrial walls. Strain curves were generated for 12 left atrium LA segments to calculate global longitudinal strain (GLS) for reservoir, conduit, and contractile phases. Reservoir strain was measured during systole, conduit strain during passive LA emptying, and contractile strain during active atrial contraction.

Diastolic function was assessed by measuring mitral peak early (E) and atrial (A) flow velocities, mitral annular septal and lateral velocities (e'), and calculating E/A and E/e' ratios. LA dimensions were measured in the parasternal long-axis view, and LA volumes (maximal and minimal) were calculated using the biplane area-length method.

STE measurements in this study were independently reviewed by more than one experienced echocardiographer. In cases of discrepancy, consensus was reached through joint review to ensure accuracy and consistency of the measurements. This consensus-based approach, performed by skilled operators following standardized protocols, enhances the reliability of the reported strain values.

Sample Size Calculation

The sample size was calculated using the power analysis and sample size 15 program, with a power of 80% and an alpha error of 5%. Based on the findings of D'Andrea et al.[3], which demonstrated that HIIT led to reverse cardiac remodeling and improved diastolic and systolic function as assessed by standard echocardiography, an effect size difference of 0.8 was assumed between the two groups for LA function parameters. Accounting for a 10% dropout rate, a total of 60 patients (30 per group) were deemed necessary.

Statistical Analysis

Data were analyzed using the (SPSS, version 21). Continuous variables were described using appropriate measures of central tendency and dispersion, expressed as mean ± standart deviation, and compared using t-tests. Categorical variables were summarized as percentages and analyzed using chi-square tests. Pearson correlation and multivariate linear regression analyses were performed to evaluate the relationships between variables. All statistical tests were two-tailed, with statistical significance set at $P \leq 0.05$.

RESULTS

The demographic and risk factor profiles were comparable between the moderate- and high-intensity groups, with no statistically significant differences observed. Age, gender distribution, smoking habits, and comorbidities such as diabetes mellitus, hypertension (HTN), and ischemic heart disease (IHD) were comparable, providing a balanced baseline between the study groups ($P > 0.05$ for all variables) Table 1.

Table 1: Demographic data and risk factors among the study groups

		Moderate intensity (n=30)	High intensity (n=30)	*P*-value
Age	Mean ± SD	54.13±10.47	49.5±11.58	0.109
	Range	33-70	24-68	
Gender				
Female	n (%)	4 (13.3%)	1 (3.3%)	0.161
Male	n (%)	26 (86.7%)	29 (96.7%)	
Smoker	n (%)	18 (60.0%)	21 (70.0%)	0.417
Shisha	n (%)	3 (10.0%)	1 (3.3%)	0.301
Hashish	n (%)	2 (6.7%)	6 (20.0%)	0.129
DM	n (%)	13 (43.3%)	6 (20.0%)	0.052
HTN	n (%)	9 (30.0%)	11 (36.7%)	0.584
IHD	n (%)	3 (10.0%)	4 (13.3%)	0.688
CVS	n (%)	3 (10.0%)	1 (3.3%)	0.301
Alcohol	n (%)	0 (0.0%)	1 (3.3%)	0.313
Single Kidney	n (%)	1 (3.3%)	0 (0.0%)	0.313
Tramadol	n (%)	1 (3.3%)	1 (3.3%)	>0.99
Paroxysmal AF	n (%)	1 (3.3%)	0 (0.0%)	0.313
Hypothyroidism	n (%)	1 (3.3%)	1 (3.3%)	>0.99
HCV	n (%)	0 (0.0%)	1 (3.3%)	0.313
Dyslipidemic	n (%)	1 (3.3%)	0 (0.0%)	0.313
Family History	n (%)	3 (10.0%)	2 (6.7%)	0.64

P-value < 0.05 was considered statistically significant.

DM: Diabetes mellitus, HTN: Hypertension, IHD: Ischemic heart disease, CVS: Cerebrovascular stroke, AF: Atrial fibrillation, HCV: Hepatitis C virus, SD: Standard deviation

Table 2: Echocardiographic parameters before and after exercise among continuous high intensity group

Continuous high intensity group		Before (n=30)	After (n=30)	*P*-value
LA reservoir strain %	Mean ± SD	21.6±7.79	27.27±10.08	**<0.001**
	Range	6-36	7-45	
LA conduit strain %	Median (IQR)	-11.5 (-15- -7)	-14 (-19--10)	**<0.001**
	Range	-23--3	-31--3	
LA contractile strain %	Median (IQR)	-10 (-14--5)	-13 (-16--9)	**<0.001**
	Range	-21--1	-24--2	
LA diameter	Mean ± SD	38.57±4.48	38.57±4.48	-
	Range	32-47	32-47	
LA volume max (biplane)	Mean ± SD	51.87±22.17	50.6±19.82	**<0.001**
	Range	22-132	26-107	
E/A	Mean ± SD	1.17±0.22	1.03±0.14	**<0.001**
	Range	0.9-1.5	0.9-1.3	
E/E'	Mean ± SD	7.73±0.92	7.48±0.9	**<0.001**
	Range	6.25-9.3	6-9	

P-value < 0.05 was considered statistically significant.

LA: Left atrial, E/A. Early-to-atrial diastolic velocity ratio, E/E': Early diastolic velocity to annular velocity ratio, SD: Standard deviation, IQR: Interquantile range

Table 3: Echocardiographic parameters before and after exercise in moderate intensity group.

Moderate intensity group		Before (n=30)	After (n=30)	*P*-value
LA reservoir strain %	Mean ± SD	27.3±8.88	31.1±8.63	**<0.001**
	Range	10-46	17-47	
LA conduit strain %	Median (IQR)	-13 (-19--7)	-17.5 (-23--10)	**<0.001**
	Range	-31-0	-33--5	
LA contractile strain %	Median (IQR)	-13.5 (-16--10)	-15 (-18--12)	0.014
	Range	-24--4	-25--6	
LA diameter	Mean ± SD	37.23±4.09	37.23±4.09	–
	Range	29-47	29-47	
LA volume max (biplane)	Mean ± SD	45±18.97	42.03±14.24	0.336
	Range	21-110	18-74	
E/A	Mean ± SD	1.17±0.2	1.03±0.15	**<0.001**
	Range	0.9-1.6	0.9 -1.5	
E/E'	Mean ± SD	8.03±1.14	7.73±1.02	**<0.001**
	Range	6-10	6-9.5	

P-value < 0.05 was considered statistically significant.

LA: Left atrial, E/A. Early-to-atrial diastolic velocity ratio, E/E': Early diastolic velocity to annular velocity ratio, SD: Standard deviation, IQR: Interquantile range

Table 4: Mean differences of echocardiographic parameters between both groups

	Moderate intensity (n=30)	High intensity (n=30)	*P*-value
LA reservoir strain %	3.80±3.32	5.67±4.39	0.115
LA conduit strain %	-3.13±3.66	-3.03±3.97	0.789
LA contractile strain %	-1.33±3.74	-2.93±4.27	0.110
LA volume max (biplane)	-2.97±16.59	-1.27±13.45	0.778
E/A	-0.14±0.14	-0.14±0.12	0.927
E/E'	-0.30±0.34	-0.25±0.16	0.568

Date are are presented in mean ± standard deviation. *P*-value < 0.05 was considered statistically significant.

LA: Left atrial, E/A: Early-to-atrial diastolic velocity ratio, E/E': Early diastolic velocity to annular velocity ratio

In the group that exercised at HICT, significant improvements were observed in echocardiographic parameters after exercise. LA reservoir strain, LA conduit strain, and LA contractile strain all showed statistically significant increases ($P < 0.001$. Additionally, LA volume maximum and E/A ratio significantly decreased ($P < 0.001$ for both), while E/E' showed a modest but significant reduction ($P < 0.001$). The LA diameter remained unchanged Table 2.

In the group that exercised at MICT, significant increases were noted in LA reservoir strain, LA conduit strain, and LA contractile strain after exercise ($P < 0.001$, < 0.001, and < 0.014, respectively). E/A and E/E' ratios showed significant decreases ($P < 0.001$ for both). No significant changes were observed in LA diameter or LA volume maximum ($P = 0.336$) Table 3.

The mean differences in echocardiographic parameters between MICT and HICT groups were not statistically significant for any variable ($P > 0.05$). Changes in LA reservoir strain, LA conduit strain, LA contractile strain, LA volume maximum, E/A, and E/E' were comparable between the two groups Table 4.

DISCUSSION

Current guidelines for CR in anterior STEMI patients post-primary PCI emphasize moderate-intensity training. However, emerging evidence indicates that high-intensity training (e.g., HIIT) may offer superior improvements in cardiac function compared to traditional moderate-intensity regimens, with HIIT being demonstrated as safe and effective.[3] Despite this, a critical evidence gap persists regarding the safety and efficacy of HICT in this population. Further research is needed to validate HICT's role in optimizing recovery and cardiovascular outcomes.

Echocardiographic GLS is increasingly recognized as a more sensitive marker than traditional ejection fraction for detecting subtle LV dysfunction. Post-myocardial infarction,

LA strain (LAS) serves as a prognostic tool, where progressive improvement may signal positive remodeling and atrial functional recovery, while persistently reduced strain could indicate ongoing dysfunction.[10] Serial monitoring of LAS during follow-up enables clinicians to assess therapeutic efficacy and tailor treatment strategies, offering a dynamic approach to optimizing patient management in cardiovascular care.

This study evaluated the effects of (HICT, Group 1) versus (MICT, Group 2), on LAS in 60 anterior STEMI patients post-primary PCI, randomized during cardiac rehabilitation. The cohort had a mean age of 51.82 years, with a pronounced male predominance (91.7%), consistent with established gender disparities in cardiovascular disease prevalence.[11] Both groups exhibited similar baseline age and gender profile, minimizing confounding variables when assessing exercise intensity impact. These findings align with prior research (e.g., Elbarbary et al.[12]) which identified higher STEMI incidence in males, particularly those aged 56-65, underscoring the demographic relevance of this population for CR studies.

The male predominance in this study (91.7% male) poses a significant limitation to the generalizability of findings, particularly for CR applications in women. Physiologically, women typically exhibit lower baseline peak oxygen uptake (VO_2 peak) than men, and while both sexes benefit from CR, men often achieve greater improvements in VO_2 peak post-rehabilitation.[13] This sex-based disparity in exercise responsiveness suggests that training modalities optimized for male-dominated cohorts may not equally benefit female patients. Consequently, the results of this study, derived from a predominantly male sample, may not fully represent outcomes for the broader cardiac population, underscoring the need for future research with gender-balanced cohorts to validate and refine sex-specific CR strategies.

This study identified HTN (33.3%), smoking (65%), dyslipidemia (53.3%), and diabetes (48.3%) as dominant comorbidities in anterior STEMI patients, reinforcing the critical role of risk factor management in IHD. These findings align with global patterns: Bhardwaj et al.[14] reported similar risk profiles [smoking, HTN, low high-density lipoprotein (HDL), high triglycerides] in young Indian AMI patients, noting the predominance of STEMI in males and frequent left anterior descending artery (LAD) involvement. Similarly, Elkersh et al.[15] observed high rates of smoking (63.5%), HTN (57.5%), diabetes (60.5%), and dyslipidemia (57%) in Egyptian acute coronary syndrome (ACS) patients. Collectively, these studies highlight smoking and metabolic disorders as pivotal, modifiable drivers of cardiovascular events, particularly in males, and underscore the need for targeted preventive strategies across diverse populations.

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Both MICT and HICT groups demonstrated significant improvements in LA strain parameters-reservoir, conduit, and contractile strains-following cardiac rehabilitation, suggesting exercise-induced benefits on atrial function regardless of intensity. These enhancements likely stem from mechanisms such as improved blood flow, reduced atrial stiffness, and adaptive myocardial remodeling.[16] Increased LA reservoir strain reflects greater atrial compliance and optimized ventricular filling, while elevated conduit strain indicates enhanced passive cardiac filling. Improved contractile strain underscores more effective atrial contraction, critical for maintaining cardiac output.[17,18] Importantly, LA strain improvements correlated with reduced diastolic dysfunction severity, as evidenced by inverse relationships with LV filling pressures (E/E' ratio).[19] While both regimens promoted favorable cardiac adaptations, the study highlights exercise's broad role in ameliorating atrial mechanics and diastolic function, independent of intensity.

Our findings align with those of Huang et al.[20], who observed notable enhancements in LA strain measurements after engaging in moderate-intensity exercise. A study by Reddy et al.[21] further showed that high-intensity interval exercise notably enhanced LAS highlighting its significance as a marker of improved atrial function.

The study found no statistically significant differences in LA reservoir, or conduit strain improvements between HICT and MICT groups, though a non-significant trend favored HICT. Both regimens similarly enhanced LA reservoir, conduit, and contractile strains, suggesting comparable efficacy in improving atrial function. These findings align with prior studies Yang et al.[22] and Zheng et al.[23] which reported equivalent LA strain improvements across exercise intensities, implying a potential functional threshold where further intensity increases may not yield additional benefits. The lack of significance may reflect insufficient sample size to detect subtle differences, highlighting the need for larger trials to clarify optimal exercise intensity for atrial remodeling.

The study observed no significant changes in structural LA parameters-LA diameter and maximum LA volume-across both moderate-intensity (MICT) and HICT groups, despite functional improvements in atrial mechanics. Exercise enhanced myocardial efficiency and functional performance (e.g., strain metrics) without inducing structural remodeling, a finding consistent across exercise intensities. These results align with Andrea et al.[3], Fukuta[24], and Caminiti et al.[16], who similarly reported stable LA dimensions despite functional gains, even in older adults.[24] Collectively, these studies suggest that exercise-driven benefits in LA function arise from adaptive physiological mechanisms (e.g., improved compliance, contractility) rather than structural alterations, reinforcing the concept that functional improvements can occur independently of changes in atrial size or volume.

Both MICT and HICT groups exhibited significant improvements in diastolic function, marked by reductions in E/A and E/E' ratios, indicative of enhanced ventricular filling and reduced LV filling pressures. These findings align with prior studies: Alves et al.[25] and Pearson et al.[26] demonstrated diastolic improvements with moderate exercise, while Amundsen et al.[27] reported similar benefits with high-intensity interval training. Notably, no statistically significant differences in E/A or E/E' improvements were observed between MICT and HICT groups, consistent with the study by Trachsel et al.[28], which found comparable efficacy across exercise intensities. This underscores that both regimens similarly optimize diastolic function, likely through shared mechanisms such as improved myocardial compliance and reduced stiffness.

No complications were reported in either the moderate-intensity or high-intensity exercise groups, indicating that both exercise intensities are safe.

Our study compared the effects of HICT and MICT on LA mechanics in cardiac patients. Both regimens were safe and equally effective in improving LA and diastolic function, with no statistical differences observed between groups. The lack of significance may reflect true equivalence in efficacy, as both intensities could induce similar physiological adaptations (e.g., cardiovascular strain sufficient for beneficial remodeling). This supports personalized exercise prescriptions-HICT for time efficiency in tolerant patients; and MICT as a safer alternative for others. However, limitations such as a small sample size (increasing type II error risk). Larger studies are needed to confirm these findings and clarify whether minimal true differences exist.

Study Limitation

This study has several limitations. First, its single-center design, relatively small sample size, and male-predominant cohort may restrict the generalizability of the results to broader populations, including women and diverse clinical settings. Second, the short follow-up period limited the ability to assess the long-term effects of high-intensity exercise on cardiac function and cardiovascular health outcomes. Third, the reliance on HR monitoring without complementary measures such as the Rate of Perceived Exertion may have provided an incomplete picture of exercise intensity and patient effort.

The non-significant differences in secondary outcomes may be attributed to the study not being adequately powered to detect them.

Despite these limitations, the findings support integrating supervised high-intensity exercise programs into CR protocols, particularly given their benefits in improving LAS. To optimize outcomes, programs should be personalized to patient tolerance and implemented with stringent safety protocols, including screening for contraindications and continuous physiological monitoring. Future research should prioritize multi-center trials with larger, more representative cohorts, extended follow-up periods, and standardized intensity assessments (e.g., combining RPE with HR) to evaluate long-term efficacy, safety, adherence, and cardiovascular outcomes.

CONCLUSION

HICT and MICT show comparable safety and efficacy in enhancing cardiac function, suggesting exercise intensity may be tailored to patient preference or tolerance. While statistical equivalence could reflect true biological similarity, limitations like underpowered design or participant heterogeneity warrant further research to validate clinical implications.

Ethics

Ethics Committee Approval: This study was approved by the Ain Shams University Faculty of Medicine Research Ethics Committee (approval number: MS 215/2024, date: 13.03.2025).

Informed Consent: Written informed consent was obtained, confidentiality and privacy were assured for all participants, and the study was secured.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.H.A.H., R.R.E., Concept: A.K.A.A., T.K.A., Design: A.H.A.H., T.K.A., R.R.E., Data Collection or Processing: A.K.A.A., A.H.A.H., R.R.E., Analysis or Interpretation: A.K.A.A., T.K.A., R.R.E., Literature Search: A.K.A.A., A.H.A.H., R.R.E., Writing: A.H.A.H., T.K.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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RESEARCH ARTICLE

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Study on Clinical and Echocardiographic Assessment of Right Ventricular Function in Patients with Mitral Valve Disease in Medical College Kolkata

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Abstract

Background and Aim: Mitral valve disease (MVD) is a significant cardiovascular condition requiring comprehensive evaluation of right ventricular (RV) function. The present study aims to assess the RV function using clinical methods and echocardiography in patients with MVD.

Materials and Methods: This cross-sectional, observational study included 100 patients with moderate and severe MVD at a tertiary care center in India. RV function was assessed through clinical examination and comprehensive echocardiography using 2D, M-mode, color Doppler, pulsed wave Doppler, and tissue Doppler imaging (TDI).

Results: Among the total of 100 patients, 43 (43%) patients had mitral stenosis, 31 (31%) had mitral regurgitation, and 26 (26%) had mixed lesions. RV function was assessed using various parameters, 28 (28%) by eye estimation, 43 (40%) by tricuspid annular plane systolic excursion, 38 (38%) by RV fractional area change, 47 (47%) by TDI S'velocity, and 42 (42%) by RV myocardial performance index. RV dysfunction was more prevalent in patients with: atrial fibrillation, those classified as New York Heart Association class III and IV, and severe mitral valve involvement.

Conclusion: RV dysfunction is common in MVD patients, particularly in those with atrial fibrillation, left atrial dilatation, severe symptoms, and severe valvular involvement. Comprehensive echocardiographic assessment of RV function should be an integral part of the evaluation in MVD patients, as it provides valuable information for risk stratification and clinical management.

Keywords: Atrial fibrillation, echocardiography, heart valve diseases, mitral valve stenosis, ventricular dysfunction, right

INTRODUCTION

Valvular heart disease (VHD) represents a significant global health burden, with mitral valve disease (MVD) emerging as one of its most common manifestations. MVD stands as a major contributor to cardiovascular morbidity and mortality worldwide. The demographic landscape of MVD is particularly noteworthy, as its prevalence demonstrates a striking age-dependent pattern, with a marked increase in the elderly population. Indeed, epidemiological studies have revealed that up to 10% of individuals over 75 years of age are affected by this condition.[1] From the current estimate of 1.5 million individuals aged 65 and above, this number is projected to reach double its present value by 2046, ultimately escalating to approximately 3.3 million affected individuals by 2056.[2] Evaluation of MVD by cardiovascular imaging plays a pivotal role in multiple critical functions in patient care. The fundamental aspects of imaging assessment encompass detailed valve morphology for etiological

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determination, quantification of valvular dysfunction, its hemodynamic impact, and the evaluation of right and left ventricles. Among the various imaging modalities available, echocardiography remains the cornerstone diagnostic tool for mitral valve visualization and assessment.[3] Right ventricular (RV) performance has emerged as a crucial prognostic indicator across numerous cardiovascular conditions. While multiple validated echocardiographic parameters exist for evaluating RV function, each individual measure carries inherent limitations and constraints. A more comprehensive approach, integrating various complementary parameters, offers enhanced reliability in distinguishing between normal and impaired RV function. The diagnostic measurement includes visual assessment, RV myocardial performance index, tricuspid annular plane systolic excursion (TAPSE), 2D RV fractional area change (RVFAC), 2D RV ejection fraction (RVEF), and 3D RVEF. Additionally, advanced techniques like tissue doppler imaging (TDI) are used to derive tricuspid lateral annular systolic velocity (S').[4]

Hence, the aim of the present study was to assess the RV function using clinical methods and echocardiography in patients with MVD.

METHODS

Study Design and Population

This is a cross-sectional, observational study conducted at a tertiary care center in India from July 2017 to December 2018. Patients diagnosed with MVD, attending outpatient department/inpatient department, department of cardiology, were included in the study. A total of 100 patients with a moderate to severe degree of MVD were present in the study. Patients who were not willing to give consent for the study with less than 18 years, pregnant women, with multi-valvular disease with significant aortic valve lesion or organic tricuspid valve lesion, with a medical history of chronic pulmonary disease, co-morbid conditions like diabetes mellitus, severe anemia, and chronic kidney disease, with significant left- to-right shunt or who were hemodynamically unstable were excluded from the study.

Data Collection

After taking informed consent from the eligible patients, a detailed history along with clinical and laboratory investigation was also performed. RV function of each patient was assessed through clinical examination as well as echocardiography examination using GE Vivid 7 echocardiography machine, which included 2D, M mode, color Doppler, pulsed wave Doppler, and TDI. Patients were examined for any history of symptoms of dyspnea, fatigue, palpitation, chest pain and were classified based on New York Heart Association (NYHA) classification. Clinical examination of the patients included pulse rate, blood pressure, jugular venous pressure, dependent edema, precordial examination with particular emphasis on the RV impulse. Atrial fibrillation/flutter or other types of arrhythmias, RV hypertrophy, RV strain, right axis deviation, right bundle branch block, and right atrium enlargement were detected using 12 lead electrocardiography with long lead II. any symptoms related to congestive cardiac failure (CCF) were also noted.

Definition

Mitral Stenosis and Mitral Regurgitation

Reference ranges for mitral stenosis and mitral regurgitation were taken in this study based on the 2014 American Heart Association/American College of Cardiology[5] and are depicted in Table 1 and Table 2. Mitral valve area was calculated by 2D echocardiography planimetry from the parasternal short axis views. MV mean pressure gradient was calculated using continuous wave Doppler in apical-4 chamber view. Mitral regurgitation was calculated using 2D, colour Doppler, proximal isovelocity area method, jet area, vena contracta, effective regurgitant orifice, regurgitant volume, and regurgitant fraction.

Congestive Cardiac Failure

CCF was assessed based on the Framingham criteria of congestive heart failure.[6] The Framingham Heart Study criteria are 100% sensitive and 78% specific for identifying persons with definite congestive heart failure. Major criteria included: paroxysmal nocturnal dyspnea, neck vein distension, rales, radiographic cardiomegaly, acute pulmonary oedema, S3 gallop, increased central venous pressure (>16 cm H_2O at right atrium), hepatojugular reflux, weight loss >4.5 kg, in 5 days in response to treatment while minor criteria included bilateral ankle oedema, nocturnal cough, dyspnea on ordinary exertion, hepatomegaly, pleural effusion, decrease in vital capacity by one third from maximum recorded, and tachycardia (heart rate > 120 beats/min).

NYHA was used to classify the severity of symptoms like dyspnea, fatigue, palpitation, and chest pain. Classification is as follows:

Class I: Patients with no limitation of activities; they suffer no symptoms from ordinary activities.

Class II: Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

Class III: Patients with marked limitation of activity; they are comfortable only at rest.

Class IV: Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Right Ventricular Parameters

RV systolic and diastolic parameters were taken for reference from 2015 guidelines of the American Society of Echocardiography as shown in Figure 1.[7] RV diameter: measured in end-diastole from the RV focused apical 4-chamber view at the mid-level. A value >35 mm was considered abnormal.[7] Pulmonary artery systolic pressure is calculated from the tricuspid regurgitation (TR) jet peak velocity using the Bernoulli equation: pressure =4× (velocity)². The estimated right atrial (RA) pressure was added to the TR peak gradient calculated in this manner.[8]

Mean pulmonary artery pressure (MPAP) is calculated from the pulmonary regurgitation (PR) jet peak velocity using a similar method, after adding the estimated RA pressure to the PR peak gradient. In some patients, it was also calculated from the RV outflow tract acceleration time (RVOT AT) using the standard equation: MPAP = 90 - 0.6×(RVOT AT).[8]

Inferior vena cava (IVC) size and respiratory variation: used as an indicator of RA pressure. Measured from the subcostal view. IVC diameter >2.1 cm that collapses <50% with a sniff suggests high RA pressure of 15 mm Hg (range: 10-20 mm Hg).[7]

Ethical Committee Information

The study was approved by the Institutional Ethics Committee of the Institute and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants (approval number: MC/Kol/IEC/Non-spon/580/07-2017, date: 26.08.2017).

Outcomes

To assess the RV function using clinical methods and echocardiography in patients with MVD.

Table 1: Mitral valve stenosis-severity assessment criteria

Grade	MVA (cm^2)	MV mean PG (mmHg)
Mild	>1.5	<5
Moderate	1-1.5	5-10
Severe	≤1.0	>10

MVA: Mitral valve area, PG: Pressure gradient

Table 2: Severity assessment criteria for mitral valve regurgitation

Definition	Valve hemodynamics
Mild	Central jet area <20% of LA; eccentric holosystolic jet <0.2 cm^2; regurgitant volume <30 mL
Moderate	Central jet area 20-40 of LA%; ERO =0.20-0.39 cm^2; regurgitant volume = 30-59 mL
Severe	Central jet area >40% of LA or eccentric holosystolic jet; vena contracta ≥0.7 cm, ERO ≥0.40 cm^2, regurgitant volume ≥60 mL, regurgitant fraction ≥50%

ERO: Effective regurgitant orifice, LA: Left atrium

Statistical Analysis

Data were analysed using GraphPad InStat (version 3.0). Continuous variables were expressed as mean ± standard deviation. Chi-square and Fisher's exact tests were used to compare data between the two groups. Pearson's correlation coefficient was used to assess relationships between pairs of parameters. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 100 patients with MVD were included in this study. The demographic and clinical characteristics of the patient population are presented in Table 3. The study cohort was predominantly female, with the majority of patients falling within the 20- to 50-year old age group, representing the most prevalent demographic in this population. Rheumatic heart disease was the most common aetiology for MVD in our study. According to the severity of symptoms, most of the patients belong to NHYA class II and III. Figure 2 shows the types of mitral valve involvement.

RV dysfunction, estimated through eye examination, was identified in 28 patients (28%), with the highest prevalence in mitral stenosis (34.8%) compared to regurgitation (19.35%) and mixed lesions (26.9%). Severe mitral stenosis showed higher rates than moderate stenosis (44% vs 22.22%, *P* =0.19), while regurgitation severity showed no significant relationship (*P* =1.0). Despite its subjective nature, eye estimation effectively identifies clinically significant RV dysfunction, particularly in symptomatic patients with stenotic lesions.

Various parameters showing RV systolic and diastolic dysfunction are illustrated in Table 4. The RV dysfunction was observed in 40 (43%) patients by TAPSE, 38 (38%) patients by RVFAC, 47 (47%) patients by TDI S' velocity, and 42 (42%) by RV myocardial performance index/Tei.

Pulsed wave doppler was used to identify the ratio of early diastole to atrial systole, wave velocity right ventricle in flow (A) wave velocity right ventricle inflow (E) at the tricuspid valve in 66 patients without atrial fibrillation, with a mean E/A ratio of 0.79±0.2032 and a mean E wave deceleration time (EDT) of 220.33±32.779 msec. Among these 66 patients, an abnormal E/A ratio <0.8 was found in 44 (66.7%) patients, early diastolic velocity at the tricuspid lateral annulus by TDI early diastolic velocity at tricuspid lateral annulus by TDI (e') in 37 (56%) patients, abnormal E/e' >6 in 47 (71%) patients, e'/ late diastolic velocity at tricuspid lateral annulus by tissue doppler image (a') ratio in 38 (58%) patients, abnormal EDT in 38 (57%) patients, dilated IVC in 34 (52%) patients, and decreased IVC collapse in 26 (40%) patients, suggesting RV diastolic dysfunction.

Parameter	Mean ± SD	Abnormality threshold
TAPSE (mm)	24 ± 3.5	<17
Pulsed Doppler S wave (cm/sec)	14.1 ± 2.3	<9.5
Color Doppler S wave (cm/sec)	9.7 ± 1.85	<6.0
RV fractional area change (%)	49 ± 7	<35
RV free wall 2D strain* (%)	−29 ± 4.5	>−20 (<20 in magnitude with the negative sign)
RV 3D EF (%)	58 ± 6.5	<45
Pulsed Doppler MPI	0.26 ± 0.085	>0.43
Tissue Doppler MPI	0.38 ± 0.08	>0.54
E wave deceleration time (msec)	180 ± 31	<119 or >242
E/A	1.4 ± 0.3	<0.8 or >2.0
e′/a′	1.18 ± 0.33	<0.52
e′	14.0 ± 3.1	<7.8
E/e′	4.0 ± 1.0	>6.0

Figure 1: Normal RV parameters as per American Society of Echocardiography

RV: Right ventricle, MPI:Myocardial performance index, EF: Eection fraction, TAPSE: Tricuspid annular plane systolic excursion, SD: Standard deviation

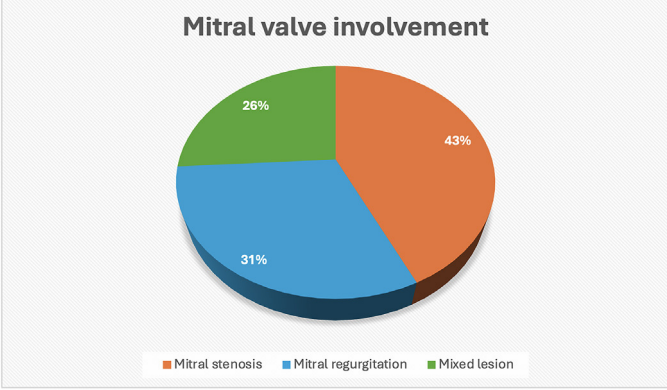

Figure 2: Types of mitral valve involvement

Figure 3 shows correlations of RVFAC with LA size (diameter), left ventricular EF (LVEF), and MPAP. Figure 3A shows a significant linear correlation between RVFAC values and the corresponding LA diameter of patients, suggesting that a larger left atrial diameter was associated with poorer RV systolic function. The linear correlation coefficient (r) was -0.6237 with a 95% confidence interval (CI) of -0.7106 to -0.4869, and significance of p <0.0001. Figure 3B shows that lower LVEF, suggestive of poor LV systolic function, was associated with lower RVFAC (r=0.6387, 95% CI: 0.5057 to 0.7420, P <0.0001). Figure 3C shows that higher MPAP, indicating greater mean pulmonary pressure RV afterload, was associated with lower RVFAC, indicating worse RV systolic function (r=-0.5941, 95% CI: -0.7080 to -0.4502, P <0.0001).

Table 5 demonstrates the relationship between RV function and atrial fibrillation/flutter. All parameters of RV function were significantly affected in patients with atrial fibrillation. The evaluation of RV function using TAPSE, RVFAC, TDI S' vel, TDI Tei, and decreased IVC collapsibility showed significant changes in patients with atrial fibrillation (P <0.05), while e', E/e', and e'/a' also showed significant changes with P <0.0001. When comparing the occurrence of RV systolic dysfunction (RVFAC <35%) between patient groups with and without atrial fibrillation/flutter using Fisher's exact test, a significant association was found (P =0.0318, relative risk=1.747, 95% CI: 1.077 to 2.835).

The correlation between RV function and NYHA class of symptoms is shown in Table 6. All parameters of RV function were significantly affected in the NYHA class III and IV. The RV function, measured by mean E and mean A, showed significant changes in the more symptomatic group (P <0.05), while TAPSE, RVFAC, TDI S' vel, RV Tei index, decreased IVC collapse, e', E/e', and e'/a' were significant with P <0.0001. Table 7 and Table 8 demonstrate the correlation between RV function and mitral stenosis and regurgitation. Patients with severe MVD showed significantly more RV dysfunction compared to those with moderate MVD.

Figure 4 shows a relationship between e'/a' and LA diameter. The graph demonstrates that increased left atrial diameter was associated with a lower e'/a' ratio, suggesting more significant RV diastolic dysfunction. The coefficient of correlation (r) was -0.6053 (95% CI: -0.7166 to -0.4640, P <0.0001).

Table 3: Demographic and clinical characteristics of the patient population

Variables	n=100 patients
Age, years	
<20	0 (0)
20-30	35 (35)
30-40	35 (35)
40-50	21 (21)
50-60	5 (5)
>60	4 (4)
Female	70 (70)
Male	30 (30)
Etiology of mitral valve lesion	
RHD	82 (82)
IHD	4 (4)
ICMP	4 (4)
MVP	4 (4)
SLE	2 (2)
DCM	2 (2)
MAC	2 (2)
NYHA classification	
NYHA class I	12 (12)
NYHA class II	32 (32)
NYHA class III	46 (46)
NYHA class IV	10 (10)
Atrial fibrillation/flutter	
Mitral stenosis	13 (38.2)
Mitral regurgitation	7 (20.6)
Mixed lesions	14 (41.2)
Mean pulse rate (pulse/min)	87.04±9.812
Mean SBP (mmHg)	102.96±11.272
Mean DBP (mmHg)	71.08±6.627
Mean PASP (mmHg)	46.65±10.167
MPAP (mmHg)	31.5±6.984
Right ventricular impulse (%)	
Yes	74 (74)
No	26 (26)
Jugular venous pressure	
Mitral stenosis	25 (58.14)
Mitral regurgitation	13 (41.9)
Mixed lesions	23 (79.31)
Congestive cardiac failure	
Mitral stenosis	21 (48.84)
Mitral regurgitation	13 (41.9)
Mixed lesions	19 (73.1)

Data are presented as n (%) and mean ± standard deviation.

DBP: Diastolic blood pressure, DCM: Dilated cardiomyopathy, ICMP: Ischemic cardiomyopathy, IHD: Ischemic heart disease, MAC: Mitral annular calcification, MPAP: Mean pulmonary artery pressure, NYHA: New York Heart Association, PASP: Pulmonary artery systolic pressure, RHD: Rheumatic heart disease, SLE: Systemic lupus erythematosus, SBP: Systolic blood pressure

Among the 47 patients who did not have clinical heart failure at the time of examination, echocardiographic assessment revealed varying degrees of cardiac dysfunction, which identified RV systolic dysfunction in 4 (8.5%) patients by RVFAC, and 5 (10.6%) patients, by RV Tei method. The RV diastolic dysfunction was found in 23 (62.16%) out of 37 patients by E/A ratio (without atrial fibrillation), 16 (34.04%) out of 47 patients by E/e' ratio, and 10 (21.27) out of 47 patients by both e' and e'/a' ratios.

DISCUSSION

This study demonstrated that RV dysfunction (RVD) is prevalent in patients with MVD, manifesting across various combinations of valvular lesions. The analysis revealed significant correlations between RV systolic dysfunction and multiple hemodynamic parameters, including left atrial size, LV systolic function, and MPAP. Additionally, the correlation between e'/a' ratio and left atrial diameter provided evidence of associated diastolic dysfunction.

A study by Kammoun et al.[9] which characterized RVD in patients with moderate to severe rheumatic mitral stenosis using TAPSE, FSA, and S' measurements, found that RV systolic function was impaired in 35% of patients. This dysfunction was notably more prevalent among patients who had atrial fibrillation and left atrial dilation, which aligns with our observations of higher RVD rates in patients with atrial fibrillation.

A comparative study utilizing TDI and velocity vector imaging demonstrated progressive deterioration of RV systolic performance correlating with stenosis severity, establishing a proportional relationship between mitral stenosis severity and RVD magnitude.[10] These concordant findings validate our observations and reinforce that RV impairment represents a predictable hemodynamic consequence of progressive mitral valve obstruction.

Furthermore, TDI studies have revealed that RV diastolic function can be impaired in symptomatic patients with isolated mitral stenosis, even when RV systolic function remains normal.[11] This supports our finding of abnormal diastolic dysfunction parameters in a significant proportion of patients.

In the present study, several significant correlations were identified that elucidate the complex hemodynamic relationships in MVD. A strong negative correlation was observed between RVFAC and left atrial diameter (r=-0.6237, P <0.0001), indicating that progressive left atrial enlargement is associated with deteriorating RV function. Conversely, a moderate to strong positive correlation between RVFAC and LV ejection fraction (r=0.6387, P <0.0001) demonstrated that improvements in LV systolic performance are accompanied by corresponding enhancements in RV function, reflecting

Table 4: Right ventricular systolic and diastolic dysfunction of the patient population based on different parameters

Variables	Total (n=100)	Mitral stenosis (n=43)	Mitral regurgitation (n=31)	Mixed lesions (n=26)
Mean LA size (mm)	50.22±8.764	47.53±6.642	50.0±10.096	54.84±8.545
Mean LVEF (%)	55.03±8.290	57.56±5.607	52.58±11.587	53.77±6.173
RV diameter (mm)	27.9 ± 4.58	27.26	25.71	30.00
Mean IVC diameter (mm)	16.95±3.29	16.72	16.16	18.27
Dilated IVC (≥18 mm)	52 (52)	20 (46.5)	15 (48.4)	17 (65.4)
Less than adequate IVC collapse	40 (40)	18 (41.86)	10 (32.23)	12 (46.15)
Mean TAPSE (mm)	15.67±2.94	15.56±3.25	16.71±2.53	14.62±2.52
Abnormal TAPSE	43 (40)	18 (41.86)	10 (32.25)	15 (57.7)
Mean RV FAC (%)	40.44±9.733	41.58±10.012	42.39±8.48	36.23±9.750
Abnormal RV FAC <35%	38 (38)	16 (37.2)	8 (25.8)	14 (53.8)
Mean TDI-S' vel (cm/sec)	9.41±2.638	9.37±2.966	10.03±2.313	8.73±2.320
Abnormal TDI-S' vel (<9.5 cm/sec)	47 (47)	22 (51.2)	10 (32.2)	15 (57.7)
RV MPI/Tei index	0.53±0.117	0.526±0.127	0.48±0.933	0.58±0.106
Abnormal MPI/Tei index (>0.54)	42 (42)	18 (41.9)	9 (29)	15 (57.7)
Mean e'	7.52±2.819	7.88±2.803	8.45±3.161	5.81±1.393
e' (<7.8)	56 (56)	23 (53.5)	13 (41.9)	20 (76.9)
E/e' ratio	7.782±2.72	7.69±2.670	6.97±2.088	8.91±1.031
Abnormal E/e' (>6)	71 (71)	29 (67.4)	19 (61.3)	23 (88.5)
e'/a'	0.54±0.190	0.59±0.176	0.55±0.223	0.42±0.110
Abnormal e'/a' (<0.52)	58 (58)	23 (53.5)	15 (48.4)	20 (76.9)
Abnormal EDT (msec) (>220)	57 (57)	19 (44.2)	18 (58.1)	20 (76.9)

Data are presented as n (%) and mean ± standard deviation.

a': Late diastolic velocity at tricuspid lateral annulus by tissue doppler image, E: E wave velocity right ventricle inflow, EDT: E wave deceleration time, e': Early diastolic velocity at tricuspid lateral annulus by tissue doppler imaging, FAC: Fractional area change, IVC: Inferior vena cava, LA: Left atrium, LVEF: Left ventricular ejection fraction, MPI: Myocardial performance index, RV: Right ventricle, TAPSE: Tricuspid annular plane systolic excursion, TDI S' vel: Tissue doppler image S' wave velocity

ventricular interdependence. Additionally, a strong negative correlation between RVFAC and MPAP (r=-0.5941, *P* <0.0001) was identified, confirming that elevated pulmonary pressures directly compromise RV systolic performance.

Our findings have important clinical implications for the management of patients with MVD. RVD was detected even in patients without clinical evidence of CCF, suggesting subclinical impairment that precedes overt heart failure symptoms. The prevalence of RVD was markedly higher among patients with advanced functional limitations (NYHA class III and IV) and in patients with severe forms of both mitral stenosis and mitral regurgitation, underscoring the progressive nature of right heart involvement as valvular disease severity increases. Giannini et al.[12] in their study of survival outcomes in patients with severe functional mitral regurgitation and advanced heart failure who underwent percutaneous mitral valve repair, concluded that the assessment of RV systolic function plays a crucial role in risk stratification for these patients.

In a multi-centre large cohort study of patients diagnosed with degenerative mitral regurgitation, it was observed that RVD assessed by transthoracic echocardiography was a major and independent determinant of long-term survival in response to conservative or surgical management, and RV systolic function should be included in routine DMR evaluation and in the clinical decision-making process.[13]

The strong association between functional class and RV impairment emphasizes the importance of comprehensive RV evaluation in symptomatic patients. The severity-dependent nature of RVD across different types of MVD suggests that RV function parameters could serve as important markers for surgical timing and prognostic assessment, particularly in patients with severe disease who may benefit from earlier intervention to preserve RV function and improve long-term outcomes.

Study Limitation

The present study has several limitations, which should be considered during interpretation of the results. It was a single centre study with a relatively small sample size, which may limit the generalizability of the study findings. A significant

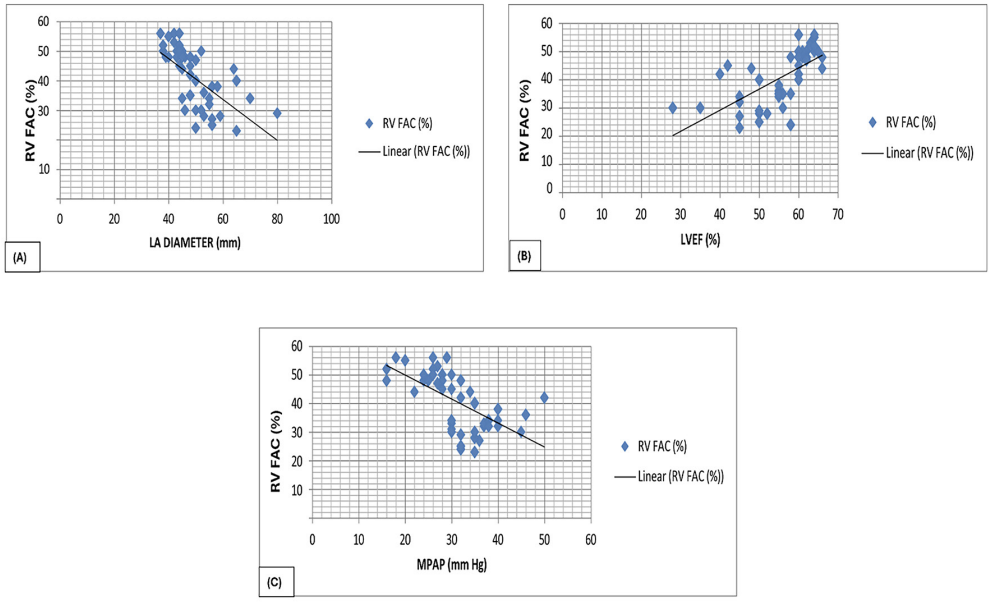

Figure 3: Correlation of RV FAC with LA size (diameter), LVEF and MPAP

(A) Shows a significant linear correlation between RVFAC values and the corresponding LA diameter of patients, suggesting that a larger left atrial diameter was associated with poorer RV systolic function. The linear correlation coefficient (r) was -0.6237 with a 95% confidence interval (CI) of -0.7106 to -0.4869, and significance of P <0.0001. (B) Shows that lower LVEF, suggestive of poor LV systolic function, was associated with lower RVFAC (r=0.6387, 95% CI: 0.5057 to 0.7420, P <0.0001). (C) Shows that higher MPAP, indicating greater mean pulmonary pressure RV afterload, was associated with lower RVFAC, indicating worse RV systolic function (r=-0.5941, 95% CI: -0.7080 to -0.4502, P <0.0001).

LA: Left atrium, LVEF: Left ventricular ejection fraction, MPAP: Mean pulmonary artery pressure, RVFAC: Right ventricular fractional area change

Table 5: Correlation of right ventricular function and atrial fibrillation/flutter

Variables	Atrial fibrillation/ flutter (n=34)	No atrial fibrillation/ flutter (n=66)	*P* -value
Mean TAPSE (mm)	14.65±2.460	16.97±3.049	0.0075
Mean RV FAC (%)	37.41±8.482	42±10.025	0.0186
Mean TDI S' (cm/s)	8.32±2.215	9.97±2.677	0.0016
Mean TDI Tei	0.56±0.107	0.51±0.122	0.0395
Mean E (cm/sec)	51.53±7.195	53.26±8.642	0.292
Mean e'	5.97±1.255	8.32±3.067	<0.0001
Mean E/e'	9.29±1.082	7.004±2.337	<0.0001
Mean e'/a'	0.42±0.084	0.59±0.205	<0.0001
Mean EDT (msec)	225.32±26.047	219.27±32.863	0.318
Patients with less than adequate IVC collapse	19 (55.9)	21 (31.8)	0.031

Data are presented as n (%) and mean ± standard deviation.

a': Late diastolic velocity at tricuspid lateral annulus by tissue doppler image, E: E wave velocity right ventricle inflow, EDT: E wave deceleration time, e': Early diastolic velocity at tricuspid lateral annulus by tissue doppler imaging, FAC: Fractional area change, IVC: Inferior vena cava, RV: Right ventricle, TAPSE: Tricuspid annular plane systolic excursion, TDI S' vel: Tissue doppler image S' wave velocity

Table 6: Correlation of right ventricular function and NYHA class of symptoms

Variables	NYHA class I-II (n=44)	NYHA class III-IV (n=56)	*P* -value
Mean TAPSE (mm)	17.95±1.589	13.87±2.494	<0.0001
Mean RV FAC (%)	48.57±5.884	34.054±7.005	<0.0001
Mean TDI S' (cm/s)	11.52±1.422	7.75±2.136	<0.0001
Mean TDI Tei	0.44±0.72	0.597±0.968	<0.0001
Mean E (cm/sec)	56.023±7.663	50.036±7.654	0.0002
Mean A (cm/sec)	72.57±10.241	64.69±9.064	0.0017
Mean E/A	0.8±0.199	0.77±0.211	0.4933
Mean e'	9.36±2.727	6.07±1.908	<0.0001
Mean E/e'	6.36±2.070	8.89±1.751	<0.0001
Mean e'/a'	0.65±0.178	0.44±0.147	<0.0001
Mean EDT (msec)	221.18±20.871	219.66±39.906	0.8065
Patients with less than adequate IVC collapse	6 (13.6)	34 (60.7)	<0.0001

Data are presented as n (%) and mean ± standard deviation.

A: A wave velocity right ventricle in flow, a': Late diastolic velocity at tricuspid lateral annulus by tissue doppler image, E: E wave velocity right ventricle inflow, EDT: E wave deceleration time, e': Early diastolic velocity at tricuspid lateral annulus by tissue doppler imaging, FAC: Fractional area change, IVC: Inferior vena cava, RV: Right ventricle, TAPSE: Tricuspid annular plane systolic excursion, TDI S' vel: Tissue doppler image S' wave velocity

Table 7: Correlation of right ventricular function and severity of mitral stenosis

Variables	Severe mitral stenosis (n=25)	Moderate mitral stenosis (n=18)	*P* -value
Mean TAPSE (mm)	14.32±3.185	17.28±2.54	0.0022
Mean RV FAC (%)	37.28±9.204	47.56±7.943	0.001
Mean TDI S' (cm/s)	8.24±2.7	10.94±2.62	0.0026
Mean TDI Tei	0.57±0.117	0.47±0.123	0.015
Mean E (cm/sec)	50.4±8.155	60.56±7.579	0.0005
Mean A (cm/sec)	65.67±11.159	71.33±11.568	0.15
Mean E/A	0.776±0.25	0.896±0.25	0.13
Mean e'	6.56±2.038	9.72±2.718	0.0002
Mean E/e'	8.34±2.759	6.766±2.307	0.0225
Mean e'/a'	0.53±0.16	0.704±0.136	0.0012
Mean EDT (msec)	203.12±49.17	218.11±28.004	0.62
Patients with less than adequate IVC collapse	14 (56)	4 (22.22)	0.034

Data are presented as n (%) and mean ± standard deviation.

A: A wave velocity right ventricle in flow, a': Late diastolic velocity at tricuspid lateral annulus by tissue doppler image, E: E wave velocity right ventricle inflow, EDT: E wave deceleration time, e': Early diastolic velocity at tricuspid lateral annulus by tissue doppler imaging, FAC: Fractional area change, IVC: Inferior vena cava, RV: Right ventricle, TAPSE: Tricuspid annular plane systolic excursion, TDI S' vel: Tissue doppler image S' wave velocity

Table 8: Correlation of right ventricular function and severity of mitral regurgitation

Variables	Severe mitral regurgitation (n=19)	Moderate mitral regurgitation (n=12)	*P* -value
Mean TAPSE (mm)	15.79±2.123	18.167±2.517	0.0017
Mean RV FAC (%)	39.26±6.94	47.33±8.585	0.0016
Mean TDI S' (cm/s)	9.316±2.129	11.167±2.209	0.0273
Mean TDI Tei	0.51±0.088	0.44±0.089	0.0184
Mean E (cm/sec)	49.05±4.743	56±4.671	0.0010
Mean A (cm/sec)	69.167±6.337	68.333±10.731	0.93
Mean E/A	0.702±0.068	0.817±0.189	0.07
Mean e'	7.58±3.372	9.83±2.290	0.0371
Mean E/e'	7.677±2.171	5.843±1.389	0.0237
Mean e'/a'	0.482±0.222	0.668±0.180	0.0234
Mean EDT (msec)	233.11±16.22	216.33±21.35	0.0285
Patients with less than adequate IVC collapse	8 (42.10)	2 (66.66)	0.24

Data are presented as n (%) and mean ± standard deviation.

A: A wave velocity right ventricle in flow, a': Late diastolic velocity at tricuspid lateral annulus by tissue doppler image, E: E wave velocity right ventricle inflow, EDT: E wave deceleration time, e': Early diastolic velocity at tricuspid lateral annulus by tissue doppler imaging, FAC: Fractional area change, IVC: Inferior vena cava, RV: Right ventricle, TAPSE: Tricuspid annular plane systolic excursion, TDI S' vel: Tissue doppler image S' wave velocity

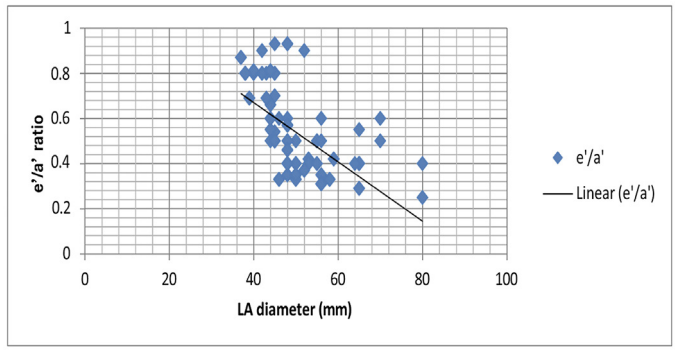

Figure 4: Relation between e'/a' ratio and LA diameter

a': Late diastolic velocity at tricuspid lateral annulus by tissue doppler image, e': Early diastolic velocity at tricuspid lateral annulus by tissue doppler index

limitation is the absence of longitudinal follow-up evaluation, which prevents assessment of the prognostic implications and long-term outcomes of RVD identified in this study. This is particularly important given that RV function is an established prognostic indicator in MVD; however, our cross-sectional design cannot provide insights into survival outcomes, disease progression, or optimal timing for interventions. While our exclusion criteria attempted to minimize confounding factors, the potential influence of different etiological entities on RV function remains a consideration. Future studies incorporating advanced imaging techniques such as 3D echocardiography, strain imaging, and cardiac magnetic resonance imaging could provide a more comprehensive assessment of RV function, though attention to image quality and operator experience would be essential. Prospective multi-centre studies with long-term follow-up are needed to establish the prognostic significance of these findings and enhance generalizability.

CONCLUSION

Despite its critical prognostic value, RV function assessment often receives insufficient attention in the context of VHD. Careful assessment of RV function should be prioritized in patients presenting with MVD in various forms. Simple echocardiography techniques using 2D, M mode, pulsed wave Doppler, TDI, and others can reveal the status of RV function, systolic as well as diastolic, in great detail. Our study demonstrates significant associations between impaired RV function and several clinical parameters, including atrial fibrillation, left atrial dilatation, and more severe symptoms and valvular involvement in patients with MVD. However, the cross-sectional design of this study limits our ability to establish causal relationships or determine the temporal sequence of these associations. These findings carry substantial clinical implications, serving as valuable predictors of symptom progression, risk stratification for adverse events, timing of intervention, and post-procedural outcomes. Such

comprehensive evaluation of RV function therefore emerges as an indispensable component in the optimal management of patients with MVD. Future longitudinal studies are warranted to establish the causal relationships and temporal progression of RVD in this patient population.

Ethics

Ethics Committee Approval: The study was approved by the Institutional Ethics Committee of the Institute and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants (approval number: MC/Kol/IEC/Non-spon/580/07-2017, date: 26.08.2017).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.N.D., B.C., Concept: S.N.D., Design: S.N.D., Data Collection or Processing: B.C., Analysis or Interpretation: S.N.D., B.C., Literature Search: S.N.D., B.C., Writing: S.N.D., B.C.

Conflict of Interest: No conflict of interest was declared by the authors.

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LETTER TO THE EDITOR

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Addressing Methodological Gaps in the Relationship Between Vitamin D and Coronary Atherosclerosis

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Abstract

Keywords: Acute coronary syndrome, coronary artery disease, cardiovascular health, ventricular dysfunction, vitamin D

To the Editor,

I read with great interest the article by Sahani and Gupta[1], titled "*Association between Vitamin D Deficiency and Angiographic Severity in Patients with Coronary Artery Disease*", published in the *International Journal of Cardiovascular Academy* [2024;10:132-8].[1] While the primary focus of vitamin D research is its role in bone health, immune function, and other systemic effects, its potential impact on cardiovascular health is noteworthy. This study provides important insights into the relationship between serum vitamin D levels and the severity of coronary artery disease (CAD). However, I would like to share some of my thoughts on some methodological aspects and contextual considerations.

Vitamin D cut-off thresholds vary significantly across populations and health conditions, reflecting the complexity of establishing a universal standard. Given the ongoing debates surrounding optimal serum vitamin D concentrations, the definitions of sufficiency, insufficiency, and deficiency are inherently approximate.[2] In this study, the authors reference a Malaysian study to define vitamin D cut-off values.[3] Considering the substantial variability in vitamin D levels across regions and populations, it would have been valuable to use India-specific reference values or provide a detailed rationale for adopting these particular thresholds. Furthermore, the study does not explain why specific cut-offs such as ≤10, 11-20, 21-30, and >30 ng/mL were chosen or whether these thresholds align with the clinical and demographic characteristics of patients with acute coronary syndrome (ACS) in India. Addressing these points would enhance the applicability and contextual relevance of this study's findings.

The timing of vitamin D measurement is another critical factor that remains unclear. It is not specified whether vitamin D levels were not assessed prior to the onset of ACS, during hospital admission, or during subsequent follow-ups. This distinction is particularly important because ACS triggers an inflammatory response characterized by elevated markers, such as C-reactive protein and interleukin-6, which are known to influence vitamin D metabolism.[4] Without this information, it becomes challenging to distinguish baseline vitamin D levels from those affected by the acute inflammatory state. Including dynamic vitamin D measurements alongside inflammatory markers could provide more robust insights into the interplay between inflammation and vitamin D levels.

Additionally, the exclusion criteria used in this study require further elaboration. Patients with chronic kidney disease and parathyroid disorders were excluded, but other potential

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confounding factors, such as dietary habits, seasonal variations, and the use of statins or antihypertensive medications, were not addressed.[5] These variables can significantly influence serum vitamin D levels and CAD progression, potentially affecting the observed associations. A more comprehensive consideration of these factors would have strengthened the findings of this study.

The absence of a control group in the study limited the robust assessment of the relationship between vitamin D levels and CAD severity or left ventricular function. This deficiency leads to an emphasis on correlation rather than causality. The observed differences in left ventricular ejection fraction between patients with optimal and vitamin D deficiency also raise intriguing questions about the mechanisms involved. Although the authors attribute this to the anti-inflammatory and endothelial-modulating properties of vitamin D, alternative explanations, such as reduced physical activity in vitamin D-deficient patients, should be considered. This finding warrants further investigation to distinguish direct effects from potential confounders.

In conclusion, while Sahani and Gupta's[1] study offers valuable contributions to understanding the relationship between vitamin D and CAD severity, addressing the aforementioned methodological considerations could enhance its robustness and applicability. I commend the authors for their important work and encourage continued exploration of the role of vitamin D in cardiovascular disease.

Footnotes

Authorship Contributions

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