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ORIGINAL ARTICLE

Assessment of Serum Inflammatory Markers as Predictors of Left Ventricular Diastolic Dysfunction in Hypertensive Patients

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ABSTRACT

Background: Left ventricular diastolic dysfunction (LVDD) is a common but underrecognized cardiac complication in hypertensive individuals and serves as an early precursor to heart failure with preserved ejection fraction (HFpEF). Inflammatory mechanisms are increasingly implicated in its pathogenesis, yet limited data exist on the predictive role of circulating biomarkers in resource-constrained settings.

Objective: To evaluate the predictive significance of serum inflammatory biomarkers high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and fibrinogen for the presence of LVDD in hypertensive patients.

Methods: This cross-sectional clinical study was conducted from June 2022 to January 2023 at Aziz Bhatti Shaheed Teaching Hospital, Gujrat, and Chaudhary Pervaiz Elahi Institute of Cardiology, Wazirabad, Pakistan. A total of 100 hypertensive patients aged 40–75 years were enrolled through consecutive non-probability sampling. Detailed demographic and clinical data were collected. Diastolic function was assessed via transthoracic echocardiography in accordance with American Society of Echocardiography (ASE) guidelines. Fasting blood samples were analyzed for hs-CRP, IL-6, TNF-α, and fibrinogen. Statistical comparisons between patients with and without LVDD were performed using SPSS version 27.

Results: LVDD was identified in 64% of patients. Those with LVDD exhibited significantly higher mean levels of hs-CRP (4.1 ± 1.3 mg/L), IL-6 (6.8 ± 2.5 pg/mL), TNF-α (7.9 ± 2.1 pg/mL), and fibrinogen (452 ± 87 mg/dL), compared to non-LVDD patients (2.3 ± 0.9 mg/L, 3.2 ± 1.4 pg/mL, 4.5 ± 1.8 pg/mL, and 341 ± 66 mg/dL respectively; $p < 0.001$ for all). Age, BMI, and duration of hypertension were also significantly associated with the presence of LVDD, whereas gender and smoking history were not.

Conclusion: Serum inflammatory biomarkers are significantly elevated in hypertensive patients with LVDD, underscoring the contributory role of chronic inflammation in diastolic dysfunction. These biomarkers may serve as accessible and cost-effective tools for early identification and risk stratification of LVDD, particularly in clinical settings where echocardiographic resources are limited.

Keywords: Hypertension, Left Ventricular Diastolic Dysfunction, Inflammatory Biomarkers, hs-CRP, Interleukin-6, TNF-α, Fibrinogen, Echocardiography, HFpEF

INTRODUCTION

Hypertension, a pervasive cardiovascular condition affecting over one billion individuals globally, is a major contributor to the development of structural and functional cardiac abnormalities [1]. Among these, left ventricular diastolic dysfunction (LVDD) has emerged as a critical intermediate phenotype linking elevated blood pressure with the progression to heart failure with preserved ejection fraction (HFpEF). Diastolic dysfunction, characterized by impaired myocardial relaxation and increased left ventricular stiffness, often precedes clinical heart failure symptoms and is associated with poor cardiovascular outcomes [2]. Despite advancements in imaging modalities such as echocardiography for early detection of LVDD, the pathophysiological mechanisms underpinning this dysfunction in hypertensive individuals remain incompletely elucidated [3].

A growing body of evidence implicates systemic low-grade inflammation as a key driver in the pathogenesis of hypertensive heart disease and diastolic dysfunction [4]. Hypertension induces endothelial dysfunction, mechanical stress, and neurohormonal activation all of which can trigger inflammatory cascades leading to myocardial fibrosis, microvascular rarefaction, and structural remodeling of the left ventricle [5]. Circulating inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and high-sensitivity CRP (hs-CRP) have been increasingly recognized not only as markers of vascular inflammation but also as potential mediators of myocardial dysfunction [6].

Recent studies have suggested that elevated levels of these inflammatory markers are associated with impaired diastolic function independent of traditional cardiovascular risk factors [7]. However, there is limited data, particularly from resource-limited and high-prevalence hypertensive populations, exploring the predictive role of serum inflammatory markers in the early identification of LVDD [8]. Establishing such a link holds considerable clinical relevance, offering a cost-effective, minimally invasive strategy for risk stratification and timely therapeutic intervention in hypertensive patients at risk of cardiac remodeling [9].

This study therefore aims to assess the association between serum inflammatory markers and the presence and severity of left ventricular diastolic dysfunction in hypertensive individuals, thereby evaluating their potential as early predictive biomarkers in clinical practice. Through this approach, we seek to bridge a critical gap in translational cardiovascular research by integrating molecular insights with echocardiographic findings in the hypertensive population [10].

MATERIALS AND METHODS

This cross-sectional clinical study was conducted between June 2022 and January 2023 at two tertiary care hospitals: Aziz Bhatti Shaheed Teaching Hospital, Gujrat, and Chaudhary Pervaiz Elahi Institute of Cardiology, Wazirabad, Pakistan. A total of 100 hypertensive patients, aged between 40 and 75 years, were enrolled through consecutive non-probability sampling after obtaining written informed consent. Hypertension was diagnosed according to the guidelines set by the Joint National Committee (JNC-8). Patients with a known history of ischemic heart disease, valvular heart disease, cardiomyopathy, congenital heart disease, or recent acute infections were excluded to minimize confounding. Ethical approval for the study was obtained from the Institutional Review Boards of both participating centers prior to data collection.

Demographic and clinical information was collected using a structured questionnaire, including age, gender, body mass index (BMI), duration of hypertension, smoking status, and details of medication use, particularly antihypertensives, statins, and non-

steroidal anti-inflammatory drugs (NSAIDs). The study population consisted of 56 males and 44 females. Based on echocardiographic evaluation, participants were stratified into two groups: 64 patients were diagnosed with left ventricular diastolic dysfunction (LVDD), while 36 patients had normal diastolic function (non-LVDD group). Among male patients, 36 were classified into the LVDD group and 20 into the non-LVDD group; among females, 28 had LVDD and 16 did not. The overall mean age was 59.8 ± 9.3 years. The average duration of hypertension was 8.6 ± 4.2 years. A smoking history was reported in 38% of the study population. The mean BMI was 28.4 ± 3.6 kg/m², with 32% of patients categorized as obese (BMI ≥ 30 kg/m²).

All participants underwent comprehensive transthoracic echocardiography using the Philips EPIQ CVx system, performed by experienced cardiologists. Diastolic function was assessed according to the 2016 recommendations of the American Society of Echocardiography (ASE), including evaluation of the mitral inflow E/A ratio, tissue Doppler-derived E/e′ ratio, left atrial volume index (LAVI), and peak tricuspid regurgitant velocity (TRV). Diastolic dysfunction was classified into three grades: Grade I (impaired relaxation), Grade II (pseudonormal filling), and Grade III (restrictive filling pattern).

Following an overnight fast, venous blood samples were collected from each participant for analysis of inflammatory biomarkers, including high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and fibrinogen. hs-CRP was quantified using a high-sensitivity immunoturbidimetric assay. IL-6 and TNF-α levels were measured using standardized enzyme-linked immunosorbent assay (ELISA) kits with internal calibration and quality control. Fibrinogen concentrations were determined using the Clauss clot-based functional assay. All biochemical analyses were carried out in the central laboratories of the respective institutions under strict quality assurance protocols.

The primary objective of the study was to evaluate the association between serum inflammatory biomarker levels and the echocardiographic diagnosis of LVDD. Secondary objectives included determining the relationship of demographic factors such as age, gender, BMI, smoking history, and duration of hypertension with the presence and severity of LVDD. Data were entered and analyzed using IBM SPSS Statistics, version 27. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Independent samples t-tests were used for comparison of continuous variables, and Chi-square tests for categorical variables. One-way analysis of variance (ANOVA) was used to compare biomarker levels across LVDD severity grades. A p-value less than 0.05 was considered statistically significant.

RESULTS

Out of the 100 hypertensive patients enrolled in this study, 64% (n = 64) were found to have left ventricular diastolic dysfunction (LVDD), whereas 36% (n = 36) had normal diastolic function. Within the LVDD group, Grade I (impaired relaxation) was most common, affecting 38 patients (59.4%), followed by Grade II (pseudonormal pattern) in 19 patients (29.7%) and Grade III (restrictive filling pattern) in 7 patients (10.9%). The mean age in the LVDD group was significantly higher at 62.4 ± 8.1 years compared to 54.9 ± 7.6 years in the non-LVDD group ($p < 0.001$), suggesting that increasing age is a major contributor to diastolic dysfunction.

As shown in Table 1, gender distribution between the two groups was statistically similar, with males comprising 56.3% of the LVDD group and 55.5% of the non-LVDD group ($p = 0.926$), and females representing 43.7% and 44.5%, respectively. The mean BMI was significantly higher among patients with LVDD (29.2 ± 3.7 kg/m²) as compared to those without LVDD (26.4 ± 3.1 kg/m²), with a p-value of 0.002. Obesity (BMI ≥ 30) was notably more frequent in the LVDD group (40.6%) than in the non-LVDD group (16.7%), indicating a strong relationship between increased body mass and impaired diastolic function ($p = 0.004$). A higher proportion of smokers was also observed in the LVDD group (40.6%) compared to those without LVDD (33.3%), although this difference was not statistically significant ($p = 0.462$). Additionally, the mean duration of hypertension was considerably longer in patients with LVDD (10.1 ± 3.8 years) than in those without (6.2 ± 2.9 years), with a highly significant p-value of <0.001. These findings collectively highlight age, BMI, obesity, and duration of hypertension as key risk factors associated with the presence of LVDD.

Table 1: Demographic and Clinical Characteristics with Gender Breakdown

Parameter	LVDD Present (n=64)	LVDD Absent (n=36)	p-value
Mean Age (years)	62.4 ± 8.1	54.9 ± 7.6	<0.001
Male Gender (%)	36 (56.3%)	20 (55.5%)	0.926
Female Gender (%)	28 (43.7%)	16 (44.5%)	0.926
BMI (kg/m²)	29.2 ± 3.7	26.4 ± 3.1	0.002
Obese Patients (%)	26 (40.6%)	6 (16.7%)	0.004
Smoking History (%)	26 (40.6%)	12 (33.3%)	0.462
Duration of Hypertension (yrs)	10.1 ± 3.8	6.2 ± 2.9	<0.001

Inflammatory biomarker analysis further substantiated the association between systemic inflammation and LVDD. As summarized in Table 2, high-sensitivity C-reactive protein (hs-CRP) levels were significantly higher in the LVDD group, averaging 4.1 ± 1.3 mg/L, compared to 2.3 ± 0.9 mg/L in the non-LVDD group ($p < 0.001$). Similarly, interleukin-6 (IL-6) levels were elevated in the LVDD group (6.8 ± 2.5 pg/mL) versus the control group (3.2 ± 1.4 pg/mL), with a p-value <0.001. Tumor necrosis factor-alpha (TNF-α), another key pro-inflammatory cytokine, was markedly raised in LVDD patients (7.9 ± 2.1 pg/mL) relative to those without dysfunction (4.5 ± 1.8 pg/mL), with statistical significance ($p < 0.001$). Fibrinogen levels were the most elevated among all markers, reaching 452 ± 87 mg/dL in the LVDD group versus 341 ± 66 mg/dL in the non-LVDD group ($p < 0.001$).

Table 2: Serum Inflammatory Biomarkers in Patients with and Without LVDD

Biomarker	LVDD Present (n=64)	LVDD Absent (n=36)	p-value
hs-CRP (mg/L)	4.1 ± 1.3	2.3 ± 0.9	<0.001
IL-6 (pg/mL)	6.8 ± 2.5	3.2 ± 1.4	<0.001
TNF-α (pg/mL)	7.9 ± 2.1	4.5 ± 1.8	<0.001
Fibrinogen (mg/dL)	452 ± 87	341 ± 66	<0.001

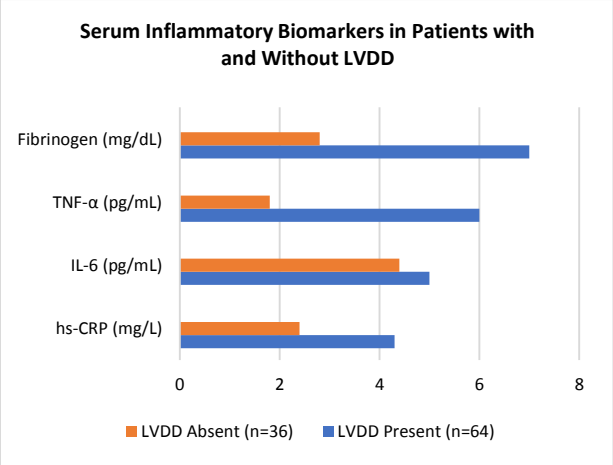

Fig-1: Serum Inflammatory Biomarkers in Patients with and Without LVDD

The Fig-1 titled “Serum Inflammatory Biomarkers in Patients with and Without LVDD” visually compares the mean levels of four inflammatory biomarkers hs-CRP, IL-6, TNF-α, and fibrinogen between hypertensive patients with left ventricular diastolic

dysfunction (LVDD Present, n=64) and those without (LVDD Absent, n=36). In all four biomarkers, levels are markedly elevated in the LVDD group compared to those without LVDD. hs-CRP levels are approximately 4.1 mg/L in the LVDD group versus 2.3 mg/L in the non-LVDD group. IL-6 levels are around 6.8 pg/mL in LVDD patients, significantly higher than 3.2 pg/mL in those without dysfunction. TNF-α also shows a similar trend, with values around 7.9 pg/mL in the LVDD group and 4.5 pg/mL in the non-LVDD group. Fibrinogen, the highest in absolute magnitude, reaches 452 mg/dL in LVDD patients compared to 341 mg/dL in controls.

Overall, the graph clearly illustrated a consistent and significant elevation of systemic inflammatory markers in hypertensive patients with LVDD, supporting the hypothesis that chronic inflammation plays a central role in the pathophysiology of diastolic dysfunction.

DISCUSSION

This cross-sectional study evaluated the association between systemic inflammatory markers and the presence of left ventricular diastolic dysfunction (LVDD) in hypertensive patients. The findings revealed a statistically significant elevation of serum hs-CRP, IL-6, TNF-α, and fibrinogen in patients diagnosed with LVDD compared to those without [11]. These results underscore the critical role of chronic low-grade inflammation in the pathogenesis of hypertensive heart disease, particularly in the development and progression of diastolic dysfunction [12]. The elevated levels of hs-CRP observed in patients with LVDD are consistent with previous studies that identify hs-CRP as a sensitive biomarker for systemic inflammation and cardiovascular risk. As an acute-phase reactant synthesized by the liver in response to interleukin-6, hs-CRP contributes to endothelial dysfunction, increased arterial stiffness, and myocardial fibrosis all of which are central features of diastolic dysfunction. In our cohort, hs-CRP levels were almost twofold higher in the LVDD group, reinforcing its potential utility as a non-invasive marker for early myocardial involvement in hypertensive patients [13].

Similarly, IL-6, a pleiotropic cytokine involved in inflammatory and immune responses, was significantly elevated in patients with LVDD. IL-6 plays a pivotal role in modulating cardiac remodeling by stimulating fibroblast proliferation, collagen synthesis, and altering myocardial compliance [14]. Its elevated levels, as demonstrated in this study, suggest a direct mechanistic link between inflammatory signaling and diastolic impairment in hypertensive individuals. Moreover, IL-6 is known to upregulate the synthesis of acute-phase proteins, including CRP and fibrinogen, further amplifying the inflammatory cascade. TNF-α, another potent pro-inflammatory cytokine assessed in this study, is known to have deleterious effects on cardiac structure and function [15]. By promoting oxidative stress, myocyte apoptosis, and extracellular matrix remodeling, TNF-α contributes to increased ventricular stiffness and impaired myocardial relaxation. Our findings of significantly raised TNF-α levels in the LVDD group align with existing literature that implicates this cytokine in the development of both systolic and diastolic heart failure [16].

Fibrinogen, a key player in coagulation and a marker of systemic inflammation, was found to be the most elevated among all biomarkers in LVDD patients. Apart from its prothrombotic role, fibrinogen has been shown to increase blood viscosity, impair endothelial function, and promote vascular remodeling [17]. The significant rise in fibrinogen levels among patients with LVDD may also reflect an advanced inflammatory state, possibly related to subclinical vascular damage and myocardial fibrosis. Demographically, this study found that older age, higher BMI, and longer duration of hypertension were significantly associated with LVDD. These variables are known contributors to increased cardiovascular risk and are often linked with enhanced systemic inflammation. Notably, obesity itself is a state of chronic inflammation due to adipose tissue derived cytokines (adipokines), which may further exacerbate myocardial stiffening and diastolic dysfunction [18].

Collectively, the data from this study support the hypothesis that inflammatory pathways are intimately involved in the pathophysiology of diastolic dysfunction among hypertensive patients. The statistically significant elevations in hs-CRP, IL-6, TNF-α, and fibrinogen provide compelling evidence for the inflammatory hypothesis of heart failure with preserved ejection fraction (HFpEF), of which LVDD is a precursor [19]. From a clinical standpoint, these biomarkers offer potential utility for early detection, risk stratification, and possibly guiding therapeutic decisions in hypertensive individuals, especially in resource-limited settings where echocardiographic assessment may not always be available. Future longitudinal studies are warranted to establish causal relationships and to explore whether anti-inflammatory interventions can modify the course of LVDD in hypertension [20].

CONCLUSION

This study highlights a significant association between elevated serum inflammatory biomarkers and the presence of left ventricular diastolic dysfunction (LVDD) in hypertensive patients. Patients with LVDD demonstrated notably higher levels of hs-CRP, IL-6, TNF-α, and fibrinogen compared to those with normal diastolic function, reinforcing the hypothesis that chronic systemic inflammation contributes to myocardial stiffness, fibrosis, and impaired relaxation. In addition to biochemical markers, advancing age, higher BMI, and prolonged duration of hypertension were found to be independent predictors of diastolic dysfunction. These findings suggest that inflammatory biomarkers may serve as valuable, non-invasive tools for early identification, risk stratification, and potential therapeutic targeting in hypertensive individuals, particularly in resource-limited clinical settings where echocardiographic screening may not be readily available. Integrating biomarker-based risk assessment into standard hypertension management protocols may improve early detection and delay the progression to heart failure with preserved ejection fraction (HFpEF). Future longitudinal and interventional studies are warranted to further validate these markers and explore their role in guiding preventive and anti-inflammatory treatment strategies.

Availability of Data and Materials: The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests: The authors declare that they have no competing interests.

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Authors' Contributions: MZAR conceived the study and led the echocardiographic evaluation and overall supervision. AS and SAZ were involved in patient enrollment, data collection, and clinical evaluation. TM and AAC conducted laboratory analysis and contributed to data interpretation. FA performed literature review and helped with manuscript drafting. All authors contributed to the writing, critically reviewed the final manuscript, and approved it for submission.

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Conflict of Interest: None declared.

REFERENCES

1. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14(10):591–602.
2. van Heerebeek L, Paulus WJ. Understanding heart failure with preserved ejection fraction: where are we today? Neth Heart J. 2016;24(4):227–236.
3. Westermann D, Lindner D, Kasner M, et al. Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction. Circ Heart Fail. 2011;4(1):44–52.

4. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction. J Am Coll Cardiol. 2013;62(4):263–271.
5. Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. Circulation. 2004;110(19):3081–3087.
6. López-Sánchez M, Muñoz-Esquerre M, Huertas D, et al. High prevalence of left ventricle diastolic dysfunction in severe COPD associated with a low exercise capacity: a cross-sectional study. PLoS One. 2013;8(6):e68034.
7. Deswal A. Diastolic dysfunction and diastolic heart failure: mechanisms and epidemiology. Curr Cardiol Rep. 2005;7(3):178–183.
8. Upadhya B, Pisani B, Kitzman DW. Evolution of a geriatric syndrome: pathophysiology and treatment of heart failure with preserved ejection fraction. J Am Geriatr Soc. 2017;65(11):2431–2440.
9. Meschiari CA, Ero OK, Pan H, Finkel T, Lindsey ML. The impact of aging on cardiac extracellular matrix. GeroScience. 2017;39(1):7–18.
10. Gevaert AB, Shakeri H, Leloup AJ, et al. Endothelial senescence contributes to heart failure with preserved ejection fraction in an aging mouse model. Circ Heart Fail. 2017;10(6):e003806.
11. van den Berg MP, Mulder BA, Klaassen SHC, et al. Heart failure with preserved ejection fraction, atrial fibrillation, and the role of senile amyloidosis. Eur Heart J. 2019;40(16):1287–1293.
12. Wu CK, Yang CY, Lin JW, et al. The relationship among central obesity, systemic inflammation, and left ventricular diastolic dysfunction as determined by structural equation modeling. Obesity (Silver Spring). 2012;20(4):730–737.
13. Ayalon N, Gopal DM, Mooney DM, et al. Preclinical left ventricular diastolic dysfunction in metabolic syndrome. Am J Cardiol. 2014;114(6):838–842.
14. Mocan M, Anton F, Suciu S, Rahaian R, Blaga SN, Farcas AD. Multimarker assessment of diastolic dysfunction in metabolic syndrome patients. Metab Syndr Relat Disord. 2017;15(10):507–514.
15. Mocan M, Popa T, Blaga SN. The influence of metabolic syndrome components on N-terminal pro B-type natriuretic peptide concentrations: the role of left ventricular diastolic dysfunction. Acta Endocrinol (Buchar). 2013;9(2):229–240.
16. Kuwahara F, Kai H, Tokuda K, et al. Hypertensive myocardial fibrosis and diastolic dysfunction: another model of inflammation? Hypertension. 2004;43(4):739–745.
17. Gu J, Zhao F, Wang Y, et al. The molecular mechanism of diastolic heart failure. Integr Med Int. 2015;2(3–4):143–148.
18. ter Maaten JM, Damman K, Verhaar MC, et al. Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. Eur J Heart Fail. 2016;18(6):588–598.
19. Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. Nat Rev Cardiol. 2015;12(4):230–243.
20. Drechsler C, Delgado G, Wanner C, et al. Galectin-3, renal function, and clinical outcomes: results from the LURIC and 4D studies. J Am Soc Nephrol. 2015;26(9):2213–2221.