Original Article

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Correlation of Left Atrial Volume Index with Pro-BNP in Heart Failure with Preserved Ejection Fraction

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ABSTRACT

Objective: To determine the correlation between left atrial (LA) volume index and Pro- BNP in heart failure patients with preserved ejection fraction.

Methodology: This descriptive Cross-Sectional Study was conducted at Department of Cardiology, Liaquat University of Medical & Health Sciences (LUMHS), Jamshoro, Pakistan, during Six months after the approval of synopsis from March 26, 2021 to September 25, 2021. All patients who fulfilled the inclusion criteria and visited to LUMHS, Jamshoro were included in the study. Informed consent was taken after explaining the procedure, risks and benefits of the study. Peripheral venous blood samples were obtained for assessment of pro- BNP level. A detailed comprehensive echocardiography was performed in all patients. All the collected data were entered into the proforma attached at the end and used electronically for research purpose.

Results: The age of the patients ranged from 19 to 59 years with a median of 58 with interquartile range 12. In distribution of gender, 20 (60.5%) patients were male while 13 (39.4%) were female. Pearson's correlation coefficient showed weak and non-significantly linear correlation between left atrial volume index and Pro-BNP levels i.e. (r= 0.134) in the region $P < 0.05$.

Conclusion: It is to be concluded that there was a weak correlation between left atrial volume index and Pro-BNP levels. More studies are necessary to evaluate the statistical association with a larger sample size and with more parameters in multiple study centers in Pakistan are needed to validate the findings of the present study.

Keywords: Correlation, Heart Failure, Left Atrial Volume Index, Preserved Ejection Fraction, Pro-BNP.

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Introduction

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome characterized by symptoms of heart failure despite a normal or nearly normal left ventricular ejection fraction, typically defined as 50% or higher. Rather than a single disorder, HFpEF arises from a variety of underlying conditions, making management complex. The prevalence of HFpEF is increasing rapidly, driven by an aging population and a rise in risk factors like obesity, diabetes and the hypertension.[1-3] The Pro-B-type natriuretic peptide (Pro-BNP) hormone levels rise in cases of acute or chronic heart failure, whether due to systolic or diastolic dysfunction. Even in patients without symptoms, a slight elevation in left ventricular (LV) filling pressure can lead to an increase in Pro-BNP levels.[4,5] Diastolic function can be evaluated by estimating LV filling pressure using the ratio of early transmitral inflow to the diastolic velocity of the mitral annulus (E/E′). In cases of diastolic dysfunction, elevated

LV filling pressure increases myocardial wall tension and stiffness, causing left atrial (LA) distension and an enlargement in LA volume. Recently, LA volume has gained recognition as an indicator of both the severity and duration of diastolic dysfunction and is associated with cardiovascular risk.[4-6] Kim et al in his study has shown that higher left atrial (LA) stiffness has been linked to a greater risk of all-cause mortality and heart failure-related hospitalizations in patients with HFpEF.

Its prognostic significance appears to be stronger than that of left ventricular filling pressure indices.[8] A study reported correlation coefficient between left atrial volume index and NT-proBNP as 0.474 and p value of 0.007.[9] While another study reported the correlation 0.387 with significant p(<0.001).[10] Brain natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are released by cardiomyocytes in response to stretching, and their levels increase in the presence of ventricular dysfunction. However, plasma concentrations of these peptides can also be influenced by factors such as gender, age, renal failure and the obesity.[11] The correlation between BNP values and ventricular function parameters is not particularly strong, leading to a "grey area" where BNP levels do not provide definitive evidence to confirm or exclude the presence of ventricular dysfunction.[12]

While an elevated E/E' ratio is associated with NT-pro-BNP levels in congestive heart failure (CHF), the relationship between these two parameters does not exhibit a consistent correlation.[9-10] Additionally, it remains uncertain which factors, aside from the E/E' ratio, significantly contribute to the elevation of NT-pro-BNP levels, especially in patients with heart failure with preserved ejection fraction (HFPEF). As a result, we aimed to determine whether left atrial (LA) volume could serve as a predictor or correlate with NT-pro-BNP levels in this patient population. The relationship between left atrial volume index and Pro-BNP remains debated in clinical practice, with some studies reporting a moderate correlation and others a weak one. To clarify this inconsistency, it is crucial to investigate this correlation more closely to establish stronger evidence, particularly by addressing the gap in local data on the correlation coefficient (r). Additionally, continuous research is essential to refine clinical conclusions and adapt to advancements in medical science, ensuring improvements in standard care. This study, by providing the coefficient of correlation (r), offers a reliable statistical measure for evaluating this relationship. The findings can provide consultants with valuable insights to guide clinical practice and patient care.

Methodology

A descriptive cross-sectional Study was done at Department of Cardiology, Liaquat University of Medical & Health Sciences (LUMHS). Duration of the study was six months from 26th March 2021 to 25th September 2021 after taking Ethical approval. Subject between age of 19 to 59 years, both gender, with LV ejection fraction >50%, without regional wall motion abnormalities, patients presented with heart failure with preserved ejection fraction (as mentioned in operational definition) irrespective the duration of HF and patients with HF class I, II, or III according to Framingham Criteria irrespective were included. Patients with other comorbid such as chronic liver disease, chronic lung disease, or chronic kidney disease, moderate to severe valvular heart disease, NYHA Class IV and Non-Sinus rhythm were excluded. Informed consent was taken from each patient after explaining the study protocol. Venous blood samples from the periphery were obtained for pro- BNP level measurement immediately after the echocardiographic study. Blood samples were collected in tubes containing EDTA and were centrifuged within 1 hour. The pro-BNP was determined in serum using an electro- chemiluminescence immunoassay on a Modular analytics E170 (Roche Diagnostics, Mannheim, Germany); the analytic range of the pro-BNP was 5-35000[pg/ml].

All patients underwent comprehensive echocardiographic study using a Vivid 7 digital ultrasound system, while echocardiographic images were obtained in the standard parasternal and apical views. Measurements of LV dimension and wall thickness and LA dimension were performed according to the recommendations of the American Society of Echocardiography. Measurements of the LVEF done from apical four and two chamber views (modified biplane Simpson's method). LA volume was obtained by means of the formula for biplane area-length method, and LA volume index (LAVI) was calculated as LA volume-to-body surface area ratio. Early transmitral inflow (E) velocity, its decelerating time (DT), late transmitral flow (A) velocity, and isovolumic relaxation time was assessed by using pulsed-wave tissue Doppler image (TDI) (systolic (S′), early diastolic (E′), and late diastolic (A′) mitral annular velocity were obtained at the septal mitral annulus level in apical four-chamber view with septal annulus movement aligned with sample volume line, and E/E′ ratio was derived. Biasness of the study was controlled by strictly followed

the inclusion criteria. Statistical Package for Social Sciences (SPSS) Version 26.0 was used for data processing and analysis.

Results

In this study 33 patients were included to assess the correlation between left atrial volume index and Pro-BNP levels in heart failure patients with preserved ejection fraction and the results were analyzed. The study sample had a mean age of 51.15 ±12.47 years. The average body mass index (BMI) was 30.70 ±5.20 kg/m², and the left atrial (LA) volume index averaged 31.12±6.36 ml/m²). Pro-BNP levels were recorded at a mean of 112.91±9.31 pg/ml). Out of all, 60.6% of participants were male and 39.4% were female. Hypertensive cases were 42.4% and 45.5% had diabetes mellitus. Participants were categorized into NYHA classes as follows: Class I, 21.2%, Class II, 42.4% and Class III, 36.4%. (Table I)

A Pearson correlation test was done to assess the relationship between LA volume and Pro-BNP levels. Mean LA volume was 31.12±6.36 ml/m², while the mean Pro-BNP level was 112.91±9.31 pg/ml. The correlation coefficient (r) was found to be 0.134, with a p-value of 0.457, indicating no statistically significant correlation between LA volume and Pro-BNP levels in this sample. (Table II)

Table I: Statistics for demographic information. (n=33)

Variables		Statistics
Age (mean+SD)		51.15±12.47 years
Weight		80.62±10.26 kg
Height		64.50±3.49 cm
Body mass index		30.70±5.20 kg/m^2
LA volume index		31.12±6.36 ml/m^2
Pro-BNP levels		112.91±9.31 pg/ml
Gender	Male	20(60.6%)
	Female	13(39.4%)
Hypertension	Yes	14(42.4%)
	No	19(57.6%)
Diabetes mellitus	Yes	15(45.5%)
	No	18(54.5%)
NYHA class	I	7(21.2%)
	II	14(42.4%)
	III	12(36.4%)

Table II: Correlation between LA volume and PRO-BNP level. (n=33)

OUTCOME	MEAN±SD	Coefficient of Correlation (r)	P-VALUE
La Volume	31.12 6.368		
Pro-BNP level	112.91 9.315	0.134	0.457

On the stratification by age, gender, BMI, hypertension, diabetes, and NYHA class showed no significant correlations between LA volume and Pro-BNP levels across all categories. Despite some variations in mean

Table III: Stratification with respect to the age, gender, BMI, hypertension , diabetes and NYHA class. (n=33)

Variables			MEAN	±SD	Coefficient correlation (r)	P-value
Age groups	19 – 50	La Volume	31.00	6.815		
		Pro-BNP level	109.70	8.341	0.465	0.175
	> 50	La Volume	31.17	6.322		
		Pro-BNP level	114.30	9.541	0.008	0.971
Gender	Male	La Volume	29.95	6.894		
		Pro-BNP level	112.90	8.735	0.176	0.457
	Female	La Volume	32.92	5.204		
		Pro-BNP level	112.92	10.516	0.079	0.797
BMI kg/m^2	25 –28 Kg/m^2	La Volume	30.16	5.439		
		Pro-BNP level	112.79	9.484	0.414	0.078
	> 28 Kg/m^2	La Volume	32.43	7.460		
		Pro-BNP level	113.07	9.434	-0.148	0.614
Hypertension	Hypertensive	La Volume	31.86	7.199		
		Pro-BNP level	113.00	9.282	-0.073	0.805
	Non-Hypertensive	La Volume	30.58	5.824		
		Pro-BNP level	112.84	9.593	0.314	0.191
Diabetes	Diabetic	La Volume	31.27	7.255		
		Pro-BNP level	113.60	8.959	0.229	0.411
	Non- Diabetic	La Volume	31.00	5.739		
		Pro-BNP level	112.33	9.822	0.045	0.860
NYHA class	I	La Volume	32.00	7.211		
		Pro-BNP level	116.71	8.538	0.084	0.858
	II	La Volume	32.29	5.823		
		Pro-BNP level	114.71	8.686	0.167	0.567
	III	La Volume	29.25	6.594		
		Pro-BNP level	108.58	9.472	-0.053	0.869

values, none of the Pearson correlation coefficients were statistically significant, indicating no strong association between these variables within the studied group of 33 participants as shown in table III.

Discussion

Heart failure with preserved ejection fraction (HFpEF) is characterized by elevated left ventricular (LV) diastolic pressures, even though LV end-diastolic volumes remain largely normal. Patients with HFpEF typically exhibit left ventricular wall hypertrophy, accompanied by increased interstitial collagen deposition and cellular infiltration within the myocardium. These histological alterations result in LV stiffness, leading to a reduction in distensibility and elasticity. The stiffness of the LV subsequently elevates left atrial (LA) pressure, which ultimately contributes to increased pulmonary venous pressure.[13,14] While the exact pathophysiological mechanisms behind heart failure with preserved ejection fraction (HFpEF) are not fully understood, patients with this condition are often more likely to present with left ventricular (LV) hypertrophy or concentric remodeling, diastolic dysfunction of the LV, and enlargement of the left atrium (LA).[15]

This study has been conducted to evaluate the correlation between left atrial volume index and Pro- BNP in heart failure patients with preserved ejection fraction, on 33 patients with an overall mean age of 51.15 ±12.47 years and male predominance. Consistently in a study by Tromp J et al[16] involving 1,203 patients with heart failure with preserved ejection fraction (HFpEF), the mean age was 68.4 years (±12.2), with women making up 50% of the sample. Notably, 37% of the participants were under 65 years old, which included 157 individuals (13%) categorized as very young (under 55 years) and 284 individuals (24%) identified as young (aged 55 to 64 years).[16] In the study conducted by Kim H et al., the mean age of participants was reported as 68 ±12 years.[10] Similarly, Telles F et al. documented an average age of 69.4 ±8.0 years.[17] In the present study, there was a notable gender distribution among the patients, with 20 (60.5%) identified as male and 13 (39.4%) as female. This inconsistent with the findings from Kim H et al., where female participants constituted 76 (51%) of the

sample.[10] Conversely, Telles F et al. reported a higher prevalence of males, with 35 (71.4%) male patients compared to 14 (28.6%) females.[17] This variation in gender representation highlights the differing demographics across studies involving heart failure with preserved ejection fraction (HFpEF).

In the current study, hypertension was identified in 14 patients, accounting for 42.4% of the cohort. This finding contrasts with previous studies, where hypertension was reported in 86 cases (58%),[10] and in 33 cases (67%).[17]

Similarly, diabetes was documented in 15 patients (45.5%) in our study, whereas Kim H et al. found that diabetic patients comprised 37 cases (25%),[10] and Telles F et al. reported diabetes in only 7 patients (14%).[17] Regarding the distribution of NYHA class in our study, class I was noted in 7 patients (21.2%), class II in 14 patients (42.4%), and class III in 12 patients (36.4%). In comparison, Kim H et al. reported a higher prevalence of NYHA class I in 68 patients (46%), class II in 40 patients (27%), and class III in 40 patients (27%).[10] These differences in the prevalence of hypertension, diabetes, and NYHA classification among studies may reflect variations in patient demographics and clinical characteristics within the heart failure with preserved ejection fraction (HFpEF) population.

In the present study, the correlation between left atrial (LA) volume and Pro-BNP levels was observed, with mean values of 31.12±6.368 ml/m² for LA volume and 112.91±9.315 pg/ml for Pro-BNP. The coefficient of correlation was found to be r=0.134, with a non-significant p-value of 0.457. This contrasts with other studies that reported stronger correlations; one study found a correlation coefficient of 0.474 with a significant p-value of 0.007,[9] while another reported a coefficient of 0.387 and a highly significant p-value (<0.001).[10]

Diastolic function can be assessed by estimating left ventricular (LV) filling pressure, typically through the ratio of early transmitral inflow to diastolic velocity of the mitral annulus (E/E′).[18,19] In cases of diastolic dysfunction, increased LV filling pressure raises wall tension and myocardial stiffness, leading to LA distension and an increase in LA volume. Recently, LA volume has been recognized as a marker for the severity and duration of diastolic dysfunction, which is also related to cardiovascular risk. Moreover, it remains unclear what other factors, apart from the E/E′ ratio, significantly influence the elevation of NT-pro-BNP levels, particularly in patients with heart failure with preserved ejection fraction (HFpEF). This study also has several significant limitations, which highlights the need for further investigation into the determinants of NT-pro-BNP levels in this patient population.

Conclusion

It is to be concluded that weak correlation was noted between left atrial volume index and Pro-BNP levels. More studies are necessary to evaluate the statistical association with a larger sample size and with more parameters in multiple study centers in Pakistan are needed to validate the findings of the present study.

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