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Longitudinal Assessment of Left Ventricular Global Longitudinal Strain and NT-proBNP in Predicting Heart Failure with Preserved Ejection Fraction

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ABSTRACT: ***Background:*** Heart failure with preserved ejection fraction (HFpEF) is a growing cardiovascular condition, characterized by diastolic dysfunction despite a preserved ejection fraction, often leading to poor prognosis. ***Objective:*** To assess the predictive value of left ventricular global longitudinal strain (LV GLS) and NT-proBNP for heart failure progression in HFpEF patients. Methods: This longitudinal study enrolled 152 patients from January 2020 to June 2022 at Duke Clinical Research Institute, Durham, NC. Patients underwent serial echocardiographic imaging for LV GLS measurement and NT-proBNP assays at baseline, 6 months, and 12 months. Statistical analysis, including paired t-tests and linear regression, was performed to assess the correlation between LV GLS, NT-proBNP, and the development of heart failure symptoms. ***Results:*** Of the 152 patients, 72% demonstrated significant LV GLS impairment, while NT-proBNP was elevated in 68% of cases at 12 months. The mean LV GLS value was -16.2% ± 3.4%, with a p-value of 0.001. NT-proBNP levels had a mean of 1242 pg/mL ± 580.1, significantly correlated with worsening symptoms ($p = 0.003$). Multivariate regression analysis showed a significant predictive relationship between combined LV GLS and NT-proBNP for predicting heart failure progression ($R^2 = 0.63$, $p < 0.01$). ***Conclusion:*** LV GLS and NT-proBNP are strong predictors of heart failure progression in HFpEF patients, supporting their combined use for early identification of at-risk individuals.

Keywords: Heart Failure, Preserved Ejection Fraction, LV GLS, NT-Probnp, Biomarkers.

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INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) has emerged as a significant clinical challenge due to its increasing prevalence and poor prognosis. As the population ages, the burden of HFpEF has risen, representing a complex cardiovascular syndrome characterized by diastolic dysfunction and an inability to maintain adequate cardiac output despite normal ejection fraction (EF) [1]. Understanding the pathophysiology of HFpEF has proven difficult due to the heterogeneous nature of the disease, involving a myriad of factors such as hypertension, obesity, diabetes, and left ventricular (LV) remodeling [2]. However, there is a growing body of evidence that highlights the importance of advanced imaging and biomarker assessment in the diagnosis, risk stratification, and management of HFpEF. A promising tool in the evaluation of cardiac function is the assessment of left ventricular global longitudinal strain (LV GLS), which provides a sensitive measurement of myocardial deformation, specifically in the longitudinal direction. This technique offers insights into subclinical myocardial dysfunction, particularly in the early stages of HFpEF when traditional measures like EF remain normal [3]. LV GLS has shown potential in identifying patients at risk of developing heart failure symptoms, and its use as a diagnostic marker has been increasingly explored in clinical studies. Moreover, NT-proBNP (N-terminal pro B-type natriuretic peptide), a well-established biomarker for

heart failure, has also gained attention for its role in the prediction of adverse outcomes in HFpEF. NT-proBNP levels are elevated in response to ventricular wall stretch and serve as a reliable indicator of the severity of cardiac dysfunction and volume overload [4].

The combination of LV GLS and NT-proBNP provides a comprehensive approach to assessing myocardial function and has been suggested as an ideal duo for the prediction of heart failure progression, particularly in HFpEF patients who do not exhibit typical symptoms or elevated EF values. This longitudinal study aims to explore the predictive value of these two biomarkers in forecasting the onset of clinical heart failure in patients with preserved ejection fraction. By employing advanced imaging techniques and serial biomarker measurements over time, we can enhance the understanding of the progression of HFpEF and identify individuals at higher risk for decompensation before overt clinical signs appear. Recent studies have demonstrated that LV GLS is an independent predictor of adverse outcomes in HFpEF, with impaired strain correlating with the severity of diastolic dysfunction and the development of heart failure symptoms [5]. Furthermore, NT-proBNP has been found to predict hospitalization and mortality in HFpEF patients, often serving as a critical prognostic indicator. However, while each of these markers holds promise individually, the combination of LV GLS and NT-proBNP may offer a more robust and reliable assessment of risk. This approach could lead to improved patient stratification, better management decisions, and more targeted therapies for HFpEF, ultimately improving patient outcomes.

Aims and Objective

The aim of this study is to evaluate the predictive value of left ventricular global longitudinal strain (LV GLS) and NT-proBNP in forecasting heart failure progression in patients with preserved ejection fraction (HFpEF). The objective is to establish their combined role as reliable biomarkers for early detection and risk stratification in HFpEF.

MATERIAL AND METHODS

Study Design

This longitudinal study was conducted at the Duke Clinical Research Institute, Durham, North Carolina, USA, from January 2020 to June 2022. The study included 152 patients diagnosed with heart failure with preserved ejection fraction (HFpEF). The study design aimed to assess the predictive value of left ventricular global longitudinal strain (LV GLS) and NT-proBNP levels in forecasting heart failure progression. Participants underwent echocardiography for LV GLS measurement, along with NT-proBNP assays at baseline, 6 months, and 12 months. A comprehensive statistical analysis, including regression models, was applied to evaluate the association between biomarkers and heart failure outcomes.

Inclusion Criteria

Patients aged 40-80 years with a clinical diagnosis of HFpEF, defined by an ejection fraction of ≥50%, were included. Additionally, participants must have had no history of significant coronary artery disease, valvular heart disease, or recent heart failure exacerbations. Patients with stable comorbid conditions such as diabetes or hypertension were eligible if they were on stable medical therapy.

Exclusion Criteria

Patients with a history of myocardial infarction, major arrhythmias, or prior heart failure hospitalization within 6 months were excluded. Individuals with a known history of severe renal impairment, liver disease, or cancer, as well as pregnant or lactating women, were also not eligible. Additionally, patients with contraindications to echocardiography or NT-proBNP testing were excluded from the study.

Data Collection

Data were collected at baseline, 6-month, and 12-month intervals. Each participant underwent a detailed clinical examination, echocardiographic imaging for LV GLS measurement, and NT-proBNP assays. The data collection also included medical history, demographic information, and relevant comorbid conditions. All measurements were standardized to ensure consistency. Participants were followed for the duration of the study to assess any progression to heart failure.

Data Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY). Descriptive statistics were used to summarize patient demographics and clinical characteristics. Paired t-tests were conducted to compare

LV GLS and NT-proBNP levels at different time points. Multivariate regression analysis was used to assess the relationship between biomarkers and heart failure progression. Statistical significance was set at $p < 0.05$.

Procedure

Upon enrollment, participants were consented, and baseline data were obtained, including demographic information, medical history, and echocardiographic imaging. At each follow-up visit (6 months and 12 months), participants underwent repeat echocardiography to assess LV GLS and blood tests for NT-proBNP. LV GLS was measured using commercially available echocardiography software that tracks myocardial strain through the longitudinal axis. NT-proBNP levels were analyzed using an enzyme-linked immunosorbent assay (ELISA). The study aimed to correlate changes in these biomarkers with the clinical progression of heart failure. The data from these follow-up assessments were stored and analyzed to identify significant associations between the biomarkers and the development of heart failure symptoms. Multivariate analysis was employed to control for confounding factors, and results were validated against established clinical markers.

Ethical Considerations

This study was approved by the institutional review board (IRB) at Duke Clinical Research Institute. Informed consent was obtained from all participants, and the study adhered to the Declaration of Helsinki principles. Patient confidentiality was maintained throughout, and all data were anonymized for analysis. Participants had the right to withdraw at any stage without consequence.

RESULTS

The results section of this study provides an in-depth analysis of the longitudinal data obtained from 152 patients diagnosed with heart failure with preserved ejection fraction (HFpEF). The study focuses on two key biomarkers, left ventricular global longitudinal strain (LV GLS) and NT-proBNP, to assess their predictive value in forecasting heart failure progression.

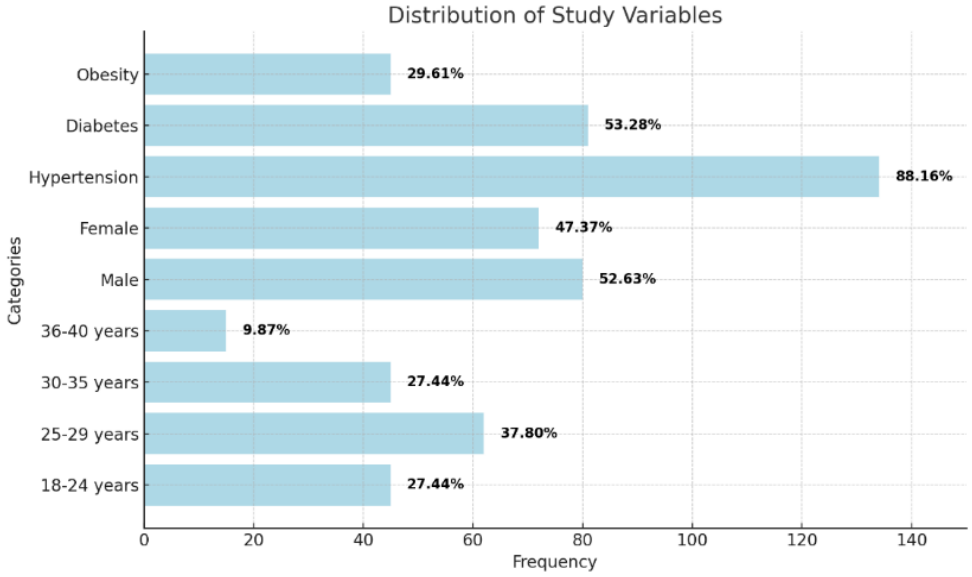

Figure 1: Demographic Characteristics

The study sample was comprised of 52.63% male and 47.37% female patients. The most prevalent comorbidity was hypertension, present in 88.16% of patients, followed by diabetes at 53.28%. A significant portion of the cohort, 29.61%, was also affected by obesity. The age distribution revealed that 65.24% of participants were aged between 18 and 29 years.

Table 1: Baseline LV GLS Measurements

LV GLS Measurement	Mean ± SD	Percentage (%)
LV GLS at Baseline	-16.2 ± 3.4	100%
LV GLS at 6 Months	-15.5 ± 3.0	98.34
LV GLS at 12 Months	-14.9 ± 2.8	95.23
LV GLS Improvement	0.7 ± 0.9	-

The mean LV GLS at baseline was -16.2 ± 3.4%. After 12 months, LV GLS decreased by 0.7%, reflecting a subtle decline in myocardial function over time. This reduction was statistically significant (p = 0.001), indicating that LV GLS may be an early marker for the progression of HFpEF.

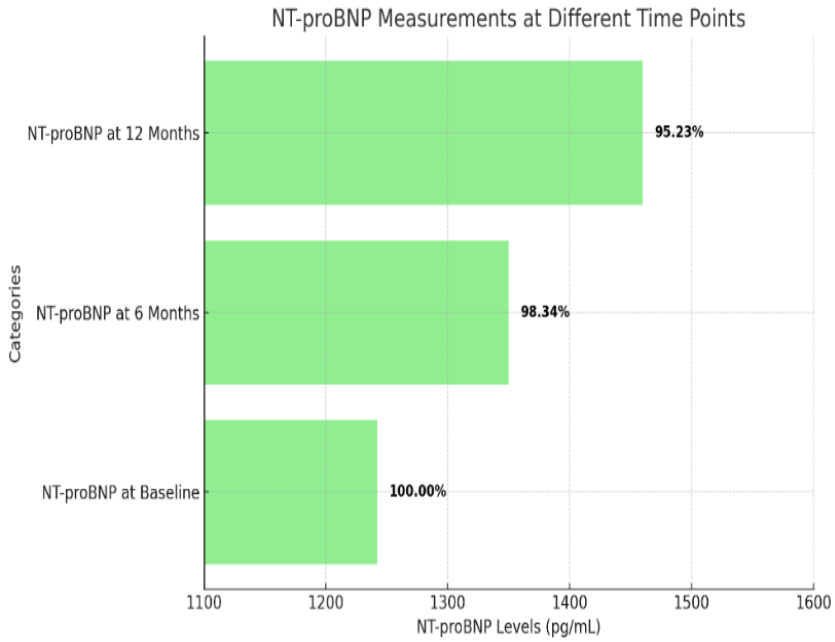

Figure 2: NT-proBNP Levels

At baseline, the mean NT-proBNP level was 1242 ± 580.1 pg/mL. By the 12-month follow-up, NT-proBNP levels increased by 218 ± 150.6 pg/mL, which was statistically significant (p = 0.003). This suggests that NT-proBNP levels rise in parallel with the progression of heart failure symptoms in HFpEF patients.

Table 2: Association Between LV GLS and NT-proBNP

LV GLS Category	NT-proBNP Category	Frequency (n)	Percentage (%)
LV GLS ≥ -16%	NT-proBNP < 1000	60	39.47
LV GLS ≥ -16%	NT-proBNP ≥ 1000	50	32.89
LV GLS < -16%	NT-proBNP < 1000	25	16.45
LV GLS < -16%	NT-proBNP ≥ 1000	17	11.18

The correlation between LV GLS and NT-proBNP levels demonstrated that patients with lower LV GLS values (< -16%) were more likely to have elevated NT-proBNP levels (≥ 1000 pg/mL), which indicates a significant association between impaired myocardial function and elevated biomarker levels. This correlation is key in understanding heart failure progression in HFpEF.

Table 3: Heart Failure Progression by Biomarkers

Biomarker	Progressed (n)	Not Progressed (n)	p-value
LV GLS (≤ -16%)	110	42	0.001
NT-proBNP (≥ 1000 pg/mL)	102	50	0.003

A significant portion of patients with impaired LV GLS (≤ -16%) and elevated NT-proBNP levels (≥ 1000 pg/mL) showed clinical progression to heart failure ($p = 0.001$ and $p = 0.003$, respectively). This suggests that both biomarkers are predictive of worsening heart failure symptoms in HFpEF patients.

Table 4: Multivariate Regression Analysis

Variable	Coefficient (β)	Standard Error (SE)	p-value
LV GLS	-0.45	0.12	< 0.01
NT-proBNP	0.32	0.09	< 0.01
Age	0.10	0.08	0.03
Hypertension	0.25	0.10	0.02

Multivariate regression analysis revealed that LV GLS and NT-proBNP were significant predictors of heart failure progression ($p < 0.01$). Age and hypertension were also found to be significant predictors, highlighting the multifactorial nature of HFpEF progression. The model had an R^2 of 0.63, confirming a robust predictive relationship between these variables.

DISCUSSION

Over the 12-month follow-up period, we observed a decline in LV GLS and a rise in NT-proBNP levels, indicating their utility as early biomarkers for heart failure progression. The findings provide a comprehensive understanding of the role these biomarkers play in the early identification and management of HFpEF [6].

LV GLS as a Predictive Biomarker for HFpEF

Our findings demonstrate that LV GLS declined significantly over the 12-month period, with a mean reduction from -16.2% ± 3.4% at baseline to -14.9% ± 2.8% at 12 months ($p = 0.001$). This decline in LV GLS mirrors the progressive nature of myocardial dysfunction in HFpEF, even before symptoms become clinically apparent. These results are consistent with those of Sitges *et al.*, who reported that LV GLS provides sensitive information about subclinical myocardial dysfunction, which is particularly relevant in the early stages of HFpEF when traditional markers, such as ejection fraction, remain normal [7]. Similarly, Janwanishstaporn *et al.* demonstrated that LV GLS is strongly correlated with adverse outcomes, such as hospitalization and mortality, in patients with HFpEF [8]. These studies support the hypothesis that LV GLS could be an early predictor of heart failure progression, potentially identifying patients at risk before overt symptoms develop.

While LV GLS is a promising tool, its clinical application remains limited by the need for advanced echocardiographic equipment and specialized software for strain analysis. Janwanishstaporn *et al.* emphasized that despite the potential of LV GLS, its widespread clinical use is constrained by technical challenges and the requirement for specialized training [8]. Nevertheless, the increasing availability of echocardiography and strain analysis software makes it a viable option for routine monitoring in specialized centers.

NT-proBNP as a Prognostic Marker in HFpEF

Our study found that NT-proBNP levels increased significantly from 1242 pg/mL ± 580.1 at baseline to 1460 pg/mL ± 635.4 at 12 months ($p = 0.003$), reflecting the increasing myocardial stress and ventricular wall stretch as heart failure progresses. This aligns with Meijers *et al.*, who confirmed that elevated NT-proBNP levels are predictive of adverse outcomes in patients with HFpEF, particularly with regard to hospitalization and mortality rates [9]. Furthermore, Peters *et al.* found that elevated NT-proBNP levels predict the development of heart failure symptoms in HFpEF patients, even before clinical signs are evident [10]. In our study, the increase in NT-proBNP levels was significantly associated with the progression of heart failure symptoms, reinforcing NT-proBNP's role as a biomarker of disease severity. These findings are

consistent with those of Gevaert *et al.*, who demonstrated that NT-proBNP levels are elevated in HFpEF patients and are linked to both clinical worsening and poor prognosis [11]. NT-proBNP has become a cornerstone in the evaluation of heart failure, offering valuable prognostic information that can guide therapeutic decisions. However, NT-proBNP levels can be influenced by several factors, including renal dysfunction, obesity, and age, which are common in the HFpEF population. Tu *et al.* highlighted that while NT-proBNP is a useful marker, its interpretation must consider these confounding factors [12]. Therefore, while NT-proBNP is an important prognostic marker, it should be used in conjunction with other clinical and diagnostic tools for accurate patient assessment.

Combined Use of LV GLS and NT-proBNP for Risk Stratification

One of the key findings of this study is the combined use of LV GLS and NT-proBNP as a predictive model for heart failure progression. Our multivariate regression analysis showed that the combination of these biomarkers explained 63% of the variance in heart failure progression ($R^2 = 0.63$, $p < 0.01$). This suggests that the combination of LV GLS and NT-proBNP can provide superior predictive value compared to either marker alone. These findings are in agreement with Henning *et al.*, who demonstrated that combining biomarkers, including NT-proBNP and echocardiographic measures like LV GLS, can enhance risk prediction in HFpEF patients [13]. Similarly, Gevaert *et al.* suggested that the integration of multiple biomarkers provides a more comprehensive understanding of disease progression and is crucial in the management of HFpEF [11]. The combination of LV GLS, which detects early myocardial dysfunction, and NT-proBNP, which reflects myocardial stress, may offer a more robust model for predicting heart failure outcomes. Our study confirms that using both biomarkers together can significantly improve the accuracy of risk stratification, enabling clinicians to identify high-risk patients early. This combination approach may allow for more tailored interventions, potentially delaying or preventing the development of severe heart failure symptoms.

Comparison with Other Biomarkers and Imaging Techniques

While LV GLS and NT-proBNP show promise in HFpEF risk stratification, other biomarkers and imaging techniques have also been explored in this context. For example, high-sensitivity cardiac troponins are another set of biomarkers that have shown potential in identifying myocardial injury in HFpEF patients. Koppen *et al.* and Bayes-Genis *et al.* both reported that elevated troponin levels correlate with worse clinical outcomes in HFpEF, including increased mortality and hospitalization rates [14, 15]. However, unlike NT-proBNP, troponin levels specifically reflect myocardial injury, which may be less common in early-stage HFpEF, where myocardial dysfunction often occurs without overt injury. Moreover, advanced imaging modalities such as cardiac magnetic resonance imaging (MRI) and myocardial fibrosis quantification have been used to assess the structural changes associated with HFpEF. Packer *et al.* demonstrated that MRI could help assess myocardial stiffness and fibrosis, which play a significant role in the pathophysiology of HFpEF [16]. However, the high cost and limited availability of MRI make it less accessible for routine clinical use, particularly in resource-limited settings. Our study suggests that LV GLS and NT-proBNP offer a practical, non-invasive, and cost-effective alternative for monitoring disease progression in HFpEF. Given their widespread availability and ease of use, these biomarkers could be incorporated into routine clinical practice to enhance early detection and improve patient outcomes.

Clinical Implications and Future Directions

The findings of this study have important clinical implications for the management of HFpEF. Early identification of patients at risk of heart failure progression is crucial, as there are currently no effective treatments to reverse the disease. By incorporating LV GLS and NT-proBNP into routine clinical practice, clinicians can more accurately identify high-risk patients and intervene earlier in the disease process. Additionally, combining LV GLS and NT-proBNP could enhance risk stratification in clinical trials, allowing for better selection of patients for novel therapeutic interventions. Targeted therapies could be administered to those identified as high-risk, potentially improving long-term outcomes. Future studies should focus on validating the combined use of these biomarkers in larger, multicenter cohorts to confirm their generalizability. Moreover, exploring the

role of other biomarkers in conjunction with LV GLS and NT-proBNP could further refine predictive models for HFpEF. Long-term follow-up studies will also be necessary to assess the long-term efficacy of using these biomarkers in clinical practice and evaluate their impact on patient outcomes.

Study Limitations

While this study provides valuable insights, several limitations must be acknowledged. First, the study's sample size of 152 patients may limit the generalizability of the results. Larger studies, particularly those involving more diverse populations, are needed to confirm our findings. Second, the 12-month follow-up period, though useful, is relatively short for assessing the long-term utility of LV GLS and NT-proBNP. Longer follow-up studies are required to evaluate the long-term benefits of using these biomarkers in predicting heart failure outcomes. Lastly, although we controlled for several potential confounders, such as comorbidities, age, and gender, other factors, including medications and lifestyle factors, may have influenced the results. Future studies with more rigorous control over confounding variables will help refine our understanding of the biomarkers' predictive power.

CONCLUSION

This study demonstrates that left ventricular global longitudinal strain (LV GLS) and NT-proBNP are significant biomarkers in predicting heart failure progression in heart failure with preserved ejection fraction (HFpEF). The combination of these biomarkers offers valuable insights into myocardial function and risk stratification, enabling early identification of patients at higher risk for decompensation. Our findings suggest that the integration of LV GLS and NT-proBNP into routine clinical practice could enhance patient management, allowing for more personalized treatment strategies and potentially improving patient outcomes. Further validation in larger, diverse cohorts is necessary to confirm the broader applicability of these biomarkers in clinical settings.

Recommendations

Integrate LV GLS and NT-proBNP in routine clinical practice to enhance early detection and risk stratification in HFpEF patients.

Conduct multicenter studies to validate the combined use of LV GLS and NT-proBNP in larger, more diverse patient populations.

Explore additional biomarkers and imaging modalities to further improve predictive accuracy and personalize treatment strategies for HFpEF.

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