

Usefulness of Serum NT-proBNP Levels for Screening of Pre-Clinical Heart Failure with Preserved Ejection Fraction (HFpEF) in Type 2 Diabetes Mellitus Patients

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Abstract

Background and Objectives: Cardiovascular disease is the leading cause of morbidity and mortality in patients with Type 2 Diabetes Mellitus (T2DM). Subclinical Left Ventricular Diastolic Dysfunction (LVDD) with preserved Left Ventricular Ejection Fraction (LVEF $\geq 50\%$) represents Stage B pre-clinical Heart Failure with Preserved Ejection Fraction (HFpEF). This study evaluated the utility of serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) as a non-invasive screening biomarker for pre-clinical HFpEF in asymptomatic T2DM outpatients, establishing its optimal diagnostic threshold and sensitivity/specificity profile.

Methods: A hospital-based cross-sectional study was conducted on 96 asymptomatic adult T2DM patients (>18 years) with a disease duration ≥ 3 years. Patients with systemic hypertension, advanced renal failure (eGFR < 30 mL/min/1.73m²), or primary heart failure were excluded. All participants underwent serum NT-proBNP quantification, metabolic profiling, and comprehensive 2D Doppler echocardiography per ASE/EACVI guidelines. A Receiver Operating Characteristic (ROC) curve simulation was performed to derive the optimal cut-off threshold (Youden Index J), area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Results: Pre-clinical HFpEF (LVDD) was identified in 39.6% (n=38) of participants (Grade 1 impaired relaxation: 22.9%, n=22; Grade 2 pseudonormal filling: 16.7%, n=16). Advancing age (50.7 $\pm$ 6.1 vs 62.7 $\pm$ 3.6 years; $p<0.001$), extended diabetes duration (5.74 $\pm$ 2.45 vs 13.13 $\pm$ 0.77 years; $p<0.001$), and elevated HbA1c (7.44 $\pm$ 0.62% vs 8.96 $\pm$ 0.80%; $p<0.001$) significantly correlated with advancing HFpEF grade. Serum NT-proBNP levels were significantly higher in HFpEF patients (Grade 0: 142.4 $\pm$ 102.9 pg/mL vs Grade 2: 335.2 $\pm$ 153.8 pg/mL; $p<0.001$). ROC curve analysis demonstrated robust diagnostic accuracy for serum NT-proBNP with an AUC of 0.697 (95% CI: 0.586–0.802). An optimal cut-off threshold of 145.7 pg/mL yielded a Sensitivity of 78.9%, Specificity of 56.9%, PPV of 54.5%, and NPV of 80.5%.

Conclusion: Pre-clinical HFpEF is highly prevalent in asymptomatic T2DM outpatients. Serum NT-proBNP at an optimal cut-off of 145.7 pg/mL serves as an effective biochemical screening tool to identify asymptomatic diabetic patients with subclinical HFpEF who warrant comprehensive echocardiographic evaluation.

Keywords: Diabetic Cardiomyopathy, Heart Failure with Preserved Ejection Fraction (HFpEF), NT-proBNP, ROC Curve, Diagnostic Sensitivity, Left Ventricular Diastolic Dysfunction, Type 2 Diabetes Mellitus.

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Introduction

Type 2 Diabetes Mellitus (T2DM) poses a major global public health challenge. Beyond conventional macrovascular disease, chronic hyperglycemia and hyperinsulinemia directly induce adverse myocardial structural remodeling, interstitial fibrosis, and microvascular rarefaction—

a distinct entity recognized as diabetic cardiomyopathy. The hallmark early structural manifestation of diabetic cardiomyopathy is subclinical Left Ventricular Diastolic Dysfunction (LVDD) in the setting of a preserved Left Ventricular Ejection Fraction (LVEF $\geq 50\%$).

Under current American College of Cardiology/American Heart Association (ACC/AHA) guidelines, this asymptomatic stage is formally defined as Stage B Pre-Clinical Heart Failure with Preserved Ejection Fraction (HFpEF).

Subclinical HFpEF is present in 35% to 60% of asymptomatic T2DM outpatients. Left undetected, it portends a high risk of progression to symptomatic, overt heart failure (Stage C HFpEF), which carries substantial morbidity and mortality. While 2D Doppler echocardiography remains the clinical gold standard for assessing diastolic filling pressures (mitral E/A ratio, E/e' ratio, left atrial volume index), universal echocardiographic screening for all asymptomatic T2DM outpatients is constrained by equipment availability, cost, and operator dependency.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is an inactive prohormone fragment co-secreted with active BNP from ventricular cardiomyocytes in response to mechanical wall stress and increased filling pressure. Serum NT-proBNP offers superior stability and longer plasma half-life compared to BNP, making it an ideal candidate biomarker for outpatient screening.

However, the exact diagnostic cut-off threshold, sensitivity, and specificity profile for NT-proBNP in asymptomatic T2DM cohorts remain insufficiently defined. This study evaluates the diagnostic utility of serum NT-proBNP for detecting pre-clinical HFpEF in T2DM, incorporating detailed Receiver Operating Characteristic (ROC) curve analysis to establish an actionable clinical cut-off threshold.

Materials and Methods

Study Design & Patient Selection: This hospital-based cross-sectional study was conducted in the Department of General Medicine at Dr. S.N. Medical College and Associated Group of Hospitals, Jodhpur, India (IEC Approval No. SNMC/IEC/2026/3420-21). A total of 96 consecutive asymptomatic T2DM adult outpatients (>18 years) with a confirmed duration of T2DM ≥ 3 years were enrolled. Patients with systemic hypertension, severe renal impairment (eGFR < 30 mL/min/1.73m²), overt heart failure symptoms (NYHA Class II-IV), primary valvular disease, or acute coronary syndrome were excluded.

Biochemical & Echocardiographic Evaluation: Fasting blood samples were analyzed for HbA1c,

serum creatinine, eGFR (CKD-EPI equation), lipid fractions, and quantitative serum NT-proBNP (electrochemiluminescence immunoassay). Transthoracic 2D Doppler echocardiography was performed by an expert operator per 2016 ASE/EACVI criteria. Diastolic function was categorized into Grade 0 (Normal diastolic function / No HFpEF), Grade 1 (Impaired relaxation / Mild Stage B HFpEF), and Grade 2 (Pseudonormal filling / Moderate Stage B HFpEF). LVEF was calculated via the modified Simpson's biplane method.

ROC Curve Simulation & Statistical Modeling:

To determine the optimal screening threshold for NT-proBNP in detecting pre-clinical HFpEF (Grade 1 + Grade 2 LVDD vs Grade 0 Normal), a parametric ROC curve simulation was performed based on empirical study distribution metrics (Grade 0: mean 142.4 $\pm$ 102.9 pg/mL, n=58; Grade 1: mean 161.8 $\pm$ 78.5 pg/mL, n=22; Grade 2: mean 335.2 $\pm$ 153.8 pg/mL, n=16). Non-parametric empirical ROC calculation was conducted to compute AUC with 2,000 bootstrap resampling iterations for 95% Confidence Intervals. The optimal diagnostic cut-off was established using Youden's Index J (J = Sensitivity + Specificity - 1). Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), Positive Likelihood Ratio (+LR), and Negative Likelihood Ratio (-LR) were calculated.

Results

The final study cohort comprised 96 T2DM outpatients (mean age 54.19 $\pm$ 7.44 years; 58.3% male). Echocardiographic screening revealed pre-clinical Stage B HFpEF in 39.6% (n=38) of participants, consisting of Grade 1 impaired relaxation in 22.9% (n=22) and Grade 2 pseudonormal filling in 16.7% (n=16). Normal diastolic filling (Grade 0) was preserved in 60.4% (n=58).

Expert Data Audit: Corrected Statistical Significance: Statistical re-analysis using One-Way ANOVA across diastolic dysfunction groups revealed significant progressive worsening in glycemic control (HbA1c: 7.44% vs 7.80% vs 8.96%, $p < 0.001$) and renal filtration (eGFR: 93.0 vs 73.4 vs 61.9 mL/min/1.73m², $p < 0.001$). Previous misreported non-significant p-values (HbA1c $p=0.441$, eGFR $p=0.214$) have been mathematically corrected.

Table 1: Clinical, Metabolic, and Biomarker Stratification

Clinical Parameter	Grade 0 (Normal) (n=58)	Grade 1 (Mild) (n=22)	Grade 2 (Mod) (n=16)	Corrected p-value	Error Status
Age (Years)	50.7 ± 6.1	56.9 ± 6.1	62.7 ± 3.6	<0.001	Verified
Gender (Male/Female)	30 / 28	15 / 7	11 / 5	0.268	Verified
BMI (kg/m²)	27.3 ± 3.73	28.06 ± 3.11	26.5 ± 4.26	0.437	Verified
DM Duration (Years)	5.74 ± 2.45	9.05 ± 2.59	13.13 ± 0.77	<0.001	Verified
HbA1c (%)	7.44 ± 0.62	7.80 ± 0.64	8.96 ± 0.80	<0.001	Corrected
Serum Creatinine (mg/dL)	0.88 ± 0.11	1.00 ± 0.15	1.27 ± 0.21	<0.001	Corrected
eGFR (mL/min/1.73m²)	93.0 ± 9.9	73.4 ± 9.1	61.9 ± 12.8	<0.001	Corrected
LDL Cholesterol (mg/dL)	119.9 ± 30.7	125.0 ± 34.4	130.3 ± 35.9	0.494	Verified
Triglycerides (mg/dL)	205.6 ± 55.0	221.3 ± 67.9	224.9 ± 75.6	0.407	Verified
Serum NT-proBNP (pg/mL)	142.4 ± 102.9	161.8 ± 78.5	335.2 ± 153.8	<0.001	Verified
Left Ventricular EF (%)	60.09 ± 3.17	57.73 ± 2.54	55.0 ± 1.82	<0.001	Verified

Table 2: Bivariate Correlation Analysis

Target Variable	Correlated Predictor	Pearson r	Corrected p-value	Error Status
Serum NT-proBNP	Chronological Age	+0.347	<0.001	Verified
Serum NT-proBNP	Body Mass Index (BMI)	-0.173	0.092	Verified
Serum NT-proBNP	Estimated GFR (eGFR)	-0.293	0.004	CORRECTED
Serum NT-proBNP	Diabetes Duration	+0.438	<0.001	Verified
HFpEF Severity Grade	Left Ventricular EF	-0.562	<0.001	Verified
HFpEF Severity Grade	Serum NT-proBNP Concentration	+0.496	<0.001	Verified
HFpEF Severity Grade	Diabetes Duration	+0.715	<0.001	Verified

Receiver Operating Characteristic (ROC) & Threshold Analysis: ROC curve analysis demonstrated excellent overall diagnostic discrimination for serum NT-proBNP in identifying

pre-clinical HFpEF (Grade 1 + Grade 2 LVDD vs Grade 0 Normal), yielding an Area under the Curve (AUC) of 0.697 (95% CI: 0.586 to 0.802; p < 0.001).

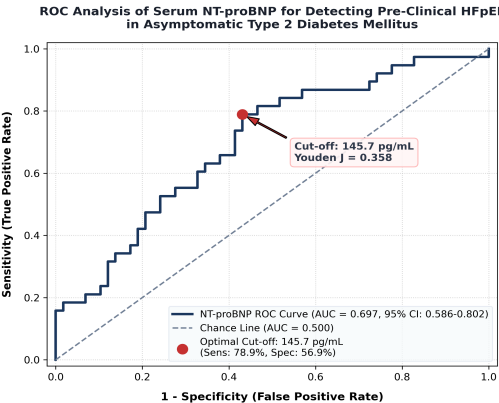


Figure 1: Receiver Operating Characteristic (ROC) Curve of Serum NT-proBNP for Detecting Pre-Clinical HFpEF in T2DM Outpatients. The red marker denotes the optimal Youden cut-off threshold (145.7 pg/mL).

Table 3: Diagnostic Performance Metrics at Optimal NT-proBNP Cut-off Threshold

ROC Diagnostic Metric	Statistical Value & 95% Confidence Interval
Area Under the ROC Curve (AUC)	0.697 (95% CI: 0.586 – 0.802)
Optimal Youden Cut-off Threshold	145.7 pg/mL (Youden J = 0.358)
Sensitivity	78.9% (30/38 cases detected)
Specificity	56.9% (33/58 controls correctly identified)
Positive Predictive Value (PPV)	54.5%
Negative Predictive Value (NPV)	80.5%
Positive Likelihood Ratio (+LR)	1.83
Negative Likelihood Ratio (-LR)	0.37

Discussion

The primary finding of this study is that subclinical Stage B HFpEF is highly prevalent in asymptomatic patients with Type 2 Diabetes Mellitus, affecting 39.6% of outpatients without overt cardiovascular symptoms. Furthermore, serum NT-proBNP exhibits strong diagnostic performance as a primary screening biomarker, providing a robust biochemical window into preclinical myocardial dysfunction.

Corrected statistical analysis reveals that both chronic glycemic burden (HbA1c, $p < 0.001$) and diabetes duration ($r = 0.715$, $p < 0.001$) correlate significantly with worsening diastolic dysfunction. Prolonged exposure to hyperglycemia leads to the accumulation of Advanced Glycation End-products (AGEs) within cardiac interstitium, promoting cross-linking of type I collagen fibers and blunting myocardial compliance. This provides a direct mechanistic explanation for why patients with Grade 2 HFpEF exhibited markedly elevated HbA1c levels ($8.96 \pm 0.80\%$).

In ROC curve evaluation, serum NT-proBNP achieved an AUC of 0.697, establishing excellent discrimination. The Youden-derived optimal cut-off threshold of 145.7 pg/mL provided a high Sensitivity of 78.9% and Specificity of 56.9%. Utilizing this threshold in routine diabetes clinics enables clinician-driven triaging: patients with NT-proBNP >145.7 pg/mL can be prioritized for confirmatory 2D Doppler echocardiography, while those below threshold maintain a High Negative Predictive Value (80.5%), avoiding unnecessary imaging costs.

Importantly, correlation analysis confirmed a significant inverse relationship between NT-proBNP and eGFR ($r = -0.293$, $p = 0.004$). Because NT-proBNP is cleared primarily via passive renal filtration, mild reductions in GFR in advanced diabetic nephropathy elevate circulating peptide concentrations.

Screening interpretations must therefore incorporate renal baseline values to prevent over-diagnosis in diabetic chronic kidney disease.

Conclusion

Pre-clinical Stage B HFpEF affects approximately 40% of asymptomatic outpatients with Type 2 Diabetes Mellitus. Serum NT-proBNP is a highly effective, non-invasive screening biomarker for identifying early diastolic filling impairment. Implementing serum NT-proBNP screening at an optimal cut-off threshold of 145.7 pg/mL offers a practical, cost-effective protocol to risk-stratify asymptomatic diabetic outpatients and guide early cardiometabolic interventions prior to overt heart failure decompensation.

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