Septal Tissue Doppler Velocity and Left Atrial Volume Index as Predictors of Heart Failure with Preserved Ejection Fraction in Patients with Type 2 Diabetes Mellitus: A Cross-sectional Study

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a major risk factor for heart failure with preserved ejection fraction (HFpEF). Early detection of diastolic dysfunction in diabetic patients is essential but challenging in routine practice.

Objective: To determine the prevalence of HFpEF among T2DM patients in a tertiary centre and to evaluate septal early diastolic mitral annular velocity (septal e′) and left atrial volume index (LAVI) as predictors of HFpEF using the 2019 Heart Failure Association (HFA)–European Society of Cardiology (ESC) consensus criteria.

Methods: In this cross-sectional study, 201 adults with T2DM under follow-up at Hospital UiTM over six months were randomly selected. Clinical evaluation, biochemical profiling, N-terminal pro–B-type natriuretic peptide (NT-proBNP), and comprehensive transthoracic echocardiography were performed. HFpEF was diagnosed using HFA–ESC 2019 recommendations (symptoms/signs of HF, LVEF ≥50%, structural/functional abnormalities, and elevated NT-proBNP). Septal e′, LAVI, basal septal hypertrophy, and serum cortisol (exploratory) were assessed. Group comparisons and multiple linear regression were used to identify independent predictors of HFpEF.

Keywords: Type 2 diabetes mellitus; heart failure with preserved ejection fraction; diastolic dysfunction; echocardiography; septal e′; left atrial volume index; NT-proBNP

1. Introduction

Heart failure with preserved ejection fraction (HFpEF) represents at least half of all heart failure (HF) cases worldwide and is associated with morbidity and mortality comparable to HF with reduced ejection fraction (HFrEF). Unlike HFrEF, however, evidence-based therapies for HFpEF remain limited, making **early identification and prevention** particularly important.

Type 2 diabetes mellitus (T2DM) is highly prevalent and confers an increased risk of HF through multiple mechanisms including microvascular dysfunction, myocardial fibrosis, metabolic derangements, and neurohormonal activation. Diastolic dysfunction is common in T2DM, and HFpEF is considered a key clinical expression of **diabetic cardiomyopathy**.

Diagnosis of HFpEF is challenging because patients often present with nonspecific symptoms such as exertional dyspnoea, and left ventricular ejection fraction (LVEF) is preserved by definition. The 2019 Heart Failure

Association (HFA)–European Society of Cardiology (ESC) consensus proposes an integrated algorithm incorporating symptoms, LVEF, natriuretic peptides, and echocardiographic markers of structural and functional abnormalities.

Among these echocardiographic parameters, **septal early diastolic mitral annular velocity (septal e′)** and **left atrial volume index (LAVI)** are particularly useful. Septal e′ reflects **myocardial relaxation**, while LAVI reflects **chronic elevation of left ventricular (LV) filling pressures**. Both are highly relevant in the context of T2DM, where subclinical diastolic dysfunction is frequent.

Despite this, data on HFpEF prevalence and simple echocardiographic predictors in diabetic populations from Southeast Asia, including Malaysia, remain sparse.

Aim: This study aimed to (i) determine the prevalence of HFpEF among adults with T2DM in a Malaysian tertiary centre using HFA–ESC criteria, and (ii) assess whether septal e′ and LAVI are independent predictors of HFpEF. Basal septal hypertrophy and serum cortisol were evaluated as exploratory markers.

2. Materials and Methods

2.1 Study Design and Setting

This was a single-centre, cross-sectional study conducted at Hospital UiTM, a tertiary teaching hospital in Malaysia. The study period was six months (December 2020 to May 2021).

2.2 Study Population

Adult patients (≥18 years) with established T2DM on regular follow-up in medical and diabetes clinics were eligible. A sampling frame was generated from clinic registries, and participants were selected using simple random sampling. All participants provided informed consent.

2.2.1 Inclusion Criteria

- Age ≥ 18 years
- Confirmed diagnosis of T2DM
- At least one year of clinical follow-up at Hospital UiTM

2.2.2 Exclusion Criteria

- Known HF with reduced ejection fraction (LVEF < 50%)
- Significant valvular heart disease (moderate/severe stenosis or regurgitation)
- Known primary cardiomyopathy (e.g., hypertrophic cardiomyopathy unrelated to hypertension)
- Acute coronary syndrome or HF hospitalization within the previous 3 months
- Inadequate echocardiographic window
- Pregnancy or severe systemic illness likely to confound NT-proBNP or cortisol (e.g., sepsis, advanced malignancy)

2.3 Clinical and Laboratory Assessment

A structured proforma was used to collect:

- Demographic data: age, sex, ethnicity
- Clinical data: duration of T2DM, history of hypertension, dyslipidaemia, coronary artery disease, stroke, and chronic kidney disease
- Lifestyle: smoking status (current, ex-smoker, never)

- Medications: antidiabetic agents, antihypertensives, statins, diuretics, etc.
- Physical examination: blood pressure (BP), heart rate, height, weight (for BMI)

Symptoms of HF (exertional dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, peripheral oedema) were documented, and functional capacity was graded using the New York Heart Association (NYHA) classification.

Morning fasting blood samples were obtained for:

- Fasting plasma glucose
- Glycated haemoglobin (HbA1c)
- Lipid profile (total cholesterol, LDL, HDL, triglycerides)
- Serum urea and creatinine, estimated glomerular filtration rate (eGFR)
- N-terminal pro–B-type natriuretic peptide (NT-proBNP)
- Serum cortisol (measured in the morning)

2.4 Echocardiographic Assessment

All patients underwent comprehensive transthoracic echocardiography using standard equipment and protocols. Studies were performed by experienced operators and interpreted by a cardiologist blinded to the biochemical results.

The following parameters were recorded:

- **LVEF**: assessed using the biplane Simpson method from apical four- and two-chamber views.
- **LV structure**: interventricular septal thickness, posterior wall thickness, LV internal diameters; LV mass calculated and indexed to body surface area.
- **Left atrial volume index (LAVI)**: left atrial volume measured by the biplane area-length method and indexed to body surface area (mL/m²).
- **Diastolic function indices**:
  - Transmitral Doppler: E and A waves, E/A ratio, deceleration time
  - Tissue Doppler imaging (TDI): septal early diastolic mitral annular velocity (septal e′, cm/s)
  - E/e′ ratio: E wave divided by septal e′
- **Basal septal hypertrophy**: visually and quantitatively assessed as localized thickening of basal interventricular septum beyond reference ranges.
- **Other**: right ventricular size and systolic function, estimated pulmonary artery systolic pressure when tricuspid regurgitation jet was adequate, and presence of pericardial effusion or major structural abnormalities.

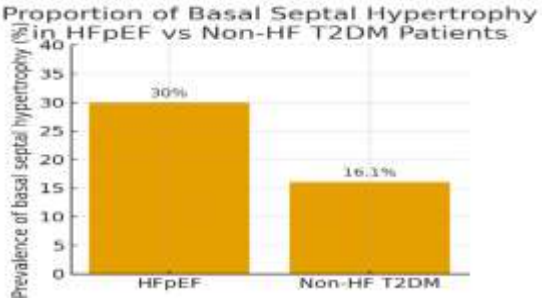

Figure 1. Proportion of basal septal hypertrophy in HFpEF vs non-HF T2DM patients.

2.5 Definition of HFpEF

HFpEF was diagnosed using the HFA–ESC 2019 algorithm. The following criteria had to be fulfilled:

1. **Presence of HF symptoms and/or signs** (e.g., exertional dyspnoea, orthopnoea, peripheral oedema);
2. **LVEF ≥ 50%**;
3. Evidence of **structural and/or functional cardiac abnormalities**, such as elevated LAVI, LV hypertrophy, reduced e′, elevated E/e′, or increased pulmonary pressures;
4. **Elevated NT-proBNP**, using age-appropriate cut-offs in sinus rhythm.

Patients fulfilling all criteria were classified as HFpEF. Those who did not meet these criteria and had no clinical HF were categorized as **non-HF diabetics**.

2.6 Statistical Analysis

Data were analysed using standard statistical software.

- Continuous variables were expressed as **mean ± standard deviation (SD)** or median (interquartile range) as appropriate.
- Categorical variables were expressed as **numbers (percentages)**.
- Comparisons between HFpEF and non-HF groups were made using **independent samples t-tests** for normally distributed continuous variables and **chi-square tests** for categorical variables.
- A **multiple linear regression model** was constructed to identify independent predictors of HFpEF status, including septal e′, LAVI, basal septal hypertrophy, cortisol, and selected clinical covariates.
- A p-value < 0.05 was considered statistically significant.

3. Results

3.1 Study Population and Prevalence of HFpEF

A total of 201 T2DM patients were included. HFpEF was diagnosed in **40 patients (19.9%)**, while 161 patients had no evidence of HF and served as the comparison group.

The mean age of HFpEF patients was **61 ± 5.4 years**. There was a modest female predominance overall, in keeping with known HFpEF epidemiology.

3.2 Baseline Clinical Characteristics

HFpEF patients tended to be older and had a higher prevalence of comorbid hypertension and dyslipidaemia compared with non-HF diabetics, although these trends did not reach statistical significance for all variables. BMI was generally elevated in both groups, reflecting a high burden of obesity. Many patients were on ACE inhibitors or angiotensin receptor blockers, statins, and oral antidiabetic medications.

Table 1. Baseline Clinical and Biochemical Characteristics of the Study Population

Variable	*All T2DM (n = 201)*	*HFpEF (n = 40)*	*Non-HF T2DM (n = 161)*	*p-value**
Age, years	*59.8 ± 6.1*	*61.0 ± 5.4*	*59.5 ± 6.3*	*0.12*
Female sex, n (%)	*112 (55.7)*	*25 (62.5)*	*87 (54.0)*	*0.34*
Duration of diabetes, years	*11.2 ± 4.9*	*12.0 ± 5.2*	*11.0 ± 4.8*	*0.29*
BMI, kg/m²	*29.7 ± 4.3*	*30.1 ± 4.5*	*29.6 ± 4.2*	*0.52*

Variable	*All T2DM (n = 201)*	*HFpEF (n = 40)*	*Non-HF T2DM (n = 161)*	*p-value**
Systolic BP, mmHg	*137 ± 14*	*140 ± 15*	*136 ± 13*	*0.09*
Diastolic BP, mmHg	*80 ± 8*	*81 ± 9*	*80 ± 8*	*0.41*
Hypertension, n (%)	*151 (75.1)*	*33 (82.5)*	*118 (73.3)*	*0.23*
Dyslipidaemia, n (%)	*139 (69.2)*	*30 (75.0)*	*109 (67.7)*	*0.37*
Known CAD, n (%)	*48 (23.9)*	*13 (32.5)*	*35 (21.7)*	*0.15*
Current smoker, n (%)	*39 (19.4)*	*9 (22.5)*	*30 (18.6)*	*0.56*
HbA1c, %	*8.1 ± 1.3*	*8.2 ± 1.4*	*8.1 ± 1.3*	*0.68*
Fasting plasma glucose, mmol/L	*8.9 ± 2.4*	*9.2 ± 2.5*	*8.8 ± 2.3*	*0.33*
Total cholesterol, mmol/L	*4.6 ± 0.9*	*4.7 ± 0.9*	*4.6 ± 0.9*	*0.57*
LDL cholesterol, mmol/L	*2.6 ± 0.7*	*2.7 ± 0.7*	*2.6 ± 0.7*	*0.46*
HDL cholesterol, mmol/L	*1.1 ± 0.3*	*1.0 ± 0.3*	*1.1 ± 0.3*	*0.18*
Triglycerides, mmol/L	*1.8 ± 0.8*	*1.9 ± 0.8*	*1.8 ± 0.8*	*0.40*
eGFR, mL/min/1.73 m²	*72 ± 18*	*70 ± 17*	*73 ± 18*	*0.39*
NT-proBNP, pg/mL (median, IQR)	*162 (90–310)*	*285 (190–420)*	*140 (80–260)*	*<0.001*
ACEI/ARB use, n (%)	*132 (65.7)*	*29 (72.5)*	*103 (64.0)*	*0.30*
β-blocker use, n (%)	*74 (36.8)*	*17 (42.5)*	*57 (35.4)*	*0.40*
Statin use, n (%)	*149 (74.1)*	*32 (80.0)*	*117 (72.7)*	*0.35*
Insulin therapy, n (%)	*67 (33.3)*	*16 (40.0)*	*51 (31.7)*	*0.31*

**p-value for comparison between HFpEF and non-HF T2DM groups (t-test or chi-square as appropriate). Values are mean ± SD unless otherwise stated.*

3.3 Echocardiographic Parameters

3.3.1 Septal e′

Septal e′ was significantly reduced in HFpEF patients:

- HFpEF: **5.5 ± 1.5 cm/s**
- Non-HF: **7.6 ± 1.0 cm/s**
- **p < 0.001**, 95% CI for difference: –2.40 to –1.49 cm/s

This indicates more pronounced impairment of LV relaxation in the HFpEF group.

3.3.2 Left Atrial Volume Index (LAVI)

LAVI was significantly higher in HFpEF patients:

- HFpEF: **35.5 ± 1.5 mL/m²**
- Non-HF: **28.6 ± 1.0 mL/m²**
- **p < 0.001**, 95% CI for difference: –2.50 to –1.33 mL/m²

This is consistent with chronic elevation of LV filling pressures in HFpEF.

3.3.3 Basal Septal Hypertrophy

Basal septal hypertrophy was present in **30%** of HFpEF patients and less frequently in the non-HF group. The difference approached, but did not reach, conventional statistical significance (**p = 0.081**), suggesting a possible association.

(Suggested Figure 1: Proportion of basal septal hypertrophy in HFpEF vs non-HF.)

3.4 NT-proBNP and Cortisol

HFpEF patients had higher NT-proBNP levels than non-HF diabetics, consistent with increased wall stress and filling pressures. When patients were stratified into NT-proBNP categories, a **stepwise increase in serum cortisol** was observed with increasing NT-proBNP (trend p = 0.061). This suggests possible interaction between neurohormonal activation and HF severity, although the finding did not reach strict statistical significance.

3.5 Multivariable Analysis

On multiple linear regression analysis incorporating echocardiographic parameters and selected clinical variables:

- **Lower septal e′** and **higher LAVI** were **independent predictors** of HFpEF status.
- The final model explained approximately **25%** of the variance in HFpEF (model $r^2 = 0.249$, $p < 0.001$).

Basal septal hypertrophy and cortisol did not remain independently significant after adjustment but retained suggestive trends as potential contributory markers.

Table 2. Echocardiographic Characteristics in HFpEF vs Non-HF T2DM Patients

Parameter	***HFpEF (n = 40)***	***Non-HF T2DM (n = 161)***	***p-value***
LVEF, %	*58.7 ± 3.2*	*59.4 ± 3.0*	*0.21*
LV end-diastolic diameter, mm	*47.1 ± 3.8*	*46.5 ± 4.0*	*0.39*
Interventricular septal thickness, mm	*12.1 ± 1.8*	*11.4 ± 1.7*	*0.06*
Posterior wall thickness, mm	*11.2 ± 1.6*	*10.9 ± 1.5*	*0.29*
LV mass index, g/m²	*103 ± 22*	*96 ± 20*	*0.07*
Septal e', cm/s	***5.5 ± 1.5***	***7.6 ± 1.0***	***<0.001***
E wave velocity, m/s	*0.83 ± 0.15*	*0.78 ± 0.14*	*0.09*
A wave velocity, m/s	*0.96 ± 0.18*	*0.91 ± 0.17*	*0.11*
E/A ratio	*0.88 ± 0.21*	*0.87 ± 0.19*	*0.81*
E/e' ratio (septal)	*15.2 ± 3.0*	*10.6 ± 2.4*	*<0.001*
Left atrial volume index, mL/m² (LAVI)	***35.5 ± 1.5***	***28.6 ± 1.0***	***<0.001***
Basal septal hypertrophy, n (%)	*12 (30.0)*	*26 (16.1)*	*0.081*
*Estimated PASP, mmHg**	*33 ± 6*	*30 ± 5*	*0.02*
Mild mitral regurgitation, n (%)	*11 (27.5)*	*31 (19.3)*	*0.25*

**PASP: pulmonary artery systolic pressure (measured when tricuspid regurgitation jet adequate). Values are mean ± SD unless otherwise stated.*

4. Discussion

This study demonstrates that HFpEF is common among patients with T2DM in a Malaysian tertiary centre, with a prevalence of about **20%** using contemporary HFA–ESC diagnostic criteria. Importantly, two simple echocardiographic parameters—**septal e′ and LAVI**—were identified as **independent predictors** of HFpEF in this population.

4.1 High Prevalence of HFpEF in T2DM

The observed HFpEF prevalence underscores the substantial burden of **subclinical and overt cardiac dysfunction in T2DM**, even among patients attending routine follow-up rather than specialized HF clinics. This aligns with the concept of diabetic cardiomyopathy, in which myocardial structural and functional changes develop independently of overt coronary disease.

4.2 Septal e′ and Diastolic Dysfunction

Reduced septal e′ in HFpEF patients reflects **impaired active relaxation** of the LV, a hallmark of diastolic dysfunction. Hyperglycaemia, insulin resistance, microvascular dysfunction, and interstitial fibrosis in T2DM all contribute to depressed myocardial relaxation. Our findings support the use of septal e′ as a **practical, easily measured marker** for detecting early diastolic abnormalities in diabetics.

4.3 LAVI and Chronic Filling Pressure

LAVI was significantly higher in HFpEF patients, reflecting **chronic elevation of LV filling pressures** and long-standing diastolic overload. Enlargement of the left atrium has been associated not only with HF but also with atrial fibrillation, stroke, and overall cardiovascular risk. The independent predictive value of LAVI in our study reinforces its role as a **"diastolic memory"** marker that integrates the cumulative impact of elevated LV filling pressures over time.

4.4 Basal Septal Hypertrophy and Cortisol as Emerging Markers

Basal septal hypertrophy was more frequently observed in HFpEF patients, suggesting that localized hypertrophic remodeling may be associated with diastolic dysfunction in T2DM. Although the association did not achieve conventional statistical significance, the trend justifies further investigation.

The borderline association between higher cortisol levels and higher NT-proBNP supports a possible relationship between **stress hormone activation and myocardial dysfunction**. Chronic elevation of cortisol can promote hypertension, insulin resistance, visceral obesity, and myocardial remodeling—all relevant to HFpEF. However, the exploratory nature and limited power of the current analysis mean that these findings should be interpreted cautiously.

4.5 Clinical Implications

This study has several important clinical implications:

1. **Diastolic assessment should be routine in T2DM**: Echocardiography for diabetic patients should go beyond measuring LVEF and include diastolic indices such as septal e′ and LAVI, particularly in symptomatic individuals and older patients.
2. **Risk stratification**: T2DM patients with reduced septal e′ and increased LAVI should be considered at **high risk for HFpEF** and might benefit from more intensive cardiovascular risk factor control, including blood pressure optimization, weight management, and careful glycaemic control.

3. **Integrated care**: The findings support closer collaboration between endocrinology and cardiology services, emphasizing HF prevention and early detection in T2DM.
4. **Potential for monitoring**: Septal e′ and LAVI could also serve as outcome measures in future interventional trials evaluating therapies (e.g., SGLT2 inhibitors, lifestyle interventions) targeting diastolic dysfunction in T2DM.

4.6 Strengths and Limitations

Strengths of this study include the application of up-to-date HFA–ESC HFpEF criteria, systematic echocardiographic evaluation, and focus on a high-risk T2DM cohort in a Southeast Asian setting.

Limitations include the cross-sectional design, single-centre nature, and modest sample size of the HFpEF group, which limit generalizability and preclude causal inference or prognostic analysis. Echocardiographic assessment was resting only; exercise echocardiography or invasive hemodynamics could detect milder or early HFpEF. Furthermore, cortisol measurements were limited to single morning values, and other biomarkers of fibrosis or inflammation were not assessed.

5. Conclusion

In a tertiary cohort of adults with type 2 diabetes mellitus, **approximately one in five** patients fulfilled diagnostic criteria for HFpEF. **Septal e′ and LAVI** were identified as **independent echocardiographic predictors** of HFpEF, reflecting impaired LV relaxation and chronic elevation of filling pressures, respectively.

These parameters are simple to obtain, widely available, and should be considered for routine incorporation into echocardiographic assessment of diabetic patients, particularly those with symptoms suggestive of HF. Early identification of high-risk individuals offers an opportunity for targeted intervention to delay or prevent progression to overt HFpEF.

Basal septal hypertrophy and cortisol–NT-proBNP associations appear promising as emerging markers and warrant evaluation in larger, longitudinal studies.

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