

Left Atrial Volume Index in Diagnosis of Heart Failure With Preserved Ejection Fraction

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Research Article

Keywords: heart failure with preserved ejection fraction, left ventricular end-diastolic pressure, left atrium volume index

Posted Date: September 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-593762/v1>

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Abstract

Objective To assess the value of left atrium volume index (LAVI) for diagnosing heart failure with preserved ejection fraction (HFpEF) based on the invasive determination of left ventricular end-diastolic pressure (LVEDP).

Methods A total of 710 cases of patients with dyspnea (LVEF \geq 50%) were enrolled in this retrospective study. Left ventricular end-diastolic pressure (LVEDP) was measured through selective coronary angiography. According to the value of LVEDP, cases were divided into the HFpEF group (LVEDP \geq 15mmHg) and the control group (LVEDP $<$ 15mmHg). LAVI was calculated based on cardiac compartment diameter, as measured by echocardiography, and body surface area (BSA). Differences of LAVI between the HFpEF group and the control group, and between subgroups in the HFpEF group were analyzed.

Results The difference in LAVI between the control group and the HFpEF group was statistically significant (41.35 ± 2.28 vs. 46.78 ± 2.63 ml/m², $p=0.008$). LVEDP was positively correlated with LAVI (Pearson: $r=0.787$, $P<0.001$). When LAVI took the best cutoff value of 43.7 mm/m², the sensitivity and specificity of diagnosis of HFpEF were 92.0% and 88.9%. When the boundary value of LAVI was from 41.7 to 45.7 mm/m², the sensitivity of the diagnosis of ejection fraction retention heart failure was from 97.4% to 64.4% and the specificity was from 51.2.0% to 92.2%.

Conclusion In patients with dyspnea after exclusion of heart failure with reduced ejection fraction (HFrEF), LAVI is positively correlated with LVEDP. LAVI can be used to diagnose HFpEF when HFrEF is excluded.

Introduction:

The clinical diagnosis of heart failure with preserved ejection fraction (HFpEF) is difficult^[1-2]. HFpEF is diagnosed as heart failure based on typical signs and symptoms in association with a diastolic dysfunction and a relevant structural heart disease^[2-4]. Heart failure associated symptoms and signs lack specificity due to the drawbacks of imaging and biomarkers in many clinical settings. Left atrial enlargement has been suggested by studies and guidelines as evidence for diagnosing HFpEF, but its efficacy has not been evaluated by left ventricular end-diastolic pressure (LVEDP), which is accepted as the gold standard for diagnosing HFpEF^[5, 6]. This study aims to evaluate the value of left atrium volume index (LAVI) in diagnosis of HFpEF based on the invasive determination of LVEDP.

Materials And Methods

1. Research population

The retrospective study included cases admitted between January 2015 and December 2018 to the emergency or cardiology department of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine. This study has been reviewed by the ethics committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine. Due to its retrospective nature, the study did not obtain informed consent forms.

2. Inclusion and exclusion criteria

Inclusion criteria: (i) age > 18 years old ; (ii) patients with acute dyspnea; (iii) patients with LVEF \geq 50% determined by cardiac color Doppler examination.

Exclusion criteria: (i) incomplete medical history data, loss of related examination results or existence of uncertain values; (ii) pericardial disease or pericardial effusion; (ii) severe anemia (HGB \leq 60g/L); (iv) no history of selective coronary angiography; (v) presence of serious changes of illness during cardiac color Doppler examination or selective coronary angiography; (vi) presence of serious adverse events during examinations; (vii) Moderate to severe mitral regurgitation.

3. Diagnostic criteria

LVEDP is considered to be the gold standard for diagnosing HFpEF, and heart failure can be diagnosed with LVEDP \geq 15mmHg.

4. Collection of general information

Patients' medical history, age, sex, height, weight, BMI (kg/m²), heart rate, and blood pressure (mmHg) were recorded. Blood sugar, serum creatinine, blood urea nitrogen, blood lipids, peripheral blood leukocytes, hemoglobin, smoking history, drinking history, chest X-ray, echocardiography, cardiogram, 12-lead electrocardiogram, and types and names of medications were also recorded.

5. Echocardiography

The Philips iu 22 color doppler ultrasound system (probe frequency 2.5MHZ) was used. All patients were told to remain in the left lateral position and do calm breathing for the transthoracic ultrasound examination, according to standard procedures. The following indicators were recorded: 1. left atrial diameter LAd; 2. left ventricular end diastolic diameter (Left ventricular end diastolic diameter, LVEDd); 3. interventricular septum diameter (IVSd); 4. left ventricular posterior wall diameter (LVPWd); 5. left ventricular ejection fraction (Left Ventricle Ejection Fraction, LVEF); 6. early mitral diastolic blood flow spectrum: E; 7. mitral regurgitation late anterior blood flow spectrum: A; 8. mitral regurgitation; 9. LAVI was obtained through the following steps^[7]: Obtain the left heart apex four-chamber view and the left-heart two-chamber view (Fig. 1), and plot the area of the left atrium (A1, A2) at the maximum volume of the left atrium. Also, measure the distance from the midpoint of the mitral annulus to the top of the left atrium (L1, L2). left atrial volume = $8 / 3\pi (A1 \times A2 / L) = 0.85 \times A1 \times A2 / L$, L for the apex Lavi = atrial volume / body surface area (BSA), BSA (m²) = $0.0061 \times \text{height (cm)} + 0.0128 \times \text{body weight (kg)} - 0.1529$.

6. Selective coronary angiography and left ventricular end-diastolic pressure measurement

Selective coronary angiography was performed using the Judkins method. After selective coronary angiography was completed, a pigtail catheter was slowly delivered to the left ventricle along the guide wire. There was no irritative ventricular premature contraction or adjustment before the contraction disappeared. The external pressure sensor was connected and left ventricular end-diastolic pressure was printed after the pressure screen was clearly displayed on the test screen.

7. Statistical analysis and control

(1) Data entry and control

All data were entered in an EpiData database (EpiData Association, Odense, Denmark) by the researchers using the double entry method, and cross-validation was used for control. All researchers have received professional training in reading relevant indicators.

(2) Bias control

In order to avoid control bias, the people who analyze the results of the index examination did not know the grouping.

(3) Statistical analysis

The data were imported into SPSS (Version 20.0, SPSS, Inc., Chicago, IL, USA) software for data processing. The normal distribution of continuous measurement data was expressed as mean \pm standard deviation. The Pearson chi-square test was used to analyze the categorical variables, and the Student t test was used to compare the two sets of measurement data (two-tailed test, $p < 0.05$ was considered statistically significant). LVEDP ≥ 15 mmHg was used as the gold standard for diagnosing HFpEF. The ROC curves of LAVI and N terminal pro B-type natriuretic peptide (NTpro-BNP) in diagnosing HFpEF were drew and the diagnostic efficacy between the two was compared according to the study diagnostic gold standard. The diagnostic test method was used to explore the optimal cutoff value for LAVI in diagnosing HFpEF, and the authenticity evaluation (the degree the results obtained by the diagnostic test is consistent with the actual situation) was conducted. The sensitivity, specificity, missed diagnosis rate, misdiagnosis rate, diagnosis ratio, Youden index, likelihood ratio, and the area under the ROC curve were calculated.

Results

1. Inclusion feature

Among the 829 cases enrolled, 119 withdrew due to no selective coronary angiography and 710 cases were divided into HFpEF group ($n = 239$, age 77.2 ± 9.4 years) and control group ($n = 471$, age 70.7 ± 11.9

years) according to LVEDP. The HFpEF group was divided into atrial fibrillation (Af) subgroup (n = 112) and non-atrial fibrillation (non-Af) subgroup (n = 127) (Fig. 2).

2. Baseline data

Baseline data of patients with normal heart function and the HFpEF group are shown in Table 1. There were no significant differences between the two groups in age and sex. Both groups had normal hepatic and renal functions. But levels of total cholesterol and low-density lipoprotein cholesterol (LDL-C) were higher in the HFpEF group than in the control group. Ratios of concomitant diseases such as hyperlipidemia, hypertension, diabetes, hypertrophic cardiomyopathy (HCM), atrial fibrillation and coronary artery disease were higher in the HFpEF group than in the control group whereas ratios of COPD, pulmonary interstitial fibrosis (PIF), pulmonary infection, pleural effusion and asthma were higher in the control group than in the HFpEF group. These phenomena may reflect the intrinsic features of cardiac and non-cardiac dyspnea.

3. Left atrial volume index

Levels of LAD (46.78 ± 2.63 ml/m² vs. 41.35 ± 2.28 ml/m², $p < 0.001$), LAVI (46.78 ± 2.63 ml/m² vs. 41.35 ± 2.28 ml/m², $p < 0.001$), LVEDP (25.47 ± 7.56 mmHg vs. 4.97 ± 4.12 mmHg, $p < 0.001$), NTpro-BNP (1692.73 ± 1435 pg/ml vs. 790.24 ± 497 pg/ml, $p < 0.001$) and LVEF ($72 \pm 18\%$ vs. $59 \pm 14\%$, $p < 0.001$) were higher in the HFpEF group than in the control group, while no significant difference was found in LVEDd (44.2 ± 11 mm vs. 45.4 ± 11 mm, $p = 0.32$) between the two groups. Levels of LAD, LVEDP, LAVI, NT-proBNP and LVEF were higher in the atrial fibrillation subgroup than non-atrial fibrillation subgroup (53 ± 10 mm vs. 49 ± 11 mm, $p < 0.01$); (26.71 ± 3.4 mmHg vs. 22.26 ± 6.16 mmHg, $p < 0.01$); (47.78 ± 3.35 ml/m² vs. 45.26 ± 2.71 ml/m², $p < 0.01$); (1832.42 ± 1017 pg/ml vs. 1384.73 ± 975 pg/ml, $p < 0.01$); ($75 \pm 17\%$ vs. $71 \pm 13\%$, $p < 0.01$), respectively). See Table 2.

4. Correlation of LAVI and LVEDP

LAVI was positively correlated with LVEDP (Pearson correlation: $r = 0.787$, $P < 0.001$). See Fig. 3.

Left atrial volume index and the efficacy of NT-proBNP in the diagnosis of HFpEF.

LAVI diagnosis using the HFpEF ROC curve.

The ROC curve of LAVI for diagnosing HFpEF was plotted using LVEDP ≥ 15 mmHg as the standard. AUC is 0.949 (95% CI: 0.930–0.967, $p < 0.001$). See Fig. 4.

5. ROC curve of NT-proBNP for diagnosing HFpEF

The ROC curve of NT-proBNP for diagnosing HFpEF was drawn with LVEDP ≥ 15 mmHg as the standard. The area under the curve (AUC) for the NT-proBNP diagnosing HFpEF was 0.76 (95% CI: 0.723 ~ 0.797, p

< 0.001). See Fig. 5. LAVI is superior to NT-proBNP in diagnosing HFpEF. The difference between AUC of LAVI and that of NTpro-BNP was significant (0.949 vs.0.760, $p=0.0001$).

6.Diagnostic test parameters of LAVI for diagnosing HFpEF

When LAVI took the best cutoff value of 43.7mm/m², with reference to LVEDP \geq 15mmHg as the standard for diagnosing HFpEF, the sensitivity and specificity for diagnosis of heart failure were 92.0% and 88.9%. The area under the curve was 0.949. When the LAVI threshold was from 41.7 to 45.7 mm/m², the sensitivity for diagnosis of ejection fraction retention heart failure ranged from 97.4–64.4%, and the specificity ranged from 51.2–92.2%, as shown in Table 3.

Discussion

Heart failure with preserved ejection fraction (HFpEF) is difficult to diagnose. If LVEF is in the normal range, further identification of HFpEF is difficult^[8]. Ultrasound assessment of diastolic function indexes such as E/A and E/E' are not easy to carry out under many clinical conditions. However, measuring the size of the left atrium as LVEF is comparatively easier. Epidemiological studies suggest that the size of the left atrium is associated with HFpEF and that left atrial volume index can be used to aid in the diagnosis of HFpEF^[9]. But the efficacy of this method has not been evaluated by LVEDP, which is accepted as the gold standard for diagnosing HFpEF^[10]. To further clarify the value of LAVI in the diagnosis of HFpEF, this study used LVEDP to evaluate the value of LAVI for diagnosing HFpEF.

In this study, LVEDP, LAD and LAVI were collected from cases of patients with dyspnea whose diagnoses have excluded the possibility of HFrEF. Left ventricular end-diastolic pressure (LVEDP) was measured by catheterization, the left atrial diameter was measured by cardiac color Doppler examination and LAVI was calculated thereby. Cases of patients with dyspnea were divided into an HFpEF group and a control group according to LVEDP^[5]. The correlation between LAVI and LVEDP in the HFpEF group showed that LAVI was positively correlated with LVEDP ($r = 0.787$, $P < 0.001$). The value of LAVI for diagnosing HFpEF was evaluated by using LVEDP \geq 15mmHg as the gold standard. The results show that LAVI is a valuable indicator for diagnosing HFpEF, and consistent with our hypotheses, its value is superior than that of NT-proBNP (ROC: 0.949 vs. 0.760, $p < 0.0001$).

In the subgroup analysis, though the level of LAVI was higher in atrial fibrillation subgroup than in non-atrial fibrillation group (47.78 ± 3.35 ml/m² vs. 45.26 ± 2.71 ml/m², $p=0.01$), all its level was higher than the best cutoff value of 43.7mm/m². The efficacy of LAVI for diagnosing HFpEF were reserved in our study population.

The role of changes in left atrial structure and function in heart failure is receiving growing interest^[11]. The pathophysiological mechanism of HFpEF is mainly characterized by myocardial hypertrophy, fibrosis, impaired dysfunction, left ventricular remodeling in patients with HFpEF, increased left ventricular mass, reduced left ventricular long axis shortening, left ventricular geometry changes, and concomitant

diastolic dysfunction [12-13]. When left atrial mass begins to increase in moderate left ventricular diastolic dysfunction, it is likely that the volume of the left atrium has not increased and that left atrial enlargement is a sign of a sustained increase in left ventricular filling pressure [14-15]. Continued elevated left atrial pressure and volume load increase left atrial hypertrophy and its mass [16-19], and thus the left atrium is considered to be closely related to HFpEF [24].

Currently there is no invasive method to explore the relation between left atrial volume and left ventricular end-diastolic pressure in patients with HFpEF although previous studies have shown that left atrial volume is closely related to the prognosis of HFpEF [20-21], or suggest that left atrial volume is associated with HFpEF comorbidities such as atrial fibrillation [22-23] or with diabetes [24]. Recently, Melenovsky and his colleagues used hemodynamics and echocardiography to study the structure and function of the left atrium in 198 cases (51% with HFpEF) with heart failure. They found that patients with HFpEF have higher left atrial peak pressure, left atrial stiffness, and pulsation index [25]. Impaired left atrial function is associated with right ventricular dysfunction and elevated pulmonary vascular resistance. Gani Bajraktari believed that, in addition to the effects of elevated left ventricular filling pressure, impaired compliance of the left atrium also leads to enlargement of the left atrium [26]. These studies suggest that the structure and function of the damaged left atrium are prevalent in HFpEF and play an important role in the pathophysiological changes of HFpEF. The structural changes of HFpEF in the left atrium (left atrial remodeling and enlargement) can be used as diagnostic indicators for HFpEF. Our study confirmed that LVEDP elevation is closely related to LAVI and can be used to diagnose HFpEF. It is an inexpensive and convenient means of diagnosis [25, 27].

Limitations

Some patients received treatment during the interval between selective coronary angiography and echocardiography, so the results may be affected and the errors were not excluded.

Conclusions

The left atrial volume index gradually increased with the increase of left ventricular end-diastolic pressure, and they were positively correlated. LAVI can be used to diagnose HFpEF. In the differential diagnosis of clinical dyspnea, if left ventricular ejection fraction is normal whereas the left atrium is enlarged, HFpEF should be considered. LAVI is superior to NTproBNP in the diagnosis of HFpEF.

Abbreviations

Full name	abbreviation
Mitral regurgitation late anterior blood flow spectrum	A
Atrial fibrillation	Af
Alanine transaminase	ALT
Aspartate aminotransferase	AST
Area under the curve	AUC
Body mass index	BMI
Body surface area	BSA
Blood urea nitrogen	BUN
Coronary artery disease	CAD
Chronic obstructive pulmonary diseases	COPD
Early mitral diastolic blood flow spectrum	E
High-density lipoprotein	HDL-C
Heart failure with preserved ejection fraction	HFpEF
Heart failure with reduced ejection fraction	HFrEF
Interventricular septum diameter	IVSd
Left atrial diameter	Lad
Left atrium volume index	LAVI
Low-density lipoprotein cholesterol	LDL-C
Left ventricular end diastolic diameter	LVEDd
Left ventricular end-diastolic pressure	LVEDP
Left ventricular ejection fraction	LVEF
Left ventricular posterior wall diameter	LVPWd
N terminal pro B-type natriuretic peptide	NTpro-BNP
Pulmonary interstitial fibrosis	PIF
Receiver operating characteristic	ROC
Total bilirubin	TBIL
Triglyceride	TG
Uric acid	UA

Declarations

Ethics approval and consent to participate

This study has been reviewed by the Ethics committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine. The ethics number is 2021DZMEC-111. Due to its retrospective nature, the study did not obtain informed consent forms, and the protocol was performed in accordance with the **Measures for the Ethical Review of Biomedical Research Involving Humans** (2016) published by National Health Commission of the People's Republic of China. Ethics committee of Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine agreed that there is no need for consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

No conflict of interest exists in the submission of this manuscript.

Funding

No funding.

Authors' contributions

Xingxue Pang and Peng Zhao wrote the main manuscript text, Ruoyi Liu and Li Xu prepared figures 1-3, Xuezheng Hao and Haiyan Zhu prepared figures 4-5, Cuiyun Zhao prepared tables 1-3 and Xin Tao polished the language. All authors reviewed the manuscript.

Acknowledgements

Not applicable.

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Tables

Due to technical limitations, table 1 to 3 is only available as a download in the Supplemental Files section.

Figures

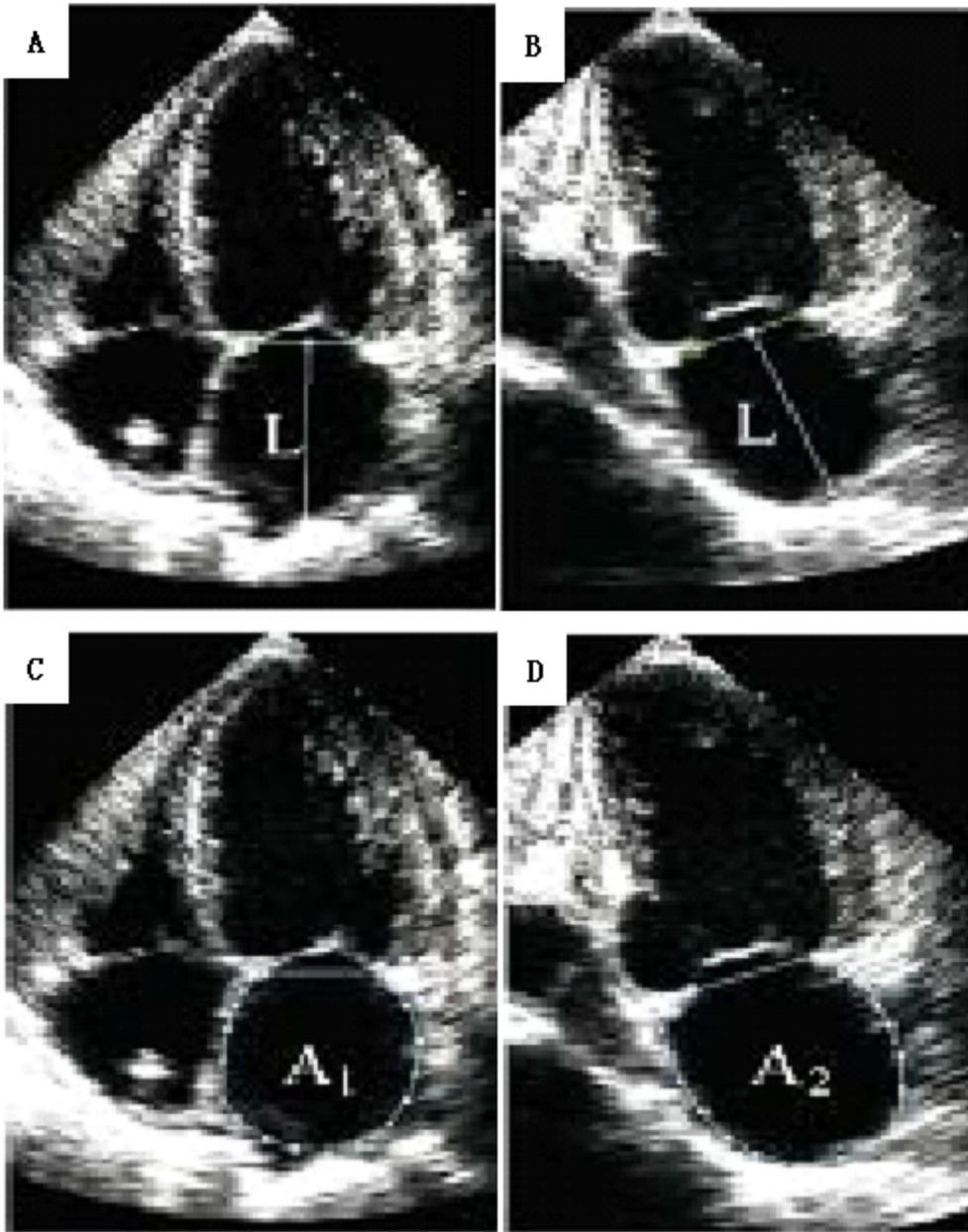


Figure 1

Schematic diagram of left atrial volume measurement Upper figure: L: distance from the midpoint of the mitral annulus to the top of the left atrium, A: a type of left atrium shape; B: another type of left atrium shape Lower figure: C: plotting the area of the left atrium, A1: a type of left atrium shape D: A2: another type of left atrium shape

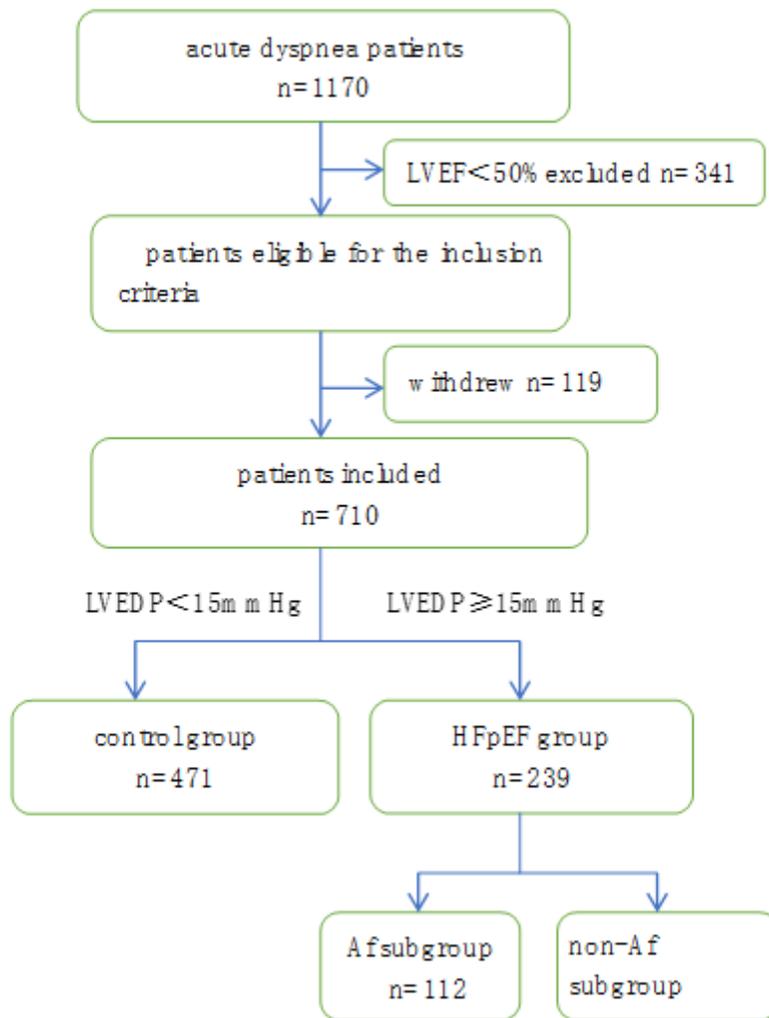


Figure 2

Schematic representation of the study

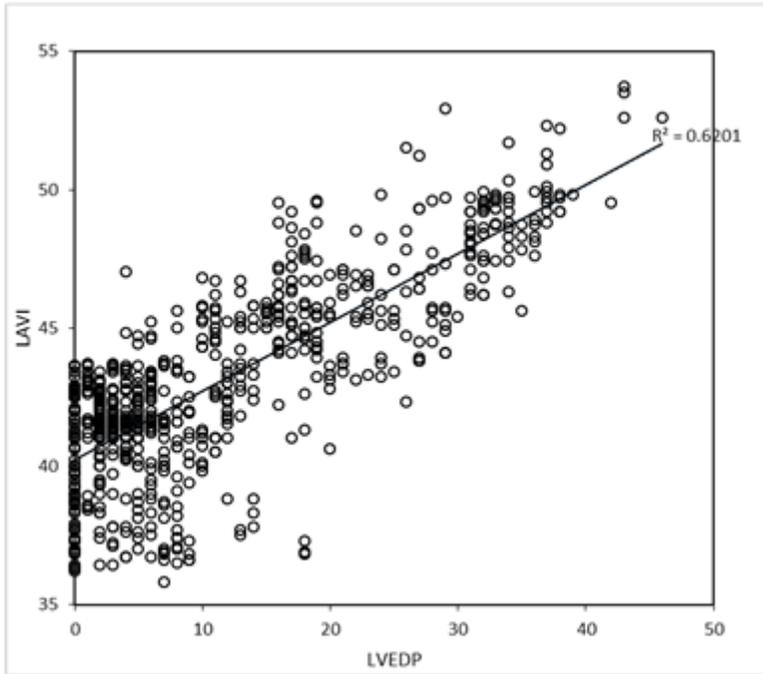


Figure 3

Scatter plot of LVI and LVEDP The figure shows that LVI was positively correlated with LVEDP ($r=0.787$, $P<0.001$).

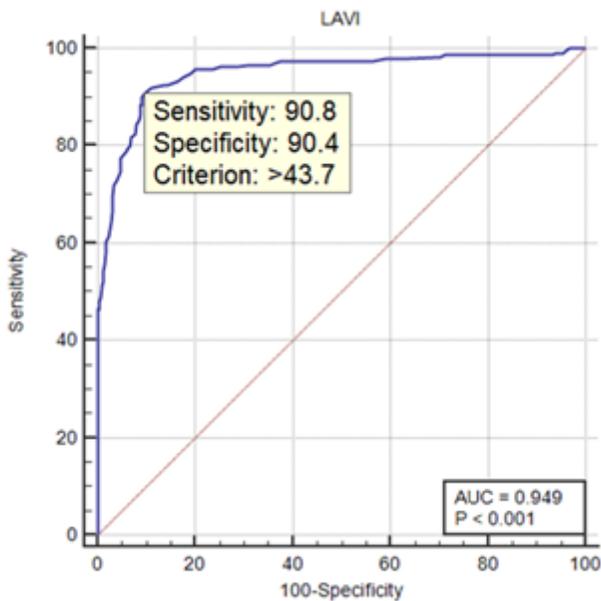


Figure 4

ROC curve of LVI for diagnosing HFpEF The AUC acquired from the ROC curve of LVI for diagnosing HFpEF is 0.949 with sensitivity of 90.8% and specificity of 90.4% ($P<0.001$).

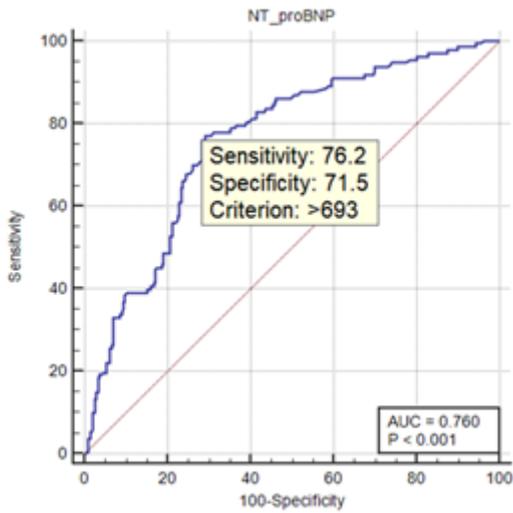


Figure 5

ROC curve of NT-proBNP for diagnosing HFpEF The AUC acquired from the ROC curve of NT-proBNP for diagnosing HFpEF is 0.760, with sensitivity of 76.2% and specificity of 71.5% $P < 0.001$

Supplementary Files

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