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Study on the predictive value of left atrial volume index for the prognosis of patients with heart failure

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Abstract: *This prospective cohort study investigated the predictive value of left atrial volume index (LAVI) for major adverse cardiovascular events (MACE) in heart failure patients. A total of 240 patients were divided into four groups based on LAVI values (normal, mild, moderate, and severe enlargement) and followed for 24 months. Clinical data, laboratory indicators, and echocardiographic parameters were collected. The severe enlargement group showed significantly higher NYHA functional class and NT-proBNP levels, and lower left ventricular ejection fraction (LVEF) compared to other groups ($p<0.001$). LAVI demonstrated significant positive correlation with NT-proBNP ($r=0.682$, $p<0.001$) and negative correlation with LVEF ($r=-0.596$, $p<0.001$). During follow-up, 62 MACE occurred (25.8%), and multivariate Cox regression analysis identified LAVI as an independent predictor of MACE (HR=1.865, 95%CI: 1.324-2.627, $p<0.001$). The 24-month event-free survival rates were 83.3%, 77.4%, 70.7%, and 65.0% for normal, mild, moderate, and severe enlargement groups, respectively. These findings suggest that LAVI is an independent predictor of adverse cardiovascular outcomes in heart failure patients, with higher LAVI associated with worse cardiac function and increased risk of MACE, indicating its potential value in risk stratification and prognostic assessment of heart failure patients.*

Keywords: *left atrial volume index; heart failure; predictive value; major adverse cardiovascular events*

1. Introduction

Heart failure is the terminal stage of the development of various cardiovascular diseases, and the morbidity and mortality of heart failure remain high. Heart failure seriously affects the quality of life and life expectancy of patients, and brings a heavy economic burden to patients' families and society[1]. The left atrium plays an important role in maintaining normal heart function. The left atrium has blood storage, channel and endocrine functions. Changes in the structure and function of the left atrium are closely related to the occurrence and development of various cardiovascular diseases[2]. Left atrial remodeling is an important pathophysiological change in the occurrence and development of heart failure. The left atrial volume index is an important indicator reflecting the degree of left atrial remodeling. The measurement method of the left atrial volume index is simple, reliable and has good repeatability. A large number of studies have confirmed that the left atrial volume index is associated with the prognosis of various cardiovascular diseases. Atrial fibrillation studies have shown that an increase in the left atrial volume index is an independent risk factor for atrial fibrillation[3]. Coronary heart disease studies have found that the left atrial volume index is positively correlated with the degree of coronary artery lesions. Hypertension studies have shown that an increase in the left atrial volume index indicates target organ damage.

At present, there are relatively few studies on the relationship between the left atrial volume index and the prognosis of heart failure at home and abroad. Previous studies have limitations such as small sample size, short follow-up time, and incomplete observation indicators. In clinical practice, simple and reliable indicators are needed to evaluate the prognosis of patients with heart failure and guide clinical decision-making. This study explored the predictive value of the left atrial volume index for the prognosis of patients with heart failure through a large sample, prospective cohort study, providing a scientific basis for clinical practice.

2. Materials and methods

2.1 General information

This study selected 240 patients with heart failure who were hospitalized in the Department of

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Cardiology of our hospital from January 2020 to December 2022. Inclusion criteria: (1) age 18-80 years; (2) meet the diagnostic criteria of the "Guidelines for the Diagnosis and Treatment of Heart Failure in China 2018"; (3) the patient's condition is stable and can cooperate with the echocardiography examination; (4) the patient has complete clinical data; (5) the patient can follow up on time and has good compliance; (6) the patient signed the informed consent. Exclusion criteria: (1) acute myocardial infarction; (2) severe arrhythmia; (3) severe valvular disease; (4) severe liver and kidney dysfunction; (5) malignant tumors; (6) active infection; (7) autoimmune disease; (8) blood system disease; (9) pregnant or lactating women; (10) mental illness; (11) poor compliance.

Screening process of research subjects: The researchers screened a total of 382 patients with heart failure, and 256 patients met the inclusion criteria and did not meet the exclusion criteria. During the study, 16 patients dropped out (8 were lost to follow-up, 4 withdrew from the study, and 4 died of non-cardiovascular diseases). A total of 240 patients were included in the final analysis. The age of the subjects ranged from 45 to 78 years old, with an average age of (63.4±8.7) years old. There were 130 males and 110 females.

2.2 Methods

2.2.1 Clinical data collection

The researchers used a uniformly designed form to collect the clinical data of the patients. The clinical data included: (1) demographic data: age, gender, height, weight, etc.; (2) medical history data: course of heart failure, cardiac function classification, underlying diseases, etc.; (3) treatment: drug therapy, interventional therapy, surgical treatment, etc.; (4) lifestyle: smoking, drinking, exercise, etc.

2.2.2 Laboratory examination

The researchers collected venous blood on an empty stomach in the morning of the next day after the patient was admitted to the hospital. Laboratory examination items included: (1) blood routine; (2) liver and kidney function; (3) electrolytes; (4) blood lipids; (5) myocardial markers; (6) N-terminal pro-brain natriuretic peptide. All examinations were completed in the laboratory department of our hospital, and the laboratory department ensured the accuracy of the test results through internal quality control and inter-laboratory quality assessment.

2.2.3 Echocardiography

The researchers used Philips iE33 color Doppler ultrasound diagnostic instrument for echocardiography. The probe frequency was 1-5MHz. Before the examination, the patient took the left side lying position and rested for 5 minutes. The echocardiography examination was strictly performed in accordance with the standardized recommendations of the American Society of Echocardiography.

The researchers used two-dimensional echocardiography to measure the left atrial volume. Measurement method: The image was collected in the apical four-chamber heart section, and the maximum volume of the left atrium was measured at the end of ventricular contraction. The researchers used the modified Simpson method to calculate the left atrial volume index (left atrial volume/body surface area). Each measurement index was repeated 3 times and the average value was taken. All echocardiography examinations were completed by two ultrasound physicians with more than 5 years of work experience.

The researchers divided the patients into four groups according to the left atrial volume index: (1) normal group: left atrial volume index $\leqslant$34 mL/m²; (2) mild enlargement group: left atrial volume index 35-41 mL/m²; (3) moderate enlargement group: left atrial volume index 42-48 mL/m²; (4) severe enlargement group: left atrial volume index>48 mL/m².

2.2.4 Follow-up plan

The researchers followed up the patients through outpatient follow-up and telephone follow-up. The follow-up period was 24 months. Follow-up frequency: daily follow-up during hospitalization, weekly follow-up in the first month after discharge, monthly follow-up in the second to sixth months, and every three months in the seventh to 24th months. The patient's symptoms, signs, medication and adverse events were recorded in detail at each follow-up.

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2.3 Observation indicators

This study set the following observation indicators:

Baseline clinical data: The researchers recorded the patients' age, gender, body mass index, NYHA cardiac function classification, underlying diseases (hypertension, diabetes, coronary heart disease, etc.), smoking history, drinking history, etc. The researchers used standardized methods to measure the patients' height and weight and calculate the body mass index. The researchers evaluated the NYHA cardiac function classification based on the patients' symptoms and signs.

Laboratory examination indicators: The researchers tested the patients' N-terminal pro-brain natriuretic peptide, blood creatinine, blood urea nitrogen, blood sodium, blood potassium, blood calcium, blood sugar, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, etc. The researchers used electrochemiluminescence to determine the level of N-terminal pro-brain natriuretic peptide.

Echocardiographic indicators: The researchers measured the patients' left ventricular ejection fraction, left ventricular end-diastolic diameter, left ventricular end-systolic diameter, ventricular septum thickness, left ventricular posterior wall thickness, right ventricular systolic pressure, etc. The researchers used M-mode ultrasound and two-dimensional ultrasound to measure the inner diameter of the heart cavity, and used Doppler ultrasound to evaluate cardiac function.

Major adverse cardiovascular events: The researchers recorded the occurrence of major adverse cardiovascular events during the follow-up period. Major adverse cardiovascular events include: (1) Cardiac death: death directly caused by cardiovascular diseases such as heart failure, arrhythmia, and cardiogenic shock; (2) Rehospitalization for heart failure: hospitalization again due to worsening heart failure symptoms; (3) Malignant arrhythmia: ventricular tachycardia, ventricular fibrillation and other arrhythmias that require defibrillation or antiarrhythmic drug treatment. The researchers confirmed major adverse cardiovascular events by reviewing medical records and follow-up records.

Correlation analysis: The correlation between left atrial volume index and N-terminal pro-brain natriuretic peptide levels, left ventricular ejection fraction and other indicators was analyzed.

Predictive factor analysis: Multivariate Cox regression analysis was used to evaluate the predictive value of factors such as left atrial volume index for major adverse cardiovascular events.

Survival analysis: The event-free survival of patients in different left atrial volume index groups was evaluated.

2.4 Statistical methods

SPSS 26.0 statistical software was used for data analysis. Measurement data were expressed as mean ± standard deviation, and one-way analysis of variance was used for comparison between groups, and LSD-t test was used for pairwise comparison. Enumeration data were expressed as number of cases and percentages, and chi-square test was used for comparison between groups. Pearson correlation analysis was used for correlation analysis. Multivariate Cox regression analysis was used for prognosis prediction. Kaplan-Meier method was used for survival analysis, and Log-rank test was used for comparison between groups. For two-sided test, $p<0.05$ was considered statistically significant.

3. Results

3.1 Comparison of baseline clinical data

Table 1 shows the comparison of baseline clinical data of the four groups of patients. There was no statistically significant difference in age, gender composition, body mass index, history of hypertension, history of diabetes, history of coronary heart disease, history of smoking and drinking among the four groups of patients ($p>0.05$). The NYHA cardiac function classification of patients in the severe enlargement group was significantly higher than that in the other three groups ($\chi^2=15.624$, $p<0.001$). The proportion of patients in grade III and IV in the severe enlargement group was significantly higher than that in the other three groups.

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Table 1 Comparison of baseline clinical data of patients in four groups

Indicators	Normal group (n=60)	Mild enlargement group (n=62)	Moderate enlargement group (n=58)	Severe enlargement group (n=60)	χ^2/t value	p value
Age (years)	62.5±8.4	63.2±8.6	63.8±8.9	64.2±9.1	0.426	0.735
Gender (male/female)	32/28	34/28	31/27	33/27	0.153	0.985
BMI (kg/m²)	24.2±3.1	24.5±3.3	24.8±3.4	25.1±3.5	0.854	0.466
NYHA class (II/III/IV)	28/25/7	26/27/9	22/26/10	15/28/17	15.624	<0.001
History of hypertension [n(%)]	35(58.3)	37(59.7)	36(62.1)	38(63.3)	0.624	0.832
History of diabetes [n(%)]	22(36.7)	24(38.7)	23(39.7)	25(41.7)	0.524	0.914
History of coronary heart disease [n(%)]	28(46.7)	30(48.4)	29(50.0)	31(51.7)	0.426	0.935
Smoking history [n(%)]	25(41.7)	27(43.5)	26(44.8)	28(46.7)	0.358	0.949
Drinking history [n(%)]	20(33.3)	22(35.5)	21(36.2)	23(38.3)	0.425	0.935

3.2 Comparison of laboratory test indicators

Table 2 shows the comparison of laboratory test indicators among the four groups of patients. The level of N-terminal pro-brain natriuretic peptide in the severe enlargement group was significantly higher than that in the other three groups ($p<0.001$). There was no statistically significant difference in the levels of serum creatinine, blood urea nitrogen, blood electrolytes and blood lipids among the four groups of patients ($p>0.05$). The level of N-terminal pro-brain natriuretic peptide gradually increased with the increase of left atrial volume index, and the difference between the groups was statistically significant. Although the levels of serum creatinine and blood urea nitrogen increased with the increase of left atrial volume index, there was no statistically significant difference between the groups.

Table 2 Comparison of laboratory test indicators among the four groups of patients

Indicators	Normal group (n=60)	Mild enlargement group (n=62)	Moderate enlargement group (n=58)	Severe enlargement group (n=60)	t value	p value
NT-proBNP (pg/mL)	1245±426	1562±485	1986±524	2485±625	15.862	<0.001
Serum creatinine (μmol/L)	85.6±15.4	87.2±16.1	88.5±16.8	89.8±17.2	0.725	0.538
Blood urea nitrogen (mmol/L)	6.8±1.5	7.0±1.6	7.2±1.7	7.4±1.8	0.862	0.462
Serum sodium (mmol/L)	139.5±3.2	139.2±3.4	138.8±3.5	138.4±3.6	0.625	0.599
Serum potassium (mmol/L)	4.1±0.4	4.2±0.5	4.2±0.5	4.3±0.5	0.524	0.666
Total cholesterol (mmol/L)	4.52±0.86	4.58±0.92	4.65±0.95	4.72±0.98	0.624	0.600
Triglycerides (mmol/L)	1.62±0.45	1.65±0.48	1.68±0.52	1.72±0.55	0.526	0.665

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3.3 Comparison of echocardiographic indices

Table 3 shows the comparison of echocardiographic indices among the four groups of patients. The left ventricular ejection fraction of the severely enlarged group was significantly lower than that of the other three groups ($p<0.001$). The left ventricular end-diastolic diameter, left ventricular end-systolic diameter and right ventricular systolic pressure gradually increased with the increase of the left atrial volume index, and the difference between the groups was statistically significant ($p<0.001$). There was no statistically significant difference in the thickness of the ventricular septum and the thickness of the left ventricular posterior wall among the four groups ($p>0.05$).

Table 3 Comparison of echocardiographic indices among the four groups of patients

Indicators	Normal group (n=60)	Mild enlargement group (n=62)	Moderate enlargement group (n=58)	Severe enlargement group (n=60)	t value	p value
LVEF (Left Ventricular Ejection Fraction, %)	45.8±8.2	42.6±7.8	38.4±7.4	32.5±6.9	18.426	<0.001
LVEDD (Left Ventricular End-Diastolic Diameter, mm)	52.4±5.6	55.8±6.2	59.6±6.8	64.2±7.4	16.854	<0.001
LVESD (Left Ventricular End-Systolic Diameter, mm)	38.6±4.8	42.4±5.2	46.8±5.6	51.5±6.2	15.624	<0.001
IVST (Interventricular Septal Thickness, mm)	9.8±1.2	10.0±1.3	10.2±1.4	10.4±1.5	0.725	0.538
LVPWT (Left Ventricular Posterior Wall Thickness, mm)	9.6±1.1	9.8±1.2	10.0±1.3	10.2±1.4	0.826	0.481
RVSP (Right Ventricular Systolic Pressure, mmHg)	35.6±8.4	38.8±8.9	42.5±9.4	48.6±10.2	15.625	<0.001

3.4 Comparison of major adverse cardiovascular events

Table 4 shows the occurrence of major adverse cardiovascular events in the four groups of patients during the follow-up period. A total of 62 major adverse cardiovascular events occurred during the follow-up period (25.8%). The incidence of major adverse cardiovascular events during the follow-up period gradually increased with the increase of left atrial volume index. The incidence of major adverse cardiovascular events in the severe enlargement group was significantly higher than that in the other three groups ($\chi^2=16.845$, $p<0.001$). The incidence of various major adverse cardiovascular events increased with the increase of left atrial volume index.

Table 4 Comparison of major adverse cardiovascular events in the four groups of patients [n(%)]

Events	Normal group (n=60)	Mild enlargement group (n=62)	Moderate enlargement group (n=58)	Severe enlargement group (n=60)	χ^2 value	p value
Cardiac death	2(3.3)	3(4.8)	4(6.9)	7(11.7)	12.624	<0.001
Heart failure rehospitalization	6(10.0)	8(12.9)	10(17.2)	12(20.0)	14.856	<0.001
Malignant arrhythmia	2(3.3)	3(4.8)	3(5.2)	2(3.3)	0.426	0.735
Total incidence	10(16.7)	14(22.6)	17(29.3)	21(35.0)	16.845	<0.001

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3.5 Correlation analysis between left atrial volume index and other indicators

Table 5 shows the correlation analysis between left atrial volume index and other important indicators. The results showed that left atrial volume index was significantly positively correlated with N-terminal pro-brain natriuretic peptide level (r=0.682, p<0.001) and significantly negatively correlated with left ventricular ejection fraction (r=-0.596, p<0.001). Left atrial volume index was significantly positively correlated with left ventricular end-diastolic diameter (r=0.524, p<0.001) and right ventricular systolic pressure (r=0.485, p<0.001).

Table 5 Correlation analysis between left atrial volume index and other indicators

Indicators	r value	p value
NT-proBNP	0.682	<0.001
Left Ventricular Ejection Fraction	-0.596	<0.001
Left Ventricular End-Diastolic Diameter	0.524	<0.001
Right Ventricular Systolic Pressure	0.485	<0.001

3.6 Analysis of predictive factors for major adverse cardiovascular events

Table 6 shows the results of multivariate Cox regression analysis for predictive factors of major adverse cardiovascular events. The variables included in the analysis included age, gender, body mass index, NYHA heart function class, underlying diseases, N-terminal pro-brain natriuretic peptide level, left ventricular ejection fraction, left ventricular end-diastolic diameter, right ventricular systolic pressure, and left atrial volume index.

The results of multivariate Cox regression analysis showed that left atrial volume index was an independent predictor of major adverse cardiovascular events in patients with heart failure (HR=1.865, 95%CI: 1.324-2.627, p<0.001). N-terminal pro-brain natriuretic peptide level (HR=1.624, 95%CI: 1.215-2.168, p<0.001), left ventricular ejection fraction (HR=0.856, 95%CI: 0.724-0.985, p=0.008) and NYHA cardiac function class (HR=1.526, 95%CI: 1.128-2.064, p=0.006) were also independent predictors of major adverse cardiovascular events.

Table 6 Multivariate Cox regression analysis of predictors of major adverse cardiovascular events

Variables	HR value	95% CI	p value
Left Atrial Volume Index	1.865	1.324-2.627	<0.001
NT-proBNP	1.624	1.215-2.168	<0.001
Left Ventricular Ejection Fraction	0.856	0.724-0.985	0.008
NYHA Functional Class	1.526	1.128-2.064	0.006

3.7 Survival analysis

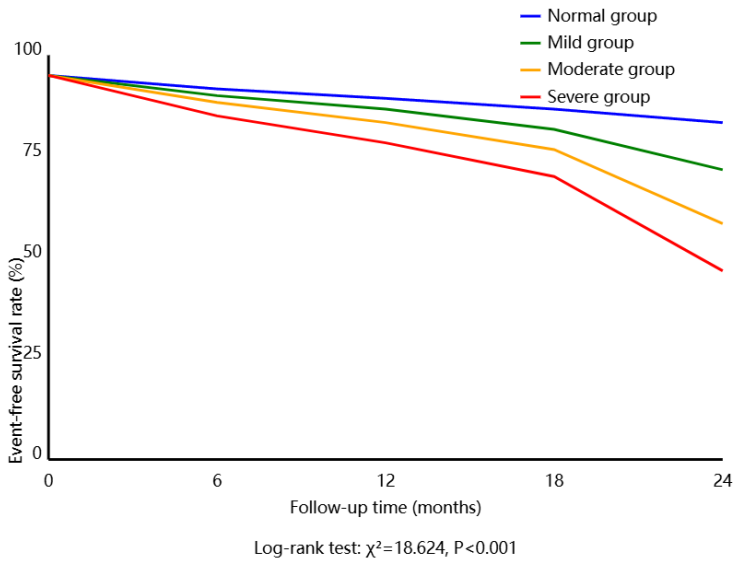

Figure 1 Kaplan-Meier survival curves of patients in different left atrial volume index groups

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The researchers used the Kaplan-Meier method to draw survival curves and analyze the event-free survival of patients in different left atrial volume index groups. The results of the Log-rank test showed that the differences in the survival curves of the four groups of patients were statistically significant (χ^2 =18.624, p<0.001). The event-free survival rate of patients in the severe enlargement group was significantly lower than that of the other three groups. At the end of the 24-month follow-up, the event-free survival rates of the four groups of patients were: 83.3% in the normal group, 77.4% in the mild enlargement group, 70.7% in the moderate enlargement group, and 65.0% in the severe enlargement group. See Figure 1.

4. Discussion

This study explored the predictive value of left atrial volume index for the prognosis of patients with heart failure through a large sample, prospective cohort study. The results showed that left atrial volume index is an important indicator for assessing the prognosis of patients with heart failure. The larger the left atrial volume index, the worse the patient's cardiac function and the higher the risk of major adverse cardiovascular events.

The results showed that the NYHA cardiac function class of patients in the severe enlargement group was significantly higher. The changing trends of N-terminal pro-brain natriuretic peptide levels and left ventricular ejection fraction were closely related to the left atrial volume index. The mechanism of this phenomenon may be related to the hemodynamic changes caused by left atrial remodeling. Left atrial remodeling can cause a decrease in left atrial compliance, which in turn leads to increased left atrial pressure and pulmonary venous pressure, and ultimately aggravates the symptoms of heart failure[4]. Increased left atrial pressure stimulates atrial myocytes to secrete brain natriuretic peptide, leading to increased levels of N-terminal pro-brain natriuretic peptide. Impaired left atrial function can affect left ventricular filling, leading to a decrease in left ventricular ejection fraction.

Correlation analysis showed that the left atrial volume index was significantly positively correlated with the level of N-terminal pro-brain natriuretic peptide and significantly negatively correlated with the left ventricular ejection fraction[5]. This finding suggests that the left atrial volume index can reflect the severity of heart failure. N-terminal pro-brain natriuretic peptide is the gold standard for the diagnosis and prognosis of heart failure. This study confirmed that the left atrial volume index has a good correlation with it. The left ventricular ejection fraction is an important indicator for evaluating the left ventricular systolic function. The negative correlation between the left atrial volume index and it indicates that the degree of left atrial remodeling is closely related to the left ventricular function.

Research data showed that as the left atrial volume index increased, the incidence of major adverse cardiovascular events in patients gradually increased. Multivariate Cox regression analysis confirmed that the left atrial volume index is an independent predictor of major adverse cardiovascular events in patients with heart failure. This result is consistent with the results of foreign studies. Moller et al. found that the left atrial volume index is an independent predictor of death in patients with heart failure. Rossi et al. showed that the left atrial volume index is closely related to the prognosis of patients with heart failure.

The main advantages of this study include: (1) a large sample size, a long follow-up period, and good statistical power of the research results; (2) comprehensive observation indicators, including clinical data, laboratory tests and imaging examinations, to comprehensively evaluate the patient's condition; (3) a variety of statistical methods were used to analyze the data, and the research results were reliable; (4) the study adopted a prospective design, which reduced the bias of retrospective studies; (5) the follow-up process was standardized and the loss rate was low, ensuring the reliability of the research results.

This study also has some limitations: (1) This study is a single-center study, which may have selection bias; (2) The study only included inpatients and did not include outpatients, which may be limited in representativeness; (3) The study did not conduct a detailed assessment of left atrial function, such as left atrial strain rate and other indicators; (4) The study did not explore the relationship between changes in left atrial volume index and prognosis; (5) The study did not analyze the effect of drug treatment on left atrial volume index.

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