



N-terminal pro-B-type Natriuretic peptide levels and left atrial appendage thrombosis in patients with persistent atrial fibrillation

Niveles de péptido natriurético N-terminal pro-B y trombosis de la orejuela auricular izquierda en pacientes con fibrilación auricular persistente

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ABSTRACT

Introduction: In hospitalized patients, atrial fibrillation is the most common arrhythmia, and leading cause of cardio-embolic stroke.

Objective: To evaluate the association between N-terminal b-type natriuretic peptide pro (NT-proBNP) and left atrial appendage thrombus in persistent atrial fibrillation patients.

Methods: A cross-sectional study, enrolled 139 patients with persistent non-valvular atrial fibrillation. Transthoracic and trans-esophageal echocardiographs were performed in all patients.

Results: Mean age was 70.5 ± 10.6 years, 80.6% male. In patients with LAAT, NT-proBNP was positively correlated with left ventricular end diastolic diameter (LVEDD) ($r=0.345$), left ventricular end-systolic diameter (LVEDS) ($r=0.449$), E/e' ($r=0.445$), and left atrial spontaneous echo contrast (LA SEC) ($r=0.478$), and negatively correlated with left ventricular ejection fraction (LVEF) ($r=-0.473$), left



atrial strain ($r = -0.301$), strain rate ($r = -0.283$), and e' ($r = -0.458$). In patients without LAAT, NT-proBNP was positively correlated with LVEDD ($r = 0.333$), LVESD ($r = 0.358$), E ($r = 0.318$), E/e' ($r = 0.411$), left atrial volume index (LAVI) ($r = 0.421$), and negatively correlated with LVEF ($r = -0.307$). Plasma NT-proBNP (> 1279 pg/mL) could be used to predict LAAT (AUC= 0.639; Se= 67.7%, Sp= 60.2%). In patients with ejection fraction $> 50\%$, the cutoff value of NT-proBNP to predict LAAT was 1325 pg/mL (AUC= 0.572; Se= 57.9%, Sp= 78.3%). Multiple logistic regression analysis showed that prior stroke, E/e' index, and NT-proBNP correlated with LAAT ($r = 0.887$; $p < 0.001$; $r = -0.092$, $p = 0.035$ and 0.022 ; $p = 0.004$, respectively).

Conclusion: Plasma NT-proBNP levels and E/e' index are associated with LAAT in patients with persistent atrial fibrillation.

Keywords: NT-proBNP, left atrial appendage, thrombosis, atrial fibrillation.

RESUMEN

Introducción: En pacientes hospitalizados, la fibrilación auricular es la arritmia más común y causa principal de ictus cardioembólico.

Objetivo: Evaluar la asociación entre el péptido natriurético NT proBNP y el trombo en la orejuela auricular izquierda en pacientes con fibrilación auricular persistente.

Métodos: Se reclutaron prospectivamente 139 pacientes con fibrilación auricular no valvular persistente. Se realizaron ecocardiografías transtorácicas y transesofágicas en todos los pacientes.

Resultados: Edad media, $70,5 \pm 10,6$ años; 80,6 % hombres. En pacientes con LAAT, NT-proBNP correlacionó positivamente con el diámetro telediastólico del ventrículo izquierdo (DDVI) ($r = 0,345$), diámetro sistólico final del ventrículo izquierdo (DSVI) ($r = 0,449$), E/e' ($r = 0,445$) y contraste de eco espontáneo auricular izquierdo (LA SEC) ($r = 0,478$), y negativamente con la fracción de eyección del ventrículo izquierdo (FEVI) ($r = -0,473$), tensión auricular izquierda ($r = -0,301$), tasa de tensión ($r = 0,283$) y e' ($r = -0,458$). En pacientes sin LAAT, NT-proBNP correlacionó positivamente con LVEDD ($r = 0,333$), LVESD ($r = 0,358$), E ($r = 0,318$), E/e' ($r = 0,411$), índice de volumen auricular izquierdo (LAVI) ($r = 0,421$), y negativamente con FEVI ($r = -0,307$). NT-proBNP plasmático (> 1279 pg/mL) podría usarse para predecir LAAT (AUC=0,639; Se=67,7 %, Sp=60,2 %). En pacientes con fracción de eyección > 50 %;



valor de corte de NT-proBNP para predecir LAAT fue 1325 pg/mL (AUC=0,572; Se=57,9 %, Sp=78,3 %). Según regresión logística múltiple, el accidente cerebrovascular previo, el índice E/e' y NT-proBNP se correlacionaron con LAAT ($r=0,887$; $p<0,001$; $r=0,092$, $p=0,035$ y $0,022$; $p=0,004$, respectivamente).

Conclusiones: Los niveles plasmáticos de NT-proBNP y el índice E/e' se asocian con el OAI en pacientes con FA persistente.

Palabras clave: NT-proBNP, orejuela auricular izquierda, trombosis, fibrilación auricular.

Received: 03/06/2023

Approved: 14/10/2023

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia in hospitalized patients, and it is the main cause of cardio-embolic stroke in clinical practice.⁽¹⁾ The prevalence of AF is significantly increasing in general population as life expectancy is increasing worldwide. Moreover, the recent evidences showed that AF is underdiagnosed and its real prevalence is much higher than it is reported.⁽²⁾ During paroxysmal or persistent AF episodes, left atrial appendage thromboembolism may occur as a result of previously prescribed mechanisms by Virchow.^(3,4) Trans-esophageal echocardiography (TEE) is a widely accepted method to detect atrial appendage thrombus⁽⁵⁾ and spontaneous echo contrast.⁽⁶⁾ However, they are invasive methods which not every patient can tolerate.

In AF patients, both systolic and diastolic left ventricular function are impaired significantly. Diastolic dysfunction can lead to increase of left ventricular filling pressure and subsequently cause formation of left atrial appendage thrombus (LAAT).⁽⁷⁾ Prior studies have shown that several echocardiographic parameters such as left ventricular ejection fraction (LVEF), left ventricular mass index (LVMI), left atrial volume index (LAVI), left atrial strain are predictors for LAAT in AF patients.^(8,9,10,11) Moreover,



Doukky et al.⁽⁷⁾ reported that diastolic function indices such as E/e' and e' are independently associated with LAA thrombus and these echo parameters can help to identify patients at risk of thromboembolism. N-terminal-pro-B type natriuretic peptide is a well-known marker of left ventricular and atrial wall stretching which can be produced by atria and ventricle during AF.⁽¹²⁾ *Yu et al.*⁽¹³⁾ reported that elevated plasma NT-proBNP concentrations and LV filling pressure represented by LAA dysfunction may be reliable surrogate markers for predicting thromboembolic risk in patients with AF. NT-proBNP is also well correlated with Doppler echocardiographic parameters of diastolic function in AF patients.⁽¹⁴⁾ There are growing evidences to show that NT-proBNP and diastolic echocardiographic indexes are associated with LAAT in AF patients. However, should these parameters be used to predict LAA thrombus?

This study aims to reveal the association between NT-proBNP and LAAT and its predictive value for LAAT.

METHODS

Design: Cross-sectional study.

Subject: From September 2016 to November 2019, 139 patients were recruited. All patients were diagnosed having persistent AF according to American College of Cardiology (ACC) guidelines 2014.⁽¹⁵⁾ The concomitant diseases were well controlled with medications according to the recent guidelines. Heart rate should be lower than 90 at the time of performing echocardiography. All patients who were not willing to participate into study or deny transesophageal echocardiography (TEE) were excluded, and also patients with valvular diseases.

Variables: Patients were interviewed to collect anthropometric and clinical indicators (age, sex, body mass index -BMI-, heart rate, blood pressure), medical history, and calculate CHA_2DS_2-VASc score. All patients with suspicion of left atrial appendage thrombus underwent transthoracic echocardiography (TTE), TEE and blood test to obtain LVEDD (left ventricular end diastolic diameter), LVEDS (left ventricular end systolic diameter), LVEF (left ventricular ejection fraction), LAVi (left atrial volume



index), LA strain, LA strain rate, E velocity (m/s), $e' - e$ tissue velocity (m/s), EDT (end diastolic time) (ms), E/e, LAA SEC (spontaneous echocontrast) and NT-pro-BNP.

Procedures: TTE was performed using a high-quality ultrasound machine (VIVID 7; GE Medical Systems, Milwaukee, WI, USA), equipped with a 1.7/3.4-MHz tissue harmonic transducer. Speckle tracking and cardiac chamber measurements were conducted according to the guidelines issued by the American Society of Echocardiography⁽¹⁶⁾ and the European Association of Cardiovascular Imaging.⁽¹⁷⁾ Left ventricular systolic function was assessed by LVEF, LV filling pressure was calculated by echo E/e' index and left atrial volume was defined by area-length method as followed: $LAV = 8/3\pi[(A1) \cdot (A2)]/L$ (A1 and A2 were maximal atrial area at 2- and 4-chamber views), L was atrial length from mitral annulus to atrial ceiling. $LAVI = LAV / \text{body skin area (BSA, cm}^2\text{)}$.

TEE Evaluation: TEE was performed using the same ultrasound machine with the 3.5/7-MHz multi-plane probe. Patients fasted for at least 6 hours, received local anesthesia using lignocaine spray and, if necessary, intravenous midazolam (3–5 mg) for sedation. With the patients in the left lateral decubitus position, the transducer was slowly advanced through the mouth guard into the esophagus. All cardiac chambers were surveyed carefully to search for thrombus in the LA and LA appendage. Thrombus was defined as a fixed or mobile echogenic mass clearly distinguishable from the wall of the LA or LA appendage. Spontaneous echo contrast was diagnosed as dynamic or “smoke-like” echo signal inside the LA that could not be eliminated by changing the gain settings.

N-terminal pro-B- type natriuretic peptide analysis: NT-proBNP was analyzed by Enzym-linked Immunosorbent Assay (ELISA) method.

Processing: Continuous variables were expressed as mean \pm standard deviation, while discrete variables were expressed as frequency (percentage). Between-group comparisons were conducted using the Student's *t*-test for data with normal distribution and using the Mann–Whitney test for data with abnormal distribution. Logistic regression models were used to evaluate the association between binary and continuous variables and examine the performance of different predictive models. Receiver operating characteristic (ROC) curves were analyzed to identify the optimal cutoff values of echocardiographic variables for predicting the presence of LAAT, and the results were expressed as the area under the ROC



curve (AUC). The quality of the models was expressed in terms of odds ratios (ORs) with 95% confidence intervals (95% CIs). p values ≤ 0.05 were considered to indicate statistical significance.

Bioethical aspects: This study was approved by the Medical Ethical Committee of 108 Military Central Hospital. The diagnostic methods used in this study were included in the list of techniques allowed to be used at 108 Military Central Hospital, issued by the Ministry of Health. All patients agreed to participate in the study through informed consents.

RESULTS

A convenient sample was intentionally selected, so the number of patients with LAAT accounted for a significant proportion (36 patients). Among them, 83.3% had prior stroke in contrast to the group of patients without LAAT (no case previous stroke). The average $\text{CHA}_2\text{DS}_2\text{-VASc}$ score in patients with LAAT (3.78 ± 0.86) was higher than group without LAAT (1.47 ± 0.95). In terms of echocardiography, longitudinal atrial strain is lower in patients with LAAT ($7.21 \pm 3.64\%$) compared to patients without LAAT ($9.24 \pm 4.88\%$). All the other demographic and characteristics of the 2 groups were comparable. Noticeably, the grade of spontaneous echo-contrast in patients with or without LAAT is not statistically significant (table 1).

Using univariate regression analysis, the results showed that in patients with LAAT, NT-proBNP was positively correlated with LVEDD ($r= 0.345$), LVEDS ($r= 0.449$), E/e' ($r= 0.445$) and LA SEC ($r= 0.478$). NT-proBNP was negatively correlated with LVEF ($r= -0.473$), LA strain ($r= -0.301$), strain rate ($r= -0.283$) and e' ($r= -0.458$). In patients without LAAT, NT-proBNP was positively correlated with LVEDD ($r= 0.333$), LVESD ($r= 0.358$), E ($r= 0.318$) and E/e' ($r= 0.411$) and negatively correlated with LVEF ($r= -0.307$) (table 2).



Table 1 - Patients characteristics according to the presence of LAAT

Parameters	Total AF (n=139)	With LAAT (n=36)	Without LAAT (n=103)	p (between with and without LAAT)
Age, years	70.5 ± 10.6	69.6 ± 9.6	70.8 ± 10.9	0.563
Male sex, n(%)	112 (80.6)	32 (88.9)	80 (77.7)	0.143
Body mass index, kg/m ²	22.2 ± 3.0	22.1 ± 2.9	22.2 ± 3.0	0.775
Systolic BP, mmHg	127.9 ± 13.8	127.2 ± 14.5	128.3 ± 13.7	0.702
Diastolic BP, mmHg	78.8 ± 9.8	77.9 ± 9.4	79.1 ± 9.9	0.543
Heart rate, bpm	82.6 ± 8.1	83.5 ± 6.3	82.3 ± 8.7	0.423
CHF, n(%)	42 (30.2)	14 (38.9)	28 (27.2)	0.188
Hypertension, n. (%)	95 (68.3)	29 (80.6)	66 (64.1)	0.067
Diabetes mellitus, n (%)	23 (16.5)	5 (13.9)	18 (17.5)	0.812
Stroke, n (%)	30 (21.6)	30 (83.3)	0	<0.001
Vascular disease, n (%)	15 (10.8)	6 (16.7)	9 (8.7)	0.314
CHA ₂ DS ₂ -VASc score	2.06 ± 1.37	3.78 ± 0.86	1.47 ± 0.95	<0.001
LVEDD, mm	50.51 ± 8.12	52.17 ± 7.69	49.93 ± 8.22	0.156
LVESD, mm	36.23 ± 9.08	38.14 ± 9.52	35.56 ± 8.87	0.143
LVEF (%)	54.65 ± 13.11	52.25 ± 14.56	55.49 ± 12.53	0.204
LAVi (ml/m ²)	59.37 ± 20.66	60.89 ± 15.91	58.84 ± 22.13	0.610
LA strain (%)	8.71 ± 4.66	7.21 ± 3.64	9.24 ± 4.88	0.029
LA strain rate (s ⁻¹)	-0.85 ± 0.39	-0.82 ± 0.35	-0.86 ± 0.39	0.639
E (m/s)	98.0 ± 21.57	99.89 ± 23.89	97.34 ± 20.78	0.544
e' (m/s)	8.90 ± 2.54	8.49 ± 2.40	9.05 ± 2.59	0.255
EDT (ms)	158.44 ± 27.29	157.69 ± 32.49	158.69 ± 25.39	0.850
E/e'	11.99 ± 4.53	12.79 ± 5.02	11.72 ± 4.33	0.255
LAA SEC	1.16 ± 1.35	1.44 ± 1.44	1.05 ± 1.31	0.150

BP – blood pressure; CHF – congestive heart failure; AF – atrial fibrillation; LAAT – left atrial appendage thrombus; E – septal tissue velocity; e' – lateral tissue velocity; EDT – end diastolic time; LVEDD – left ventricular end diastolic diameter; LVESD – left ventricular end diastolic diameter; LVEF – left ventricular ejection fraction; LAVi – left atrial volume index; LA- left atrium; LAA – left atrial appendage; SEC – spontaneous echocontrast.



Table 2 - Correlation between left ventricular echocardiographic indices with plasma NT-proBNP levels and LAAT

Parameters	NT-proBNP			
	With LAAT		Without LAAT	
	r	p	r	p
LVEDD, mm	0.345	< 0.05	0.333	< 0.05
LVESD, mm	0.449	< 0.05	0.359	< 0.05
LVEF, %	- 0.473	< 0.05	- 0.307	< 0.05
LAVi, ml/ m ²	0.129	> 0.05	0.421	< 0.05
LA strain, %	- 0.301	< 0.05	0.014	> 0.05
LA strain rate, s ⁻¹	- 0.283	< 0.05	- 0.077	> 0.05
E, m/s	0.041	> 0.05	0.318	< 0.05
EDT, ms	- 0.247	> 0.05	- 0.071	> 0.05
e', m/ s	- 0.458	< 0.05	- 0.267	> 0.05
E/ e'	0.445	< 0.05	0.411	< 0.05
LA SEC	0.478	< 0.05	- 0.043	> 0.05

LVEDD-left ventricular end diastolic diameter, LVESD – left ventricular end systolic diameter; LVEF- left ventricular ejection fraction; LAVi- Left atrial volume index; LA – left atrium; E – E velocity; EDT – end diastolic time, e' – e tissue velocity; SEC- spontaneous echocontrast; LAAT – left atrial appendage thrombus.

Using ROC to predictive LAAT: Overall, NT-proBNP with cutoff value of 1279 pg/mL can be used to predict LAAT with AUC of 0.639 and sensitivity of 67.7%, specificity of 60.2%. In patients with EF > 50%, the cutoff value of NT-proBNP to predict LAAT was 1325 pg/mL with AUC of 0.572; sensitivity of 57.9% and specificity of 78.3%. In patients with CHA₂-DS₂-VASc < 4, the echocardiographic and NT-proBNP were invaluable to predict LAAT (table 3).



Table 3 - Predictive value of plasma NT-proBNP levels and left ventricular diastolic echocardiographic indices for left atrial appendage thrombus

Parameters	Cutoff	Sensitivity	Specificity	AUC	95% CI	p
Total (n= 139)						
E/ e'	> 9.79	69.4	42.7	0.55	0.46-0.63	0.34
NT-proBNP(pg/ mL)	> 1279	67.6	60.2	0.63	0.55-0.72	0.007
LVEF ≥ 50 (n= 95)						
E/ e'	> 9.79	71.4	51.4	0.57	0.46-0.67	0.26
NT-proBNP(pg/mL)	> 1325	57.9	78.3	0.66	0.55-0.76	0.01
Patients with CHA ₂ DS ₂ -VASc score < 4 (n=117)						
E/ e'	≤ 13	86.7	36.3	0.55	0.45-0.64	0.50
NT-proBNP(pg/ mL)	> 1401	61.5	67.0	0.59	0.50-0.69	0.23

AUC – area under curve; E – velocity; e' – tissue velocity; LVEF – left ventricular ejection fraction.

Multiple logistic regression analysis showed that among clinical, echocardiographic and NT-proBNP, only NT-proBNP had predictive value for LAAT with beta coefficient of 0.116, r= 0.229 and p= 0.004. Using multiple logistic regression analysis, this study found that among different factors prior stroke, E/e' index and NT-proBNP correlated with LAAT (r= 0.887; p< 0.001; r= -0.092, p= 0.035 and 0.022; p= 0.004, respectively) (table 4 and figure 1).

Table 4 - Multivariate logistic regression analyses for left atrial appendage thrombus prediction

Variable	Beta coefficient	r	p
(Constant)	-0.032	-	-
Prior stroke	0.940	0.887	< 0.0001
Diabetes	-0.035	-0.042	0.445
Hypertension	0.039	0.155	0.285
Heart failure	-0.032	0.111	0.431
Coronary diseases	-0.043	0.111	0.431
E/e'	-0.092	0.109	0.035
NT-proBNP	0.116	0.229	0.004

E – velocity, e' – tissue velocity.

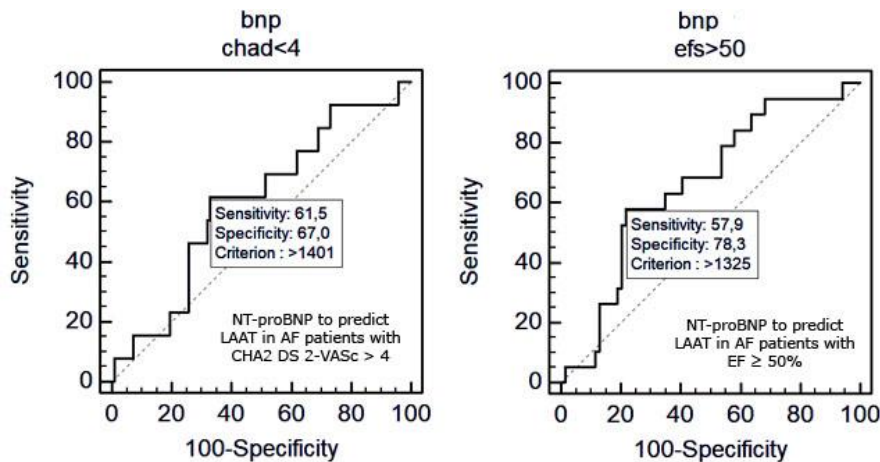


Fig. 1 - ROC curve for NT-proBNP to predict LAAT.

DISCUSSION

Atrial fibrillation is associated with increased risk of death, systemic embolism (SE), particularly stroke, and bleeding (associated with antithrombotic therapy).⁽¹⁸⁾ Conventional risk factors for the development of AF are older age, male sex, hypertension, diabetes, left atrial enlargement and history of myocardial infarction, valvular heart disease, or congestive heart failure.^(19,20,21) The left atrial appendage is the foremost common location of thrombus formation-related morbidity, particularly in patients with non-valvular AF. Previous researchers found that AF-induced thrombogenicity of the left atrial was much higher compared with the right atrial.⁽²²⁾ Although embolism of cardiac thrombi can include any vascular domain, there has been an authentic center on cerebral embolism, a result correlated with significant disability and mortality. Subsequently, increasing studies are attempting to discover a predictive model of the risk of thrombosis in patients with persistent AF. In persistent AF, the prediction of LAAT is challenging work that needs more intensive research. Previous studies have shown that NT-proBNP and diastolic echocardiographic indices such as E/e' and e' may have potential in predicting LAAT.^(7,9,23) The mean age of 139 patients was 70.5 ± 10.6 years with 80.6% male. There were 36 patients with LAAT, accounting for 25.9% patients in all groups. The reason for that is that a convenience sample was chosen to ensure that the sample size is large enough for comparison 2 groups. The average CHA₂DS₂-VASc



score in patients with LAAT was significantly higher than patients without LAAT. In terms of echocardiographic figures, LA strain in patients with LAAT was significantly lower than that of patients without LAAT. These results were similar to many other findings. *Douky R et al.*⁽²⁴⁾ conducted a prospective study of 266 nonvalvular AF patients resulted that mean CHA₂DS₂-VASc score in patients with LAAT was 4.6 ± 1.7 compared to 3.0 ± 1.8 in patients without LAAT ($p= 0.001$). Also, patients with LAAT had a higher rate in history of stroke or TIA (29%) than patients without LAAT (12%) ($p= 0.04$). *Kupczynska K et al.*⁽²⁵⁾ demonstrated that patients with LAAT had lower LA reservoir function (expressed by LASp and LASRr) as well as conduit function (expressed by LASRc) compared to patients without LAAT.

NT-proBNP is an endogenous biomarker, which is secreted primarily by ventricular as well as atrial myocardial cells in response to the overload of volume and pressure in the heart chamber.⁽²⁶⁾ Earlier studies figured out that NT-proBNP is an independent predictor for the risk of death and major cardiac adverse events in AF patients.⁽²⁷⁾ The results showed that in patients with LAAT, NT-proBNP was positively correlated with LVEDD, LVEDS, E/e' and LA SEC; negatively correlated with LVEF, LA strain, strain rate and e'. Additionally, in patients without LAAT, NT-proBNP was positively correlated with LVEDD, LVEDS, E and E/e' and negatively correlated with LVEF. It can be seen that in patients without LAAT, there was a moderate positive correlation between NT-proBNP and E ($r= 0.318$), LAVI ($r= 0.421$). Studies of *Kurt M et al.*⁽²⁸⁾ and *Yu et al.*⁽¹³⁾ also gave similar results. It can be explained that LA is the main source of BNP in patients with AF, the hemodynamic and morphology disorders due to pathological changes in the atrium with AF (including hypertrophy, fibrosis, and inflammation) leading to the overload of LA pressure and LV end diastolic filling pressure. This is also the cause of the release and increase of plasma NT-proBNP as well as predicts LAAT.

When evaluating the ability of NT-proBNP to predict LAAT, the ROC curve demonstrated that plasma NT-proBNP > 1279 pg/mL can be used to predict LAAT with good sensitivity and specificity. Predicting LAAT in persistent AF is important work because LAAT is considered the main cause of cardio-embolic stroke. The gold methods to detect LAAT are still TEE, computed tomography with contrast or magnetic resonance imaging which are expensive, invasive and time-consuming. In clinical practice, CHA₂DS₂-VASc score has been used as a risk stratification to predict stroke and thromboembolic events in such



groups of patients. According to recent ESC guidelines, patients with $CHA_2DS_2-VASc > 2$ in men or > 1 in women should be beneficial from anticoagulation.⁽²⁹⁾ However, the study showed that patients with $CHA_2DS_2-VASc < 2$ had stroke. Besides, when patients have normal LVEF, the definition of CHF is even more difficult. Our study found that in patients with $EF > 50\%$, the cutoff value of NT-proBNP to predict LAAT was 1325pg/ml, higher than that of all AF patients. Moreover, multiple logistic regression analysis showed that among clinical, echocardiographic and NT-pro-BNP, only NT-proBNP correlated with LAAT ($r = 0.229$; $p = 0.004$). That was why we should add plasma NT-proBNP as a risk factor for LAAT in AF patients.

It is physiologically plausible that impaired diastolic function and consequent elevation in the left ventricular filling pressure lead to left atrial stasis. As a result, these characteristics increase the risk of LAAT formation, followed by the risk of systemic thromboembolism. Prior reports suggest that two-dimensional echocardiographic parameters such as LVEF, LAVI and LVEF/LAVI as well as E/e' are associated with LAAT in patients with AF (9).⁽²⁴⁾ Yu et al.⁽¹³⁾ reported that high NT-proBNP level (> 249.7 pg/mL) (OR 6.79, $p < 0.001$) and E/e' (> 10) (OR 4.41, $p < 0.001$) were independent predictors of LAA dysfunction after adjustment of known thromboembolic risk factors. The main findings in this study were that besides the proven prior stroke, plasma NT-proBNP and E/e' index are the independent predictors of LAAT based on the multiple regression logistics analysis.

It is concluded that plasma NT-proBNP levels and E/e' index are associated with left atrial appendage thrombus in patients with persistent atrial fibrillation.

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Conflicts of interest

The authors declare that there are not conflicts of interest regarding to the study.

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