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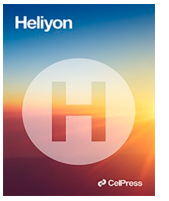

L1 cell adhesion molecule may be a protective molecule for atrial fibrillation in patients with valvular heart disease

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ABSTRACT

Background: Atrial fibrillation (AF) is the most prevalent sustained arrhythmia. L1 cell adhesion molecule (L1CAM) served as a crucial regulator of signaling pathways. This research sought to examine the clinical value and functions of soluble L1CAM in the serum of AF patients.
Methods: In total, 118 patients (valvular heart disease patients [VHD, total: n = 93; AF: n = 47; sinus rhythm (SR): n = 46] and healthy controls [n = 25]) were recruited in this retrospective study. Plasma levels of L1CAM were detected by enzyme-linked immunosorbent assays. The Pearson's correlation approach, as applicable, was used for analyzing the correlations. The L1CAM was shown to independently serve as a risk indicator of AF in VHD after being analyzed by the multivariable logistic regression. To examine the specificity and sensitivity of AF, receiver operating characteristic (ROC) curves and the area under the curve (AUC) were used. A nomogram was developed for the visualisation of the model. We further evaluate the prediction model for AF using calibration plot and decision curve analysis.
Results: The plasma level of L1CAM was substantially decreased in AF patients as opposed to healthy control and SR patients (healthy control = 46.79 ± 12.55 pg/ml, SR = 32.86 ± 6.11 pg/ml, AF = 22.48 ± 5.39 pg/ml; SR vs. AF, $P < 0.001$; control vs. AF, $P < 0.001$). L1CAM was significantly and negatively correlated with LA and NT-proBNP (LA: $r = -0.344$, $P = 0.002$; NT-proBNP: $r = -0.380$, $P = 0.001$). Analyses using logistic regression showed a substantial correlation between L1CAM and AF in patients with VHD (For L1CAM, Model 1: OR = 0.704, 95%CI = 0.607–0.814, $P < 0.001$; Model 2: OR = 0.650, 95% CI = 0.529–0.798, $P < 0.001$; Model 3: OR = 0.650, 95% CI = 0.529–0.798, $P < 0.001$). ROC analysis showed that inclusion of L1CAM in the model significantly improved the ability of other clinical indicators to predict AF. The predictive model including L1CAM, LA, NT-proBNP and LVDd had excellent discrimination and a nomogram was developed. The model had good the calibration and clinical utility.
Conclusion: L1CAM was shown to independently serve as a risk indicator for AF in VHD. In AF patients with VHD, the prognostic and predictive effectiveness of models incorporating L1CAM

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was satisfactory. Collectively, L1CAM may be a protective molecule for atrial fibrillation in patients with valvular heart disease.

1. Introduction

Atrial fibrillation (AF) is the most prevalent kind of cardiac arrhythmia and is associated with considerably elevated morbidity and mortality [1]. AF could contribute to a greater risk of dementia, stroke, heart failure, and death [2]. Despite a growing comprehension of the significance of AF, a lack of understanding of the processes that underlie its development has resulted in a lack of knowledge of the circulating biological markers that might guide the therapeutic management of AF patients.

L1 cell adhesion molecule (L1CAM) is a type of transmembrane protein that is a member of the immunoglobulin (Ig) superfamily. The L1CAM extracellular domains could serve as a signal transduction or the mediator between cells and the microenvironment by interacting with other L1CAM molecules, extracellular matrix proteins, neuropilin-1, integrins, and growth factor receptors [3–5]. Therefore, L1CAM has important biological functions in different tissue and human disease and is increased in a variety of malignancies, where it serves as a carcinogenic driver [6–8].

Atrial fibrosis, inflammatory response, and oxidative stress are thought to be important mechanisms in the development of AF, and L1CAM is closely associated with these mechanisms [9]. First, L1CAM has been shown to be closely associated with endothelial-mesenchymal transition (EndMT) in pancreatic cancer and lung cancer [10,11], while EndMT in cardiovascular cells has been reported to cause cardiac fibrosis [12]. Furthermore, L1CAM has been implicated as an important regulator of inflammation and immunity. L1CAM may regulate transendothelial migration and trafficking of dendritic cells [13], the response to pro-inflammatory T cells [14], and the innate lymphoid cell signaling [15]. Inflammation contributes to atrial remodeling, including the structural and electrophysiological changes that constitute atrial fibrillation. Finally, the upregulation of L1CAM has been reported to reduce superoxide production, decrease oxidative stress, and suppress inflammation in neuronal cells [16,17]. Therefore, we speculate that L1CAM may be involved in the development of AF. However, the investigation of the function of L1CAM in AF, as well as other cardiac disease, was extremely rare. By modulating the extent of persistent DNA damage, an antibody that targets the L1 cell adhesion molecule may suppress cardiotoxicity [18]. L1CAM was an essential component in the cell adhesion process, working in conjunction with neural cell adhesion molecule (NCAM). Its level was shown to be elevated under metabolic stress in cardiomyocytes and it was found to be linked to the growth of cardiac vessels [19,20].

In this research, we sought to examine if the soluble L1CAM might function as a useful biomarker for AF patients.

2. Methods

2.1. Participants' clinical information

This research included 93 individuals diagnosed with valvular heart disease (VHD) and hospitalized in the Cardiology department of Guangzhou Panyu Central Hospital in China between January 2021 and June 2022. Among them, 46 VHD patients had sinus rhythm (SR). 47 patients experienced persistent AF. Patients undergoing pharmaceutical treatment were considered to have persistent atrial fibrillation if they had AF that had persisted without interruption for seven days or more, or for whom electrical cardioversion was needed to terminate the arrhythmia. While there were some differences amongst patients, in general, the severity of the condition was

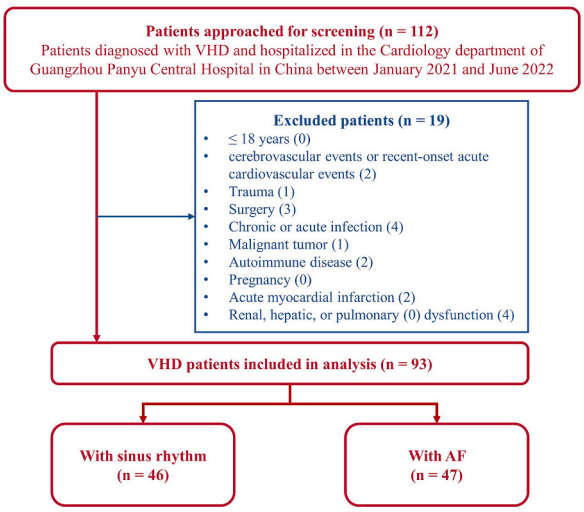

Fig. 1. Patient flowchart.

comparable as determined by their AF history (>1 year) and the outcomes of the ultrasound. As a healthy control group, we chose 25 participants who did not have VHD and did not exhibit any symptoms of cardiovascular disease.

The following were among the standards for exclusion: aged below 18 years, cerebrovascular events or recent-onset acute cardiovascular events such as acute myocardial infarction, trauma, surgery, chronic or acute infection, malignant tumor, autoimmune disease, pregnancy, and renal, hepatic, or pulmonary, dysfunction. The patients' clinical records were analyzed and gathered for evaluation. The clinical research and experimental animal ethics committee granted its approval to the project (PYRC-2020-128), and before participation in the trial, all patients included in this investigation offered informed consent. The flowchart for patient inclusion as shown in Fig. 1.

2.2. Collection and detection of blood samples

The method has been reported before [21]. Patients with VHD as well as healthy controls both had blood specimens collected from forearm veins utilizing vacutainer tubes (6 ml) (BD, Plymouth, United Kingdom) that contained ethylenediamine tetraacetic acid. Plasma samples were obtained using a centrifugation process that lasted for 15 min at a rate of 2500 rpm and then refrigerated at −80 °C within one day for subsequent detection using enzyme-linked immunosorbent assays (ELISAs). ELISAs were used to analyze the plasma samples to ascertain the levels of L1CAM following the guidelines stipulated by the manufacturer (Sino Biological Inc., Beijing, USA).

2.3. Statistical analysis

The results are expressed as numbers (percentages) or means (±standard deviation). Categorical variables were compared using the Chi-square test. Comparisons between the three groups were made using one-way ANOVA and LSD for pairwise comparisons. Correlations of L1CAM levels with continuous characteristic variables were characterized using the Pearson correlation coefficient. To further determinate the relationship of L1CAM and AF, univariable and multivariable logistic regression analysis were conducted. In the multivariable logistic analysis, we developed three models to illustrate L1CAM as an independent risk factor for AF after

Table 1
Clinical characteristics of the study groups.

Parameters	Control (n = 25)	VHD with SR (n = 46)	*P* value (SR vs. C)	VHD with AF (n = 47)	*P* value (AF vs. C)	*P* value (AF vs. SR)
Age (years)	38.28 ± 9.46	55.65 ± 10.21	**<0.001**	55.89 ± 9.44	**<0.001**	0.907
Male, n (%)	13 (52.00)	26 (56.52)	0.715	24 (51.06)	0.939	0.598
BMI (kg/m^2)	21.53 ± 3.79	22.75 ± 2.51	0.108	23.77 ± 3.84	**0.021**	0.134
Hypertension, n (%)	0 (0.00)	14 (30.43)	**0.002**	6 (12.77)	0.062	**0.038**
Diabetes, n (%)	0 (0.00)	6 (13.04)	0.059	2 (4.26)	0.295	0.131
Stroke, n (%)	0 (0.00)	2 (4.35)	0.290	4 (8.51)	0.133	0.414
Old Myocardial infarction, n (%)	0 (0.00)	0 (0.00)	1.000	2 (4.26)	**0.043**	0.157
Smokers, n (%)	7 (28.00)	14 (30.43)	0.830	18 (38.30)	0.382	0.424
β-blocker treatment, n (%)	0 (0.00)	12 (26.09)	**0.005**	15 (31.91)	**0.002**	0.536
Statin treatment, n (%)	0 (0.00)	7 (15.22)	**0.040**	8 (7.02)	0.175	0.208
NYHA, n (%)						
I	–	3 (6.52)	–	1 (2.13)	–	–
II	–	19 (41.30)	–	18 (38.30)	–	–
III	–	20 (43.48)	–	23 (48.94)	–	–
IV	–	4 (8.70)	–	5 (10.64)	–	–
LA, mm	26.62 ± 4.94	41.66 ± 8.96	**<0.001**	51.48 ± 8.91	**<0.001**	**<0.001**
LVDd, mm	50.18 ± 4.62	55.37 ± 10.49	**0.022**	50.22 ± 9.63	0.985	**0.016**
LVDs, mm	29.23 ± 3.29	35.87 ± 10.73	**0.004**	33.71 ± 7.52	**0.006**	0.263
IVSd, mm	9.34 ± 1.23	11.16 ± 3.53	**0.015**	9.72 ± 2.64	0.499	**0.028**
RV, mm	20.93 ± 2.21	23.45 ± 3.02	**<0.001**	24.71 ± 6.89	**<0.001**	0.258
LVEF, %	78.54 ± 9.91	69.48 ± 8.92	**<0.001**	63.69 ± 8.32	**<0.001**	**0.002**
NT-proBNP, pg/ml	358 ± 163	1748 ± 1173	**<0.001**	1781 ± 1690	**<0.001**	0.9133
WBC, 10^9/L	5.34 ± 2.93	6.27 ± 2.96	0.209	6.59 ± 2.44	0.058	0.571
Neutrophils (Percentage)	0.56 ± 0.08	0.56 ± 0.07	1.000	0.57 ± 0.10	0.667	0.579
Lymphocytes (Percentage)	0.40 ± 0.05	0.33 ± 0.08	**<0.001**	0.34 ± 0.09	**0.003**	0.573
CRP, mg/L	3.28 ± 1.25	37.67 ± 23.93	**<0.001**	4.29 ± 4.19	0.244	**<0.001**
Creatinine, μmol/L	81.43 ± 17.42	88.89 ± 49.49	0.469	83.18 ± 28.61	0.781	0.496
DBP, mmHg	111.36 ± 17.09	130.24 ± 16.73	**<0.001**	118.47 ± 14.22	0.064	**<0.001**
SBP, mmHg	77.39 ± 18.21	72.49 ± 11.67	0.172	74.25 ± 12.68	0.395	0.488

The results are expressed as numbers (percentages) or means (±standard deviation). Chi-squared values were used for categorical data, and ANOVA tests for continuous variables. VHD, valvular heart disease; SR, sinus rhythm; AF, atrial fibrillation; BMI, body mass index; NYHA, New York Heart Association; LA, left atrium diameter; LVDd, end-diastolic left ventricular internal diameter; LVDs, end-systolic left ventricular internal diameter; IVSd, end-diastolic interventricular septum diameter; RV, right atrium diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; WBC, white blood cell; CRP, C-reactive protein; DBP, diastolic blood pressure; SBP, systolic blood pressure.

adjustment. The risk factors in the multivariable logistic regression included the factors identified in the univariable logistic regression analysis and also included other recognized risk factors for AF. Model 1 was adjusted for age, gender, and NT-proBNP. Model 2 was adjusted for age, gender, NT-proBNP and LA. Model 3 was adjusted for age, gender, NT-proBNP, LA and LVEF. The receiver operating characteristic (ROC) curves and the area under the curve (AUC) data were utilized to perform to determine the sensitivity and selectivity of L1CAM and its gain over other models. The parameters of these prediction models were chosen from predictive markers previously reported in the literature for predicting atrial fibrillation, such as NT-proBNP [22], LA [23] and LVDd [24]. A nomogram for the prediction of AF based these variables was developed. We further evaluate the model using calibration plot and decision curve analysis. For all tests, $P < 0.05$ was established as the criterion of statistical significance. STATA, version 14.0 (StataCorp, College Station, TX, United States), GraphPad Prism Software (Version 8, La Jolla, California, United States of America) and SPSS 22 (IBM, Chicago, IL) were adopted to execute all analyses of statistical data.

3. Results

3.1. Baseline characteristics

The flowchart for patient inclusion as shown in Fig. 1. The demographic information of the patients who participated in this research was depicted in Table 1. Compared with healthy controls, patients with AF were older, had higher BMI, LA, LVDs, RV, NT-proBNP levels, higher proportions of old myocardial infarction and β-blocker treatment, and lower LVEF and lymphocytes levels. Compared to the SR patients, patients diagnosed with AF had larger left atria, lower LVDd, LVDs, IVSd, LVEF, CRP and DBP levels, higher proportion of hypertension.

3.2. L1CAM levels in participants with AF and SR, and in healthy controls

Fig. 2 shows the difference in serum L1CAM levels between patients diagnosed with AF and SR and healthy controls. Patients diagnosed with AF had remarkably lowered plasma levels of L1CAM in contrast with those of healthy controls and SR patients (healthy control = 46.79 ± 12.55 pg/ml, SR = 32.86 ± 6.11 pg/ml, AF = 22.48 ± 5.39 pg/ml; SR *vs.* AF, $P < 0.001$; control *vs.* AF, $P < 0.001$). These findings illustrated that L1CAM down-regulation could be implicated in VHD and AF.

3.3. Correlation of L1CAM level with clinical variables in VHD

The correlation of L1CAM level with clinical variables in VHD was shown in Table 3. There was a substantial inverse link between L1CAM and LA and NT-proBNP (LA: r = −0.344, $P = 0.002$; NT-proBNP: r = −0.380, $P = 0.001$). No remarkable association was discovered between L1CAM and other clinical variables in this study. These results suggested that L1CAM down-regulation was associated with worse cardiac function.

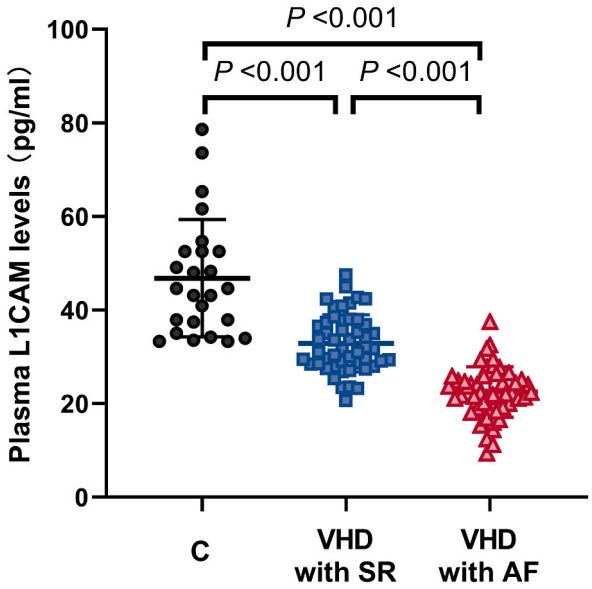

Fig. 2. Plasma levels of LICAM detection in the clinical samples. The plasma samples were analyzed from three groups: normal healthy controls (Normal, n = 25), VHD patients with SR (n = 46), and VHD patients who had persistent AF (n = 47). Data are shown as the mean ± SD.

Table 2
Correlation of L1CAM level with clinical variables.

	r	*P* value
LA, mm	−0.344	**0.002**
LVDd, mm	0.107	0.338
LVDs, mm	0.034	0.761
IVSd, mm	0.041	0.719
RV, mm	−0.013	0.911
LVEF, %	0.029	0.801
NT-proBNP, pg/ml	−0.380	**0.001**
WBC, 10^9/L	0.054	0.592
Neutrophils, %	−0.032	0.778
Lymphocytes, %	0.051	0.652
CRP, mg/L	−0.074	0.511
Creatinine, μmol/L	0.063	0.577

L1CAM, L1 cell adhesion molecule; LA, left atrium diameter; LVDd, end-diastolic left ventricular internal diameter; LVDs, end-systolic left ventricular internal diameter; IVSd, end-diastolic interventricular septum diameter; RV, right atrium diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; WBC, white blood cell; CRP, C-reactive protein.

Table 3
Univariable Logistic regression analyses for Atrial fibrillation in VHD patients.

	OR (95%CI)	*P* value
L1CAM	0.698 (0.604–0.805)	**< 0.001**
LA, mm	1.197 (1.107–1.294)	**< 0.001**
LVDd, mm	0.958 (0.919–0.998)	**0.038**
LVDs, mm	0.975 (0.934–1.018)	0.253
IVSd, mm	0.735 (0.609–0.888)	**0.001**
RV, mm	1.081 (0.985–1.188)	0.101
LVEF, %	0.991 (0.952–1.029)	0.613
NT-proBNP, pg/ml	1.000 (0.999–1.001)	0.069
WBC, 10^9/L	0.882 (0.736–1.056)	0.172
Neutrophils, %	0.362 (0.046–27.876)	0.646
Lymphocytes, %	2.998 (0.022–42.669)	0.663
CRP, mg/L	0.989 (0.963–1.018)	0.480
Creatinine, μmol/L	0.998 (0.990–1.006)	0.657

VHD, valvular heart disease; L1CAM, L1 cell adhesion molecule; LA, left atrium diameter; LVDd, end-diastolic left ventricular internal diameter; LVDs, end-systolic left ventricular internal diameter; IVSd, end-diastolic interventricular septum diameter; RV, right atrium diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; WBC, white blood cell; CRP, C-reactive protein.

3.4. Correlation of L1CAM level with AF in VHD

To further determinate the relationship of L1CAM and AF, univariable and multivariable logistic regression analysis were conducted and the findings were displayed in Tables 3 and 4. For univariable logistic regression analyses, L1CAM, LA, LVDd and IVSd were significantly correlated with AF in VHD (L1CAM: OR = 0.698, 95%CI = 0.604–0.805, $P < 0.001$; LA: OR = 1.197, 95%CI = 1.107–1.294, $P < 0.001$; LVDd: OR = 0.958, 95%CI = 0.919–0.998, $P = 0.038$; IVSd: OR = 0.735, 95%CI = 0.609–0.888, $P = 0.001$)

Table 4
Multivariable analysis of LICAM for Atrial fibrillation in VHD patients.

	L1CAM	
	OR (95%CI)	*P* value
Model 1	0.704 (0.607–0.814)	**< 0.001**
Model 2	0.650 (0.529–0.798)	**< 0.001**
Model 3	0.650 (0.529–0.798)	**< 0.001**

Model 1 was adjusted for age, gender and NT-proBNP.
Model 2 was adjusted for age, gender, NT-proBNP, and LA.
Model 3 was adjusted for age, gender, NT-proBNP, LA and LVEF.
L1CAM, L1 cell adhesion molecule; VHD, valvular heart disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; LA, left atrium diameter; LVEF, left ventricular ejection fraction.

(Table 3). The findings of the multivariable analysis were depicted in Table 4. When conducting multivariable analyses, adjustments were made. Model 1 was adjusted for age, gender and NT-proBNP. Model 2 was adjusted for age, gender, NT-proBNP and LA. Model 3 was adjusted for age, gender, NT-proBNP, LA and LVEF (For L1CAM, Model 1: OR = 0.704, 95%CI = 0.607–0.814, $P < 0.001$; Model 2: OR = 0.650, 95%CI = 0.529–0.798, $P < 0.001$; Model 3: OR = 0.650, 95%CI = 0.529–0.798, $P < 0.001$).

3.5. Predictive ability of L1CAM for AF in VHD

To evaluate the predictive model combining the L1CAM and other clinical variables for AF, a ROC curve analysis was performed. The addition of L1CAM to the model significantly improved the accuracy of LA (AUC = 0.95, 95%CI = 0.92–0.99 *vs.* 0.82, 95%CI: 0.74–0.91; $P < 0.001$; Fig. 3A), NT-proBNP (AUC = 0.91, 95%CI = 0.85–0.97 *vs.* 0.70, 95%CI: 0.59–0.81; $P < 0.001$; Fig. 3B) and LVDd (AUC = 0.92, 95%CI = 0.87–0.97 *vs.* 0.38, 95%CI: 0.27–0.49; $P < 0.001$; Fig. 3C) alone in predicting atrial fibrillation. Furthermore, even though the composite model of LA, NT-proBNP and LVDd achieved an accuracy of 0.86 (95%CI = 0.78–0.94) in predicting atrial fibrillation, the addition of L1CAM further improved the model (AUC = 0.97, 95%CI = 0.93–1.00, $P < 0.01$; Fig. 3D).

As the model consisting of L1CAM, LA, NT-proBNP and LVDd has a high degree of discrimination in predicting atrial fibrillation, we further evaluate the model using calibration plot and decision curve analysis (DCA). To make the model more convenient to use, a nomogram for the prediction of AF based on the model was developed. A score was assigned to each variable and the total score was calculated by adding all the individual scores (Fig. 4A). The calibration plot of the model showed a good consistency between the predicted probability and observed probability (Fig. 4B). DCA was performed to evaluate the clinical utility of the model. As shown in Fig. 4C, the model provided greater benefits than treat-all or treat-no scheme. Therefore, the model had a good clinical utility.

4. Discussion

In the current investigation, we discovered that the plasma level of L1CAM was considerably lowered in patients with AF in contrast with healthy control subjects and SR patients in VHD. L1CAM was significantly and negatively correlated with LA and NT-proBNP. L1CAM was found to independently serve as a risk indicator for AF in VHD. The models composed of L1CAM exhibited an excellent prognostic prediction capacity for AF in VHD. Altogether, L1CAM may be a protective molecule for AF. To our knowledge, this was

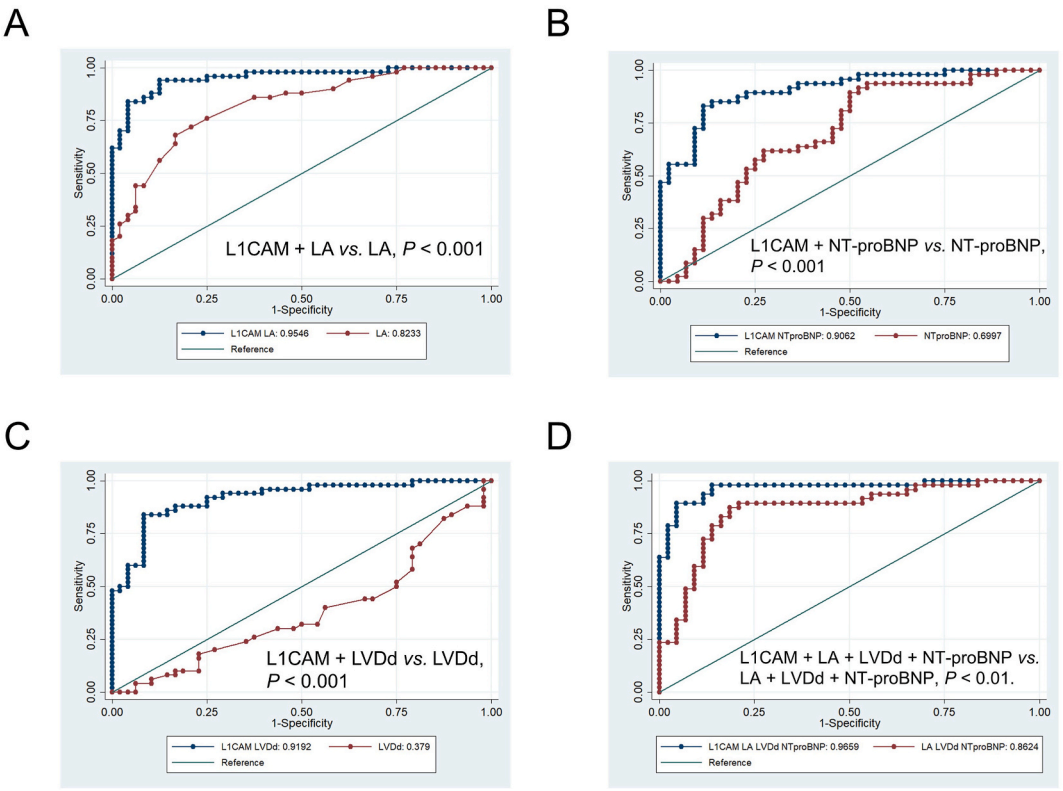

Fig. 3. ROC curves for the predictive model combining the L1CAM and other clinical variables in AF of the VHD patients. (A) ROC for LA and the model with L1CAM + LA. L1CAM + LA vs. LA, $P < 0.001$. (B) ROC for NT-proBNP and the model with L1CAM + NT-proBNP. L1CAM + NT-proBNP vs. NT-proBNP, $P < 0.001$. (C) ROC for LVDd and the model with L1CAM + LVDd. L1CAM + LVDd vs. LVDd, $P < 0.001$. (D) ROC for the model with L1CAM + LA + LVDd + NT-proBNP and the model with LA + LVDd + NT-proBNP. L1CAM + LA + LVDd + NT-proBNP vs. LA + LVDd + NT-proBNP, $P < 0.01$.

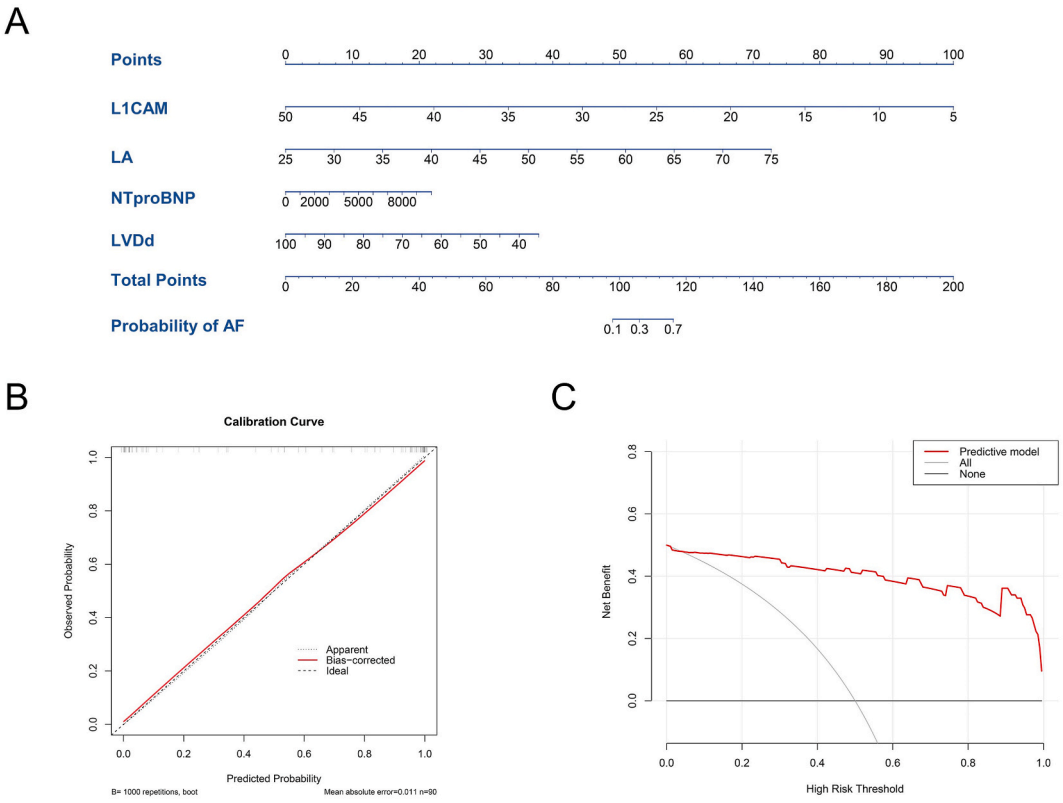

Fig. 4. Nomogram, calibration plot and decision curve analysis (DCA) of the model consisting of L1CAM, LA, NT-proBNP and LVDd in the prediction of atrial fibrillation. (A) Nomogram for model was developed. (B) Calibration curves of the model. (C) DCA was performed to validate the clinical applicability of the prediction model.

the first study connecting L1CAM and AF.

Patients diagnosed with AF have a mortality rate that is two times higher than patients who do not have AF [25]. To properly risk-stratify patients who were diagnosed with AF, clinicians relied primarily on clinical indicators that produce risk scores to develop treatment regimens. In studies of risk assessment of AF, mounting research efforts have been directed towards identifying possible biological markers in the blood that may more accurately evaluate the risk of AF complications as well as the risk of developing AF. Some markers reflected the pathophysiology of AF, while others were related to severity or comorbidities associated with an elevated AF risk. Even though the majority of biological markers demonstrated an elevation in AF, the optimal value of these markers relies on the diverse patient subgroups and the environments in which they are assessed. For example, many newly discovered biological markers have been demonstrated to have a link to AF, including carbohydrate antigen 125 [26], galectin-3 [27,28], growth differentiation factor-15 [29], a member of the interleukin 1 receptor family [30], IL1RL1 (ST2) [31], and NT-proBNP [32]. For heart failure patients, carbohydrate antigen 125, NT-proBNP, and growth differentiation factor-15 were successful in identifying the existence of AF in new-onset AF, while galectin-3 and sST2 effectively predicted the AF recurrence following ablation [31,33–36]. Another REGARDS study showed that a variety of biological markers was shown to be related to a greater risk of incident ischemic stroke in participants who had AF, including NT-proBNP, interleukin-6, factor VIII antigen, and cystatin-C, indicating that a stroke risk stratification based on these biomarkers could significantly enhance the ability to predict the risk of ischemic stroke in AF patients [37]. Our study showed that L1CAM was associated with LA and NT-proBNP, the important elements involved in AF (Table 2). We also illustrated that L1CAM was considerably linked to AF, and the models composed of L1CAM had an outstanding prognostic predictive ability for AF (Tables 3 and 4, Fig. 3). The close association of L1CAM with the proven AF risk indicators (including LA, NT-proBNP and LVDd) indicated that L1CAM could be a novel viable risk indicator for AF. Our study has several advantages. First, because of the possible mechanism of L1CAM in the occurrence of AF, we found this novel marker from a pathophysiological perspective. Second, we combined L1CAM with traditional risk factors, including LA, NT-proBNP and LVDd, to establish a prediction model and developed a nomogram for AF, and the model has good discrimination, calibration and clinical application.

Numerous studies have discovered that different localized L1CAMs exerted different functions by mediating different mechanisms, and participated in various disease processes. Nam JK et al. showed that fibrotic phenotype (endothelial–mesenchymal transition, EndMT) may be seen in vascular endothelial cells when persistent DNA damage has been caused by irradiation and subsequent treatment with Dox correlating with the colocalization of L1CAM and persistent DNA damage foci [18]. Moreover, the use of the anti-L1CAM antibody in therapy has the potential to attenuate L1CAM overexpression as well as nuclear translocation and persistent

DNA damage foci [18]. However, this research mainly emphasized the role of L1CAM in myocardial tissue, but not circulating L1CAM. The membrane-proximal cleavage of the L1CAM ectodomain was mediated by a disintegrin and metalloproteinases (ADAMs), resulting in the production of the whole ectodomain, which has been designated as L1-200 and, as a direct outcome of this, it becomes water-soluble [38,39]. Our studies showed that a lower level of circulating L1CAM was found in the VHD patients, and was associated with AF (Tables 2–4, Fig. 2), indicating that circulating L1CAM might be involved in the development of AF. Similar expression patterns were also found in ESCC. Elevated L1CAM levels in ESCC tissues were linked to dismal survival of patients [40], and lower circulating L1CAM and higher autoantibodies against L1CAM were found in ESCC patients [41,42]. These findings suggested that soluble L1CAM may exert diverse biological functions from the full-length one in both heart disease and ESCC. However, more research is required on the roles and the mechanism via which L1CAM cleavage is regulated in heart disease.

5. Conclusions

Overall, a lower circulating L1CAM was linked to AF in VHD. A substantial negative correlation was observed between L1CAM and LA, and NT-proBNP. Univariable and multivariable logistic regression analysis illustrated that L1CAM independently acted as a risk variable for AF in VHD. The inclusion of L1CAM in the model significantly improved the predictive ability of other clinical indicators for AF, and the predictive model including L1CAM, LA, NT-proBNP and LVDd had excellent diagnostic ability. Collectively, L1CAM may be a protective molecule for AF.

5.1. Limitation

This research suffers from all of the drawbacks that are associated with single-center retrospective observational studies. Because this was just observational research, it was not possible to determine cause-effect relationships. Additional research with a prospective design is required to verify our current results. Our research also had a limited number of participants in the sample we used. And the incidence of atrial fibrillation is low. To provide a clear landscape of the connection between L1CAM and AF, it would be helpful to conduct additional thorough research involving larger sample sizes and meta-analyses. Finally, we found that the discrimination and calibration ability of the L1CAM is poor, which indicates that the accuracy of this indicator in predicting atrial fibrillation is unsatisfactory. This may be a bias due to insufficient number of cases and further collection of more samples may be able to improve it. Larger cohorts of prospectively recruited subjects are needed to accurately assess L1CAM. So L1CAM may be a protective molecule rather than a risk marker of value in predicting AF in patients.

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Ethical standards

This research project was authorized by the institutional ethical review committee at Guangzhou Panyu Central Hospital and was conducted in conformity with the recommendations outlined in the Helsinki Declaration (PYRC-2020-128).

Informed consent

All subjects involved in the research project provided their written informed consent.

Production notes

Author contribution statement

Dayu Wang: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

Bo Hu: Guangtao Xu: Performed the experiments.

Ruibin Wei: Zhen Liu: Huajun Wu: Long Xu: Analyzed and interpreted the data.

Suiqing Huang: Jian Hou: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data included in article/supp. material/referenced in article.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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