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## Association between atrial cardiopathy and stroke severity in acute ischemic stroke

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In this hospital-based cross-sectional analytic study, we retrospectively reviewed clinical data of patients with acute ischemic stroke (AIS) between January 2017 and April 2023. Atrial cardiopathy was defined as any presence of the following: left atrial diameter  $\geq 52$  mm (males) or  $\geq 47$  mm (females), elevated P-wave terminal force in V1  $> 5000$   $\mu\text{V ms}$ , or serum N terminal pro B type natriuretic peptide  $> 250$  pg/ml. Initial stroke severity was defined by the National Institutes of Health Stroke Scale (NIHSS; moderate-to-severe,  $\geq 5$ ; and severe,  $\geq 15$ ). Univariate and multivariate binary logistic regression analyses were performed to assess the association between atrial cardiopathy and stroke severity. Among 662 AIS patients (mean age 70 years [interquartile range 61–78], 31.3% women), 303 (45.8%) had atrial cardiopathy. Multivariable logistic regression analysis showed that the presence of atrial cardiopathy was significantly associated with a higher odd of moderate-to-severe stroke (adjusted odds ratio [OR] 2.16, 95% confidence interval [CI] 1.46–3.20,  $p < 0.001$ ) and severe stroke (adjusted OR 4.89, 95%CI 2.45–9.76,  $p < 0.001$ ). This association remained significant in a sensitivity analysis excluding those with atrial fibrillation or coronary artery disease. Findings of the current study revealed that the association of atrial cardiopathy was with initial stroke severity independent of atrial fibrillation and was even confirmed in patients without atrial fibrillation; future studies to explore improved stroke prevention strategies for patients with atrial cardiopathy are needed.

**Keywords** Acute ischemic stroke, Atrial cardiopathy, Stroke severity, National institutes of health stroke scale

### Abbreviations

AIS	Acute ischemic stroke
NIHSS	National Institutes of Health Stroke Scale
OR	Odds ratio
CI	Confidence interval
PTFV1	P-wave terminal force in lead V1
LAE	Left atrial enlargement
NT-proBNP	N-terminal pro-brain natriuretic peptide
SAFAS	Stepwise screening for silent atrial fibrillation after stroke
IQR	Interquartile range
HR	Hazards ratio
CNSR-III	Third China National Stroke Registry

Atrial cardiopathy is characterized by changes in atrial structure or function, such as atrial fibrosis, impaired cardiac cell function, and atrial enlargement, which may precede and promote atrial fibrillation<sup>1–3</sup>. Although currently there is no golden standard to define atrial cardiopathy, established biomarkers of atrial cardiopathy include increased P-wave terminal force in lead V1 (PTFV1) on electrocardiogram, left atrial enlargement (LAE) on echocardiogram, and elevated serum N-terminal pro-brain natriuretic peptide (NT-proBNP)<sup>4</sup>. In stroke free

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individuals, increased PTFV1 was associated with incident stroke risk<sup>5,6</sup> in the absence of clinically apparent atrial fibrillation<sup>7</sup>. Observational evidence showed that LAE on echocardiogram was independently associated with an increased risk of ischemic stroke in the absence of atrial fibrillation<sup>8–10</sup>. Moreover, increased serum level of NT-proBNP, a biomarker of ventricular and atrial dysfunction, is also associated with ischemic stroke<sup>11,12</sup>.

Previous studies have shown that atrial cardiopathy might be useful to assess the probability of cardioembolism in patients with cryptogenic stroke<sup>13</sup>. However, whether atrial cardiopathy relates to stroke severity has been scarcely reported. The influence of initial stroke severity on stroke recovery has been increasingly recognized. For example, moderate to severe stroke has been shown to be associated with mortality, increasing the likelihood of in-hospital mortality by more than nine-fold<sup>14,15</sup>. Several previous studies assessed the association between atrial cardiopathy and stroke severity in acute ischemic stroke (AIS) patients, yielding inconsistent findings. A small cohort of the Stepwise screening for silent atrial fibrillation after stroke (SAFAS) study showed a significant difference in the National Institutes of Health Stroke Scale (NIHSS) score in patients with and without atrial cardiopathy, suggesting a potential link between atrial cardiopathy and stroke severity<sup>16</sup>. However, a small prospective cohort study showed that the proportion of a higher NIHSS score (NIHSS of 9 or above) was similar in participants with and without atrial cardiopathy (10 [14%] vs. 6 [13%],  $p = 0.91$ )<sup>17</sup>. To our knowledge, the association between atrial cardiopathy and stroke severity in AIS patients remains not fully understood. We therefore aimed to investigate whether the presence of atrial cardiopathy is associated with stroke severity in AIS population.

## Methods

### Participants

In this hospital-based cross-sectional analytic study, we retrospectively reviewed clinical data of adult patients with AIS between January 2017 and April 2023 in a university teaching hospital. The exclusion criteria were as follows: (1) Recorded rheumatic heart valve disease or artificial heart valve; (2) Without adequate electrocardiogram parameters to assess PTFV1; (3) Without transthoracic echocardiogram assessment of left atrial diameter; (4) Without NT-proBNP data. We collected the demographic and clinical characteristics including age, sex, body mass index, alcohol and cigarette consumption, history of hypertension, hyperlipidemia, diabetes, atrial fibrillation, and coronary heart disease from patients' medical notes. Atrial fibrillation included paroxysmal, persistent, and permanent atrial fibrillation, which was either previously known or diagnosed during index hospitalization<sup>18</sup>. Etiologic subtypes of ischemic stroke were classified according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria<sup>19</sup>. Laboratory findings (fasting blood glucose, triglyceride, total cholesterol, low-density lipoprotein, and high-density lipoprotein) were collected from a digital medical database. The study protocol was reviewed and approved by the Fujian Medical University Union Hospital Ethics Committees (2023KY030). Informed consent was waived, due to the nature of the retrospective study with routine anonymous and de-identified information. This study was conducted in accordance with the Declaration of Helsinki and relevant guidelines and regulations. The datasets of the current study are available from the corresponding author on reasonable request.

### Atrial cardiopathy assessment

Biomarkers of atrial cardiopathy were routinely assessed within 48 h after admission. PTFV1 in electrocardiogram was calculated by multiplying the duration (ms) of the terminal negative component of P-wave by its amplitude ( $\mu\text{V}$ ) in lead V1 recorded by manual calculation<sup>20</sup>. Left atrium size was calculated as the antero-posterior maximal diameter of the left atrium in systole on B-mode transthoracic echocardiogram. Severe left atrial enlargement was defined as left atrial diameter  $\geq 52$  mm (males) or  $\geq 47$  mm (females)<sup>21</sup>. NT-proBNP was measured by an automated electrochemiluminescence immunoassay (Elecys proBNP II assay). The coefficient of variation for the NT-proBNP assay was 2–5% during the testing period, and the analytical measurement range for NT-proBNP was 5–35,000 pg/ml. In the present study, atrial cardiopathy was defined as any of the following: severe LAE, PTFV1  $> 5000$   $\mu\text{V}$  ms, or increased serum levels of NT-proBNP  $> 250$  pg/ml<sup>22</sup>.

### Stroke severity assessment

Initial stroke severity was assessed using the NIHSS on admission. Moderate-to-severe stroke was defined as a NIHSS scored of 5 or higher, and severe stroke as a NIHSS score of 15 or higher<sup>23</sup>.

### Statistical analysis

Continuous variables were presented as means (standard deviation) if normally distributed, or medians (interquartile range, IQR) if not normally distributed. Categorical variables were expressed as frequencies with proportions. Between group differences were compared using the t-test, the Mann–Whitney test, the Chi-square test, or the Fisher's exact test as appropriate. Logistic regression models were used to calculate the unadjusted and adjusted odds ratios (ORs) of outcomes with atrial cardiopathy. Two models were used: Model 1, Age- and sex-adjusted; and Model 2, adjusted for variables with a  $p < 0.1$  in the univariate analysis for outcomes. We conducted several subgroup analyses of outcomes stratified by age group ( $< 65$  vs.  $\geq 65$  years), sex (male vs. female), smoking status (current smoker vs. not), alcohol consumption (regular vs. not), hypertension (yes vs. no), dyslipidemia (yes vs. no), coronary artery disease (yes vs. no), and atrial fibrillation (yes vs. no), with the interaction terms as covariates. We conducted a sensitivity analysis by including patients without atrial fibrillation or coronary artery disease. We additionally assessed the linear relationship between atrial cardiopathy and continuous NIHSS score. A  $p$ -value  $< 0.05$  was considered statistically significant. All statistical analyses were done using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

## Ethical approval

This study protocol was reviewed and approved by Fujian Medical University Union Hospital Ethics Committees (2023KY030). Written informed consent was waived by the Fujian Medical University Union Hospital Ethics Committees due to the nature of our retrospective study based on routine clinical data.

## Results

### Baseline characteristics

A total of 662 AIS patients (mean age 70 years [IQR 61–78], 31.3% women) who met the inclusion criteria were finally analyzed (Fig. S1). A total of 303 (45.8%) patients had atrial cardiopathy. Table 1 shows the baseline characteristics between participants in the acute ischemic stroke with and without atrial cardiopathy. Patients with atrial cardiopathy were older (74 years [IQR 65–81] vs. 66 [IQR 58–73],  $p < 0.001$ ), more likely to be female (35.3% vs. 27.9%,  $p = 0.039$ ), and less likely to be current smoker (23.1% vs. 34.3%,  $p = 0.002$ ) and regular alcohol user (9.0% vs. 17.0%,  $p = 0.008$ ). The prevalence of hypertension (74.3% vs. 60.4%,  $p < 0.001$ ), atrial fibrillation (48.2% vs. 5.0%,  $p < 0.001$ ), coronary artery disease (22.8% vs. 8.1%,  $p < 0.001$ ), pre-stroke anticoagulation (7.6% vs. 0.6%,  $p < 0.001$ ), and the level of high-density lipoprotein ( $1.14 \pm 0.31$  vs.  $1.07 \pm 0.25$  mmol/L,  $p = 0.004$ ) were higher, while the proportion of dyslipidemia and serum levels of triglyceride were lower among patients with atrial cardiopathy compared to those without atrial cardiopathy. Stroke subtypes in patients with and without atrial cardiopathy were significantly different ( $p < 0.001$ ).

### Atrial cardiopathy and stroke severity

Patients with atrial cardiopathy had a higher NIHSS score (5 [IQR 2–12] vs. 3 [IQR 1–5],  $p < 0.001$ ). A total of 261 (39.4%) patients had a moderate-to-severe stroke, and 70 (10.6%) had a severe stroke. Table 2 summarizes the differences in characteristics in patients with and without moderate-to-severe stroke. Compared to those with mild stroke (NIHSS  $< 5$ ), those with moderate-to-severe stroke (NIHSS  $\geq 5$ ) were more likely to be female (36.8% vs. 27.7%,  $p = 0.014$ ) and had a higher proportion of atrial fibrillation (29.9% vs. 21.4%,  $p = 0.014$ ), coronary artery disease (18.8% vs. 12.2%,  $p = 0.020$ ), a higher serum level of fasting blood glucose (6.53 [5.38–8.09] vs. 5.83 [5.05–7.56] mmol/L,  $p < 0.001$ ), and a lower triglyceride level (1.16 [0.92–1.48] vs. 1.25 [0.96–1.75] mmol/L,  $p = 0.016$ ). Stroke subtypes in patients with and without moderate-to-severe stroke were significantly different ( $p < 0.001$ ). Of the individual atrial cardiopathy biomarkers, patients with moderate-to-severe stroke were more

Characteristics	Total (n = 662)	Without atrial cardiopathy (n = 359)	With atrial cardiopathy (n = 303)	p
Age, y, median (IQR)	70 (61–78)	66 (58–73)	74 (65–81)	<0.001
Sex, female, n (%)	207 (31.3)	100 (27.9)	107 (35.3)	0.039
NIHSS score, median (IQR)	3 (1–8)	3 (1–5)	5 (2–12)	<0.001
BMI, kg/m <sup>2</sup> , mean $\pm$ SD	23.7 $\pm$ 3.5	23.7 $\pm$ 3.2	23.7 $\pm$ 3.9	0.218
Current smoker, n (%)	193 (29.2)	123 (34.3)	70 (23.1)	0.002
Regular alcohol user, n (%)	91 (13.7)	61 (17.0)	30 (9.0)	0.008
Hypertension, n (%)	442 (66.8)	217 (60.4)	225 (74.3)	<0.001
Diabetes, n (%)	218 (32.9)	121 (33.7)	97 (32.0)	0.645
Atrial fibrillation, n (%)	164 (24.8)	18 (5.0)	146 (48.2)	<0.001
Dyslipidemia, n (%)	166 (25.1)	104 (29.0)	62 (20.5)	0.012
Coronary artery disease, n (%)	98 (14.8)	29 (8.1)	69 (22.8)	<0.001
Pre-stroke anticoagulation, n (%)	25 (3.8)	2 (0.6)	23 (7.6)	<0.001
Pre-stroke antiplatelet drug, n (%)	24 (3.6)	10 (2.8)	14 (4.6)	0.208
Wake-up stroke, n (%)	89 (13.4)	49 (13.6)	40 (13.2)	0.866
TOAST subtypes, n (%)				<0.001
Large artery atherosclerosis	436 (65.9)	284 (79.1)	152 (50.2)	
Cardio-embolism	177 (26.7)	37 (10.3)	140 (46.2)	
Small vessel occlusion	22 (3.3)	16 (4.5)	6 (2.0)	
Undetermined	11 (1.7)	8 (2.2)	3 (1.0)	
Others	16 (2.4)	14 (3.9)	2 (0.7)	
FBG, mmol/L, median (IQR)	6.09 (5.14–7.74)	5.95 (5.03–7.74)	6.35 (5.32–7.83)	0.051
Triglyceride, mmol/L, median (IQR)	1.21 (0.94–1.64)	1.31 (1.01–1.78)	1.09 (0.88–1.46)	<0.001
Total cholesterol, mmol/L, mean $\pm$ SD	4.43 $\pm$ 1.07	4.45 $\pm$ 0.96	4.39 $\pm$ 0.96	0.251
LDL, mmol/L, mean $\pm$ SD	2.95 $\pm$ 0.99	2.97 $\pm$ 0.89	2.92 $\pm$ 1.10	0.227
HDL, mmol/L, mean $\pm$ SD	1.10 $\pm$ 0.28	1.07 $\pm$ 0.25	1.14 $\pm$ 0.31	0.004

**Table 1.** Baseline characteristics between patients with and without atrial cardiopathy. IQR interquartile range, NIHSS National Institutes of Health Stroke Scale, SD standard deviation, BMI body mass index, TOAST Trial of Org 10172 in Acute Stroke Treatment, FBG fasting blood glucose, LDL low-density lipoprotein, HDL high-density lipoprotein.

Characteristics	Without moderate-to-severe stroke (n = 401)	With moderate-to-severe stroke (n = 261)	p
Age, y, median (IQR)	69 (61–77)	71 (61–79)	0.198
Sex, female, n (%)	111 (27.7)	96 (36.8)	0.014
BMI, kg/m <sup>2</sup> , mean ± SD	23.8 ± 3.5	23.6 ± 3.7	0.204
Current smoker, n (%)	121 (30.2)	72 (27.6)	0.474
Regular alcohol user, n (%)	58 (14.5)	33 (12.6)	0.506
Hypertension, n (%)	269 (67.1)	173 (66.3)	0.831
Diabetes, n (%)	133 (33.2)	85 (32.6)	0.872
Atrial fibrillation, n (%)	86 (21.4)	78 (29.9)	0.014
Dyslipidemia, n (%)	110 (27.4)	56 (21.5)	0.083
Coronary artery disease, n (%)	49 (12.2)	49 (18.8)	0.020
Pre-stroke anticoagulation, n (%)	18 (4.5)	7 (2.7)	0.233
Pre-stroke antiplatelet drug, n (%)	14 (3.5)	10 (3.8)	0.819
Wake-up stroke, n (%)	46 (11.5)	43 (16.5)	0.065
TOAST subtypes, n (%)			0.009
Large artery atherosclerosis	264 (65.8)	172 (65.9)	
Cardio-embolism	99 (24.7)	78 (29.9)	
Small vessel occlusion	21 (5.2)	1 (0.4)	
Undetermined	6 (1.5)	5 (1.9)	
Others	11 (2.7)	5 (1.9)	
FBG, mmol/L, median (IQR)	5.83 (5.05–7.56)	6.53 (5.38–8.09)	<0.001
Triglyceride, mmol/L, median (IQR)	1.25 (0.96–1.75)	1.16 (0.92–1.48)	0.016
Total cholesterol, mmol/L, mean ± SD	4.39 ± 1.02	4.48 ± 1.14	0.388
LDL, mmol/L, mean ± SD	2.91 ± 0.93	3.00 ± 1.07	0.431
HDL, mmol/L, mean ± SD	1.09 ± 0.28	1.11 ± 0.29	0.378
Atrial Cardiopathy, n (%)	151 (37.7)	152 (58.2)	<0.001
PTFV1 > 5000 μV·ms, n (%)	19 (4.7)	10 (3.8)	0.577
Severe LAE, n (%)	22 (5.5)	12 (4.6)	0.613
NT-proBNP > 250 pg/ml, n (%)	142 (35.4)	146 (55.9)	<0.001

**Table 2.** Baseline characteristics in patients with and without moderate-to-severe stroke. *IQR* interquartile range, *BMI* body mass index, *SD* standard deviation, *TOAST* Trial of Org 10172 in Acute Stroke Treatment, *FBG* fasting blood glucose, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *PTFV1* P-wave terminal force in lead V1, *LAE* left atrial enlargement, *NT-proBNP* N-terminal pro-brain natriuretic peptide.

likely to have an NT-proBNP > 250 pg/mL (55.9% vs. 35.4%,  $p < 0.001$ ). Similar findings were detected in patients with severe stroke (NIHSS  $\geq 15$ ) compared to those with non-severe stroke (NIHSS < 15) (Table 3).

Table 4 shows the association between atrial cardiopathy and stroke severity. Patients with atrial cardiopathy were at a higher odd of moderate-to-severe stroke (unadjusted OR 2.31, 95%CI 1.68–3.17,  $p < 0.001$ ) and severe stroke (unadjusted OR 5.58, 95%CI 3.04–10.26,  $p = 0.001$ ). The associations remained after adjustment for age and sex. After further adjustment for those variables with a  $p < 0.1$  in the univariable analysis, atrial cardiopathy remained significantly associated with a higher odd of moderate-to-severe stroke (adjusted OR 2.16, 95%CI 1.46–3.20,  $p < 0.001$ ) and severe stroke (adjusted OR 4.89, 95%CI 2.45–9.76,  $p < 0.001$ ). This association remained significant when considering the NIHSS score as a continuous variable (unadjusted Beta 0.292, adjusted Beta 0.280,  $p < 0.001$ , respectively; Table 4).

### Subgroup analysis and sensitivity analysis

We detected no significant interactions between atrial cardiopathy and variables including age (< 65 vs.  $\geq 65$  years), sex (male vs. female), smoking status (current smoker vs. not), alcohol consumption (regular vs. not), hypertension (yes vs. no), dyslipidemia (yes vs. no), coronary artery disease (yes vs. no), and atrial fibrillation (yes vs. no) for stroke severity (Fig. 1a,b). We observed a significant association of atrial cardiopathy with moderate to severe stroke (OR 2.31, 95%CI 1.57–3.40,  $p < 0.001$ ) and severe stroke (OR 4.64, 95%CI 2.35–9.16,  $p < 0.001$ ) in patients without atrial fibrillation. In the presence of atrial fibrillation, there was trend for a higher odd of moderate to severe stroke with atrial cardiopathy, although this did not reach statistical significance (OR 2.60, 95%CI 0.88–7.67,  $p = 0.083$ ; Fig. 1a).

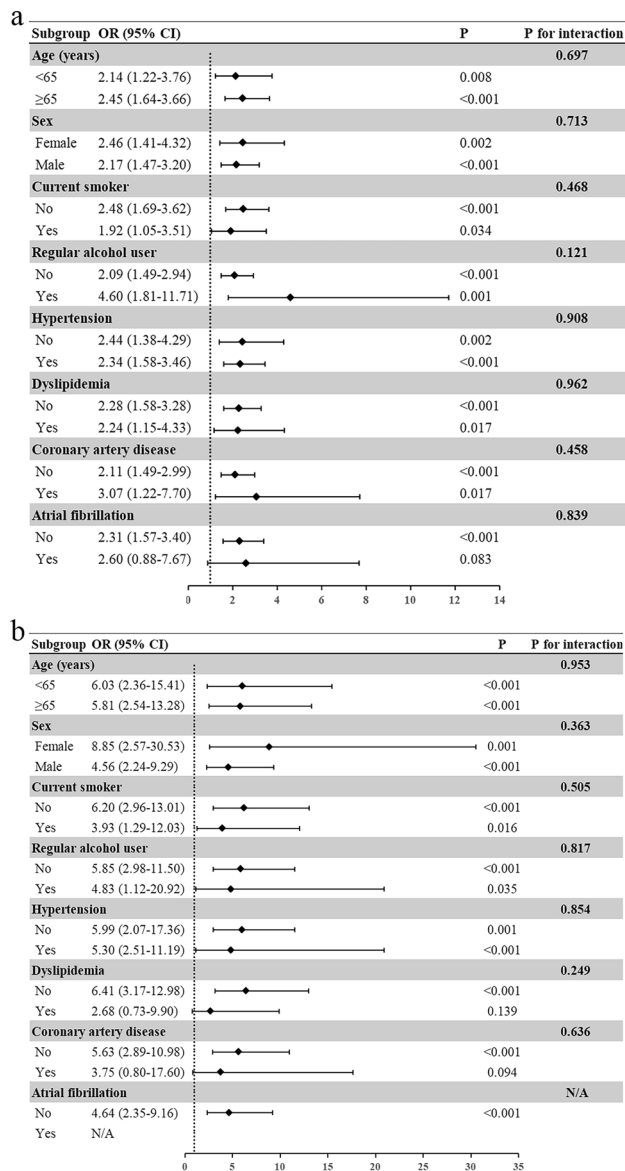
A sensitivity analysis after excluding patients with atrial fibrillation or coronary artery disease showed that atrial cardiopathy remained associated with moderate-to-severe stroke as well as severe stroke (Table 4).

Characteristics	Without severe stroke (n = 592)	With severe stroke (n = 70)	p
Age, y, median (IQR)	69 (61–77)	73 (62–83)	0.033
Sex, female, n (%)	181 (30.6)	26 (37.1)	0.262
BMI, kg/m <sup>2</sup> , mean ± SD	23.8 ± 3.5	23.5 ± 3.6	0.347
Current smoker, n (%)	178 (30.1)	15 (21.4)	0.133
Regular alcohol user, n (%)	82 (13.9)	9 (12.9)	0.819
Hypertension, n (%)	391 (66.0)	51 (72.9)	0.253
Diabetes, n (%)	201 (34.0)	17 (24.3)	0.104
Atrial fibrillation, n (%)	134 (22.6)	30 (42.9)	<0.001
Dyslipidemia, n (%)	156 (26.4)	10 (14.3)	0.028
Coronary artery disease, n (%)	81 (13.7)	17 (24.3)	0.018
Pre-stroke anticoagulation, n (%)	23 (3.9)	2 (2.9)	0.670
Pre-stroke antiplatelet drug, n (%)	20 (3.4)	4 (5.7)	0.323
Wake-up stroke, n (%)	80 (13.5)	9 (12.9)	0.879
TOAST subtypes, n (%)			0.021
Large artery atherosclerosis	397 (67.1)	39 (55.7)	
Cardio-embolism	148 (25.0)	29 (41.4)	
Small vessel occlusion	22 (3.7)	0 (0.0)	
Undetermined	11 (1.9)	0 (0.0)	
Others	14 (2.4)	2 (2.9)	
FBG, mmol/L, median (IQR)	6.03 (5.07–7.74)	6.86 (5.86–8.09)	0.001
Triglyceride, mmol/L, median (IQR)	1.23 (0.95–1.69)	1.09 (0.86–1.40)	0.004
Total cholesterol, mmol/L, mean ± SD	4.46 ± 1.13	4.11 ± 1.10	0.005
LDL, mmol/L, mean ± SD	2.98 ± 0.98	2.67 ± 0.99	0.005
HDL, mmol/L, mean ± SD	1.10 ± 0.27	1.12 ± 0.32	0.654
Atrial Cardiopathy, n (%)	247 (41.7)	56 (80.0)	<0.001
PTFV1 > 5000 μV ms, n (%)	25 (4.2)	4 (5.7)	0.564
Severe LAE, n (%)	30 (5.1)	4 (5.7)	0.817
NT-proBNP > 250 pg/ml, n (%)	234 (39.5)	54 (77.1)	<0.001

**Table 3.** Baseline characteristics in patients with and without severe stroke. *IQR* interquartile range, *SD* standard deviation, *BMI* body mass index, *TOAST* Trial of Org 10,172 in Acute Stroke Treatment, *FBG* fasting blood glucose, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *PTFV1* P-wave terminal force in lead V1, *LAE* left atrial enlargement, *NT-proBNP* N-terminal pro-brain natriuretic peptide.

	Moderate-to-severe stroke		Severe stroke		Continuous NIHSS	
	OR (95% CI)	p	OR (95% CI)	p	Beta	p
Univariate	2.31 (1.68–3.17)	<0.001	5.58 (3.04–10.26)	0.001	0.292	<0.001
Model 1	2.33 (1.67–3.26)	<0.001	5.40 (2.88–10.11)	0.001	0.287	<0.001
Model 2	2.16 (1.46–3.20)	<0.001	4.89 (2.45–9.76)	<0.001	0.280	<0.001
Sensitivity analyses						
Univariate	2.07 (1.35–3.17)	0.001	5.15 (2.45–10.83)	<0.001	0.259	<0.001
Model 1	2.37 (1.51–3.73)	<0.001	5.07 (2.34–11.02)	<0.001	0.274	<0.001
Model 2	2.23 (1.40–3.55)	<0.001	4.76 (2.13–10.61)	<0.001	0.266	<0.001

**Table 4.** Association between atrial cardiopathy and stroke severity. Model 1: Age and sex adjusted; Model 2: Adjusted for variables with a  $p < 0.1$  in the univariate analysis for outcomes; (age, sex, dyslipidemia, atrial fibrillation, coronary artery disease, wake-up stroke, TOAST, FBG, triglyceride, total cholesterol, LDL). Sensitivity analysis: excluding patients with atrial fibrillation or coronary artery disease. Two models were used: Model 1: Age and sex adjusted; Model 2: Adjusted for age, sex, dyslipidemia, wake-up stroke, TOAST, FBG, triglyceride, total cholesterol, LDL. *NIHSS* National Institutes of Health Stroke Scale, *OR* odds ratio, *CI* confidence interval, *TOAST* Trial of Org 10172 in Acute Stroke Treatment, *FBG* fasting blood glucose, *LDL* low-density lipoprotein.



**Figure 1.** The association between atrial cardiopathy and stroke severity in different subgroups. **(a)** The association between atrial cardiopathy and moderate-to-severe stroke (NIHSS  $\geq 5$ ) in different subgroups. **(b)** The association between atrial cardiopathy and severe stroke (NIHSS  $\geq 15$ ) in different subgroups. Abbreviations: OR, odds ratio; CI, confidence interval.

## Discussion

The current study showed that atrial cardiopathy was associated with initial stroke severity, suggesting that atrial cardiopathy may serve as a clinical indicator of stroke severity in AIS population. Our findings underscore the importance of increasing awareness and attention to this relationship.

Atrial cardiopathy is independently associated with incident ischemic stroke. A recent meta-analysis of observational cohort data showed that the biomarkers of atrial cardiopathy were significantly associated with the risk of ischemic stroke (increased PTFV1, hazards ratio [HR] 1.29, 95%CI 1.06–1.57; LAE, HR 1.39, 95% CI 1.06–1.82; and increased NT-proBNP, HR 2.37, 95%CI 1.61–3.50)<sup>4</sup>. In a retrospective longitudinal cohort of 32,454 community-dwelling old participants, atrial cardiopathy was independently associated with an increased risk of ischemic stroke in the absence of atrial fibrillation<sup>8</sup>. Data from the Third China National Stroke Registry (CNSR-III) also showed an association of poor prognosis with atrial cardiopathy in patients with ischemic stroke, even when patients with atrial fibrillation were excluded<sup>24</sup>. The Cardiovascular Health Study of community-dwelling elderly adults who were free of stroke and atrial fibrillation at baseline showed that atrial cardiopathy was independently associated with incident ischemic stroke<sup>25</sup>. Our results build on the above-mentioned studies by showing an independent association between atrial cardiopathy and index stroke severity, suggesting the potential prognostic role of atrial cardiopathy in AIS population. In line with our findings, an observational study of 1271 AIS patients showed that LAE was associated with more severe initial neurologic deficits of embolic subtypes

(cardioembolic and cryptogenic stroke)<sup>26</sup>. However, the small number of patients with cryptogenic stroke (n = 11) in our cohort does not allow us to assess the relationship between stroke severity and atrial cardiopathy in this subgroup. On the contrary, a retrospective analysis of the Henry Ford Health System did not detect the association between atrial cardiopathy and stroke risk<sup>27</sup>. Possible explanations for the disparities in the above-mentioned studies may include the different study population and different definition for atrial cardiopathy.

The association between atrial cardiopathy and stroke severity might be partly explained by the relationship between atrial cardiopathy and atrial fibrillation, a well-established condition that increases the risk of severe stroke<sup>28</sup>. This hypothesis is supported by our data showing that patients with atrial cardiopathy were more likely to have atrial fibrillation than those without atrial cardiopathy (48.2% vs. 5.0%,  $p < 0.001$ ). Interestingly, our subgroup analysis showed only a trend for a higher odd of moderate to severe stroke with atrial cardiopathy in those with atrial fibrillation, while this association was quite significant in patients without atrial fibrillation. This is probably attributable to the fact that most patients with atrial fibrillation have atrial cardiopathy as defined in our participants, independent of the severity of their stroke. In line with our findings, a small observational study showed that LAE, a biomarker for atrial cardiopathy, was associated with severe ischemic stroke in men with nonvalvular atrial fibrillation, suggesting that atrial cardiopathy may play a crucial role for thrombogenesis in atrial fibrillation<sup>29</sup>. Moreover, several recent studies have shown that atrial cardiopathy may be a cause of cardioembolic stroke even in the absence of atrial fibrillation<sup>5,6,30</sup>. In agreement of the aforementioned studies, our data also showed that patients with atrial cardiopathy were more likely to have a cardioembolic stroke (46.2% vs. 10.3%). Our findings need to be validated in future large prospective studies.

Our study has several limitations. First, our study is a single-center retrospective observational study with inevitable selection bias. Second, our study lacked the data of LA volume, which is a more reliable estimator of LA size<sup>31</sup>. However, LA diameter is more readily available and more widely used in clinical practice. Third, we only analyzed Chinese stroke patients; our findings may therefore not be generalizable to other populations. Moreover, our findings should be interpreted with caution due to unmeasured potential confounding effects of volume expansion for stroke management and stress-induced cardiomyopathy. Finally, we only assess the association of atrial cardiopathy with stroke severity cross-sectionally, studies with a long-term follow-up will better evaluate the relationship between atrial cardiopathy and long-term prognosis of acute ischemic stroke.

## Conclusion

This study showed that atrial cardiopathy was significantly associated with stroke severity, suggesting that atrial cardiopathy may help in predicting stroke prognosis. Future studies are needed to explore improved stroke prevention strategies for patients with atrial cardiopathy.

## Data availability

Data are available from the corresponding author on reasonable request.

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## References

- Kamel, H., Okin, P. M., Longstreth, W. T., Elkind, M. S. V. & Soliman, E. Z. Atrial cardiopathy: A broadened concept of left atrial thromboembolism beyond atrial fibrillation. *Future Cardiol.* **11**, 323–331. <https://doi.org/10.2217/fca.15.22> (2015).
- Calenda, B. W., Fuster, V., Halperin, J. L. & Granger, C. B. Stroke risk assessment in atrial fibrillation: Risk factors and markers of atrial myopathy. *Nat. Rev. Cardiol.* **13**, 549–559. <https://doi.org/10.1038/nrcardio.2016.106> (2016).
- Goette, A. *et al.* EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: Definition, characterization, and clinical implication. *Heart Rhythm* **14**, e3–e40. <https://doi.org/10.1016/j.hrthm.2016.05.028> (2017).
- Guo, J. *et al.* Atrial cardiomyopathy and incident ischemic stroke risk: A systematic review and meta-analysis. *J. Neurol.* **270**, 3391–3401. <https://doi.org/10.1007/s00415-023-11693-3> (2023).
- Kamel, H. *et al.* P-wave morphology and the risk of incident ischemic stroke in the multi-ethnic study of atherosclerosis. *Stroke* **45**, 2786–2788. <https://doi.org/10.1161/STROKEAHA.114.006364> (2014).
- Kamel, H. *et al.* Electrocardiographic left atrial abnormality and risk of stroke: Northern Manhattan study. *Stroke* **46**, 3208–3212. <https://doi.org/10.1161/STROKEAHA.115.009989> (2015).
- He, J. *et al.* P-wave indices and risk of ischemic stroke: A systematic review and meta-analysis. *Stroke* **48**, 2066–2072. <https://doi.org/10.1161/STROKEAHA.117.017293> (2017).
- Edwards, J. D., Healey, J. S., Fang, J., Yip, K. & Gladstone, D. J. Atrial cardiopathy in the absence of atrial fibrillation increases risk of ischemic stroke, incident atrial fibrillation, and mortality and improves stroke risk prediction. *J. Am. Heart Assoc.* **9**, e013227. <https://doi.org/10.1161/JAHA.119.013227> (2020).
- Barnes, M. E. *et al.* Left atrial volume in the prediction of first ischemic stroke in an elderly cohort without atrial fibrillation. *Mayo Clin. Proc.* **79**, 1008–1014 (2004).
- Benjamin, E. J., D'Agostino, R. B., Belanger, A. J., Wolf, P. A. & Levy, D. Left atrial size and the risk of stroke and death. The Framingham heart study. *Circulation* **92**, 835–841 (1995).
- Folsom, A. R. *et al.* Troponin T, N-terminal pro-B-type natriuretic peptide, and incidence of stroke: The atherosclerosis risk in communities study. *Stroke* **44**, 961–967. <https://doi.org/10.1161/STROKEAHA.111.000173> (2013).
- Cushman, M. *et al.* N-terminal pro-B-type natriuretic peptide and stroke risk: The reasons for geographic and racial differences in stroke cohort. *Stroke* **45**, 1646–1650. <https://doi.org/10.1161/STROKEAHA.114.004712> (2014).
- Jalini, S. *et al.* Atrial cardiopathy in patients with embolic strokes of unknown source and other stroke etiologies. *Neurology* **92**, e288–e294. <https://doi.org/10.1212/WNL.0000000000006748> (2019).
- Messé, S. R. *et al.* Stroke after aortic valve surgery: results from a prospective cohort. *Circulation* **129**, 2253–2261. <https://doi.org/10.1161/CIRCULATIONAHA.113.005084> (2014).
- Long, X. *et al.* Mortality, recurrence, and dependency rates are higher after acute ischemic stroke in elderly patients with diabetes compared to younger patients. *Front. Aging Neurosci.* **8**, 142. <https://doi.org/10.3389/fnagi.2016.00142> (2016).
- Didier, R. *et al.* Distribution of atrial cardiomyopathy markers and association with atrial fibrillation detected after ischaemic stroke in the SAFAS study. *Stroke Vasc. Neurol.* <https://doi.org/10.1136/svn-2023-002447> (2023).

17. Zhao, D. X., Gootee, E. & Johansen, M. C. Atrial cardiopathy is associated with cerebral microbleeds in ischemic stroke patients. *Front. Neurol.* **13**, 982926. <https://doi.org/10.3389/fneur.2022.982926> (2022).
18. Oldgren, J. *et al.* Early versus delayed non-vitamin K antagonist oral anticoagulant therapy after acute ischemic stroke in atrial fibrillation (TIMING): A registry-based randomized controlled noninferiority study. *Circulation* **146**, 1056–1066. <https://doi.org/10.1161/CIRCULATIONAHA.122.060666> (2022).
19. Adams, H. P. *et al.* Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. *Stroke* **24**, 35–41 (1993).
20. Soliman, E. Z. *et al.* Reference ranges of PR duration and P-wave indices in individuals free of cardiovascular disease: The multi-ethnic study of atherosclerosis (MESA). *J. Electrocardiol.* **46**, 702–706. <https://doi.org/10.1016/j.jelectrocard.2013.05.006> (2013).
21. Hryniewicz-Szymanska, A. *et al.* Association of the CHADS2 and CHA2DS2-VASc scores with left atrial enlargement: A prospective cohort study of unselected atrial fibrillation patients. *J. Thromb. Thrombolysis* **40**, 240–247. <https://doi.org/10.1007/s11239-014-1154-6> (2015).
22. Ning, Y., Wei, M., Song, W. & Luo, G. The relationship between atrial cardiopathy biomarkers and prognosis of patients with embolic stroke of undetermined source. *Front. Cardiovasc. Med.* **9**, 829361. <https://doi.org/10.3389/fcvm.2022.829361> (2022).
23. Viktorisson, A. *et al.* Associations of prestroke physical activity with stroke severity and mortality after intracerebral hemorrhage compared with ischemic stroke. *Neurology* **99**, e2137–e2148. <https://doi.org/10.1212/WNL.000000000000201097> (2022).
24. Wu, Y. *et al.* Prognostic significance of atrial cardiopathy in patients with acute ischemic stroke. *Eur. Stroke J.* **8**, 183–190. <https://doi.org/10.1177/23969873221126000> (2023).
25. Kamel, H. *et al.* Atrial cardiopathy and the risk of ischemic stroke in the CHS (cardiovascular health study). *Stroke* **49**, 980–986. <https://doi.org/10.1161/STROKEAHA.117.020059> (2018).
26. Xue, J. *et al.* Left atrial enlargement is associated with stroke severity with cardioembolic and cryptogenic subtypes in a Chinese population. *J. Stroke Cerebrovasc. Dis.* **29**, 104767. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104767> (2020).
27. Affan, M. *et al.* Atrial fibrillation, not atrial cardiopathy, is associated with stroke: A single center retrospective study. *J. Neurol. Sci.* **402**, 69–73. <https://doi.org/10.1016/j.jns.2019.05.012> (2019).
28. Lin, H. J. *et al.* Stroke severity in atrial fibrillation. The Framingham study. *Stroke* **27**, 1760–1764 (1996).
29. Kim, T.-W. *et al.* Left atrial dilatation is associated with severe ischemic stroke in men with non-valvular atrial fibrillation. *J. Neurol. Sci.* **354**, 97–102. <https://doi.org/10.1016/j.jns.2015.05.008> (2015).
30. Yaghi, S. *et al.* Left atrial enlargement and stroke recurrence: The northern Manhattan stroke study. *Stroke* **46**, 1488–1493. <https://doi.org/10.1161/STROKEAHA.115.008711> (2015).
31. Khankirawatana, B., Khankirawatana, S. & Porter, T. How should left atrial size be reported? Comparative assessment with use of multiple echocardiographic methods. *Am. Heart J.* **147**, 369–374 (2004).

### Author contributions

Concept and design: Y.Z., H.Lei., and H.D.; Acquisition, analysis, or interpretation of data: Y.Z., H.Lei., X.W., H.Lin. and H.D.; Drafting of the manuscript: Y.Z., H.Lei., and H.D.; Critical revision of the manuscript for important intellectual content: S.F., Q.Y., N.L.; H.D. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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### Competing interests

The authors declare no competing interests.

### Additional information

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