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*Corresponding author

Yunhan Fei, Department of Emergency, Tianjin Huanhu Hospital, No. 6 Jizhao Road, Jinnan District, Tianjin 300052, China, Tel: 86-22-59065729

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Keywords

Ischemic stroke; Atrial fibrillation; Outcomes; Risk factors; Hypertension

Research Article

Prognostic Factors Influencing Outcomes in Young Stroke Patients with Atrial Fibrillation: Evidence from a Hospital-Based Cohort Study in China

Jie Liu¹, Keliang Xie^{1#}, and Yunhan Fei^{2*}

¹Department of Critical Care Medicine, Tianjin Medical University General Hospital, China

²Department of Emergency, Tianjin Huanhu Hospital, China

[#]Author contributed equally to this manuscript

Abstract

Background : Atrial fibrillation (AF) is the established determinant of ischemic stroke and is linked to high mortality and disease burden. We aimed to assess prognosis at 3 and 12 months after stroke in Chinese patients aged <65 years with AF.

Methods : A total of 230 stroke patients with AF were recruited to this study. Outcomes at 3 and 12 months after stroke and clinical features were assessed.

Results : The rate of mortality, recurrence, and dependence at 3 months after stroke was 13.3%, 5.1%, 23.1%, respectively, while at 12 months after stroke was 17.2%, 19.0%, 36.8%, respectively. At 3 months after stroke, compared POCI, the risk of mortality and dependence increased 5.08 times and 2.27 times in PACI, respectively. Moreover, the risk of recurrence increased 3.71 times and 6.87 times in obesity (with no-obesity as the reference) and smoking (with no smoking as the reference), respectively (all $p < 0.05$). At 12 months after stroke, the risk of mortality and dependence was 4.04 times and 3.73 times compared POCI, respectively (all $P < 0.05$). Compared with mild stroke, the risk of mortality increased 2.46 times among sever stroke patients at 12 months after stroke (95% CI: 1.03-11.59; $P = 0.044$); the risk of dependence will increased 1.86 times and 2.20 times among moderate and sever stroke patients, respectively, compared to POCI stroke patients (all $P < 0.05$). However, hypertension is not a contributing factor to stroke recurrence in middle aged and young patients with AF ($P = 0.112$).

Conclusions : This study demonstrates that the mortality and dependency rates among post-stroke patients increase over time, with certain stroke types and high-risk factors significantly elevating health risks. However, arterial blood pressure does not have a significant impact on stroke recurrence. These findings highlight the need to optimize clinical strategies for managing arterial blood pressure, prioritize more influential risk factors, and develop targeted policies for the prevention, treatment, and rehabilitation of stroke and atrial fibrillation.

ABBREVIATIONS

AF: Atrial fibrillation; CT: computed Tomography; MRI: Magnetic Resonance Imaging; OCSF: Oxfordshire Community Stroke Project; TACI: Total Anterior Circulation Infarct; PACI: Partial Anterior Circulation Infarct; LACI: lacunar Infarct; POCI: Posterior Circulation Infarct; NIHSS: National Institutes of Health Stroke Scale; BI: Bethel Index; BMI: Body Mass Index; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; FG: Fasting Glucose; HbA1c: Glycosylated Hemoglobin; HR: Hazard Ratios; CI: Confidence Interval; OR: Odds Ratios; VISTA: Virtual International Stroke Trials Archive

BACKGROUND

Stroke, the second leading cause of death, worldwide, has caused increasing numbers of deaths and hospitalizations over the past 20 years [1-4]. At the national level, in 2017, stroke was the leading cause of death, years of life lost, and disability-adjusted life-years in China [5]. Presently, there are 13 million stroke patients in China, and the resultant increases in hospitalization costs are much higher than the gross domestic product growth rate [6]. National data show that, between 2005 and 2016, the proportion of patients under the age of 70 years, in China's stroke population, has continued to increase, with the age of the incident stroke gradually declining [7]. Thus, the stroke burden among young people in China is increasing, making this a major public health problem.

Atrial fibrillation (AF) is an independent risk factor for ischemic stroke and is associated with a high mortality risk and disease burden [8-11]. AF increases the stroke risk by a factor of 5 and is reported, in population studies, to contribute to 13–31% of incident ischemic strokes [12-14]. Further, AF-associated strokes are more likely to be fatal or disabling than those not associated with AF, and the stroke risk associated with AF is higher than those for other factors associated with ischemic strokes [10,15-19]. Among stroke patients with AF, previous studies have indicated that elderly patients are more likely than younger patients to have poor outcomes, including increased rates of mortality, dependency, and recurrence [20,21].

China's large population of patients with AF-associated

strokes has not, however, resulted in this important stroke type receiving sufficient attention. Thus, in this study, we assessed the outcomes and relevant determinants of AF-associated strokes in young and middle-aged adults, in China.

METHODS

Patient selection

We recruited consecutive patients with acute ischemic stroke admitted to the stroke unit, between January 2015 and December 2018, excluding those ≥ 65 years old and those who experienced transient ischemic attacks. Moreover, patients treated with thrombolysis or endovascular reperfusion were not included in this study. All patients were diagnosed according to the World Health Organization criteria, and diagnoses were confirmed using brain computed tomography or magnetic resonance imaging.

Trained neurologists collected detailed information regarding the patients with acute ischemic stroke, including stroke subtype, stroke severity, previous medical history, lifestyle factors, and 3- and 12-monthpost-stroke outcomes. AF was defined as a previous history of AF or as new-onset AF upon admission.

STROKE SUBTYPE

Upon patient admission, strokes were classified, according to the Oxfordshire Community Stroke Project (OCSF) classification, as total anterior circulation infarcts (TACIs), partial anterior circulation infarcts (PACIs), lacunar infarcts (LACIs), or posterior circulation infarcts (POCIs) [22].

CLINICAL FEATURES

Stroke severity was categorized, using the National Institutes of Health Stroke Scale (NIHSS), as: mild (NIHSS score ≤ 7), moderate (NIHSS score 8–16), or severe (NIHSS score ≥ 17) [23]. Each patient's Bethel index (BI) and modified Rankin scale (mRS) score, upon admission, were also recorded.

The examined stroke risk factors included hypertension, diabetes mellitus, dyslipidemia, brain-supplied arterial stenosis, and obesity (body mass index [BMI] ≥ 30 kg/m²); lifestyle factors included current smoking (≥ 1 cigarette per day for ≥ 1 year) and alcohol consumption (drinking alcohol at least once per week for 1 year).

OUTCOME DEFINITIONS AND FOLLOW-UP PROCESS

The assessed post-stroke outcomes were mortality, recurrence, and dependency at 3 and 12 months, post-stroke. These were assessed using both face-to-face and telephone follow-up interviews. The number of deaths included deaths due to any cause occurring within the follow-up period; death data were obtained from family member reports, including those obtained during telephone follow-up interviews. Recurrence was defined as all new-onset vascular events, including strokes, myocardial infarctions, and venous thromboses, occurring within 30 days after the incident stroke. Information regarding the diagnosis and classification of the recurrent events was obtained from the patient's medical record. Dependency was defined as a mRS score >2 [16].

Trained neurologists followed-up with all discharged stroke patients at 3, 6, 9, and 12 months after the incident stroke. Information regarding outcomes, medication use, primary risk factor control, and mRS scores was recorded following face-to-face or telephone interviews.

STATISTICAL ANALYSIS

1. All included patients were classified into either the AF or non-AF group for the analysis. Continuous variables, including the NIHSS score; BI; mRS; and age are presented as median (range interquartile); between group comparisons were performed using Student's *t*-test or the Mann-Whitney *U*-test. Categorical variables, including OCSF classification, stroke severity, conventional risk factors, and outcomes over different post-stroke periods, are presented as numbers (percentages); between-group comparisons were performed using Kaplan-Meier survival curves. A logistic regression analysis was performed to assess the outcome-associated risk factors for AF patients at 3 and 12 months, after stroke; the results are presented as relative risks (RRs) with 95% confidence intervals (CIs). A multivariate analysis was performed using the statistically significant covariates from the univariate analysis, and are presented as adjusted ORs with 95% CIs. Patients lost to follow-up were excluded from the analyses. All statistical analyses were performed using SPSS version 25.0 (SPSS, Chicago, IL); a two-tailed P -value <0.05 indicated statistical significance.

PARTICIPANTS

We recruited all consecutive acute ischemic stroke patients admitted to the stroke unit in Tianjin, China, between January 2015 and December 2018, excluding those aged 65 years and older and those who experienced transient ischemic attack. Moreover, patients treated with thrombolysis or endovascular reperfusion were not included in this study. Finally, total of 230 AF patients data were selected from the registered patients for analysis.

There were 151 (65.7%) male patients and 79 (34.3%) female patients. In this study, PACI accounts for the largest proportion of OCSF classification (60.3%). The proportion of male patients with mild stroke severity is the largest (47.0%), while female patients with more severe (40.5%). The score of NIHSS was significantly higher in women than in men ($13 > 8$; $P=0.001$). The score of BI was significantly lower in women than in men ($20 < 55$; $P=0.002$). Moreover, the smoking and drinking rate of men was significantly higher than that of women (all $P < 0.001$) [Table 1].

Influencing factors related to stroke prognosis in univariate analysis

At 3 months after stroke, the mortality rate and dependence rate were significantly higher in TACI groups, severe stroke group and obesity groups (all $P < 0.05$). The recurrence rate was higher among obesity than without obesity patients ($16.0\% > 3.5\%$, $P=0.008$); higher among smoking patients than never smoking patients ($11.8\% > 1.6\%$, $P=0.002$) [Table 2].

At 12 months after stroke, high mortality and dependence rate were found in the TACI and severe stroke patients (all $P < 0.001$). Moreover, the mortality rate was higher in hypertension patients ($22.0\% > 10.5\%$, $P=0.030$), diabetes patients ($26.4\% > 14.1\%$, $P=0.040$). In addition, the dependence rate was higher in obesity patients ($58.6\% > 33.3\%$, $P=0.009$). However, the rate of mortality was lower among current smoking patients than no smoking patients ($9.2\% < 20.8\%$, $P=0.040$); the rate of dependence was lower among current drinking patients than no drinking patients ($14.7\% < 41.1\%$, $P=0.003$) [Table 3].

DETERMINING FACTORS RELATED TO STROKE PROGNOSIS IN MULTIVARIATE ANALYSIS

Table 1. The clinical features and previous history of diseases in ischemic stroke patients aged <65 years by AF.

Characteristics	Men	Women	P
Total, n (%):	151 (65.7)	79 (34.3)	
Age, mean(SD)	56.20 (7.15)	58.73 (4.33)	0.004
OCSF classification, n (%):			0.016
PACI	89 (59.3)	49 (62.0)	
TACI	30 (20.0)	17 (21.5)	
LACU	-	4 (5.1)	
POCI	31 (20.7)	9 (11.4)	
Stroke severity, n (%):			0.032
Mild	71 (47.0)	24 (30.4)	
Moderate	40 (26.5)	23 (29.1)	
Severe	40 (26.5)	32 (40.5)	
Neurological function, median (range):			
NIHSS	8 (15)	13 (14)	0.001
BI	55 (70)	20 (65)	0.002
mRS	4 (3)	4 (2)	<0.001
Conventional risk factors, n (%):			
Hypertension	92 (60.9)	48 (60.8)	0.980
Diabetes	35 (23.2)	22 (27.8)	0.436
Dyslipidemias	45 (29.8)	25 (31.6)	0.773
Artery stenosis	15 (9.9)	14 (17.7)	0.091
Obesity	19 (12.6)	15 (19)	0.194
Current smoking	70 (46.4)	6 (7.6)	<0.001
Alcohol consumption	36 (23.8)	2 (2.5)	<0.001
Hyperhomocysteinemia	28 (18.5)	8 (10.1)	0.095

At 3 months after stroke, compared POCI, the risk of mortality and dependence increased 5.08 times (95% CI: 2.13-17.33; $P = 0.001$) and 2.27 times (95% CI: 1.44-7.46; $P = 0.001$) in PACI, respectively. Moreover, the risk of recurrence increased 3.71 times and 6.87 times in obesity (with no-obesity as the reference) and smoking (with no smoking as the reference), respectively (all $p < 0.05$) [Table 4].

2. While at 12 months after stroke, the risk of mortality and dependence was 4.04 times and 3.73 times compared POCI, respectively (all $P < 0.05$). In addition, compared with mild stroke, the risk of mortality increased 2.46 times among severe stroke patients at 12 months after stroke (95% CI: 1.03-11.59; $P = 0.044$); the risk of dependence will increased 1.86 times and 2.20 times among moderate and severe stroke patients, respectively, compared to POCI stroke patients (all $P < 0.05$). The recurrence risk decreased 16.3% with each-1 year of age increased (95% CI: 0.89-0.99; $P = 0.013$) at 12 months

after stroke. However, compared with no drinking patients, the risk of dependence will decreased 81% among current drinking patients (95% CI: 0.06-0.58; $P = 0.004$) [Table 5].

DISCUSSION

This large, hospital-based study explored the determined factors related to stroke outcomes at 3 and 12 months among young and middle-aged AF patients in China. The rate of mortality, recurrence, and dependence at 3 months after stroke was 13.3%, 5.1%, 23.1%, respectively, while at 12 months after stroke was 17.2%, 19.0%, 36.8%, respectively. In this study, the severity of stroke in men with AF was less severe than in women. At 3 months after stroke, PACI will increase the risk of mortality and dependence; the risk of recurrence was higher in obesity and smoking patients. Moreover, the risk of mortality and dependence at 12 months after stroke increased among PACI and severe stroke patients. While with increasing age, the risk of recurrence decreased at 12 months after stroke;

Table 2. The risk factors of mortality, dependency, and recurrence at 3 months after stroke among patients aged < 65 years.

Factors	Mortality		Recurrence		Dependency	
	Values	P	Values	P	Values	P
Total, n (%):	30 (13.3)		10 (5.1)		52 (23.1)	
Gender, n (%):		0.474		0.358		0.688
Men	18 (12.2)		8 (6.2)		33 (22.3)	
Women	12 (15.6)		2 (3.1)		19 (24.7)	
Age, mean(SD)	57.93 (5.32)	0.404	55.20 (5.88)	0.414	57.62 (5.10)	0.445
OCSF classification, n (%):		<0.001		0.554		<0.001
PACI	8 (5.9)		5 (3.9)		22 (16.3)	
TACI	16 (34.8)		3 (10.0)		21 (45.7)	
LACU	-		-		-	
POCI	5 (12.8)		2 (5.9)		8 (20.5)	
Stroke severity, n (%):		0.004		0.871		0.004
Mild	6 (6.4)		5 (5.7)		14 (14.9)	
Moderate	7 (11.7)		2 (3.8)		12 (20.0)	
Severe	17 (23.9)		3 (5.6)		26 (36.6)	
Hypertension		0.121		0.447		0.139
Yes	22 (16.2)		7 (6.1)		36 (26.5)	
No	8 (9.0)		3 (3.7)		16 (18.0)	
Diabetes		0.125		0.071		0.764
Yes	11 (19.3)		-		14 (24.6)	
No	19 (11.3)		10 (6.7)		38 (22.6)	
Dyslipidemias		0.977		0.469		0.555
Yes	9 (13.2)		2 (3.4)		14 (20.6)	
No	21 (13.4)		8 (5.9)		38 (24.2)	
Artery stenosis		0.663		0.213		0.236
Yes	3 (10.7)		-		4 (14.3)	
No	27 (13.7)		10 (5.9)		48 (24.4)	
Obesity		0.046		0.008		0.051
Yes	8 (24.2)		4 (16.0)		12 (36.4)	
No	22 (11.5)		6 (3.5)		40 (20.8)	
Current smoking		0.107		0.002		0.762
Yes	6 (8.1)		8 (11.8)		18 (24.3)	
No	24 (15.9)		2 (1.6)		34 (22.5)	
Alcohol consumption		0.121		0.862		0.052
Yes	2 (5.4)		2 (5.7)		4 (10.8)	
No	28 (14.9)		8 (5.0)		48 (25.5)	
Hcy		0.770		0.188		0.614
Yes	4 (11.8)		3 (10.0)		9 (26.5)	
No	26 (13.6)		7 (4.2)		43 (22.5)	

Table 3. The risk factors of mortality, dependency, and recurrence at 12 months after stroke among patients aged < 65 years.

Factors	Mortality		Recurrence		Dependency	
	Values	P	Values	P	Values	P
Total, n (%):	36 (17.2)		33 (19.0)		77 (36.8)	
Gender, n (%):		0.494		0.624		0.143
Men	22 (15.9)		21 (17.9)		46 (33.3)	
Women	14 (19.7)		12 (21.1)		31 (43.7)	
Age, mean(SD)	57.97 (5.11)	0.319	54.00 (7.79)	0.008	56.73 (6.33)	0.662
OCSP classification, n (%):		<0.001		0.052		<0.001
PACI	10 (8.3)		16 (14.3)		30 (24.8)	
TACI	18 (40.0)		9 (33.3)		30 (66.7)	
LACU	-		2 (50.0)		2 (50.0)	
POCI	7 (18.4)		6 (19.4)		14 (36.8)	
Stroke severity, n (%):		<0.001		0.064		<0.001
Mild	6 (6.9)		10 (12.2)		17 (19.5)	
Moderate	9 (16.7)		13 (28.9)		21 (38.9)	
Severe	21 (30.9)		10 (21.3)		39 (57.4)	
Conventional risk factors, n (%):						
Hypertension		0.030		0.532		0.283
Yes	27 (22.0)		20 (20.6)		49 (39.8)	
No	9 (10.5)		13 (16.9)		28 (32.6)	
Diabetes		0.040		0.099		0.876
Yes	14 (26.4)		4 (10.0)		20 (37.7)	
No	22 (14.1)		29 (21.6)		57 (36.5)	
Dyslipidemias		0.589		0.103		0.505
Yes	9 (15.0)		5 (11.5)		20 (33.3)	
No	27 (18.1)		27 (22.1)		57 (38.3)	
Artery stenosis		0.982		0.900		0.111
Yes	4 (17.4)		4 (20.0)		5 (21.7)	
No	32 (17.2)		29 (18.8)		72 (38.7)	
Obesity		0.111		0.231		0.009
Yes	8 (27.6)		6 (28.6)		17 (58.6)	
No	28 (15.6)		27 (17.6)		60 (33.3)	
Current smoking		0.040		0.286		0.361
Yes	6 (9.2)		14 (23.3)		21 (32.3)	
No	30 (20.8)		19 (16.7)		56 (38.9)	
Alcohol consumption		0.056		0.302		0.003
Yes	2 (5.9)		4 (12.5)		5 (14.7)	
No	34 (19.4)		29 (20.4)		72 (41.1)	
Hcy		0.671		0.795		0.326
Yes	5 (14.7)		6 (20.7)		10 (29.4)	
No	31 (17.7)		27 (18.6)		67 (38.3)	

Table 4. Association between outcomes and risk factors at 3 months after stroke among patients aged < 65 years.

Risk Factors	Reference	Mortality		Recurrence		Dependency	
		HR (95%CI)	P	HR (95%CI) ^a	P	HR (95%CI) ^a	P
OCSP:	POCI						
PACI		6.08 (2.13, 17.33)	0.001	-	-	3.27 (1.44, 7.46)	0.005
TACI		-	-	-	-	-	0.999
LACI		2.58 (0.77, 8.69)	0.127	-	-	1.46 (0.58, 3.66)	0.426
Severity	Mild						
Moderate		1.49 (0.43, 5.14)	0.527	-	-	1.22 (0.50, 2.95)	0.664
Severe		1.91 (0.57, 6.45)	0.296	-	-	1.87 (0.77, 4.51)	0.166
Obesity		2.04 (0.75, 5.57)	0.164	4.71 (1.16, 1.20)	0.031	-	-
Smoking		-	-	7.87 (1.59, 38.84)	0.011	-	-

Table 5. Association between outcomes and risk factors at 12 months after stroke among patients aged < 65 years.

Risk Factors	Reference	Mortality		Recurrence		Dependency	
		HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Age	-	-	-	0.937 (0.89, 0.99)	0.013	-	-
OCSP:	POCI					-	-
PACI		5.04 (1.84, 13.81)	0.002	-	-	4.73 (1.87, 11.98)	0.001
TACI		-	-	-	-	3.71 (0.44, 31.62)	0.230
LACI		2.31 (0.73, 7.27)	0.153	-	-	2.13 (0.90, 5.04)	0.084
Severity	Mild						
Moderate		3.02 (0.90, 10.13)	0.074	-	-	2.86 (1.23, 6.69)	0.015
Severe		3.46 (1.03, 11.59)	0.044	-	-	3.20 (1.31, 7.86)	0.011
Hypertension		2.17 (0.84 5.62)	0.112	-	-	-	-
Diabetes		2.46 (0.96, 6.33)	0.061	-	-	-	-
Smoking		0.33 (0.11, 1.002)	0.050	-	-	-	-
Drinking		-	-	-	-	0.19 (0.06, 0.58)	0.004
Obesity		-	-	-	-	2.04 (0.80, 5.19)	0.135

drinking alcohol also reduced the risk of stroke disability at 12 months.

A cohort study including 11 stroke centers in Ontario, Canada reported that the 12 months case fatality was 23.6% [15]. A multinational hospital-based registry from European Community Stroke Project reported that the 3 months mortality rate was 32.8% after stroke [24]. North Dublin Population Stroke Study reported that the 5-year mortality rate in patients with AF is as high as 60.8% after stroke [21]. In this study, the all case of mortality after stroke at 3 months and 12 months was 13.3% and 17.2%, respectively. This data was lower than previous studies about AF-stroke mortality. First of all, the follow-up time of this study is only 1 year, and it is younger than the study population in the above study. Secondly, the research area is Tianjin, China. The overall medical level is higher, which may be the reason for the lower mortality rate. Thus, a longer follow-up and multi-center joint study are needed to verify the results of the study.

Elderly stroke patients are more likely than younger patients to have poor outcomes after acute ischemic stroke, and they show greater short- and long-term mortality and dependency rates and a higher risk of stroke recurrence than young patients do [25-28]. A previous study have proved that age was predictors of poor post-stroke prognoses among AF patients [29]. However, the results of this study are contrary to previous studies. In this study, the risk of stroke recurrence decreased with increasing age at 12 months after stroke. The specific mechanism is not clear. The potential cause is that the research population is young and middle-aged, work and life burdens are relatively heavy, but as the age increases, life pressure gradually decreases. A meta-analysis which included 6 prospective cohort studies reported that high strain jobs were associated with increased 22% risk of stroke compared with low strain jobs [30].

It is well known that obesity paradox exists in many chronic disease [31,32]. A cohort study in Denmark showed that compared with normal-weight patients, the risk of ischemic stroke was significantly higher in overweight [33]. A previous study reported that in patients with AF over 70 years of age, obesity will increase the risk of stroke, but it has no effect on the mortality after stroke [34]. In addition, a systematic

review reported that obesity paradox existed in AF patients, particularly for all-cause and cardiovascular death outcomes [35]. In this study, obesity was the risk factor of recurrence at 3 months after stroke among AF patients. It may be due to the obesity paradox that mostly appears in the elderly, but the research population is young and middle-aged under 65.

Some studies have shown that heavy alcohol consumption increased the mortality rate of stroke [36,37]. Another previous study had also shown no strong associations between alcohol consumption and the functional outcome after stroke among AF patients [38]. A report from the China atrial fibrillation registry study showed that drinkers was associated with lower risk of poor prognosis at 2.5 years after stroke but without significance [39]. However, in this study, current drinking was protect factors of dependence at 12 months after stroke among AF patients. That may be related to the amount of alcohol consumed and the type of alcoholic beverage.

In this study, smoking and severe stroke was risk factors for poor prognosis after stroke. This result was consistent with previous research results. Many studies had reported that smoking will increase the risk of mortality and recurrence of stroke among AF patients [10,39]. Moreover, severe stroke can predict poor prognosis [14,23]. This study results were consistent with previous studies.

There were several limitations in this study. First, all patients in this study were recruited from the same city, which might limit the generalizability of the results in China. Second, there was a lack of pre-stroke information regarding anticoagulation use between the two groups, which may have affected outcome evaluation. However, the impact may be insignificant due to the lower proportion of using anticoagulation medications in China. Finally, this study did not conduct a quantitative analysis of drinking, and future follow-up will improve relevant information.

CONCLUSION

In this large, hospital-based stroke registry, we assessed differences in clinical features, risk factors, and outcomes at 3 and 12 months after stroke among young and middle-aged stroke patients with AF. Severe stroke, obesity, and smoking related to poor prognosis at 3 months after stroke in patients with AF, while drinking alcohol can reduce the dependency

rate at 12 months after stroke in patients with AF. Hypertension is not a contributing factor to stroke recurrence in middle aged and young patients with AF. Although the underlying mechanism requires more in-depth basic research, these findings have guiding significance for the prediction of stroke prognosis in young and middle-aged patients with AF.

DECLARATIONS

Ethics approval and consent to participate

This study design was approved by the ethics committee of the Ethics Committee of Tianjin Medical University General Hospital; written and informed consent was obtained from each patient or a family member or other legal guardian.

CONSENT FOR PUBLICATION

Consent for publication not applicable.

AVAILABILITY OF DATA AND MATERIALS

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

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

JL and YF were involved in conception and design, and critical review for this article. JL was involved in data analysis for this article and manuscript drafting. Y.F. and K.X. were involved in data collection, case diagnosis and confirmation for this article. All authors reviewed the manuscript.

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