Sex Differences in the Association Between Liver Fibrosis and Clinical Outcomes in Acute Cardioembolic Stroke Population With Nonvalvular Atrial Fibrillation

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Research

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Abstract

Background: Liver cirrhosis is a confirmed risk factor for worse clinical outcomes of stroke, however the contribution of liver fibrosis to cardioembolic stroke (CES) and its short-term outcomes are poorly understood. This study aimed to investigate whether liver fibrosis is associated with more severe stroke, worse short-term clinical outcomes of acute CES, due to nonvalvular atrial fibrillation (NVAF), as well as the impact of sex on the association.

Methods: Using data of 522 patients with NVAF admitted within 48 hours after acute symptom of CES onset. We calculated Fibrosis-4 score (FIB-4) and defined liver fibrosis as: likely advanced fibrosis (FIB-4>3.25), indeterminate (FIB-4, 1.45-3.25), unlikely advanced fibrosis (FIB-4<1.45). We invested the impact of liver fibrosis degree on stroke severity on admission, major disability at discharge and all cause death at 90 days stratified by sex.

Results: Among 522 acute CES patients with NVAF, the mean FIB-4 on admission reflected intermediate fibrosis, whereas liver enzymes were largely normal. After adjusting for possible confounders, multivariate analyses revealed that likely advanced liver fibrosis was associated with severe stroke (OR=2.21, 95% CI: 1.04-3.54), major disability at discharge (OR=4.59, 95% CI: 1.88-11.18), and 90-days mortality (HR=1.25, 95% CI: 1.10-1.56). Further grouped by sex, these associations were stronger in males but not significant in females.

Conclusions: In patients with largely normal liver enzyme, likely advanced liver fibrosis is associated with severe stroke, major disability and all cause death after acute CES due to NVAF; the association unfolded more obvious in males, but not for females.

Introduction

Stroke is a common disease, especially the ischemic stroke, which is the second leading cause of death and third leading cause of disability in adults worldwide.(1) Stroke induced by atrial fibrillation (AF) is more severe, with more threefold mortality and disability rates than patients without AF.(2) The severity, treatments effectiveness, outcomes of stroke may differ from sex.(3, 4) Except for sex, liver disease was associated with in-hospital death after ischemic stroke.(5) Several researches suggested that liver cirrhosis was not only associated with an increased risk of stroke, but an independent risk factor of poor prognosis after stoke.(5, 6) Although these evidences emphasized advanced liver disease possibly associated with poor stroke outcomes, the implications of subclinical liver disease—liver fibrosis for CES severity and short-term outcomes is poorly understood.

Liver fibrosis, the commonly clinical manifestation of chronic liver disease, is often undetected because of no obvious clinical symptoms.(7) Recent studies suggested that there was a significant relationship between liver fibrosis and all-cause mortality of cardiovascular disease in patients with chronic liver disease, (8, 9) as well as ischemic stroke risk.(10) As described above, data are lacking regarding to the contribution of liver fibrosis on the severity and short-term outcomes of ischemic stroke.

Currently, the China, a super aging country, have an increasing population of CES due to AF, especially the NVAF. Therefore, we focused on the CES patients with NVAF, and investigated the association between liver fibrosis, quantized by a valid liver fibrosis indictor—FIB-4, and CES outcomes using patients without overt liver disease. Furthermore, Because the severity, outcomes of stroke differ from sex, we also researched effect modification of sex on those associations. We hypothesized that liver fibrosis are associated with more severe stroke, worse functional outcomes, higher risk of death at 90 days in CES patients with NVAF.

Materials And Methods

Study Population

We performed a retrospective study using data from the First Affiliated Hospital of Xi'an JiaoTong University, a National Advanced Stroke Center which has both an acute stroke treatment center and a stroke rehabilitation center. Thus, all patients suffering acute CES admitted to the stroke center received consistent therapy in the acute and chronic phase during hospitalization. Patients were included in this study if they met the following requirements: (1) 18 years of age or older; (2) has a history of AF or presented symptom onset accompanied by AF; (3) admitted to the stroke center within 48 hours after onset; (4) without any limitation of physical activities before onset; (5) baseline assessment within 48 hours of CES, including symptom, function and imaging assessment; (6) assessment of CES recovery by cerebral imaging during hospitalization; (7) assessment of functional outcome at discharge and all cause death at 90 days after discharge;

Exclusive criteria of this study: (1) missing data on liver chemistries, baseline stroke imaging, or important clinical covariates such as cardiac function, renal function, hospital treatment and CES severity; (2) history of viral hepatitis and liver cirrhosis; (3) alcohol use (men, >30 g/day; women, >20 g/day); (4) use of medications that causes liver damage: valproic acid, amiodarone, methotrexate, and tamoxifen;(11) (5) with poor cardiac function (EF≤40%); (6) known malignancy and clinical signs of infection on admission; Over a 6-year period from January 2013 to June 2019, a total of 987 consecutive CES patients were admitted to the center for acute therapy and for further rehabilitation within 7 days of the CES onset. Of these, 522 CES patients with NVAF were included in the current study (Figure 1). The protocol for the research project has been approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiao Tong University (reference number, VL.0 2018-08-11) and that it conforms to the provisions of the Declaration of Helsinki.

Definition

We used a validated liver fibrosis indictor—FIB-4 score(12, 13), which calculated as:

$$FiB-4=\frac{age\ (years)*aspartate\ aminotransferase\left(\frac{Units}{Liter}\right)}{Platelet\ count\left(\frac{10^{9}}{liter}\right)*\sqrt{alanine\ aminotransferase\left(\frac{Units}{Liter}\right)}}$$

and defined liver fibrosis as FIB-4 >3.25, advanced fibrosis likely; 1.45-3.25, indeterminate level of fibrosis; FIB-4 <1.45, no advanced fibrosis likely.(14, 15) CES was diagnosed according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.(16) The treatment for all CES patients was performed according to the American Heart Association/American Stroke Association Guideline. (17) The diagnosis of AF was based on at least 1 electrocardiogram obtained before or after admission.(18) Stroke severity was evaluated by the National Institutes of Health Stroke Scale (NIHSS) upon admission. NIHSS score of ≥8 was considered as severe stroke,(19) as well as the consciousness state of those patient assessed by Glasgow Coma Scale (GCS).(20) The modified Rankin Scale (mRS) was used to evaluate functional outcomes at discharge, and major disability was defined as a mRS score of ≥3.(21) The primary outcomes were major disability at discharge. Our secondary outcomes were all-cause death at 90 days from discharge.

Demographics and CES Characteristics

All patients included received 12-lead electrocardiogram, transthoracic echocardiography, carotid ultrasonography, and standard blood tests upon admission. As required, some patients received 24-hours Holter electrocardiogram. Demographic and clinical data included age, sex, body mass index (BMI), hypertension, diabetes mellitus, ischemic heart disease, prior history of ischemic stroke/ transient ischemic attacks (TIA), hyperlipidemia, smoking, and the use of lipid-lowering, antiplatelet and anticoagulant medication, admission CHA2DS2-VASc score, HAS-BLED score, and blood pressure were also obtained at prespecified time points, as well as the treatment in hospital (the use of

antiplatelet and anticoagulant medication, intravenous thrombolysis, endovascular revascularization). Biochemical parameters, including platelet count, several liver chemistries (alanine aminotransferase, aspartate aminotransferase and albumin), N-terminal Pro-B-type Natriuretic Peptide (NT pro-BNP), and international normalized ratio (INR) were measured. The estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation.(22)

Statistical Analysis

Data are presented as means ± standard deviation or median and interquartile range for continuous variables and percentages for categorical variables. NT pro-BNP were lg-transformed to minimize skewness and treated as continuous variables. The population characteristics were described by FIB-4 score classification and stratified by sex to explore the distribution of each interval. Kruskal Wallis test and/or chi-square test were used to compare differences among the three groups, as appropriate. Multivariate logistic regression analyses for stroke severity on admission and major disability at discharge and COX regression analysis for all-cause death at 90 days from discharge were performed after adjusting for general risk factors. Statistical significance was defined as two-tailed $P < 0.05$. All analyses were conducted with SPSS 26.0.

Results

Characteristics of Study Population

The dataset of our study consisted of 522 CES patients with NVAF. Standard liver chemistry tests were generally in normal range of the study sample, with 11.7% of aspartate aminotransferase (AST) > 40 IU/L, 11.1% of alanine aminotransferase (ALT) > 40 IU/L. The median value of FIB-4 is 2.28 which reflect intermediate probabilities of fibrosis. 109, 280, 133 subjects were classified into unlikely advanced fibrosis group, indeterminate group, likely advanced fibrosis group based on FIB-4 score by analysis, respectively. The population in likely advanced fibrosis group had higher values for age, CHA2DS2-VASc score, HAS-BLED score and higher proportion for smoker, diabetes melitus, hyperlipidemia, ischemic heart disease, then followed by indeterminate group and unlikely advanced fibrosis group. No difference was found in sex, BMI, hypertension, prior history of ischemic stroke/TIA, drug use before admission (anticoagulant, antiplatelet and lipid-lowering use) and treatment in hospital (intravenous thrombolysis and endovascular revascularization) among three groups (Table 1).

Table 1
Characteristics of Acute CES Patients with NVAF in Different FIB-4 lever

Characteristics	Study Sample (N = 522)	FIB-4 Score<1.45 (N = 109)	(1.45–3.25) (N = 280)	FIB-4 Score>3.25 (N = 133)
Patient characteristics				
Mean age, y, (SD) **	72.61 (9.77)	64.81 (11.21)	73.55 (8.16)	77.03 (7.85)
Male sex	271 (51.9)	58 (53.2)	138 (49.3)	75 (56.4)
Smoker **	111 (21.2)	25 (22.9)	70 (25.0)	16 (12.0)
Risk stratification				
CHA2DS2-VASc score**	3 (2–4)	3 (2–4)	3 (2–4)	3 (3–4)
HAS-BLED score**	1 (1–2)	1 (0–2)	1 (1–2)	2 (1–2)
Diabetes mellitus*	127 (24.3)	28 (25.7)	76 (27.1)	23 (17.3)
Hypertension	343 (65.7)	68 (62.4)	185 (66.1)	90 (67.7)
hyperlipidemia**	122 (23.4)	35 (32.1)	61 (21.8)	26 (19.5)
Ischemic heart disease**	120 (23.0)	19 (17.4)	63 (22.5)	38 (28.6)
Prior history of Ischemic Stroke/TIA	88 (16.8)	17 (15.6)	54 (19.3)	17 (12.8)
Body Mass Index				
Mean, kg/m^2, (SD)	22.77 (3.33)	22.54 (3.12)	22.99 (3.40)	22.50 (3.35)
Obese ≥ 27.5kg/m2	41 (7.9)	6 (5.5)	26 (9.3)	9 (6.8)
Drug use before admission				
Anticoagulant use	49 (9.4)	14 (12.8)	21 (7.5)	14 (10.5)
Antiplatelet use	173 (33.1)	26 (23.9)	102 (36.6)	45 (34.1)
Lipid-lowering use	119 (22.8)	19 (17.4)	63 (22.5)	37 (27.8)
Admission laboratory data				
Platelet count, ×10^3 per microliter**	179.00 (136.75–219.00)	233.00 (196.00-286.00)	182.00 (151.25–215.00))	119.00 (102.00-151.00)
INR**	1.09 (1.04–1.17)	1.07 (1.02–1.13)	1.09 (1.03–1.16)	1.13 (1.07–1.21)
AST, units/L**	23.00 (18.00–31.00)	18.00 (15.00-24.35)	22.00 (18.00,28.75)	32.00 (24.00-44.50)
AST > 40 units/L**	61 (11.70)	2 (1.8)	21 (7.5)	38 (28.6)

Data are reported as mean ± SD, median (IQR) or number and percentage. † CES, cardioembolic stroke; NVAF, nonvalvular atrial fibrillation; FIB-4, fibrosis-4 score; TIA, transient ischemic attacks; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal Pro-B-type Natriuretic Peptide; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ‡ P-values,* for P<0.05, ** for P<0.01, *** for P<0.001.

Characteristics	Study Sample (N = 522)	FIB-4 Score<1.45 (N = 109)	(1.45–3.25) (N = 280)	FIB-4 Score>3.25 (N = 133)
ALT, units/L	18.10 (12.15-27.00)	20.00 (13.90-30.87)	18.00 (12.00-25.75)	17.33 (12.00-26.90)
ALT > 40 units/L	58 (11.1)	13 (11.9)	28 (10.0)	17 (12.8)
Albumin, g/dL	38.00 (35.20–41.00)	38.30 (35.05-42.00)	38.35 (35.53–40.90)	37.30 (34.45–40.20)
eGFR, ml/min/1.73m^2 **	90.16 (80.77-104.39)	95.91 (88.17-119.82)	89.74 (80.44-102.06)	85.61 (76.53-97.31)
Lg NT-pro BNP**	2.99 (2.73–3.27)	2.85 (2.62–3.15)	2.95 (2.69–3.25)	3.17 (2.90–3.47)
FIB-4 score***	2.28 (1.60–3.27)	1.18 (0.94–1.30)	2.19 (1.81–2.61)	4.42 (3.68–6.04)
Stroke severity on admission				
GCS	15 (11–15)	15 (12–15)	15 (12–15)	13 (9–15)
NIHSS*	8 (3–13)	5 (2–12)	7 (3–13)	8 (3–15)
NIHSS ≥ 8*	227 (43.5)	40 (36.7)	116 (41.4)	71 (53.4)
Treatment in hospital				
Antiplatelet use*	230 (44.1)	52 (47.7)	126 (45.0)	52 (39.1)
Anticoagulant use*	292 (57.9)	57 (52.3)	154 (55.0)	81 (70.9)
Intravenous thrombolysis	33 (6.3)	9 (8.3)	16 (5.7)	8 (6.0)
Endovascular revascularization*	71 (13.6)	14 (12.9)	46 (16.4)	11 (8.3)
Outcomes at discharge				
mRS*	2 (1–5)	2 (1–4)	4 (1–5)	5 (2–5)
mRS ≥ 3**	208 (39.8)	33 (30.3)	100 (35.7)	75 (56.4)
All-cause death*	39 (7.3)	9 (8.2)	16 (5.7)	14 (12.3)
Period of hospitalization, days*	30 (20–40)	30 (20–35)	28 (20–35)	35 (21–46)

Data are reported as mean ± SD, median (IQR) or number and percentage. † CES, cardioembolic stroke; NVAF, nonvalvular atrial fibrillation; FIB-4, fibrosis-4 score; TIA, transient ischemic attacks; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal Pro-B-type Natriuretic Peptide; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ‡ P-values,* for P<0.05, ** for P<0.01, *** for P<0.001.

The Short-Term Outcomes of All Study Population

Patients in the likely advanced fibrosis group had significantly higher NIHSS score on admission, mRS score at discharge, 90-days mortality and proportion of severe stroke, major disability compared with those in the indeterminate group and no advanced fibrosis likely group. The proportion for severe stroke was 32.8%, 34.8%, 46.7%,

for major disability is 25.9%, 28.3%, 49.3%, and for 90-days mortality was 5.2%, 3.6%, 8.0% in the no advanced fibrosis likely group, indeterminate group and the likely advanced fibrosis group respectively (Table 1).

Characteristics, Stroke Severity and Short-term Outcomes of Study Population Grouped by Sex

When classified by sex, the likely advanced fibrosis group had higher value for age and INR both in males and females, but beyond that, the male patients had higher CHA2DS2-VASc score, HAS-BLED score and higher proportion for smoker, hyperlipidemia, intravenous thrombolysis and endovascular revascularization in likely advanced fibrosis group, then followed by indeterminate group and unlikely advanced fibrosis group. No difference was observed in sex, BMI, hypertension, prior history of ischemic stroke/TIA, drug use before admission among three groups both for males and females (Table 2).

Table 2
Characteristics of Acute CES Patients with NVAF in different FIB-4 lever, Stratified by Sex

Characteristics	Study Sample	FIB-4 Score<1.45	(1.45–3.25)	FIB-4 Score>3.25
Male (N)	N = 271	N = 58	N = 138	N = 75
Patient characteristics				
Mean age, y, (SD) **	71.65 (10.28)	62.34 (12.02)	72.49 (8.03)	77.32 (7.26)
Smoker**	108 (39.9)	25 (42.9)	68 (49.2)	15 (20.0)
Risk stratification				
CHA2DS2-VASc score*	3 (2–4)	2 (1–3)	3 (2–4)	3 (3–4)
HAS-BLED score*	1 (1–2)	1 (0–1)	1 (1–2)	2(1–2)
Diabetes mellitus	64 (23.6)	14 (24.1)	37 (26.8)	13 (17.3)
Hypertension	164 (60.5)	31 (53.4)	83 (60.1)	50 (66.7)
Hyperlipidemia**	53 (19.6)	17 (29.3)	26 (18.8)	10 (13.3)
Ischemic heart disease	72 (26.6)	12 (20.7)	38 (27.5)	22 (29.3)
Prior history of Ischemic stroke/TIA	45 (16.6)	7 (12.0)	27 (19.5)	11 (17.3)
Body Mass Index				
Mean, kg/m^2, (SD)	23.30 (3.06)	22.71 (2.88)	22.63 (3.00)	23.15 (3.27)
Obese ≥ 27.5kg/m2	21 (7.7)	2 (3.4)	13 (9.4)	6 (8.0)
Drug use before admission				
Anticoagulant use	28 (10.3)	9 (12.0)	12 (8.7)	7 (12.1)
Antiplatelet use	91 (33.7)	15 (25.9)	53 (38.4)	23 (31.1)
Lipid-lowering use	72 (26.6)	12 (20.7)	38 (27.5)	22 (29.3)
Admission laboratory data				
Platelet count, ×10^3 per microliter**	168.00 (132.00-209.00)	236.00 (191.75-288.75)	170.00 (147.75-203.25)	113.00 (102.00-139.00)
INR*	1.10 (1.05–1.19)	1.06 (1.01–1.14)	1.08 (1.00-1.18)	1.12 (1.07–1.24)
AST, units/L**	22.00 (18.00–39.00)	18.10 (14.95-25.00)	22.00 (17.90,28.00)	27.20 (22.00-38.7)
AST > 40 units/L**	26 (9.6)	0 (0.0)	9 (6.5)	17 (22.7)
ALT, units/L	18.70 (12.50–28.00)	20.50 (14.50-31.15)	18.00 (12.23–26.25)	17.71 (11.00–28.00)

Data are reported as mean ± SD, median (IQR) or number and percentage. † CES, cardioembolic stroke; NVAF, nonvalvular atrial fibrillation; FIB-4, fibrosis-4 score; TIA, transient ischemic attacks; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal Pro-B-type Natriuretic Peptide; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ‡ P-values,* for P<0.05, ** for P<0.01, *** for P<0.001.

Characteristics	Study Sample	FIB-4 Score<1.45	(1.45–3.25)	FIB-4 Score>3.25
ALT > 40 units/L	28 (10.3)	5 (8.6)	12 (8.7)	11 (14.7)
Albumin, g/dL	37.70 (35.10–40.80)	37.40 (34.60–41.50)	37.90 (35.40–40.70)	37.30 (34.45–40.60)
eGFR, ml/min/1.73m^2 **	96.51 (79.15–115.60)	110.37 (90.47-136.23)	97.00 (79.02-114.49)	87.13 (67.55-87.13)
Lg NT pro-BNP**	2.95 (2.70–3.21)	2.79 (2.57–3.09)	2.90 (2.56–3.16)	3.13 (2.89–3.47)
FIB-4 score***	2.28 (1.56–3.43)	1.14 (0.93–1.29)	2.17 (1.76–2.59)	4.40 (3.68–5.95)
Stroke severity on admission				
GCS	15 (12–15)	15 (12–15)	15 (13–15)	15 (11–15)
NIHSS*	5 (2–13)	4 (2–12)	5 (2–13)	6 (3–15)
NIHSS ≥ 8**	102 (37.6)	19 (32.8)	48 (34.8)	35 (46.7)
Treatment in hospital				
Antiplatelet use**	134 (49.4)	34 (58.6)	71 (51.4)	29 (38.7)
Anticoagulant use**	137 (50.6)	24 (41.4)	67 (48.6)	46 (61.3)
Intravenous thrombolysis*	15 (5.5)	5 (8.6)	7 (5.1)	3 (4.0)
Endovascular revascularization*	29 (10.7)	7 (12.0)	16 (11.5)	6 (8.0)
Outcomes at discharge				
MRS*	2 (1–5)	2 (1–4)	4 (1–5)	5 (2–5)
MRS ≥ 3***	91 (33.6)	15 (25.9)	39 (28.3)	37 (49.3)
All-cause death*	14 (5.2)	3 (5.2)	5 (3.6)	6 (8.0)
Period of hospitalization, days*	25 (20–37)	22 (20–34)	24.5 (20-37.5)	27.5 (20–42)
Female (N)	N = 251	N = 51	N = 142	N = 58
Patient characteristics				
Mean age, y, (SD) **	73.65 (9.11)	67.61 (9.51)	74.59 (8.18)	76.66 (8.61)
Smoker	3 (1.2)	0 (0)	2 (1.4)	1 (1.7)
Risk stratification				
CHA2DS2-VASc score	4 (3–4)	3 (2–4)	4 (3–4)	4 (3–4)
HAS-BLED score	2 (1–2)	1 (1–2)	2 (1–2)	1 (1–2)

Data are reported as mean ± SD, median (IQR) or number and percentage. † CES, cardioembolic stroke; NVAF, nonvalvular atrial fibrillation; FIB-4, fibrosis-4 score; TIA, transient ischemic attacks; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal Pro-B-type Natriuretic Peptide; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ‡ P-values,* for P<0.05, ** for P<0.01, *** for P<0.001.

Characteristics	Study Sample	FIB-4 Score<1.45	(1.45–3.25)	FIB-4 Score>3.25
Diabetes mellitus	63 (25.3)	14 (27.5)	39 (27.5)	10 (17.2)
Hypertension	179 (71.3)	37 (72.5)	102 (71.8)	40 (69.0)
Hyperlipidemia	69 (27.5)	18 (35.3)	35 (24.6)	16 (27.6)
Ischemic heart disease*	48 (19.1)	7 (13.7)	25 (17.6)	16 (27.6)
Prior history of Ischemic stroke/TIA	43 (17.1)	10 (19.6)	27 (19.0)	6 (10.3)
Body Mass Index				
Mean, kg/m^2, (SD)	22.2 (3.52)	22.36 (3.40)	22.37 (3.66)	21.66 (3.29)
Obese ≥ 27.5kg/m2	20 (8.0)	4 (7.8)	13 (9.2)	3 (5.2)
Drug use before admission				
Anticoagulant use	21 (8.4)	7 (13.7)	9 (6.3)	5 (8.6)
Antiplatelet use	82 (32.8)	11 (21.6)	49 (34.8)	22 (37.9)
lipid-lowering use	47 (18.7)	7 (13.7)	25 (17.6)	15 (25.9)
Admission laboratory data				
Platelet count, ×10^3 per microliter**	185.00 (147.00-229.00)	233.00 (193.00-285.00)	186.50 (153.00-223.50))	128.00 (102.75–172.50)
INR*	1.08 (1.03–1.17)	1.07 (1.03–1.13)	1.08 (1.02–1.16)	1.13 (1.06–1.21)
AST, units/L**	23.75 (18.00–33.00)	17.00 (15.00–23.00)	22.00 (18.00,29.00)	34.56 (28.65-46.00)
AST > 40 units/L**	35 (13.9)	2 (3.9)	12 (8.5)	21 (36.2)
ALT, units/L	18.00 (12.00-26.80)	19.00 (13.00–28.00)	18.00 (11.77–25.25)	17.17 (12.75–26.42)
ALT > 40 units/L	30 (12.0)	8 (15.7)	16 (11.3)	6 (10.3)
Albumin, g/dL**	38.60 (35.70–41.50)	39.90 (36.10–42.10)	38.80 (36.07–41.56)	37.35 (34.28-40.00)
eGFR, ml/min/1.73m^2 **	87.48 (82.03–95.09)	93.78 (87.48-101.24)	86.96 (81.57–94.64)	85.29 (79.27-90.47)
Lg NT pro-BNP**	3.05 (2.78–3.35)	2.89 (2.70–3.23)	3.01 (2.73–3.30)	3.25 (2.92–3.52)
FIB-4 score***	2.27 (1.60–3.17)	1.19 (0.94–1.33)	2.24 (1.88–2.63)*	4.60 (3.83–6.26)
Stroke severity on admission				
GCS	14 (9–15)	14 (10–15)	14 (10–15)	10 (7–15)**&

Data are reported as mean ± SD, median (IQR) or number and percentage. † CES, cardioembolic stroke; NVAF, nonvalvular atrial fibrillation; FIB-4, fibrosis-4 score; TIA, transient ischemic attacks; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal Pro-B-type Natriuretic Peptide; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ‡ P-values,* for P<0.05, ** for P<0.01, *** for P<0.001.

Characteristics	Study Sample	FIB-4 Score<1.45	(1.45–3.25)	FIB-4 Score>3.25
NIHSS*	8 (3–15)	7 (2–13)	8 (3–14)	13 (4.75-18)
NIHSS ≥ 8*	125 (49.8)	21 (41.2)	68 (47.9)	36 (62.1)
Treatment in hospital				
Antiplatelet use	96 (38.2)	18 (35.3)	55 (38.7)	23 (39.7)
Anticoagulant use	155 (61.8)	33 (64.7)	87 (61.3)	35 (60.3)
Intravenous thrombolysis	18 (7.2)	4 (7.8)	9 (6.3)	4 (6.9)
Endovascular revascularization	42 (16.8)	7 (13.7)	30 (21.2)	5 (8.6)
Outcomes at discharge				
mRS**	3 (1–5)	2 (1–5)	3 (1–5)	4.5 (2–5)
mRS ≥ 3**	117 (46.6)	18 (35.3)	61 (43.0)	38 (65.5)
All-cause death	25 (10.0)	6 (12.0)	11 (7.7)	8 (13.8)
Period of hospitalization days*	32 (21–43)	32 (21–35)	24.5 (21–35)	42 (24.75-52)

Data are reported as mean ± SD, median (IQR) or number and percentage. † CES, cardioembolic stroke; NVAF, nonvalvular atrial fibrillation; FIB-4, fibrosis-4 score; TIA, transient ischemic attacks; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal Pro-B-type Natriuretic Peptide; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ‡ P-values,* for P<0.05, ** for P<0.01, *** for P<0.001.

Both male and female patients in likely advanced fibrosis group had the higher NIHSS score, mRS score, more severe stroke, and more major disability than their counterpart (Table 2). For 90-days mortality, 8.0% male patients suffered death in likely advanced fibrosis group at 90 days, which is higher than other two groups, but there was no significant difference among three groups in females (Table 2).

The Associations Between FIB-4 Score and Severe Stroke and Short-term Outcomes of CES patients with NVAF

Multivariate analysis for severe stroke and short-term outcomes showed that FIB-4 score levels were associated with the risk of severe stroke (OR = 1.10, 95% CI: 1.07–1.21), major disability (OR = 1.20, 95% CI: 1.06–1.37) and 90-days mortality (HR = 1.34, 95% CI: 1.08–2.01). Furthermore, FIB-4 was converted to a categorical variable, when compared with no advanced fibrosis likely, likely advanced fibrosis was significantly associated with an increased risk of severe stroke (OR = 2.21, 95% CI: 1.04–3.54), major disability (OR = 4.59, 95% CI: 1.88–11.18) and 90-days mortality (HR = 1.25, 95% CI: 1.10–1.56); indeterminate fibrosis showed an significant association with 90-days mortality (HR = 1.16, 95% CI: 1.08–1.34), but not gone for severe stroke (OR = 1.34, 95% CI: 0.80–2.24) and major disability (OR = 1.26, 95% CI: 0.59–2.70). (Model 4, Table 3, 4; Model 2, Table 5).

Table 3
Effect Modification of Sex on the Associations Between FIB-4 and Admission Stroke Severity

FIB-4	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Totality								
Continuous	1.12 (1.04,1.22)	0.006	1.11 (1.02,1.20)	0.013	1.11 (1.01,1.20)	0.022	1.10 (1.07,1.21)	0.013
Categories								
FIB-4<1.45	Reference		Reference		Reference		Reference	
1.45–3.25	1.22 (0.77,1.93)	0.393	1.29 (0.79,2.11)	0.324	1.34 (0.80,2.24)	0.267	1.34 (0.80,2.24)	0.27
FIB-4>3.25	1.98 (1.17,3.31)	0.008	1.99 (1.09,3.46)	0.025	2.03 (1.11,3.72)	0.022	2.21 (1.04,3.54)	0.036
Male								
Continuous	1.14 (1.01,1.29)	0.033	1.17 (1.03,1.35)	0.019	1.18 (1.02,1.35)	0.024	1.21 (1.10,1.32)	0.000
Categories								
FIB-4<1.45	Reference		Reference		Reference		Reference	
1.45–3.25	1.31 (0.68,2.50)	0.410	1.59 (0.76,3.38)	0.217	1.72 (0.80,3.72)	0.165	1.71 (0.78,3.74)	0.177
FIB-4>3.25	2.39 (1.08,5.05)	0.031	2.73 (1.15,6.46)	0.023	2.97 (1.19,7.42)	0.020	3.12 (1.16,7.11)	0.030
Female								
Continuous	1.11 (0.99,1.24)	0.079	1.06 (0.95,1.19)	0.264	1.07 (0.95,1.21)	0.245	1.07 (0.96,1.21)	0.277
Categories								
FIB-4<1.45	Reference		Reference		Reference		Reference	
1.45–3.25	1.10 (0.57,2.10)	0.787	1.09 (0. 51,2.18)	0.804	1.12 (0.55,2.79)	0.760	1.12 (0.54,2.31)	0.761
FIB-4>3.25	1.80 (0.88,3.66)	0.107	1.77 (0.78,4.01)	0.175	1.88 (0.81,4.39)	0.145	1.89 (0.79,4.52)	0.151

Data are reported as mean ± SD, median (IQR) or number and percentage. † Model 1: adjusted for none. Model 2: adjusted for age, BMI. Model 3: adjusted for age, BMI, smoker (not for females), lg NT pro-BNP, eGFR, INR, antiplatelet use. Model 4: adjusted for all covariables in model 3 plus adjusted for diabetes mellitus, hypertension, hyperlipidemia, ischemic heart disease, prior history of ischemic stroke/TIA. ‡ FIB-4, fibrosis-4 score; BMI, Body Mass Index; TIA, transient ischemic attacks; INR, international normalized ratio; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal Pro-B-type Natriuretic Peptide; OR, odds ratio; 95% CI, 95% confidence interval.

Table 4
Effect Modification of Sex on the Associations Between FIB-4 and major disability After CES

FIB-4	Model 1		Model 2		Model 3		Model 4	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Totality								
Continuous	1.21 (1.10,1.34)	0.000	1.19 (1.08,1.32)	0.001	1.16 (1.05,1.29)	0.005	1.20 (1.06,1.37)	0.004
Categories								
FIB-4<1.45	Reference		Reference		Reference		Reference	
1.45–3.25	1.59 (0.93,2.71)	0.088	1.61 (0.91,2.87)	0.104	1.80 (0.98,3.28)	0.057	1.26 (0.59,2.70)	0.552
FIB-4>3.25	3.62 (2.01,6.53)	0.000	3.51 (1.82,6.76)	0.000	3.60 (1.79,7.25)	0.000	4.59 (1.88,11.18)	0.001
Male								
Continuous	1.38 (1.17,1.62)	0.000	1.48 (1.22,1.77)	0.000	1.48 (1.21,1.81)	0.000	1.82 (1.38,2.40)	0.000
Categories								
FIB-4<1.45	Reference		Reference		Reference		Reference	
1.45–3.25	1.59 (0.72,3.48)	0.251	2.67 (1.04,6.85)	0.047	2.60 (0.99,6.85)	0.052	2.67 (0.98,5.52)	0.078
FIB-4>3.25	3.75 (1.63,8.63)	0.002	7.97 (2.65,23.94)	0.000	7.68 (2.46,23.96)	0.000	13.21 (2.47,55.22)	0.000
Female								
Continuous	1.10 (0.99,1.25)	0.078	1.07 (0.95,1.20)	0.258	1.03 (0.91,1.16)	0.668	1.04 (0.87,1.26)	0.649
Categories								
FIB-4<1.45	Reference		Reference		Reference		Reference	
1.45–3.25	1.57 (0.75,3.27)	0.229	1.33 (0. 61,2.89)	0.471	1.52 (0.67,3.42)	0.316	1.06 (0.33,3.43)	0.924
FIB-4>3.25	3.89 (1.64,9.22)	0.002	3.00 (1.21,7.46)	0.018	2.96 (1.12,7.81)	0.028	3.05 (0.76,12.36)	0.118

Data are reported as mean ± SD, median (IQR) or number and percentage. † Model 1: adjusted for none. Model 2: adjusted for age, BMI. Model 3: adjusted for age, BMI, smoker (not for females), lg NT pro-BNP, eGFR, diabetes mellitus, hypertension, hyperlipidemia, ischemic heart disease, prior history of ischemic stroke/TIA. Model 4: adjusted for all covariables in model 3 plus adjusted for treatment in hospital, NIHSS on admission. ‡ CES, cardioembolic stroke; FIB-4, fibrosis-4 score; BMI, Body Mass Index; TIA, transient ischemic attacks; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal Pro-B-type Natriuretic Peptide; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; 95% CI, 95% confidence interval.

Table 5
Effect Modification of Sex on the Associations Between FIB-4 and All-cause Death After CES

FIB-4	Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value
Totality				
Continuous	1.21 (1.10,1.34)	0.001	1.34 (1.08,2.01)	0.003
FIB-4<1.45	Reference		Reference	
1.45–3.25	1.28 (1.12,1.65)	0.003	1.12 (1.04–1.32)	0.000
FIB-4>3.25	1.40 (1.19,1.84)	0.015	1.25 (1.10–1.56)	0.001
Male				
Continuous	1.36 (1.16,1.58)	0.000	1.44 (1.20,1.72)	0.000
Categories				
FIB-4<1.45	Reference		Reference	
1.45–3.25	1.15 (1.05, 1.67)	0.03	1.16 (1.08–1.34)	0.000
FIB-4>3.25	1.27 (1.10, 1.78)	0.005	1.20 (1.05–1.74)	0.03
Female				
Continuous	1.13 (1.00,1.26)	0.054	1.08 (0.97,1.21)	0.244
FIB-4<1.45	Reference		Reference	
1.45–3.25	1.06 (0.45, 1.40)	0.173	1.48 (0.94–1.61)	0.236
FIB-4>3.25	1.01 (0.38–1.86)	0.499	1.13 (1.00-1.88)	0.034

Data are reported as mean ± SD, median (IQR) or number and percentage. † Model 1: adjusted for none. Model 2: adjusted for adjusted for age, BMI, lg NT pro-BNP, eGFR, diabetes mellitus, hypertension, hyperlipidemia, ischemic heart disease, prior history of ischemic stroke/TIA, treatment in hospital, NIHSS on admission. ‡ CES, cardioembolic stroke; FIB-4, fibrosis-4 score; BMI, Body Mass Index; TIA, transient ischemic attacks; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal Pro-B-type Natriuretic Peptide; NIHSS, National Institutes of Health Stroke Scale; HR, hazard ratio; 95% CI, 95% confidence interval.

Effect Modification of Sex on the Associations Between FIB-4 and Severe Stroke and Short-term Outcomes After CES Duo To NVAF

When classified by sex, multivariate analysis showed when each 1 point increased in FIB-4, male patients had an increased risk of severe stroke (OR = 1.21, 95% CI: 1.10–1.32), major disability (OR = 1.82, 95% CI: 1.38–2.40) and 90-days mortality (HR = 1.44, 95% CI: 1.20–1.72). When FIB-4 was converted to a categorical variable, refer to no advanced fibrosis likely, there was a significant increased contribution of likely advanced fibrosis to severe stroke (OR = 3.12, 95% CI: 1.16–7.11), major disability (OR = 13.21, 95% CI: 2.44–55.22), and 90-days mortality (HR = 1.20, 95% CI: 1.05–1.74); Indeterminate fibrosis associated with 90-days mortality (HR = 1.16, 95% CI: 1.08–1.34), but not for severe stroke and major disability (Model 4, Table 3, 4; Model 2, Table 5).

Whereas the relationship between FIB-4 and severe stroke, major disability and 90-days mortality was not significant in the female group, no matter FIB-4 as a continuous or a categorical variable (Model 4, Table 3, 4; Model 2, Table 5).

Discussion

In this study, we found that the higher FIB-4 score was independently associated with more severe strokes on admission, a less favorable functional outcome at discharge and a higher 90-days death risk among patients with CES due to NAVF. More importantly, our study also suggest that sex could modify this association, when classified by sex, the association become stronger in male patients, but not significant in females. Notably, we also observed these associations in patients with generally normal range of standard liver chemistries.

FIB-4 score is a validated non-invasive tool to assess live fibrosis in HIV and chronic hepatitis C virus co-infection, hepatitis C mono-infection and non-alcoholic fatty liver disease (NAFLD) populations.(12, 13) NAFLD is the main cause of most clinically covert liver fibrosis, especially after excluding the influence of alcohol abuse.(23) Liver imaging and pathological diagnosis of those CES patients are not available in this study. However, FIB-4 have been verified to have good accuracy in the identification of liver fibrosis in patients with NAFLD.(15) To our knowledge, there was no evidence to confirm the association between subclinical liver disease and CES characteristics due to NVAF and clinical outcomes as well as the sex hybrid effect in present studies. Liver fibrosis may be associated with the risk of cardiovascular disease or mortality in the general population.(24) Remarkably, in NAFLD, cardiovascular disease is more commonly responsible for death than is liver disease.(8) Although several previous studies have concluded that the severe abnormal liver enzyme may be significate risk factor for stroke and short-term outcome,(5, 25, 26) however they focused on the nonspecific liver enzyme index and heavy alcohol use were not excluded Or they studied validated live fibrosis but not concern for liver enzyme index and all type of stroke were included.(5) In contrast, a novel association of severe stroke on admission, major disability at discharge and 90-days death after discharge for the recognized liver fibrosis indictor (FIB-4) was observed in the CES patients with NVAF of our study which of different pathogenesis from others. Moreover this novel finding revealed that live fibrosis may represent more severe stroke on admission, worse functional outcomes at discharge and a higher 90-days mortality risk, without obvious clinical manifestations of liver disease, abnormal liver enzyme and confirmed liver disease, which share the same conclusion as those observation-studies that liver fibrosis could occur without special attention of many subjects, and almost 75% of subjects with liver fibrosis had normal liver chemistries levels.(23) To sum up, our study presented the evidence that FIB-4 index is independently associated to severe stroke, short-term outcome of CES due to NVAF.

Stroke affected on males and females differently. Stroke risk, severity, reaction to endovascular therapy and outcomes could be differ from sex, and studies generally suggested that older females suffered from more severe stroke, worse prognosis, and higher mortality than males.(3, 4, 27, 28) We also observed the higher NIHSS score, mRS score and more death in women patients (Table S1). Therefore we grouped sex to eliminate the hybrid effect, and found that liver fibrosis became a stronger risk factor for server stroke, major disability and 90-days death in males, but not in females. The results of the present study was not consistent with the observation among liver fibrosis population showed that sex would not affect the association between liver disease and stroke mortality.(29) Maybe because of the different research population which they researched almost did not suffer from AF.

The possible mechanisms in the association between live fibrosis and poor prognosis of CES patients with NVAF may include metabolic pathways, immune-inflammatory and coagulopathy.(29–31) Liver participate to a variable degree in the acute ischemic stroke, and is responsible for the synthesis and metabolism of blood coagulation factors and fibrinolytic enzymes associated with pathophysiology of stroke.(30, 32) What's more, liver also can

produced enzymes proportional to the injury size, to response signals from cerebral infarction.(32) But whether these mechanisms can also apply to explain our findings referring to subclinical liver fibrosis remain uncertain and requires further studies to verify.

Our finding about sex can modify the relationship of liver fibrosis and the short-time outcomes of CES patients with NVAF, which share a different view of another study.(29) The disagreement might be related to discrepancies in several aspects between these two studies, including different study populations, durations of stroke after onset and timings to assess the outcomes. In Baik's study(29), all types of acute stroke were investigated, and the patients they included with younger age, little atrial fibrillation, and milder function outcome at discharge. Moreover, their follow-up time was over 3 years. Present studies concluded that traditional cardiovascular risk factors varies by sex.(33–35) Women have specific risk factors, including gestational hypertension and pre-eclampsia, gestational diabetes, and placental disorders such as intrauterine growth restriction and stillbirth.(36–38) It is worth noting that females remained an independent poor prognostic factor for CES due to AF, a prospective cohort study revealed the etiological stroke subtypes independently related to unfavorable outcomes at 90 days were CES in women, but large artery atherosclerosis in men. Those seemly suggested that AF affect females more than males in short-term outcome of stroke.(39) So in our study, AF maybe display an important role for the outcomes of females, and liver fibrosis also presented sex difference related to the outcome of CES due to AF, which may be explained for the comorbidity affect patients differently classified by sex(39) and the sex differences in liver function, disease pathogenesis and metabolic genes for maintaining homeostasis in the liver.(40) But this hypothesis still need further studies to verify.

Strengths of our study include the aimed population with strict inclusion criteria, the availability of standardized outcome assessments, and the exclusion of patients with overt liver disease.This is the first study that shows liver fibrosis is associated with stroke severity, outcomes due to NVAF, as well as sex could modify the relationship. It confirms and illustrates the high burden of liver fibrosis in CES patients with NVAF. In our study, almost 90% of subjects with liver fibrosis had normal liver chemistries levels, indicating even through the stroke patients with normal liver enzyme levels also need accept live fibrosis evaluation such as the FIB-4 sore, especially for male patients.

There were several limitations in the present study. First, it shares all the limitation of single-center observational study, so the generalizability of our results may be limited. To minimize the biases caused by an observational study, our study included consecutive patients admitted during the study period thereby. Second, although our use of liver fibrosis indice-FIB-4 is consistent with other studies(41, 42) to observe how liver fibrosis affect other disease processes, but we did not apply advanced liver imaging or liver biopsy to confirm the diagnosis of liver fibrosis in our study population. Third, self-reported alcohol use may have been imprecise.

Conclusion

We concluded that among CES patients with NVAF, liver fibrosis indictor-FIB-4 were associated with admission stroke severity, major disability at discharge, and 90-days mortality despite their liver enzymes ranged normally. When classified by sex, the association was more significant in males but not in females. Our work suggests that new risk assessment and therapeutic targets aimed at liver fibrosis, indicated as FIB-4 in CES may benefit those who with poor outcomes. Moreover, considering the sex discrepancy, different treatment options will be it will be necessary to make different treatment options in order to improve the prognosis in different sex.

Abbreviations

Cardioembolic stroke: CES; Nonvalvular atrial fibrillation: NVAF; Fibrosis-4 score: FIB-4; Atrial fibrillation: AF; Trial of Org 10172 in Acute Stroke Treatment: TOAST; National Institutes of Health Stroke Scale: NIHSS; Glasgow Coma Scale: GCS; modified Rankin Scale: mRS; Body mass index: BMI; Transient ischemic attacks: TIA; N-terminal Pro-B-type Natriuretic Peptide: NT pro-BNP; International normalized ratio: INR; estimated glomerular filtration rate: eGFR; Aspartate aminotransferase: AST; Alanine aminotransferase: ALT; non-alcoholic fatty liver disease: NAFLD

Declarations

Ethics approval and consent to participate

The protocol for the research project has been approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiao Tong University (reference number, VL.0 2018-08-11) and that it conforms to the provisions of the Declaration of Helsinki. All participants gave their written consent for participation in the study.

Consent for publication

All participants gave their written consent for publication of the anonymous data.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Lei Yang, design of the study, acquisition, analysis and interpretation of data, writing the manuscript. Ke Gao, analysis and interpretation of data, revising the manuscript. Xin-Ye Yao, analysis of data, revising the manuscript. Wan-Ying Yang: acquisition of data; Xiao-Rui Huang: revising the manuscript. Ya-Jie Gao: revising the manuscript; Xiao-Pu Zheng: design of the study, interpretation and analysis of data, revising the manuscript.

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Figures

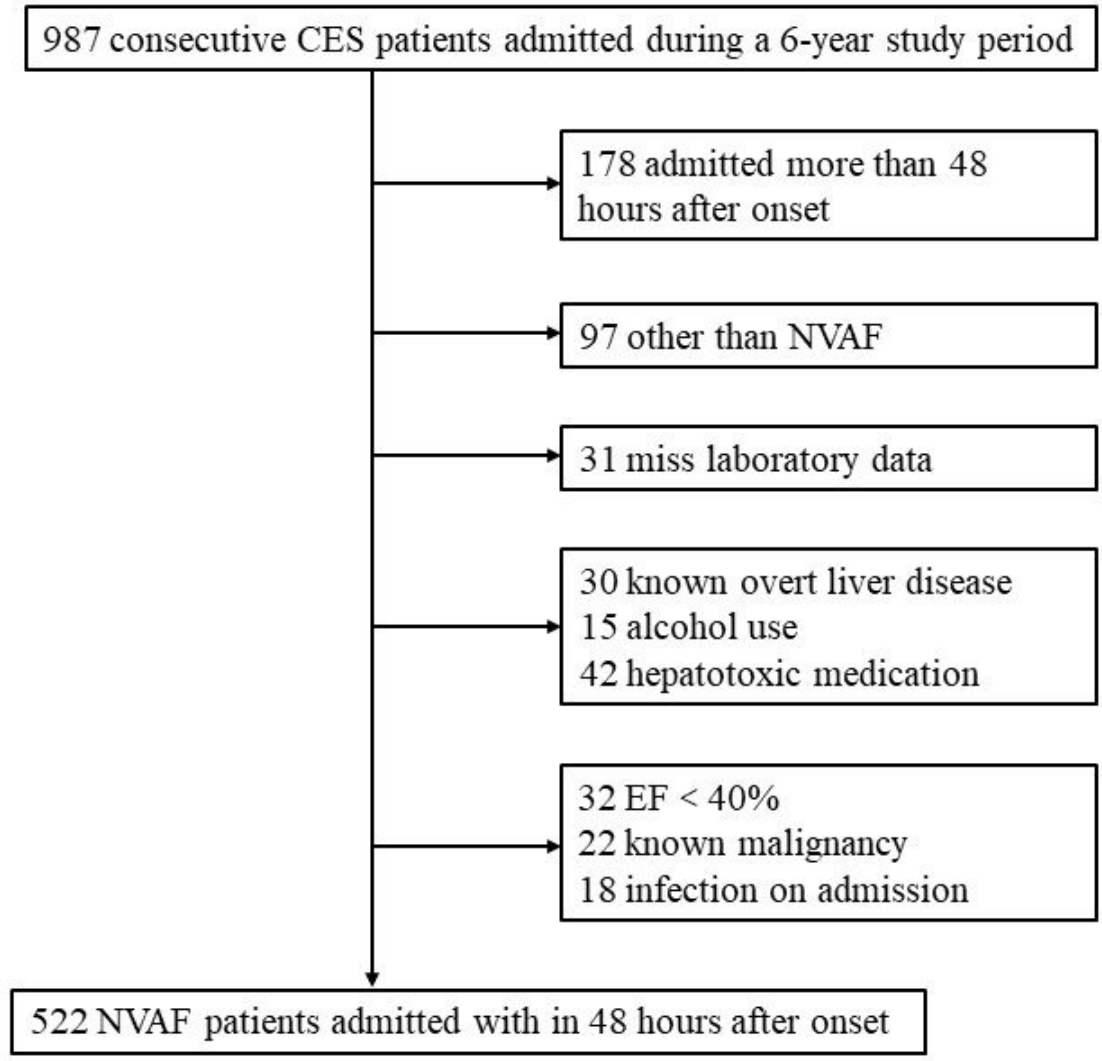

Figure1

Figure 1

Flowchart of the enrollment and analysis of the study population CES, cardioembolic stroke; NVAF, nonvalvular atrial fibrillation; EF, ejection fraction.

Supplementary Files

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