Fibrinogen Level Predicts Prognosis of Patients with Acute Ischemic Stroke or TIA

Huiqing Hou

Beijing Tiantan Hospital <https://orcid.org/0000-0003-0226-968X>

Xianglong Xiang

Beijing Tiantan Hospital

Yuesong Pan

Beijing Tiantan Hospital

Hao Li

Beijing Tiantan Hospital

Xia Meng

Beijing Tiantan Hospital

Yongjun Wang (✉ yongjunwang@ncrcnd.org.cn)

Beijing Tiantan Hospital <https://orcid.org/0000-0002-9976-2341>

Research

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Abstract

Background: Fibrinogen is involved in acute stroke. This study aimed to investigate the association between fibrinogen and prognosis in patients with acute ischemic stroke or transient ischemic attack (TIA).

Methods: Using data from the CNSR-III (Third China National Stroke Registry), this sub-study included 10 518 (69%) consecutive patients who had fibrinogen levels measured. The primary outcome was a poor functional outcome defined as modified Rankin Scale score of 3 to 6 within 90 days. The secondary outcomes were stroke recurrence, ischemic stroke recurrence, composite vascular events, and poor functional outcome during the 1-year follow-up and a new vascular event at 90 days. Multivariate logistic regression and Cox regression analyses were used to assess the associations between fibrinogen and prognosis of patients.

Results: In total, 1446 (13.9%) patients had a poor functional outcome at 90 days. High fibrinogen levels were associated with poor functional outcome (adjusted odds ratio [OR], 1.35; 95% confidence interval [CI], 1.12-1.64) at 90 days after adjustment for confounding risk factors. High fibrinogen levels also independently predicted poor functional outcome during the 1-year follow-up. Stroke recurrence occurred in 657 (6.3%) patients at 90 days. High fibrinogen levels were associated with stroke recurrence, ischemic stroke recurrence, and composite vascular events in the crude model, but further adjustment eliminated these associations in the multivariate models.

Conclusion: Our study showed that high fibrinogen level was independently associated with poor functional outcome but not with stroke recurrence in patients with acute ischemic stroke or TIA.

Background

Acute ischemic stroke and transient ischemic attack (TIA) occur frequently and are major causes of functional disability. Moreover, stroke recurrence within the 90-day follow-up period accounts for 10–15% of these patients [1, 2]. Thus, identifying potential markers associated with prognosis of stroke in addition to traditional risk factors and further developing targeted therapeutics are critical.

Fibrinogen is a pleiotropic protein secreted from the liver that plays critical roles in coagulation, the proinflammatory cascade and the inhibition of tissue repair [3]. Growing data indicate fibrinogen mediates cardiovascular risk through coagulation and inflammatory cascades, which may promote formation of thrombin substrates, platelet aggregation, endothelial activation, and smooth muscle cell proliferation and migration [3, 4]. Several large trials suggested that high fibrinogen level is a risk factor for initial stroke or vascular disease in the general population during long term follow-up period [5–7]. A higher fibrinogen level has been previously observed in patients with acute ischemic stroke [8, 9]. However, the association between fibrinogen and stroke recurrence or a new vascular event is still undefined [10–12]. On the contrary, although the association of high fibrinogen level with death after stroke has been previously expounded [13–15], only a few studies investigated the association between fibrinogen and functional outcome [16–18]. In addition, its predictive value for poor functional outcome after acute stroke is limited and inconsistent [16, 17].

The CNSR-III (Third China National Stroke Registry) is a nationwide, multicenter, prospective registry of patients with acute ischemic stroke or TIA [19]. In this subgroup study, we aimed to evaluate the association of fibrinogen levels with poor functional outcome and stroke recurrence.

Methods

Study Population

The CNSR-III study is a nationwide, consecutive, multicenter, prospective stroke registry that enrolled 15 166 patients with acute ischemic stroke or TIA within 7 days of onset who were treated at 201 hospitals in China from August 2015 to March 2018. Acute ischemic stroke was diagnosed according to the WHO criteria [20] and confirmed by brain computed tomography or magnetic resonance imaging. A subset of 10 518 patients in the CNSR-III study provided blood samples for the measurement of fibrinogen levels. All participating centers used consistent diagnostic criteria and a standard protocol.

Standard protocol approval, registration, and patient consent

The study protocol was approved by the Central Institutional Review Board at the Beijing TianTan Hospital. All participants or their legal proxies provided written informed consent.

Biochemical Measurements

EDTA treated plasma and serum samples were obtained from the CNSR-III patients at the time of enrollment and stored at -80°C. No freeze thaw cycles occurred before testing. The fibrinogen, D-dimer and high-sensitive C-reactive protein (hsCRP) levels were measured (from February 2018 to February 2019) in a center laboratory certified by the College of American Pathologists, and the laboratory personnel were blinded to the clinical data. The plasma fibrinogen and D-dimer levels were analyzed with an OLYMPUS AU2700 analyzer (Beckman, Japan) using an immunoturbidimetric assay (Kamiya Biomedical, Seattle, USA) [21–23], which is a mass-based assay with international standards. The serum hsCRP levels were measured with a Cobas c501 analyzer using a cardiac high-sensitive C-reactive protein (latex) assay (Roche, Basel, Switzerland). All measurements were performed according to the manufacturers' instructions.

Patient Follow-up and Outcome Assessment

The patients were interviewed face to face at 90 days and contacted by telephone at 1 year after enrollment by a trained research coordinator in CNSR-III [19]. Information regarding any end point event, and the functional status was collected at each follow-up interview. Modified Rankin Scale (mRS) scores ranging from 0 to 6 points were used to assess patients' functional dependence.

The primary outcome was poor functional outcome as defined by an mRS score of 3 to 6 at 90 days [24]. The secondary outcomes were stroke recurrence defined as aggravated primary neurological deficit, a new neurological deficit, rehospitalization with a diagnosis of ischemic or hemorrhagic stroke (intracerebral hemorrhage and subarachnoid hemorrhage), ischemic stroke recurrence, composite vascular events (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death), and poor functional outcome during the 1-year follow-up and a new vascular event at 90 days [24, 25].

Statistical Analysis

The baseline characteristics were compared based on the quartiles of the fibrinogen levels using the χ^2 test for the categorical variables and Kruskal–Wallis test for the continuous variables. The fibrinogen levels were examined continuously and as quartiles to investigate their association with the prognosis of ischemic stroke or TIA. The association between the fibrinogen levels and poor functional outcome was estimated using logistic regression models, while the association between the fibrinogen levels and a new vascular event was estimated using Cox proportional hazards models. The potential confounders included demographic factors, prior published clinical risk factors, stroke subtypes, complications during hospitalization, and medications used during hospitalization. All significant covariates with a P value < 0.05 in the univariate analysis were included to the multivariate model. We also evaluated the association between the fibrinogen level and the risk of poor functional outcome using a logistic regression model with restricted cubic splines for fibrinogen levels (continuous measures) that was adjusted for all potential covariates. The 5 knots of the spline were placed at the 5th, 25th, 50th, 75th, and 95th percentiles of the fibrinogen levels, and the first quartile of the fibrinogen level was treated as the reference.

All statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc., Cary, NC). All P values were 2-sided, and $P < 0.05$ was considered indicative of statistical significance.

Results

Patient Characteristics

In total, 15 166 patients with acute ischemic stroke or TIA were enrolled in the CNSR-III study. Among these patients, 4648 patients who did not provide blood samples were excluded. A subset of 10 518 patients constituted the study population for this analysis (Fig. 1).

The baseline characteristics of the 10 518 patients stratified according to the fibrinogen quartiles are shown in Table 1. The mean age was 62.3 ± 11.4 years, and 3283 (31.21%) patients were female. The median fibrinogen level was 378.0 (interquartile range [IQR], 315.0–451.5) mg/dl. The patients with higher fibrinogen levels were significantly older, more likely to be female, had a higher baseline National Institutes of Health Stroke Scale (NIHSS) score, and had a history of hypertension, diabetes mellitus, atrial fibrillation, and ischemic stroke (Table 1).

Table 1
Characteristics of the study population (n = 10 518) by fibrinogen quartiles

Characteristics	All (N = 10 518)	Quartiles of fibrinogen				P Value
		Q1 (N = 2592)	Q2 (N = 2576)	Q3 (N = 2697)	Q4 (N = 2653)*	
Age, mean (SD), y	62.3 ± 11.4	59.8 ± 11.3	61.5 ± 11.5	63.3 ± 11.1	64.4 ± 11.0	< 0.001
Female, n (%)	3283 (31.2)	637 (24.6)	747 (29.0)	890 (33.0)	1009 (38.0)	< 0.001
BMI, median (IQR)	24.5 (22.5–26.5)	24.5 (22.5–26.4)	24.4 (22.5–26.4)	24.4 (22.5–26.5)	24.5 (22.6–26.7)	0.172
Medical history, n (%)						
Hypertension	6573 (62.5)	1536 (59.3)	1568 (60.9)	1670 (61.9)	1799 (67.8)	< 0.001
Diabetes mellitus	2486 (23.6)	505 (19.5)	581 (22.6)	638 (23.7)	762 (28.7)	< 0.001
Dyslipidemia	898 (8.5)	199 (7.7)	193 (7.5)	241 (8.9)	265 (10.0)	0.003
Atrial fibrillation	763 (7.3)	161 (6.2)	164 (6.4)	196 (7.3)	242 (9.1)	< 0.001
Ischemic stroke	2,231 (21.2)	497 (19.2)	551 (21.4)	541 (20.1)	642 (24.2)	< 0.001
TIA	316 (3.0)	78 (3.0)	98 (3.8)	76 (2.8)	64 (2.4)	0.027
Myocardial infarction	228 (2.2)	45 (1.7)	56 (2.2)	56 (2.1)	71 (2.7)	0.132
Angina	411 (3.9)	95 (3.7)	93 (3.6)	96 (3.6)	127 (4.8)	0.062
Venous thrombus	39 (0.4)	11 (0.4)	9 (0.4)	8 (0.3)	11 (0.4)	0.856
Heart failure	75 (0.7)	9 (0.4)	15 (0.6)	19 (0.7)	32 (1.2)	0.002
Smoking, n (%)	3348 (31.8)	968 (37.4)	833 (32.4)	817 (30.3)	730 (27.5)	< 0.001
Drinking, n (%)	1502 (14.3)	446 (17.2)	368 (14.3)	365 (13.4)	323 (12.2)	< 0.001
Baseline NIHSS, median (IQR)	3.0 (1.0–6.0)	3.0 (1.0–5.0)	3.0 (1.0–6.0)	3.0 (1.0–6.0)	4.0 (2.0–7.0)	< 0.001
Time after event within 24 hours, n (%)	7803 (74.2)	1933 (74.6)	1947 (75.6)	1967 (72.9)	1956 (73.7)	0.149
Baseline D-dimer, median (IQR), µg/ml	1.1 (0.6–2.1)	1.1 (0.5–2.2)	1.0 (0.5–1.9)	1.2 (0.6–2.0)	1.2 (0.6–2.3)	< 0.001
Baseline hsCRP, median (IQR), mg/L	1.8 (0.8–4.8)	1.1 (0.6–2.5)	1.3 (0.7–3.1)	2.0 (1.4–7)	4.3 (1.7–12.8)	< 0.001
TOAST subtypes, n (%)						< 0.001
Large artery atherosclerosis	2625 (25.0)	580 (22.4)	630 (24.5)	668 (24.8)	747 (28.2)	
Small artery occlusion	2184 (20.8)	611 (23.6)	547 (21.2)	551 (20.4)	475 (17.9)	
Cardioembolism	685 (6.5)	155 (6.0)	165 (6.4)	163 (6.0)	202 (7.6)	
Other/undetermined	116 (1.1)	27 (1.0)	26 (1.0)	28 (1.0)	35 (1.3)	
Undefined	4908 (46.7)	1219 (47.0)	1208 (46.9)	1287 (47.7)	1194 (45.0)	
Intravenous thrombolysis, n (%)	1080 (10.3)	287 (11.1)	266 (10.3)	279 (10.3)	248 (9.4)	0.232
BMI indicates body mass index (the weight in kilograms divided by the square of the height in meters); hsCRP, high-sensitive C-reactive protein; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.						
*Quartiles of fibrinogen (mg/dl), Q1 < 315.0, Q2 = 315.0–377.9, Q3 = 378.0–451.5, Q4 > 451.5.						

Characteristics	All (N = 10 518)	Quartiles of fibrinogen				<i>P</i> Value
		Q1 (N = 2592)	Q2 (N = 2576)	Q3 (N = 2697)	Q4 (N = 2653)*	
In-hospital antithrombotics, n (%)	10 269 (97.6)	2545 (98.2)	2520 (97.8)	2627 (97.4)	2577 (97.1)	0.063
Complication during hospitalization, n (%)						
Pulmonary infection	582 (5.5)	98 (3.8)	103 (4.0)	145 (5.4)	236 (8.9)	< 0.001
Urinary infection	156 (1.5)	22 (0.9)	28 (1.1)	45 (1.7)	61 (2.3)	< 0.001
Deep vein thrombosis	63 (0.6)	11 (0.4)	12 (0.5)	12 (0.4)	28 (1.1)	0.006
BMI indicates body mass index (the weight in kilograms divided by the square of the height in meters); hsCRP, high-sensitive C-reactive protein; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.						
*Quartiles of fibrinogen (mg/dl), Q1 < 315.0, Q2 = 315.0-377.9, Q3 = 378.0-451.5, Q4 > 451.5.						

Fibrinogen and Poor Functional Outcome

In total, 1446 (13.9%) patients had a poor functional outcome at 90 days. In the quartile analyses, high fibrinogen levels were associated with an increased risk of poor functional outcome (*P* for trend < 0.001) at 90 days (Table 2).

Table 2
Clinical Outcomes

Outcome	Groups*	90-day follow-up			1-year follow-up	
		n	Events, n (%)	P for trend	Events, n (%)	P for trend
mRS score of ≥ 3				< 0.001		< 0.001
	Q1	2560	263 (10.27)		231 (9.15)	
	Q2	2558	295 (11.53)		283 (11.20)	
	Q3	2669	378 (14.16)		366 (13.90)	
	Q4	2601	510 (19.61)		491 (19.13)	
Stroke				0.014		0.002
	Q1	2592	132 (5.09)		212 (8.18)	
	Q2	2576	154 (5.98)		261 (10.13)	
	Q3	2697	185 (6.86)		284 (10.53)	
	Q4	2653	186 (7.01)		285 (10.74)	
Ischemic stroke				0.002		0.002
	Q1	2592	124 (4.78)		195 (7.52)	
	Q2	2576	145 (5.63)		239 (9.28)	
	Q3	2697	168 (6.23)		256 (9.49)	
	Q4	2653	179 (6.75)		267 (10.06)	
Composite events‡				0.001		0.001
	Q1	2592	136 (5.25)		225 (8.68)	
	Q2	2576	160 (6.21)		274 (10.64)	
	Q3	2697	190 (7.04)		298 (11.05)	
	Q4	2653	194 (7.31)		302 (11.38)	
*Quartiles of fibrinogen (mg/dl), Q1 < 315.0, Q2 = 315.0-377.9, Q3 = 378.0-451.5, Q4 > 451.5.						
‡Composite events were composed of ischemic stroke, hemorrhagic stroke, myocardial infarction, and vascular death						

After adjustment for age, sex, histories of hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, ischemic stroke, TIA, and heart failure, baseline National Institutes of Health Stroke Scale score (NIHSS), smoking, drinking, stroke subtypes, D-dimer, hsCRP, and complications during hospitalization, fibrinogen levels in Q3 (378.0-451.5 mg/dl) and Q4 (> 451.5 mg/dl) were associated with poor functional outcome (adjusted odds ratio [OR], 1.28; 95% CI, 1.06–1.55 and adjusted OR, 1.35; 95% CI, 1.12–1.64) compared with a fibrinogen level in Q1 (< 315.0 mg/dl) (Table 3). High fibrinogen levels also independently predicted poor functional outcome during the 1-year follow-up. Similar results were observed when fibrinogen was assessed as a continuous variable (Table 3).

Table 3
Odd ratio/hazard ratio of outcomes according to fibrinogen quartile categories

Outcome (90 days)	Groups*	Unadjusted Model	P Value	Adjusted Model†	P Value	Outcome (1 y)	Groups*	Unadjusted Model	P Value	Adjusted Model‡	P Value
		OR/HR† (95% CI)		OR/HR† (95% CI)				OR/HR† (95% CI)		OR/HR† (95% CI)	
mRS score of ≥ 3						mRS score of ≥ 3					
	Q1	1 (Reference)	...	1 (Reference)	...		Q1	1 (Reference)	...	1 (Reference)	...
	Q2	1.14 (0.96–1.36)	0.149	1.09 (0.89–1.33)	0.413		Q2	1.25 (1.04–1.50)	0.016	1.19 (0.97–1.46)	0.101
	Q3	1.44 (1.22–1.70)	< 0.001	1.28 (1.06–1.55)	0.012		Q3	1.60 (1.35–1.91)	< 0.001	1.36 (1.12–1.66)	0.002
	Q4	2.13 (1.82–2.50)	< 0.001	1.35 (1.12–1.64)	0.002		Q4	2.35 (1.99–2.78)	< 0.001	1.42 (1.16–1.73)	0.001
	Continuous model	6.86 (4.60–10.25)	< 0.001	1.95 (1.26–3.03)	0.003		Continuous model	8.95 (5.91–13.55)	< 0.001	2.14 (1.36–3.37)	0.001
Stroke						Stroke					
	Q1	1 (Reference)	...	1 (Reference)	...		Q1	1 (Reference)	...	1 (Reference)	...
	Q2	1.18 (0.93–1.48)	0.171	1.12 (0.88–1.41)	0.369		Q2	1.25 (1.04–1.49)	0.017	1.15 (0.95–1.38)	0.142
	Q3	1.35 (1.08–1.69)	0.008	1.23 (0.97–1.54)	0.083		Q3	1.31 (1.09–1.56)	0.003	1.18 (0.98–1.42)	0.073
	Q4	1.39 (1.11–1.74)	0.004	1.11 (0.87–1.40)	0.399		Q4	1.35 (1.13–1.61)	0.001	1.07 (0.89–1.30)	0.461
	Continuous model	1.82 (1.09–3.02)	0.022	1.11 (0.67–1.82)	0.686		Continuous model	1.63 (1.09–2.42)	0.017	1.06 (0.72–1.58)	0.758
Ischemic stroke						Ischemic stroke					
	Q1	1 (Reference)	...	1 (Reference)	...		Q1	1 (Reference)	...	1 (Reference)	...
	Q2	1.18 (0.93–1.50)	0.177	1.11 (0.87–1.42)	0.390		Q2	1.24 (1.03–1.50)	0.025	1.14 (0.94–1.38)	0.188
	Q3	1.31 (1.04–1.65)	0.024	1.17 (0.92–1.49)	0.195		Q3	1.28 (1.06–1.54)	0.011	1.14 (0.94–1.38)	0.175
	Q4	1.43 (1.13–1.79)	0.002	1.13 (0.89–1.44)	0.331		Q4	1.37 (1.14–1.65)	0.001	1.08 (0.89–1.31)	0.443

CI indicates confidence interval; HR, hazard ratio; and OR, odd ratio.

* Quartiles of fibrinogen (mg/dl), Q1 < 315.0, Q2 = 315.0–377.9, Q3 = 378.0–451.5, Q4 > 451.5.

†OR for poor functional outcome, while HR for stroke recurrence, ischemic stroke recurrence, and composite events.

‡Adjusted for age, sex, histories of hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, ischemic stroke, transient ischemic attack, and heart failure, baseline National Institutes of Health Stroke Scale score, smoking, drinking, stroke subtypes, baseline D-dimer, baseline hsCRP, pulmonary infection, urinary infection, and deep vein thrombosis during hospitalization

§Composite events were composed of ischemic stroke, hemorrhagic stroke, myocardial infarction, and vascular death

Outcome (90 days)	Groups*	Unadjusted Model	P Value	Adjusted Model†	P Value	Outcome (1 y)	Groups*	Unadjusted Model	P Value	Adjusted Model†	P Value
		OR/HR‡ (95% CI)		OR/HR‡ (95% CI)				OR/HR‡ (95% CI)		OR/HR‡ (95% CI)	
Continuous model		1.88 (1.11– 3.19)	0.019	1.13 (0.68– 1.90)	0.637	Continuous model		1.65 (1.09– 2.51)	0.018	1.05 (0.70– 1.58)	0.812
Composite events§						Composite events§					
	Q1	1 (Reference)	...	1 (Reference)	...		Q1	1 (Reference)	...	1 (Reference)	...
	Q2	1.19 (0.94– 1.49)	0.171	1.13 (0.89– 1.42)	0.323		Q2	1.23 (1.03– 1.47)	0.020	1.14 (0.95– 1.36)	0.163
	Q3	1.35 (1.08– 1.68)	0.008	1.22 (0.97– 1.53)	0.086		Q3	1.29 (1.09– 1.54)	0.004	1.16 (0.98– 1.39)	0.093
	Q4	1.41 (1.13– 1.75)	0.002	1.11 (0.88– 1.40)	0.388		Q4	1.35 (1.13– 1.60)	0.001	1.05 (0.87– 1.26)	0.616
Continuous model		1.90 (1.15– 3.13)	0.013	1.12 (0.68– 1.82)	0.662	Continuous model		1.66 (1.13– 2.45)	0.011	1.03 (0.71– 1.51)	0.871
CI indicates confidence interval; HR, hazard ratio; and OR, odd ratio.											
* Quartiles of fibrinogen (mg/dl), Q1 < 315.0, Q2 = 315.0–377.9, Q3 = 378.0–451.5, Q4 > 451.5.											
†OR for poor functional outcome, while HR for stroke recurrence, ischemic stroke recurrence, and composite events.											
‡Adjusted for age, sex, histories of hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, ischemic stroke, transient ischemic attack, and heart failure, baseline National Institutes of Health Stroke Scale score, smoking, drinking, stroke subtypes, baseline D-dimer, baseline hsCRP, pulmonary infection, urinary infection, and deep vein thrombosis during hospitalization											
§Composite events were composed of ischemic stroke, hemorrhagic stroke, myocardial infarction, and vascular death											

Using a regression model with a restricted cubic spline, we observed an association between high fibrinogen levels and an increased risk of poor functional outcome at 90 days and 1 year (Fig. 2).

Fibrinogen and Stroke Recurrence

There were 657 (6.3%) patients with stroke recurrence within 90 days. In the quartile analyses, high fibrinogen levels were significantly associated with an increased risk of 90-day stroke recurrence, ischemic stroke recurrence, and composite vascular events (P for trend = 0.014, = 0.002, and = 0.001, respectively) (Table 2). After adjustment for confounding risk factors, these associations were no longer significant (Table 3). Furthermore, fibrinogen levels were not associated with a new vascular disease during the 1-year follow-up. Similar results were observed when fibrinogen was assessed as a continuous variable (Table 3).

Discussions

In this prospective hospital-based nationwide stroke registry in China, we found that high fibrinogen levels were associated with increased risks of short-term and long-term poor functional outcome, but not stroke recurrence, ischemic stroke recurrence, and composite vascular events in patients with acute ischemic stroke or TIA.

Although previous studies confirmed that a high fibrinogen level was associated with first-ever cardiovascular disease [5, 6], the association between fibrinogen and ischemic stroke is contradictory. A large meta-analysis involving 154 211 participants proved that moderately strong associations were found between plasma fibrinogen and the risk of first stroke in healthy middle-aged adults [26]. However, subsequent studies investigating the association between fibrinogen and initial ischemic stroke showed inconsistent results [7, 27–29]. In contrast, only a few studies indicated that fibrinogen level was associated with stroke recurrence in recent TIA or minor ischemic stroke [12, 30]. A preliminary study showed that fibrinogen combined with tissue-type plasminogen activator and von Willebrand factor was associated with coronary events, but not stroke recurrence among patients with recent TIA or ischemic stroke [31]. In addition, previous studies have indicated that the association

between fibrinogen and a new vascular event was no longer significant after adjustment for confounding risk factors in patients with acute stroke [10, 11]. On the contrary, the association between fibrinogen and poor functional outcome is less established. It was previously suggested that fibrinogen was associated with poor functional outcome after adjusted simple risk factors, but further adjustment for potential factors eliminated this association [32]. Previous studies suggested that patients with lower initial fibrinogen levels had good functional outcome after acute stroke, indicating that the independent association between fibrinogen levels and functional outcomes need to be verified using a larger acute stroke dataset [16]. In the present study, the associations of fibrinogen with poor functional outcome and stroke recurrence were assessed based on a large-scale stroke registry study in China. Furthermore, D-dimer, hsCRP, and complications during hospitalization were considered in addition to the baseline NIHSS score and stroke subtype according to the Trial of Org 10172 in Acute Stroke Treatment.

In our analysis, high fibrinogen levels were associated with an increased risk of poor functional outcome. This association was independent of the stroke severity, stroke subtype, complications, D-dimer, and hsCRP. Our findings indicate that this association might depend on other potential mechanisms of fibrinogen. One possible explanation is that high fibrinogen level may affect the structure of the fibrin clot. Previous studies have suggested that high fibrinogen levels might be related to the formation of more stable fibrin clots, which determine the efficacy of arterial recanalization [33]. Another potential explanation is that high fibrinogen levels cause high blood viscosity, which could potentially compromise the microvascular blood flow in marginally perfused brain areas [16]. An additional explanation is that fibrinogen plays a critical role in interfering with tissue repair [3]. Blood–brain barrier permeability increases after ischemia and reperfusion [34], and fibrinogen enters the brain tissue, thus participating in acute tissue necrosis and causing secondary tissue damage [35, 36]. Based on our findings, high fibrinogen levels independently predict poor functional outcome, which suggest that fibrinogen might be a targeted therapeutic after acute ischemic stroke or TIA.

Consistent with previous studies, we observed no association between fibrinogen and a new vascular event in the multivariate model [11]. Potential explanation might be that fibrinogen levels were associated with other risk factors. Although fibrinogen is the most common hemostatic factor, its role in the development of atherosclerosis and vascular disease extends to a key proinflammatory player [3]. The Canakinumab Antiinflammatory Thrombosis Outcome Study showed that antiinflammatory therapy led to the reduction in hsCRP and fibrinogen, indicating that fibrinogen had potentially plays dual roles as both an acute-phase reactant and a mediator of coagulation [37]. Previous studies proved that there was a strong association between fibrinogen and hsCRP [10]. In addition, it has been suggested that hsCRP was more related to the risk of new cardiovascular events after acute ischemic stroke than fibrinogen [11]. Therefore, our findings suggest that fibrinogen might be involved in stroke recurrence through other critical risk factors.

Our study has several limitations. First, our study only included the D-dimer and hsCRP levels in addition to the fibrinogen levels, while other related coagulation or inflammatory factors may also be associated with stroke outcomes. Future studies focusing on the coagulation or inflammatory pathway could help to reveal the molecular mechanism underlying stroke outcomes. Second, this study obtained one-point fibrinogen measurements. Since fibrinogen levels persistently increase from the acute phase to the stable phase in patients after stroke [8, 9], dynamic change might be necessary to confirm its predictive value. Third, 4648 (30.6%) of the 15166 patients did not provide blood samples and were excluded because their fibrinogen levels were not measured. Although the baseline characteristics of the patients included and those excluded were well balanced, some deviation in the analysis of the associations between the fibrinogen levels and outcomes may exist. Finally, all enrolled patients were Chinese adults with acute ischemic stroke or TIA, and these results may not be generalizable to patients of other ethnicities.

Conclusions

In conclusion, our study show that high fibrinogen levels were associated with poor functional outcome, but not with stroke recurrence, ischemic stroke recurrence, or composite vascular events.

Abbreviations

BMI: Body mass index (the weight in kilograms divided by the square of the height in meters); CI: Confidence interval; CNSR: Third China National Stroke Registry; HR: Hazard ratio; hsCRP: High-sensitive C-reactive protein; IQR: Interquartile range; NIHSS: National Institutes of Health Stroke Scale; OR: Odd ratio; TIA: Transient ischemic attack; TOAST: Trial of Org 10172 in Acute Stroke Treatment.

Declarations

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Authors' contributions

YW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: YW, HH, WL, QZ and XM. Drafting of the manuscript: YW and HH. Statistical analysis: XX, YP and HL.

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Availability of data and materials

The corresponding author takes full responsibility for the data, the analyses and interpretation, and the conduct of the research; that he has full access to all of the data.

Ethics approval and consent to participate

The study protocol was approved by the Central Institutional Review Board at the Beijing TianTan Hospital. All participants or their legal proxies provided written informed consent.

Consent for publication

Not applicable.

Competing interests

None declared.

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Figures

Figure 1

Flow chart for the cohort selection process. CNSR, the Third China National Stroke Registry; mRS, modified Rankin Scale.

Figure 2

Adjusted ORs of poor functional outcome in patients stratified according to fibrinogen levels. (A) at 90 days and (B) at 1 year. The solid line indicates adjusted ORs and the dashed lines indicate the 95% CI bands. The reference is the first quartile of fibrinogen levels (315.0 mg/dl). The vertical dashed lines indicate the first, second, and third quartiles of fibrinogen levels. The data from the lowest 5% and highest 5% of patients are not shown.