Original Article

Elevated high-sensitivity C-reactive protein levels predict poor outcomes among patients with acute cardioembolic stroke

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Background: High-sensitivity C-reactive protein (hs-CRP) as a prognostic factor of stroke has been proposed and studied. However, the relationship between hs-CRP levels and outcomes among patients with cardioembolic stroke (CES) remains unclear. This study aimed to evaluate the association between hs-CRP levels in the acute phase of CES and poor patient outcomes.

Methods: We recruited 478 patients with first-onset CES. Hs-CRP and other biochemical markers were measured within 24 h after admission. Hs-CRP levels were grouped into quartiles (<2.31, 2.31 to <6.09, 6.09 to <22.30, and ≥22.30 mg/L). Stroke severity was assessed using the modified Rankin scale (mRS), with mRS scores of 0 to 2 classified as a good outcome, and scores of 3 to 6 as a poor outcome. Composite endpoints included poor outcomes, vascular death, myocardial infarction (MI), and recurrent stroke (ischemic or hemorrhagic). At 3-month and 1-year follow-ups, we used multivariate logistic regression analysis to assess the relationship between baseline hs-CRP levels, mRS scores, and composite endpoints.

Results: Among 478 patients with CES, the median hs-CRP level was 6.09 mg/L. Regarding the primary outcome, we found that hs-CRP levels ≥22.30 mg/L were positively correlated with poor outcomes at the 3-month and 1-year follow-ups [odds ratio (OR): 3.862, 95% confidence interval (CI): (1.675–8.904), P=0.002; and OR: 5.479, 95% CI: (1.692–17.744), P=0.005, respectively]. The secondary outcomes paralleled the results of the primary outcomes at the 3-month and 1-year follow-ups [OR: 3.381, 95% CI: (1.620–7.058), P=0.001; and OR: 3.181, 95% CI: (1.475–6.860), P=0.003, respectively].

Conclusions: Elevated hs-CRP in patients with CES is an independent predictor of poor outcomes; however, this association is particularly evident when hs-CRP ≥22.30 mg/L.

Keywords: Cardioembolic stroke (CES); high-sensitivity C-reactive protein (hs-CRP); outcome; predictor; stroke

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Introduction

Cardioembolic stroke (CES) is a severe subtype of cerebral infarction, accounting for 20% of cerebral infarctions (1). This condition is characterized by high in-hospital mortality rates (27.3%) (2), neurological deficits at hospital discharge, and a high risk of stroke recurrence (26%) (3). However, the prognostic indicators for patients with CES remain unclear. Acute strokes may trigger an inflammatory response, leading to elevated C-reactive protein (CRP) levels (4), which may be associated with poor prognosis as they reflect inflammation or tissue damage (5). Therefore,

CRP is a potential predictor of future cardiovascular and cerebrovascular events and prognostic markers after the event. However, compared with CRP, high-sensitivity CRP (hs-CRP) can be measured quantitatively and accurately detect low-level inflammation (6), and it can reflect minute changes in inflammation better than CRP can. Hs-CRP also has greater clinical significance in evaluating the relationship between acute inflammation and prognosis (7). Also, hs-CRP is more widely used in clinical practice, especially in the risk stratification of cardiovascular disease (CVD) (8) and stroke (9). To further clarify the role of hs-CRP in CES, we assessed hs-CRP levels as a predictor of CES prognosis. Therefore, the purpose of our study was to analyze the association between hs-CRP levels in the acute phase of CES and its outcomes.

Methods

Ethics

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Tianjin Huanhu Hospital (No. 2005012) and informed consent was taken from all individual participants.

Patient selection

We retrospectively analyzed the clinical biochemical indexes and outcomes of all patients with first ischemic stroke in the Department of Neurology of Tianjin Huanhu Hospital within 72 h after stroke onset from May 1, 2005 to December 31, 2015. Patients with thrombolysis or mechanical thrombectomy, concomitant infection, abnormal liver and kidney function, or cardiac insufficiency were not included in the study; thus, data from 9,746 patients were analyzed. Among them, there were 8,970 patients with non-CES, 776 patients with CES, and 298 patients with no data on hs-CRP levels on admission. Finally, 478 patients were included in our study.

All participants were screened according to rigorous procedures and treated according to current guidelines. A spreadsheet was used to collect and extract detailed baseline data, which included a complete medical history (100%), complete medication history (100%), complete neurological examination (100%), standard biochemical blood test (100%), head CT (100%), head MRI (89.7%), head CTA (10.9%), head MRA (26.4%), 12-lead electrocardiogram (100%), standard 12-lead dynamic electrocardiogram (61.9%), transthoracic echocardiography (100%), microemboli monitoring (13%), carotid ultrasound (100%), and transcranial Doppler ultrasound (100%).

Diagnostic criteria of CES

TOAST subtype classification, the most widely used classification of ischemic stroke, organizes ischemic stroke into five etiological subtypes (10), which include CES. Stroke classification was performed by two senior neurologists. The diagnostic criteria for CES were as follows (10): (I) symptoms appear as cortical or cerebellar dysfunction rather than lacunar syndrome; (II) infarct size (cortical, cerebellar, brain stem, or subcortical) is confirmed to be >1.5 cm through imaging (head CT and/or MRI); (III) identification of a recognized source of cardiac emboli; and (IV) no clinical evidence of extracranial internal carotid artery stenosis.

Hs-CRP and clinical assessment

Blood samples were withdrawn from all participants in the fasting state within 24 h of admission. Serum hs-CRP assays were measured using immunoturbidimetric assays. We analyzed all variables in an accredited central laboratory. Hs-CRP levels were classified according to quartiles (<2.31, 2.31 to <6.09, 6.09 to <22.30, and ≥22.30 mg/L). The basic demographic information of each patient was recorded at admission. Biochemical indicators, such as cholesterol and hemoglobin A1c (HbA1c), were recorded in the spreadsheets. The variables of interest are defined in the following section. Hypertension was defined as having a history of hypertension, having used any antihypertensive drug, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg (11). Diabetes was defined as having a history of diabetes, or having used any glucose-lowering drugs, or having a fasting glucose level of >126 mg/dL (12). Dyslipidemia was defined as having a history of dyslipidemia, having used any lipid-lowering drug, or having total cholesterol (TC) levels ≥200 mg/dL, triglycerides (TG) levels ≥150 mg/dL, high-density lipoprotein cholesterol (HDL-C) levels ≤40 mg/dL, and low-density lipoprotein cholesterol (LDL-C) levels ≥130 mg/dL (13). Current smokers were defined as those who had been smoking daily for more than 1 year. Current drinkers were defined as those who had been drinking at least once a week for more than a year. Obesity was

defined as a body mass index of ≥30 kg/m^2 (14) measured at admission. All patients obtained an index of severity on the National Institute of Health Stroke Scale (NIHSS) on admission.

Follow-up

We followed up all patients with face-to-face interviews or telephone calls at 3 months and 1 year after stroke and recorded the results in the stroke database. One week before the deadline, we called the patients or their authorized agents to remind them about the review and to set up a follow-up appointment. Most patients were assessed through outpatient services, while others who refused to go to the hospital were assessed through telephone interviews. We reclassified stroke subtypes at follow-up to ensure accurate diagnosis, and the subtype of stroke did not change during follow-up.

Study outcome

Stroke severity was assessed using the modified Rankin scale (mRS), with mRS scores of 0 to 2 classified as a good outcome, and scores of 3 to 6 as a poor outcome (15,16). Composite endpoints included poor outcomes, vascular death, myocardial infarction (MI), and recurrent stroke (ischemic or hemorrhagic). The primary outcome was determined by separating patients into two groups according to the mRS score. The secondary outcome was based on dividing patients into good outcomes and composite endpoints (17,18).

Statistical analysis

Continuous variables were presented as median (25th, 75th percentiles). The Kruskal-Wallis test or Mann-Whitney U-test was used to evaluate the significance of intergroup differences. Categorical variables were presented as counts and percentages. The chi-square test was used to analyze differences between groups. Confounder variables identified as significant in the univariate analyses (P<0.05) were entered into logistic regression analyses to determine the association between hs-CRP levels and outcomes, and results were presented as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). P<0.05 was considered statistically significant. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 24.0).

Results

Detailed demographic and baseline data

The detailed demographic and baseline data are presented in *Table 1*. A total of 478 CES patients [270 men (56.5%); median age: 71 years] were enrolled in our study. There were 398 patients with atrial fibrillation (chronic: 288 cases, paroxysmal: 82 cases, persistent: 28 cases) and four patients with atrial flutter. The patients with higher hs-CRP levels were mostly male and elderly, compared with those with lower hs-CRP levels (P<0.05). While obesity differed across the four groups, there was no significant trend. Hypertension, diabetes, dyslipidemia, smoking, alcohol consumption, and HbA1c were evenly distributed in the four groups. There were statistically significant differences in hs-CRP levels and NIHSS scores at admission among the four groups, whereby higher hs-CRP levels corresponded to a higher NIHSS score (P<0.001). Furthermore, the NIHSS score at discharge was also positively correlated with baseline CRP levels (P<0.001). Details are provided in *Table 1*.

Results at 3-month follow-up

At the 3-month follow-up, 75 patients had experienced vascular death, MI, and recurrent stroke (ischemic or hemorrhagic), and were included in the composite endpoint event. Thirty-three patients died due to other reasons, and one patient did not attend the follow-up review. Therefore, data from 444 patients were analyzed (*Figure 1*). Univariate analyses demonstrated that age, sex, hs-CRP, and NIHSS scores were associated with poor outcomes (*Table 2*). After adjusting for confounding factors such as diabetes, hypertension, dyslipidemia, alcohol consumption, smoking, obesity, and HbA1c, the primary outcomes in only the fourth quartile of hs-CRP (hs-CRP ≥22.30 mg/L) and NIHSS scores were associated with poor outcomes [OR: 3.862, 95% CI: (1.675–8.904), P=0.00; and OR: 5.438, 95% CI: (3.619–8.172), P<0.001, respectively] (*Figure 2*, model 1). The secondary outcomes were similar to the primary outcomes: the fourth quartile of hs-CRP (≥22.30 mg/L) and NIHSS scores had a significant tendency to increase the risk of composite endpoints [fourth quartile of hs-CRP: OR: 3.381, 95% CI: (1.620–7.058), P=0.001 and NIHSS score: OR: 4.246, 95% CI: (3.015–5.978), P<0.001] (*Figure 2*, model 2). There was a significant difference in outcomes among patients grouped by hs-CRP quartile at 3-month follow-up, with higher levels of hs-CRP

Table 1 Baseline demographics and clinical characteristics according to CRP groups

Factors	Quartile of CRP, mg/L				P
	<2.31 (n=119)	2.31 to <6.09 (n=120)	6.09 to <22.30 (n=119)	≥22.30 (n=120)	
Age, years (media, 25th percentile, 75th percentile)	66 (60.0, 75.0)	68 (59.3, 75.8)	73 (65.0, 77.0)	73 (66.0, 78.0)	<0.001
Male sex, n (%)	74 (62.2)	63 (52.5)	56 (47.1)	77 (64.2)	0.023
Risk factors					
Hypertension, n (%)	66 (55.5)	79 (65.8)	74 (62.2)	76 (63.3)	0.396
Diabetes, n (%)	28 (23.5)	26 (21.7)	27 (22.7)	28 (23.3)	0.986
Dyslipidemia, n (%)	25 (21.0)	36 (30.0)	25 (21.0)	23 (19.2)	0.182
Smokers, n (%)	30 (25.2)	37 (30.8)	26 (21.8)	41 (34.2)	0.143
Alcohol drinkers, n (%)	12 (10.1)	15 (12.5)	7 (5.9)	10 (8.3)	0.341
Obesity, n (%)	6 (5.0)	26 (21.7)	17 (14.3)	12 (10.0)	0.001
hs-CRP, mg/L (media, 25th percentile, 75th percentile)	1.1 (0.7, 1.6)	4.3 (3.0, 5.0)	10.1 (8.2, 16.7)	44.1 (29.8, 72.2)	<0.001
HbA1c, % (media, 25th percentile, 75th percentile)	6.2 (5.8, 7.0)	6.4 (5.8, 7.2)	6.0 (5.8, 6.5)	5.9 (5.7, 6.7)	0.388
NIHSS (on admission), n (%)					<0.001
0–6	79 (66.4)	31 (25.8)	18 (15.1)	14 (11.7)	
7–15	27 (22.7)	63 (52.5)	46 (38.7)	33 (27.5)	
≥16	13 (10.9)	26 (21.7)	55 (46.2)	73 (60.8)	
NIHSS (at discharge), n (%)					<0.001
0–6	93 (78.2)	40 (33.3)	15 (12.6)	17 (14.2)	
7–15	14 (11.7)	57 (47.5)	62 (52.1)	31 (25.8)	
≥16	12 (10.1)	23 (19.2)	42 (35.3)	72 (60.0)	

hs-CRP, high-sensitivity C-reactive protein; HbA1c, hemoglobin A1c; NIHSS, National Institute of Health Stroke Scale.

(≥22.30 mg/L) being significantly correlated with a poor outcome and composite endpoints after adjusting for confounders (*Figure 2*).

Results at 1-year follow-up

At the 1-year follow-up, 141 patients had vascular death, MI, and recurrent stroke (ischemic or hemorrhagic), and were included in the composite endpoint event. Fourteen patients died due to other reasons, and 35 patients did not attend the follow-up. Finally, data from 395 patients were analyzed (*Figure 1*). Univariate analyses demonstrated that age, sex, hs-CRP, and NIHSS scores were associated with poor outcomes (*Table 2*). After adjusting for confounding factors, such as diabetes, hypertension, dyslipidemia, alcohol consumption, smoking, obesity, and HbA1c, the three higher quartiles of hs-CRP and NIHSS scores were associated with poor outcomes for the primary endpoint (P=0.043, P=0.049, P=0.005, and P<0.001, respectively) (*Figure 2*, model 3). Furthermore, the fourth quartile of hs-CRP (≥22.30 mg/L) was significantly associated with poor outcomes [OR: 5.479, 95% CI: (1.692–17.744), P=0.005] in the multivariate analysis (*Figure 2*, model 3). Regarding the secondary outcome, the fourth quartile of hs-CRP (≥22.30 mg/L) and NIHSS scores were positively correlated with the composite endpoints (OR: 3.181, 95% CI: (1.475–6.860), P=0.003; and OR: 3.416, 95% CI: (2.407–4.848), P<0.001, respectively) (*Figure 2*, model 4). At the 1-year follow-up, higher hs-CRP levels (≥22.30 mg/L) had a significant correlation with poor

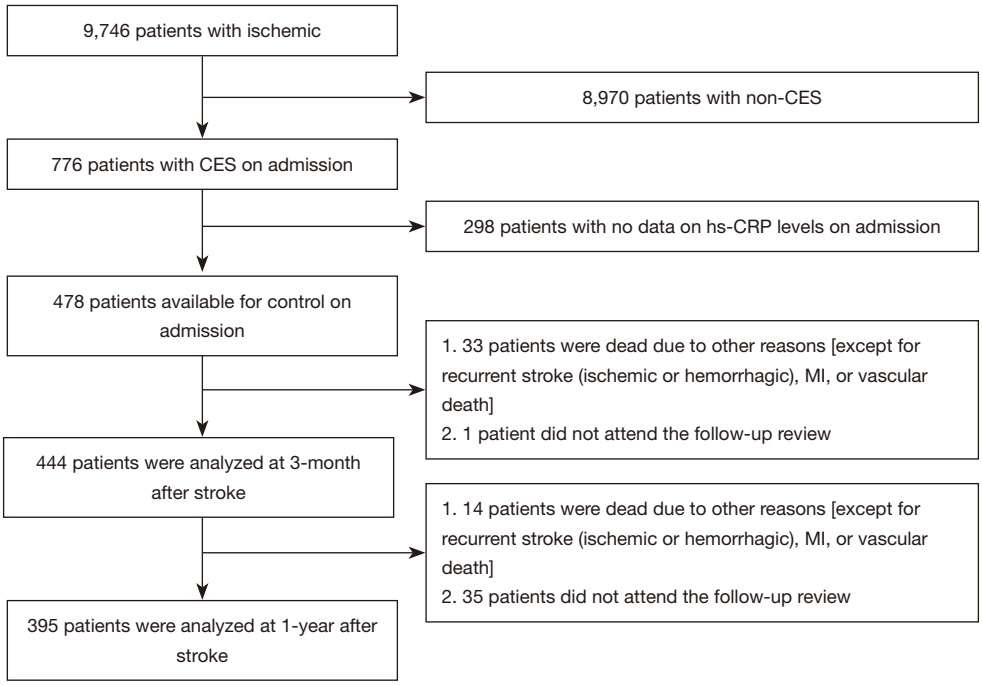

Figure 1 Flow chart of patient selection. CES, cardioembolic stroke; hs-CRP, high-sensitivity C-reactive protein; MI, myocardial infarction.

outcomes and composite endpoints.

Discussion

In our study, patients with higher hs-CRP levels were mostly elderly (P<0.001), and a previous study found that people over 56 had significantly higher CRP levels, but this only applied to healthy women (19). This is consistent with our findings. However, studies with other groups have not been reported. In the current study, CES accounted for 7.96% of ischemic strokes, which was significantly lower than that in China (about 10%) (20). The main possible reason for this is the exclusion of thrombolytic patients from our study population. Second, the average age of our study population, 71 years, was low, and CES is the most common stroke subtype in the elderly (21).

In the present study, the median hs-CRP was 6.09 mg/L, which was quite higher than what was observed in our previous studies on small-artery occlusion (1.54 mg/L) and large-artery arteriosclerosis (2.49 mg/L) (16,22). Several other studies also found higher plasma CRP levels in patients with CES than in other TOAST subtypes (23,24), and den Hertog *et al.* (5) reported that CES was more often observed in patients with CRP ≥7 mg/L. There are several potential mechanisms underlying this increased CRP in patients with CES. First, CRP is generally elevated in patients with cardiac disease (25), especially in patients with atrial fibrillation (26), which is one of the major causes of CES (27). This might explain the pre-stroke and elevated baseline CRP levels in CES. Second, in the acute phase of cerebral infarction, the extent of brain injury and blood-brain barrier (BBB) disruption may determine the degree of acute-phase inflammatory response. It has been confirmed that the degree of BBB destruction in CES patients is more serious than that in patients with other stroke subtypes (28), and this could be related to CRP levels (29). While these mechanisms may play a role in the increased CRP we observed, two studies have reported no differences in CRP levels among stroke subtypes (30,31). These conflicting results may be related to differences in the race, age, or gender of the subjects (32,33).

In this study, regarding the primary outcome, we concluded that elevated hs-CRP levels in acute CES patients can predict poor functional outcomes at 3 months and 1 year post-stroke; however, this association was only evident in the fourth quartile of hs-CRP (≥22.30 mg/L). Inflammation plays a critical role not only in the pathogenesis of stroke, but also in the deterioration following the stroke. Previous studies have found that increased CRP levels can predict the risk of poor prognosis

Table 2 Comparison of the risk factors between different groups classified by outcomes

Factors	3 m						1 y					
	mRS ≤2 (n=207)	mRS ≥3 (n=162)	P value	mRS ≤2 (n=207)	Composite endpoints (n=237)	P value	mRS ≤2 (n=170)	mRS ≥3 (n=84)	P value	mRS ≤2 (n=170)	Composite endpoints (n=225)	P value
Age, years (media, 25th percentile, 75th percentile)	67 (60.0, 75.0)	72 (63.0, 77.0)	0.005	67 (60.0, 75.0)	72 (64.0, 77.0)	0.001	65.5 (57.0, 74.3)	71 (64.0, 76.0)	0.004	65.5 (57.0, 74.3)	72 (64.0, 77.0)	<0.001
Male sex, n (%)	130 (62.8)	82 (50.6)	0.019	130 (62.8)	120 (50.6)	0.010	112 (65.9)	39 (46.4)	0.003	112 (65.9)	114 (50.7)	0.002
Hypertension, n (%)	126 (60.9)	98 (60.5)	0.942	126 (60.9)	150 (63.3)	0.600	96 (56.5)	45 (53.6)	0.662	96 (56.5)	139 (61.8)	0.287
Diabetes, n (%)	44 (21.3)	40 (24.7)	0.435	44 (21.3)	55 (23.2)	0.622	37 (21.8)	23 (27.4)	0.321	37 (21.8)	48 (21.3)	0.918
Dyslipidemia, n (%)	47 (22.7)	35 (21.6)	0.801	47 (22.7)	55 (23.2)	0.900	40 (23.5)	21 (25.0)	0.796	40 (23.5)	52 (23.1)	0.922
Smokers, n (%)	63 (30.4)	42 (25.9)	0.341	63 (30.4)	67 (28.3)	0.617	47 (27.6)	20 (23.8)	0.514	47 (27.6)	68 (30.2)	0.577
Alcohol drinkers, n (%)	19 (9.2)	18 (11.1)	0.540	19 (9.2)	25 (10.5)	0.630	17 (10.0)	10 (11.9)	0.643	17 (10.0)	19 (8.4)	0.595
Obesity, n (%)	24 (11.6)	22 (13.6)	0.567	24 (11.6)	34 (14.3)	0.391	18 (10.6)	10 (11.9)	0.753	18 (10.6)	33 (14.7)	0.231
hs-CRP, n (%)			<0.001			<0.001			<0.001			<0.001
<2.31	86 (41.5)	20 (12.3)		86 (41.5)	30 (12.7)		75 (44.1)	8 (9.5)		75 (44.1)	33 (14.7)	
≥2.31	57 (27.5)	38 (23.5)		57 (27.5)	58 (24.5)		43 (25.3)	18 (21.4)		43 (25.3)	53 (23.6)	
≥6.09	41 (19.8)	46 (28.4)		41 (19.8)	69 (29.1)		34 (20.0)	29 (34.5)		34 (20.0)	67 (29.8)	
≥22.30	23 (11.1)	58 (35.8)		23 (11.1)	80 (33.8)		18 (10.6)	29 (34.5)		18 (10.6)	72 (32.0)	
NIHSS (on admission), n (%)			<0.001			<0.001			<0.001			<0.001
0–6	110 (53.1)	14 (8.6)		110 (53.1)	29 (12.2)		91 (53.5)	4 (4.8)		91 (53.5)	36 (16.0)	
7–15	81 (39.1)	57 (35.2)		81 (39.1)	79 (33.3)		66 (38.8)	26 (31.0)		66 (38.8)	71 (31.6)	
≥16	16 (7.7)	91 (56.2)		16 (7.7)	129 (54.4)		13 (7.6)	54 (64.3)		13 (7.6)	118 (52.4)	

mRS, modified Rankin scale; hs-CRP, high-sensitivity C-reactive protein; NIHSS, National Institute of Health Stroke Scale.

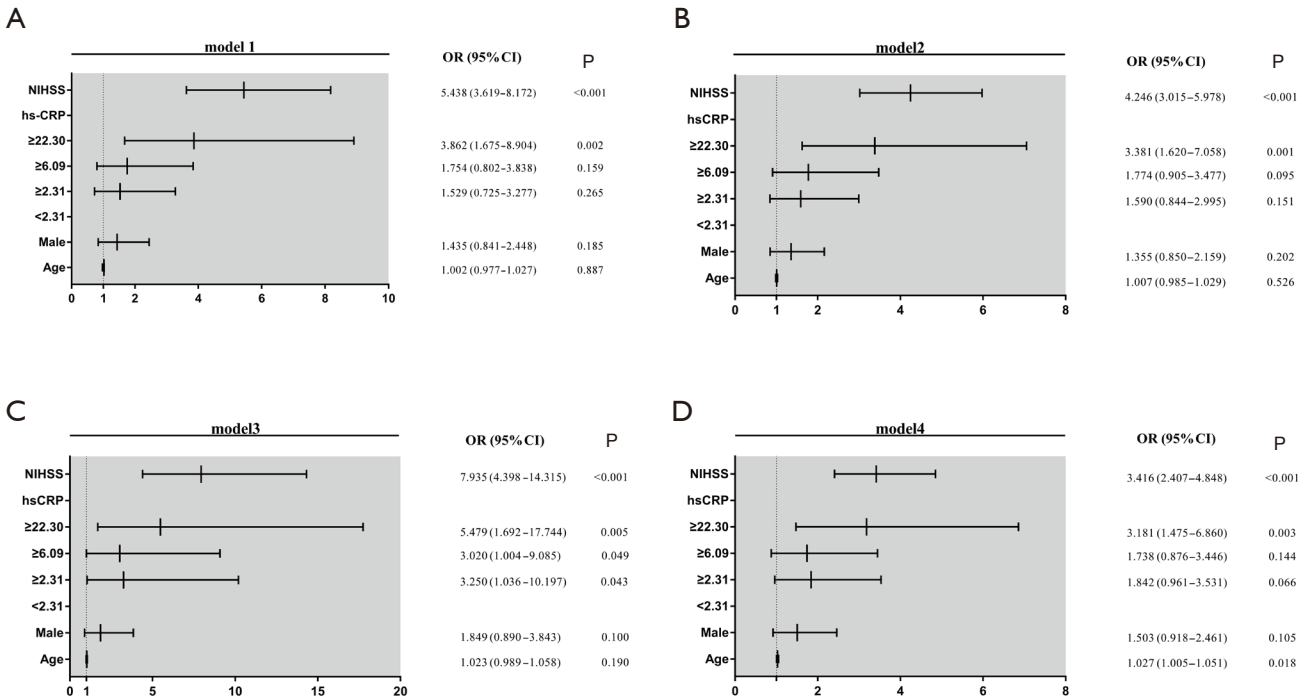

Figure 2 ORs for the hs-CRP groups-based model and the outcome variables. *Figure 2* includes the confounding variables that were identified as significant in the univariate analyses (age, sex, and National Institute of Health stroke scale score). (A) For model 1: at the 3-month follow-up, the primary outcome results showed that compared with the lowest hs-CRP levels (<2.31 mg/L), hs-CRP in the fourth quartile (≥22.30 mg/L) had a significant tendency to increase the risk of poor outcomes; (B) model 2: the secondary outcome results were similar to the primary outcome results in that the fourth quartile of hs-CRP (≥22.30 mg/L) had a significant tendency to increase the risk of composite endpoints after the 3-month follow-up; (C) model 3: at the 1 year follow-up, the results of the primary outcomes showed that compared with the lowest levels of hs-CRP (<2.31 mg/L), the three higher quartiles (2.31 to <6.09, 6.09 to <22.30, and ≥22.30 mg/L) of hs-CRP had a tendency to increase the risk of poor outcomes, and the fourth quartile was the most significant; (D) model 4: the secondary outcome results indicated that only the fourth quartile of hs-CRP (≥22.30 mg/L) was positively correlated with the composite endpoints after 1-year follow-up. OR, odds ratio; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio; CI, confidence interval; NIHSS, National Institute of Health Stroke Scale.

with acute ischemic stroke (34,35), and lower CRP levels may be related to clinical improvement and better prognosis at 3 months (36). In contrast, Modrego (37) failed to observe any relationship between CRP levels and prognosis of acute ischemic cerebrovascular disease. The explanation for these differences may be the small sample size of the study and not including the stroke subtypes in the analysis. In this study, patients with higher hs-CRP levels were mostly male, elderly, and with high NIHSS at the time of admission. Patients with high NIHSS do worse than patients with low NIHSS, those with large infarcts do worse than small infarcts, and elderly patients do worse than younger patients, all of which might explain the poor long-term outcomes.

In our present study, the findings observed for our secondary outcomes mirrored those found for our primary outcome, whereby, in acute patients with CES, hs-CRP ≥22.30 mg/L significantly correlated with composite endpoint events, which predicted new vascular events and poor functional outcome. A previous study found that elevated CRP levels in patients with acute ischemic stroke independently predicted recurrent vascular events and mortality (38). Furthermore, Christensen *et al.* (39) found that CRP +10 mg/L was independently correlated with 1-year mortality. Inflammation plays an important causal role in both vascular injury and coagulation (40); therefore, this may explain why the activation of individual inflammatory processes increases the risk of future

cardiovascular events (41).

There are some limitations to the present study. First, CRP levels are usually related to the size of tissue damage; however, the relationship between hs-CRP levels and infarct size was not analyzed. Second, genotype analysis for CRP was lacking in this study. Serum CRP levels are affected by CRP gene polymorphism (9,42). A previous study found that the CRP gene SNP rs1130864 was an independent predictor of poor short-term prognosis in patients with first ischemic stroke (43). Third, the sampling time following stroke onset may have influenced our results. Di Napoli *et al.* (44) found that CRP levels at discharge were a better predictor of prognosis. Although more well-designed studies are needed, our study clearly shows the relationship between hs-CRP levels and the outcomes of CES.

Conclusions

In this study, we can conclude that elevated hs-CRP in patients with CES is an independent predictor of poor outcomes; this association is particularly evident when hs-CRP ≥22.30 mg/L. Hs-CRP may serve as a predictor of stroke disability as well as recurrent stroke (ischemic or hemorrhagic), MI, or vascular death in patients with CES. Potential mechanisms have not yet been identified, and our findings need to be confirmed in other populations.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-1927). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study conformed to the Helsinki Declaration (as revised in 2013). The study was approved by the Ethics Committee of Tianjin Huanhu Hospital (No. 2005012) and informed consent was taken from all individual participants.

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