



# Association between high-sensitivity C-reactive protein levels and clinical outcomes in acute ischemic stroke patients treated with endovascular therapy

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**Background:** Increasing evidence demonstrates that high-sensitivity C-reactive protein (hs-CRP) is an independent prognostic predictor in acute ischemic stroke (AIS) patients. The purpose of this study is to investigate the association between hs-CRP levels and clinical outcomes in AIS patients receiving endovascular therapy (EVT).

**Methods:** This observational study was based on a prospective registry study. AIS patients receiving EVT from December 2012 to January 2019 were included. The modified Rankin Scale (mRS) scores at the 90-day and long-term follow-up were evaluated as clinical outcomes. Multivariable logistic regression analysis was conducted to adjust for confounders. Receiver operating characteristic (ROC) curve analysis was performed based on significant predictors of favorable outcomes in the logistic regression analysis. Patients were divided into two groups according to the cutoff value. Clinical outcomes were compared between groups. Survival probability was assessed using Kaplan-Meier survival analysis.

**Results:** Multivariable logistic regression analysis of the 362 enrolled AIS patients demonstrated that age ( $P=0.030$ ), National Institutes of Health Stroke Scale (NIHSS) score ( $P=0.023$ ), hs-CRP levels ( $P<0.001$ ), and symptomatic intracranial hemorrhage (sICH) ( $P=0.006$ ) were independently predictive of favorable outcomes. ROC curve analysis indicated that the hs-CRP level was predictive of favorable outcomes at the 90-day follow-up with a cutoff value of 8.255 mg/L. The mRS scores between patients with hs-CRP  $<8.255$  mg/L and patients with hs-CRP  $\geq 8.255$  mg/L at the 90-day [2 (IQR, 1–2) vs. 4 (IQR, 3–6),  $P<0.001$ ] and long-term follow-up [1 (IQR, 0–2) vs. 4 (IQR, 2–6),  $P<0.001$ ] were significantly different. Patients with hs-CRP  $\geq 8.255$  mg/L had significantly increased risk of poor clinical outcomes at the 90-day and long-term follow-up compared with those with hs-CRP  $<8.255$  mg/L ( $P<0.001$  each).

**Conclusions:** Elevated hs-CRP levels were associated with poor clinical outcomes in AIS patients receiving EVT.

**Keywords:** Ischemic stroke; endovascular therapy (EVT); high-sensitivity C-reactive protein (hs-CRP); outcome

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## Introduction

Acute ischemic stroke (AIS), a serious epidemic issue, is the second leading cause of death and long-term disability worldwide (1,2), and it places a tremendous burden on both healthcare systems and socioeconomic development (3). Endovascular therapy (EVT) is one of the established treatments for eligible AIS patients (4). With successful recanalization, most AIS patients with large vessel occlusion (LVO) can obtain benefits (5,6). Prior studies in AIS patients with EVT have identified patient-specific factors and procedural considerations as potential predictors of poor outcome or death (7-9). However, the simple and high-sensitivity hematological indexes leading to functional dependence remain unknown.

Inflammation plays an important role in the pathogenesis of AIS (10). Previous research has suggested that cerebral ischemia triggers inflammatory responses via the upregulation of acute-phase proteins such as C-reactive protein (CRP) (11). CRP, a nonspecific biomarker of inflammation, has been proposed to be an indicator of atherosclerosis and a predictor of both cardiovascular and cerebrovascular endpoints (12). A high-sensitivity CRP (hs-CRP) assay quantifies smaller incremental changes in inflammation and is more clinically relevant than CRP for evaluating the relationship between acute inflammation and prediction of the degree of long-term disability (13).

Although increasing evidence has demonstrated that hs-CRP is an independent predictor of prognosis in patients with AIS (14-18), the association between hs-CRP levels and clinical outcomes of AIS patients with EVT has not been established. Therefore, we performed this study to investigate the association between hs-CRP levels and clinical outcomes in AIS patients treated with EVT. We present the following article in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist (19) (available at <http://dx.doi.org/10.21037/atm-20-3820>).

## Methods

### Study design

This study was based on a prospective registry study in Xuanwu Hospital, Capital Medical University in Beijing, China, and it was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All consecutive AIS patients receiving EVT in our center were registered in this prospectively collected registry, which was approved by

the Ethics Committee of Xuanwu Hospital (No. 2017030), and informed consent was obtained from all the patients.

### Inclusion and exclusion criteria

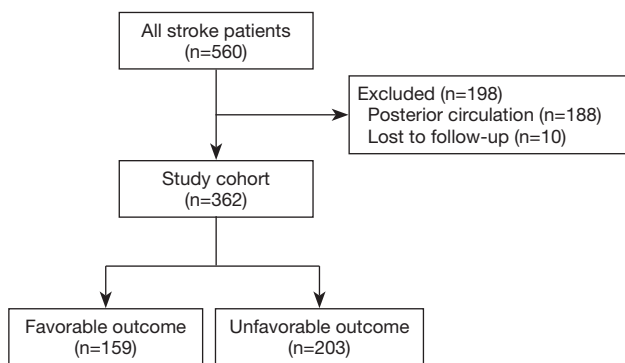
AIS patients with LVO were treated with EVT following the guidelines as soon as possible after symptom onset (4). For the present study, we enrolled AIS patients treated with EVT from December 2012 to January 2019. The inclusion criteria of this study were as follows: (I) diagnosis of AIS and (II) LVO in the anterior circulation confirmed by computed tomographic angiography, magnetic resonance angiography or digital subtraction angiography. The exclusion criteria were posterior circulation strokes and loss to follow-up.

### EVT

Based on the regulations of our center, only neurointerventionists who were trained in the technique of performing extracranial and intracranial stents were qualified to perform EVT. All procedures were performed under local or general anesthesia. Digital subtraction angiography was performed to determine the occlusion sites. Other specific intervention strategies, the type of stent retrievers, and other devices were chosen at the discretion of the treating neurointerventionist. Heparin was administered intravenously to maintain the activated coagulation time between 250 and 300 s during the procedure unless intravenous thrombolysis was implemented. After EVT, all patients were transferred to the neurological intensive care unit or acute stroke unit for further treatment.

### Clinical assessment and hs-CRP

Baseline information, including demographics, comorbidities, pathogenesis of stroke, National Institutes of Health Stroke Scale (NIHSS) score, baseline Alberta Stroke Program Early Computed Tomography Score (ASPECTS) on computed tomography (CT) scan, vital signs, time intervals, occlusion sites, interventional procedures, and recanalization conditions, was recorded from the database. Biochemical variables and other indicators were measured within 24 hours of admission in a certified central laboratory. Stroke severity on admission was assessed by certified evaluators using the NIHSS score (20). The NIHSS score is a neurologic examination stroke scale with a total score of 42; a higher NIHSS score indicates a more severe disability (20). ASPECTS is a quantitative CT score with a total of score



**Figure 1** Flowchart of patients included in this study.

of 10. A lower ASPECTS indicates a more severe ischemic change (21).

Hs-CRP levels were measured as part of routine laboratory testing for patients with AIS on admission. Hs-CRP assays were performed using the immunoturbidimetric assay. We conducted a laboratory calibration study to evaluate possible differences in hs-CRP measurements between laboratories, specimen types, assay methods, instruments, and time of measurement and found that differences in hs-CRP were not large enough to warrant calibration.

### Outcome assessment

Clinical outcomes were evaluated using the modified Rankin Scale (mRS) score. The mRS score is based on a 7-point scale, ranging from 0 (no symptoms) to 6 (death) (22). Clinical outcomes included the rates of favorable outcome (mRS, 0–2), no or minimal disability (mRS, 0–1), and mortality (mRS, 6) at 90 days as well as during long-term follow-up. In this study, an mRS score of 0–2 indicated a favorable outcome, while an mRS score of 3–6 indicated an unfavorable outcome. Outcome assessments were performed via telephone or in-person interviews by the independent evaluators who were unaware of the clinical information.

### Statistical analysis

Baseline characteristics were described. Descriptive statistics are presented as the means [standard deviation (SD)] for normally distributed continuous variables, medians [interquartile range (IQR)] for nonnormally distributed continuous variables, and percentages for categorical variables. The Kolmogorov-Smirnov test was performed for the normality assessment of continuous variables. These

variables were compared using the Student's *t*-test or the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.

To minimize the potential bias and adjust for confounders, a multivariable logistic regression analysis was conducted with favorable outcome at 90 days as the dependent variable and with age, male sex, NIHSS score, ASPECTS, atrial fibrillation, hs-CRP levels, time from stroke onset to recanalization, recanalization condition, and symptomatic intracranial hemorrhage (sICH) as the covariates. Additionally, receiver operating characteristic (ROC) curve analysis was performed based on the significant predictors of favorable outcome in the logistic regression analysis. The area under the curve (AUC) and Youden's index were further calculated to determine the cutoff value. Then, patients were divided into two groups according to the cutoff value, and the clinical outcomes at the 90-day and long-term follow-up were compared between the two groups. Furthermore, Kaplan-Meier survival analysis was performed to compare the survival probability at long-term follow-up using the log-rank test.

The significance level was set at  $P$  value  $\leq 0.05$  (two-sided). Statistical analyses were performed using SPSS 26.0 (IBM Corp., USA).

## Results

### Demographic characteristics (Figure 1 and Table 1)

Of the 560 patients who underwent EVT from December 2012 to January 2019 in our institution, 198 patients were excluded (188 patients had posterior circulation strokes, and 10 patients were lost to follow-up). Thus, a total of 362 patients were included for further analysis (Figure 1).

The mean age was 63.2 (SD, 12.7) years, and 249 patients (69.8%) were male. The median NIHSS score was 14 (IQR, 11–18), and the median ASPECTS score was 8 (IQR, 8–10) at baseline. One hundred thirty-three patients (36.7%) received intravenous alteplase before EVT. The median times from stroke onset to groin puncture (OTP), groin puncture to recanalization (PTR), and stroke onset to recanalization (OTR) were 397 (IQR, 284–519) min, 82 (IQR, 52–120) min, and 489 (IQR, 374–609) min, respectively. A total of 210 patients (58%) had middle cerebral artery occlusion, and 38 patients (10.5%) suffered sICH post procedure. The median hs-CRP value of all enrolled patients was 9.15 (IQR, 3.66–16.07) mg/L. Details of the baseline characteristics are presented in Table 1.

**Table 1** Baseline characteristics

Variables	Overall (n=362)	Favorable outcome (n=159)	Unfavorable outcome (n=203)	P value
Age, y, mean (SD)	63.2 (12.7)	61.2 (12.6)	64.8 (12.6)	0.006
Male, n (%)	249 (68.8)	119 (74.8)	130 (64.0)	0.028
BMI, median (IQR)	24.9 (22.9–27.4)	24.5 (22.9–27.1)	25.0 (22.9–27.7)	0.686
NIHSS score, median [IQR]	14 [11–18]	13 [10–16]	15.5 [12–20]	<0.001
ASPECTS, median [IQR]	9 [8–10]	9 [8–10]	9 [7–10]	0.285
Intravenous alteplase, n (%)	133 (36.7)	61 (38.4)	72 (35.5)	0.570
Systolic BP, mmHg, median [IQR]	138 [125–154]	136 [122–150]	140 [125–157]	0.142
Diastolic BP, mmHg, median [IQR]	80 [70–90]	80 [70–90]	80 [71–90]	0.276
Comorbidities, n (%)				
Hypertension	255 (62.2)	96 (60.4)	129 (63.5)	0.537
Diabetes mellitus	77 (21.3)	30 (18.9)	47 (23.2)	0.323
Hyperlipidemia	76 (21.0)	31 (19.5)	45 (22.2)	0.536
Atrial fibrillation	116 (32.0)	49 (30.8)	67 (33.0)	0.658
Smoking	145 (40.1)	67 (42.1)	78 (38.4)	0.474
Pathogenesis, n (%)				0.686
Large vessel atherosclerosis	220 (60.8)	102 (64.2)	118 (58.1)	
Cardioembolism	108 (29.8)	44 (27.7)	64 (31.5)	
Other	14 (3.9)	5 (3.1)	9 (4.4)	
Undetermined	20 (5.5)	8 (5.0)	12 (5.9)	
Laboratory assessments, median (IQR)				
Cholesterol, mmol/L	3.83 (3.31–4.60)	3.91 (3.34–4.87)	3.80 (3.25–4.55)	0.130
Triglyceride, mmol/L	1.16 (0.79–1.69)	1.10 (0.79–1.63)	1.20 (0.79–1.71)	0.606
HDL-C, mmol/L	1.15 (0.97–1.39)	1.18 (0.97–1.40)	1.14 (0.95–1.39)	0.508
LDL-C, mmol/L	2.42 (1.90–3.10)	2.49 (2.04–3.16)	2.37 (1.85–2.95)	0.076
Homocysteine, $\mu$ mol/L	12.40 (10.00–16.10)	12.90 (10.50–16.00)	12.25 (9.80–16.23)	0.556
hs-CRP, mg/L	9.15 (3.66–16.07)	3.67 (2.15–6.39)	14.53 (9.94–20.78)	<0.001
Time intervals, min, median [IQR]				
OTP	397 [284–519]	356 [228–518]	420 [320–521]	0.003
PTR	82 [52–120]	77 [48–107]	88 [60–125]	0.005
OTR	489 [374–609]	446 [324–599]	521 [401–618]	0.001
General anesthesia, n (%)	134 (37.0)	56 (35.2)	78 (38.4)	0.531
Occlusion sites, n (%)				0.388
Middle cerebral artery	210 (58.0)	97 (61.0)	113 (55.7)	
Internal carotid artery	143 (39.5)	57 (35.8)	86 (42.4)	
Anterior cerebral artery	9 (2.5)	5 (3.1)	4 (2.0)	

**Table 1** (Continued)

**Table 1** (Continued)

Variables	Overall (n=362)	Favorable outcome (n=159)	Unfavorable outcome (n=203)	P value
Interventional procedures, n (%)				
Stent retriever	298 (82.3)	127 (79.9)	171 (84.2)	0.280
Aspiration	129 (35.6)	50 (31.4)	79 (38.9)	0.229
Recanalization	304 (84.0)	143 (89.9)	161 (79.3)	0.006
sICH	38 (10.5)	5 (3.1)	33 (16.3)	<0.001

Data are expressed as the means, medians or n (%). SD, standard deviation; BMI, body mass index; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; OTP, stroke onset to groin puncture; PTR, groin puncture to recanalization; OTR, stroke onset to recanalization; sICH, symptomatic intracranial hemorrhage.

**Table 2** Predictors of favorable outcome at 90-day follow-up (multivariable analysis)

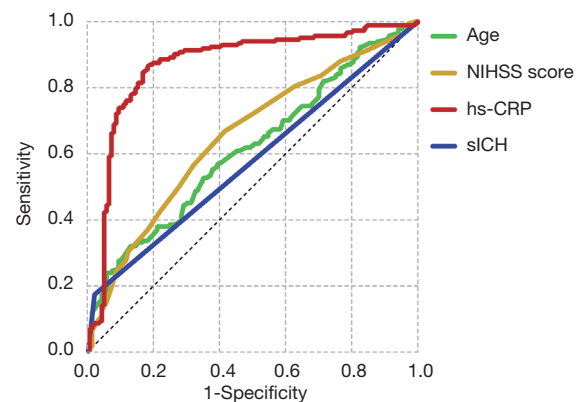
Variables	OR	95% CI	P value
Age	0.972	0.947–0.977	0.030
Male	1.752	0.897–3.420	0.100
NIHSS score	0.941	0.892–0.991	0.023
ASPECTS	1.044	0.842–1.295	0.694
Atrial fibrillation	1.792	0.876–3.666	0.110
hs-CRP	0.858	0.817–0.900	<0.001
OTR	1.000	0.998–1.001	0.752
Recanalization	2.083	0.744–5.826	0.162
sICH	0.143	0.036–0.570	0.006

OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; ASPECTS, Alberta Stroke Program Early Computed Tomography Score; hs-CRP, high-sensitivity C-reactive protein; OTR, stroke onset to recanalization; sICH, symptomatic intracranial hemorrhage.

### Outcomes

In the multivariable logistic regression analysis, after adjusting for confounding factors, age [odds ratio (OR), 0.972; 95% confidence interval (CI), 0.947–0.977;  $P=0.030$ ], NIHSS score (OR, 0.941; 95% CI, 0.892–0.991;  $P=0.023$ ), hs-CRP levels (OR, 0.858; 95% CI, 0.817–0.900;  $P<0.001$ ), and sICH (OR, 0.143; 95% CI, 0.036–0.570;  $P=0.006$ ) were significantly associated with favorable outcomes at 90 days post-EVT (Table 2).

The ROC curve analysis indicated that the hs-CRP level was a predictor of favorable outcome at the 90-day follow-



**Figure 2** ROC curves of predictors of favorable outcome at 90-day follow-up. ROC, receiver operating characteristic; NIHSS, National Institutes of Health Stroke Scale; hs-CRP, high-sensitivity C-reactive protein; sICH, symptomatic intracranial hemorrhage.

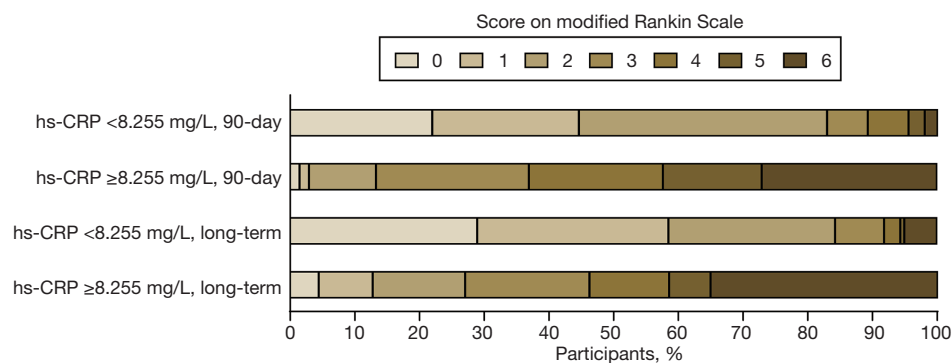
up with an AUC of 0.871 and a cutoff value of 8.255 mg/L (sensitivity, 86.7%; specificity, 83%; Figure 2).

Patients were then divided into two groups based on the cutoff value (8.255 mg/L). The median 90-day mRS scores were 2 (IQR, 1–2) in patients with hs-CRP <8.255 mg/L and 4 (IQR, 3–6) in patients with hs-CRP  $\geq$ 8.255 mg/L ( $P<0.001$ ). At long-term follow-up (median follow-up time, 15 months), the median mRS scores were 1 (IQR, 0–2) and 4 (IQR, 2–6) in patients with hs-CRP <8.255 and  $\geq$ 8.255 mg/L, respectively ( $P<0.001$ ). The rates of favorable outcome, no or minimal disability, and mortality were significantly different between the two groups at 90-day and long-term follow-up ( $P<0.001$  each). The details of functional outcomes and the distribution of

**Table 3** Functional outcomes at 90-day and long-term follow-up

Variables	Overall (n=362)	hs-CRP <8.255 mg/L (n=159)	hs-CRP ≥8.255 mg/L (n=203)	P value
90-day follow-up				
mRS, median [IQR]	3 [2–5]	2 [1–2]	4 [3–6]	<0.001
Favorable outcome, n (%)	159 (43.9)	132 (83.0)	27 (13.3)	<0.001
No or minimal disability, n (%)	77 (21.3)	71 (44.7)	6 (3.0)	<0.001
Mortality, n (%)	58 (16.0)	3 (1.9)	55 (27.1)	<0.001
Long-term follow-up				
mRS, median [IQR]	2 [1–5]	1 [0–2]	4 [2–6]	<0.001
Favorable outcome, n (%)	189 (52.2)	134 (84.3)	55 (27.1)	<0.001
No or minimal disability, n (%)	119 (32.9)	93 (58.5)	26 (12.8)	<0.001
Mortality, n (%)	79 (21.8)	8 (5.0)	71 (35.0)	<0.001

hs-CRP, high-sensitivity C-reactive protein; mRS, modified Rankin Scale; IQR, interquartile range.



**Figure 3** Distribution of the mRS scores at 90-day and long-term follow-up. The percentages are shown in each cell according to the distribution of the mRS scores. Significant differences were observed in the distribution of the mRS scores between patients with a hs-CRP level <8.255 mg/L and patients with a hs-CRP level ≥8.255 mg/L at both 90-day ( $P<0.001$ ) and long-term follow-up ( $P<0.001$ ). mRS, modified Rankin Scale; hs-CRP, high-sensitivity C-reactive protein.

the mRS categories are presented in *Table 3* and *Figure 3*.

Furthermore, Kaplan-Meier curve analysis showed that there was a significant difference between the two groups in long-term survival probability (log-rank,  $P<0.001$ ; *Figure 4*), indicating that patients with a hs-CRP level <8.255 mg/L have a better long-term survival probability.

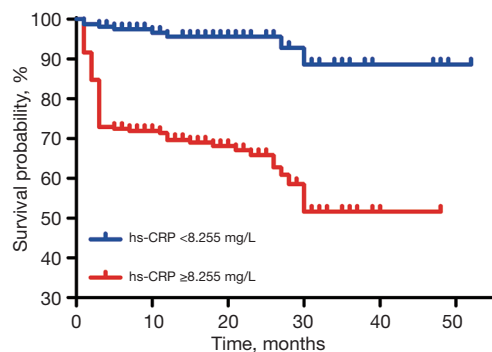
## Discussion

In the present study, we investigated the association between hs-CRP levels and clinical outcomes in AIS patients treated with EVT. We found that hs-CRP levels were independently associated with 90-day favorable outcomes.

Patients with a hs-CRP level <8.255 mg/L had better functional outcomes at 90-day and long-term follow-up and a higher long-term survival probability than those with an hs-CRP level ≥8.255 mg/L. This is the first study to show that hs-CRP levels are associated with clinical outcomes among anterior circulation stroke patients receiving EVT.

Hs-CRP is a sensitive marker of inflammation in the arterial wall (12). Increased hs-CRP levels can reflect the pre-existing situation of the presence of vascular risk factors, as it is related to inflammation of vascular stenosis or occlusion and tissue injury (23). Cerebral ischemic injury can trigger inflammatory processes that evoke acute-phase proteins and inflammatory cytokines (24), and patients with





**Figure 4** Kaplan-Meier curves for the long-term survival probability. hs-CRP, high-sensitivity C-reactive protein.

larger infarct volumes have a greater neurological deficit and worse functional outcomes (25). Thus, the hs-CRP concentration can, in part, reflect the severity of stroke.

In the present study, elevated hs-CRP levels were associated with poor prognosis at 90-day and long-term follow-up. In line with our findings, the Circulatory Risk in Communities Study (CIRCS) demonstrated a positive association between hs-CRP levels and ischemic stroke in middle-aged Japanese men and women (26). Our findings also corroborate a previous study suggesting that hs-CRP is independently predictive of all-cause mortality (23). However, in the Northern Manhattan Study (NOMAS) (27), a hs-CRP level  $>3$  mg/L was associated with ischemic stroke risk in the model adjusted for demographics, but these effects did not persist after controlling for other potential risk factors. The absence of an association with stroke may reflect the heavy risk factor burden; the prevalence of diabetes mellitus and hypertension in the NOMAS *vs.* our study was 21.5% *vs.* 21.3% and 74.6% *vs.* 62.2%, respectively. Other studies similarly found a difference in effect based on the presence or absence of other risk factors. In the Honolulu Heart Study (28), hs-CRP was not associated with stroke among men with hypertension or diabetes or among those aged  $>55$  years. Previous studies have demonstrated that advanced age, hypertension, obesity, diabetes, total cholesterol levels, and lower high-density lipoprotein cholesterol (HDL-C) levels were associated with elevated hs-CRP levels (12,27).

In this study, we investigated AIS patients with LVO in the anterior circulation. A previous study demonstrated that hs-CRP levels were elevated in all TOAST (the Trial of Org 10172 in Acute Stroke Treatment) subtypes (29), especially in patients with large artery atherosclerosis.

Rajeshwar *et al.* (30) found no significant association between hs-CRP levels and the prognosis of patients with lacunar infarcts after 3 months, but in patients with LVO, the association was positive. This was probably because LVO was associated with a larger infarct volume and stronger activation of inflammation than small artery occlusion, which was also associated with changes in hs-CRP.

Although the pathophysiological association between hs-CRP and LVO is unclear, different mechanisms may be involved. Hs-CRP is related to focal inflammation, and the inflammatory response plays an important role in patients with LVO, as it is associated with stenosis or occlusion of intracranial or extracranial large arteries, unstable plaque, artery-to-artery embolism and hypoperfusion (31). On the other hand, hs-CRP can bind to the plasma membranes and small nuclear ribonucleoprotein particles in the exposed nuclei of damaged cells (32). After such binding, the classical complement pathway can be activated, which may therefore contribute to ischemic tissue damage. A combination of these mechanisms may better explain the association between hs-CRP and LVO. Further experiments are needed to confirm the exact mechanism of prognosis.

Furthermore, the hs-CRP measurement time point at which clinical outcomes are most emblematic has not been established. In this study, the hs-CRP concentration was measured immediately upon admission. The serum hs-CRP concentration increases early and remains elevated above control values at 3 months after the index stroke (33), but to what extent the elevation reflects the inflammatory response to stroke is unclear. Previous studies suggested the usefulness of a sample taken within 12 to 72 hours after stroke onset (18,34,35). Di Napoli *et al.* (36) measured serum hs-CRP within 24 hours after index ischemic stroke, within 48 to 72 hours, and at hospital discharge; they found that hs-CRP at hospital discharge was the strongest independent marker of adverse outcome (hazard ratio, 7.42; 95% CI, 2.75–20.03;  $P=0.0001$ ), whereas further investigation suggested that the peak measurement in the first week after stroke onset was particularly valuable in relation to infarct volume and clinical outcomes (33). It is possible that discharge concentrations more closely reflect the baseline inflammatory status of the patients, and thus their intrinsic risk caused by inflammatory activity. Further prospective investigations of the optimal timing of hs-CRP for use as a prognostic marker after AIS with EVT are warranted.

This study has certain limitations. The nonrandomized

single-center design of our study had limitations in nature, and the sample population cannot represent the general population of AIS with EVT. In view of the changes in the time window of EVT for AIS patients in recent years, the median time from stroke onset to recanalization in this study has exceeded 8 hours, which is inconsistent with the traditional 8-hour time window in most previous studies. Therefore, care should be taken in generalizing these results to settings where time to recanalization is shorter, and future studies are needed to further verify our conclusions. Moreover, the timing of plasma sampling concerning stroke onset may have influenced our findings; thus, serial hs-CRP measurements should be performed. As dynamic change measurement of hs-CRP may provide more prognostic relevance in AIS, standardized serial measurements of hs-CRP concentration should be the focus in future studies to determine whether dynamic changes are related to prognosis. Finally, although multivariable logistic regression analysis was performed to adjust for relevant variables, unmeasured and residual confounding factors remained.

## Conclusions

Our present study demonstrated that hs-CRP levels were associated with clinical outcomes of AIS patients undergoing EVT with LVO in the anterior circulation. These results need to be further verified in larger multicenter prospective studies.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-3820>

*Data Sharing Statement:* Available at <http://dx.doi.org/10.21037/atm-20-3820>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-3820>).

[org/10.21037/atm-20-3820](http://dx.doi.org/10.21037/atm-20-3820)). 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 was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Xuanwu Hospital (No. 2017030), and informed consent was taken from all the patients.

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