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ORIGINAL RESEARCH

Association of C-Reactive Protein with Short-Term Outcomes in Spontaneous Intracerebral Hemorrhage Patients with or without Infection: From a Large-Scale Nationwide Longitudinal Registry

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Aim: To study the relationship between elevated C-reactive protein (CRP) levels, infection, and spontaneous intracerebral hemorrhage (ICH) outcomes.

Methods: Patients were classified into four groups (Q1–Q4). Logistic regression was used to analyze the relationship between different CRP levels and functional disability (mRS score of 3–5) at discharge, intracerebral hematoma evacuation, and in-hospital mortality. Subgroup analysis was conducted on patients with or without infection during hospitalization.

Results: A total of 14,529 patients with ICH were enrolled in this study. In the multivariate logistic regression model, compared with the reference CRP quartile group (Q1), the Q4 group had a higher proportion of functional disability (adjusted OR, 1.30, 95% CI 1.16–1.45) and hematoma evacuation (adjusted OR, 1.88, 95% CI 1.58–2.23). In patients without infection, compared with the Q1 group, the Q4 group had a higher risk of functional disability (adjusted OR, 2.16, 95% CI 1.71–2.73) and hematoma evacuation (adjusted OR, 1.15, 95% CI 1.00–1.31).

Conclusion: A significantly increased CRP level was associated with a higher risk of early functional disability and hematoma evacuation in patients with ICH, regardless of the presence or absence of infectious complications. Infection may increase the risk of poor outcomes in patients with ICH, but caution is needed when facing abnormally high CRP levels in patients with ICH without infection.

Keywords: C-reactive protein (CRP), infection, inflammation, spontaneous intracerebral hemorrhage, poor outcome

Introduction

Spontaneous intracerebral hemorrhage (ICH) is a main factor leading to stroke-related mortality and dependency, with only half of patients surviving for 1 year after ICH, leaving behind sequelae that affect their quality of life.[1]

Inflammation is believed to play an important role in the pathophysiology process of ICH.[2] C-reactive protein (CRP) is an extensively studied systemic inflammatory marker commonly considered to reflect an acute inflammatory response.[3] After ICH, CRP usually increases rapidly and is considered as a risk assessment tool and prognostic marker.[4,5] A study conducted by the Chinese Stroke Center Alliance has demonstrated that elevated CRP levels correlate with a heightened likelihood of requiring hematoma evacuation.[6] Additionally, another study has shown that plasma CRP levels, when

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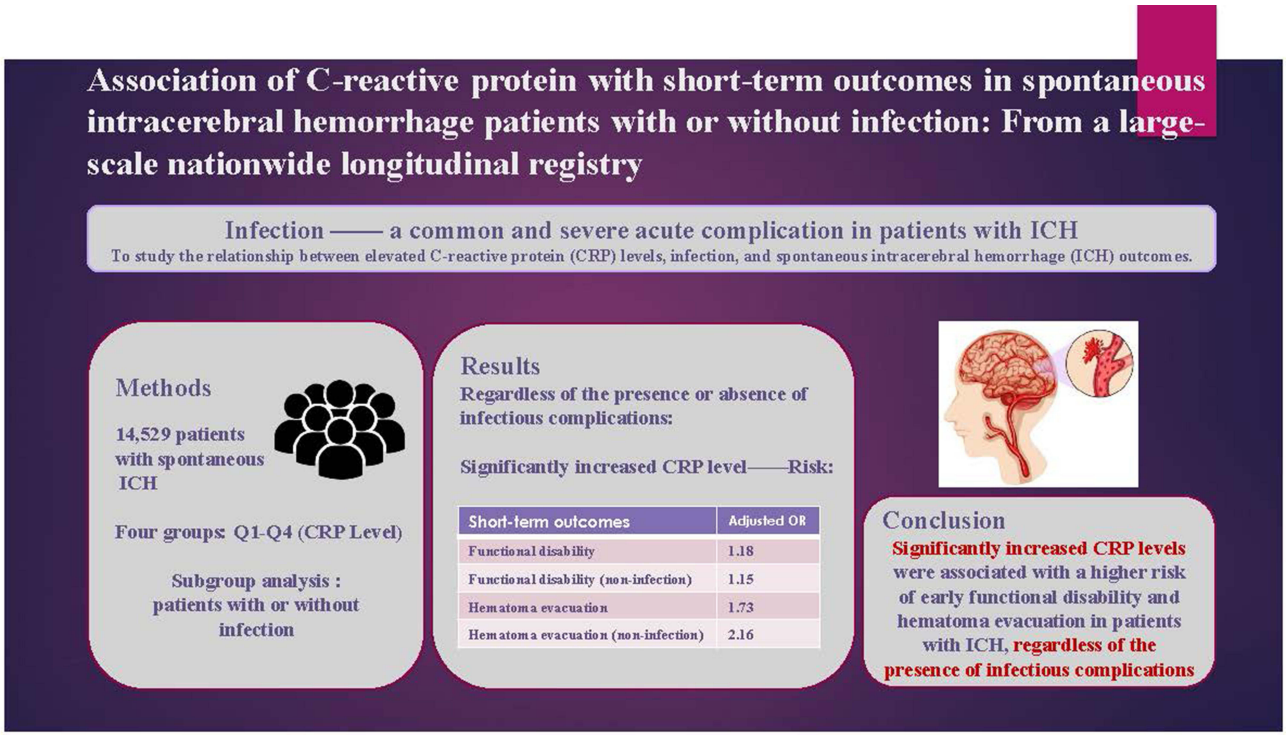
Graphical Abstract



measured within six hours post-onset, are significantly associated with the incidence of hematoma expansion and the subsequent deterioration of neurological status.[7]

While the relationship between CRP and ICH outcomes has been studied extensively, several important questions remain. Infection, a common complication in ICH patients, can lead to an acute rise in CRP levels, complicating the interpretation of CRP as a prognostic marker.[8] Therefore, while elevated CRP levels may reflect both the inflammatory response associated with ICH and the presence of infection, distinguishing these factors is critical to better understanding the role of CRP in ICH prognosis.

This study aims to fill this gap by focusing not only on the relationship between CRP levels and ICH outcomes but also on the influence of infection, within a large multicenter registry. Unlike prior studies, our research specifically addresses this complex interplay between inflammation, infection, and clinical outcomes, offering new insights into the potential for CRP as a prognostic marker. We also investigate the association between CRP levels and hematoma evacuation, an important therapeutic intervention that may further refine our understanding of CRP's role in ICH. By using a large, diverse sample, we aim to provide more robust and generalizable findings that can guide future research and clinical practice.

Methods

Patient Selection

Data were retrieved from the China Stroke Center Alliance (CSCA) multicenter database. The CSCA is a national registry cohort that enrolled patients with acute stroke/transient ischemic attack from 1,476 hospitals in China.[9] The program provides a national platform for collecting electronic data and improving stroke care in China, similar to the American Heart Association's Get With the Guidelines-Stroke (GWTG-Stroke) program in America.[10] This study was conducted according to the principles of the Declaration of Helsinki. Ethical approval was obtained from the ethical review board of Beijing Tiantan Hospital (ethical approval number: KY2018-061-02). Informed consent is obtained from

patients at the time of enrollment in the CSCA registry for the collection of clinical data. All the data were collected from routine clinical practice and the process of data collection did not alter routine clinical practice. All secondary and tertiary hospitals in China are allowed to upload the clinical data of stroke patients. A web-based patient data collection and management tool (Medicine Innovation Research Center, Beijing, China) was used to upload and preserve participants' characteristics. Only under the supervision of the China National Clinical Research Center for Neurological Diseases could data be accessed for analysis, and all identifiers for each patient were removed to protect the privacy and confidentiality of the selected patients. This study obtained the necessary data access approval and conducted the analysis under the center's oversight. From 2015 to 2019, 1,006,798 patients with stroke or transient ischemic attack (TIA), confirmed by cranial computed tomography (CT) or magnetic resonance imaging (MRI), were consecutively recruited into the CSCA cohort consecutively, and 85,705 were patients with ICH.

The inclusion criteria for this study were as follows: a) age >18 years and b) ICH diagnosis. The exclusion criteria included: a) incomplete clinical or laboratory data, particularly Glasgow Coma Scale (GCS) scores, CRP results, or infection information; b) history of conditions or medication use that could directly affect immune function, such as autoimmune diseases, cancer, or immunosuppressive therapy.

Clinical Variables and Outcome

CRP samples were collected on the second morning of admission at each sub-center. Other baseline information included age, sex, medical history (hypertension, diabetes, dyslipidemia, ischemic stroke, atrial fibrillation, heart failure, antiplatelet agents, and anticoagulation agents), smoking, drinking, GCS score, National Institutes of Health Stroke Scale (NIHSS) score, and laboratory measurements. Infections during hospitalization included pneumonia, urinary tract infections, and sepsis. Moreover, the CSCA was designed to collect the in-hospital information of participants without follow-up data after discharge.

Outcome Assessment

The primary outcome of our study was functional disability, defined as a modified Rankin Scale (mRS) score of 3–5, assessed at 14 ± 2 days post-admission, with the exception of patients who died in-hospital. The secondary study outcome was the percentage of intracerebral hematoma evacuations. In addition, we analyzed in-hospital mortality. Subgroup analysis was conducted on patients with or without infection during hospitalization.

Statistical Analysis

Statistical analyses were performed using the SAS software (version 9.4; SAS Institute, Cary, NC, USA). Participants were divided into Q1, Q2, Q3, and Q4 groups according to the quartile and median CRP levels. Continuous variables were initially assessed for normality using the Shapiro–Wilk test. Due to non-normal distribution of continuous variables, these are presented as medians (interquartile range, IQR). Non-parametric comparisons were performed using the Kruskal–Wallis test. If any continuous variables had met the assumptions of normality, parametric tests such as one-way ANOVA would have been considered. The chi-square test was used to compare categorical variables, which are expressed as numbers (proportions). Multivariate logistic regression was used to analyze the association between CRP levels and clinical outcomes. Variables with p values < 0.1 from the univariate comparison of baseline characteristics were considered for inclusion in the multivariate regression models. The covariates were selected using a stepwise selection procedure, which iteratively added or removed variables based on their statistical significance ($p < 0.05$). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each group using the first quartile (Q1) as a reference for CRP levels. Restricted cubic splines (RCS) were used to delineate the relationship between CRP levels and adjusted ORs for functional disability, hematoma evacuation, and in-hospital mortality. Results were considered significant at $p < 0.05$ (two sided).

Results

Baseline Characteristics

A total of 14,529 patients with spontaneous ICH who fulfilled the inclusion criteria were enrolled in the study (Figure 1). A comparison of the baseline characteristics is presented in Table 1. The median age was 64 (IQR 54–73) years, and 9,147 (63.0%) were males. Participants were classified into four groups according to CRP quartiles; the first, median, and third quartiles of the CAR were 1.00, 3.41, and 8.50, respectively. The CRP ranges of the quartile groups were Q1 (CRP < 1.00), Q2 (1.00 ≤ CRP <3.41), Q3 (3.41 ≤ CRP < 8.50) and Q4 (8.50 ≤CRP). The median age, NIHSS score, GCS score, total cholesterol, low-density lipoprotein cholesterol, systolic blood pressure, diastolic blood pressure, glycated hemoglobin, fasting blood glucose, percentage of males, current smokers, current drinkers, diabetes, dyslipidemia, and atrial fibrillation were significantly different among the four groups ($p < 0.05$).

CRP and Outcomes

The outcome characteristics, including functional disability, hematoma evacuation, and in-hospital mortality, showed significant overall differences among the four CRP groups ($p < 0.05$). A descriptive trend of increasing proportions of these outcomes was observed from Q1 to Q4. In addition, the percentage of infections during hospitalization was significantly different ($p < 0.05$) (Table 1).

The risks of in-hospital clinical outcomes in the CRP quartile groups are presented in Table 2. Logistic regression analyses showed that, compared with the lowest CRP quartile group (Q1), the Q2, Q3 and Q4 groups had a higher proportion of functional disability (Q2 group: crude OR, 1.11, 95% CI 1.01–1.22, $p = 0.030$; Q3 group: crude OR, 1.19, 95% CI 1.07–1.31, $p = 0.001$; Q4 group: crude OR, 1.71, 95% CI 1.55–1.88, $p < 0.001$). This association remained significant in the Q4 group after adjusting for confounding factors (Q4 group: adjusted OR, 1.30, 95% CI 1.16–1.45, $p < 0.001$). In addition, compared with the Q1 group, both the Q3 and Q4 groups had a higher risk for evacuation of

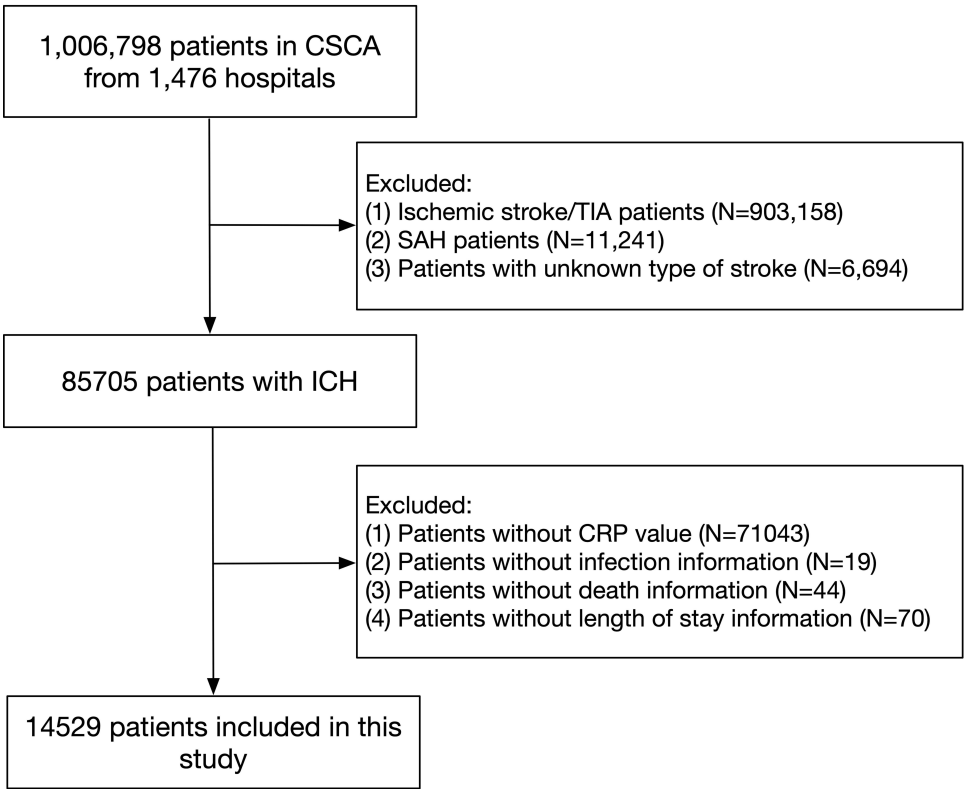


Figure 1 Flow diagram of study patients.
Abbreviations: TIA, indicates transient ischemic attack; SAH, subarachnoid hemorrhage; ICH, intracerebral hemorrhage and CRP, C-reactive protein.

Table 1 Baseline Characteristics of the Patients Stratified by the CRP

	Total N=14529	Q1 (CRP<1.00) (n=3223)	Q2 (1.00≤CRP<3.41) (n=4032)	Q3 (3.41≤CRP<8.50) (n=3639)	Q4 (8.50≤CRP) (n=3635)	P
Age (years, IQR)	64 (54–73)	63 (53–72)	63 (54–72)	64 (54–73)	65 (55–75)	<0.001
Male, n (%)	9147 (63.0)	2035 (63.1)	2471 (61.3)	2256 (62.0)	2385 (65.6)	<0.001
Smoking, n (%)	4741 (32.6)	1021 (31.7)	1271 (31.5)	1147 (31.5)	1302 (35.8)	<0.001
Drinking, n (%)	3564 (24.5)	737 (22.9)	946 (23.5)	925 (25.4)	956 (26.3)	0.002
Medical history, n (%)						
Hypertension	10439 (71.8)	2313 (71.8)	2887 (71.6)	2601 (71.5)	2638 (72.6)	0.724
Diabetes	1415 (9.7)	288 (8.9)	420 (10.4)	329 (9.0)	378 (10.4)	0.040
Dyslipidemia	579 (4.0)	99 (3.1)	159 (3.9)	154 (4.2)	167 (4.6)	0.011
Ischemic stroke	2011 (13.8)	430 (13.3)	584 (14.5)	477 (13.1)	520 (14.3)	0.224
Atrial fibrillation	223 (1.5)	38 (1.2)	57 (1.4)	51 (1.4)	77 (2.1)	0.009
Heart failure	72 (0.5)	11 (0.3)	16 (0.4)	22 (0.6)	23 (0.6)	0.202
Antiplatelet agents	1025 (7.1)	240 (7.4)	289 (7.2)	231 (6.3)	265 (7.3)	0.271
Anticoagulation agents	193 (1.3)	35 (1.1)	46 (1.1)	56 (1.5)	56 (1.5)	0.171
GCS at first admission (IQR)	13.0 (8.0–15.0)	14.0 (10.0–15.0)	14.0 (8.0–15.0)	13.0 (8.0–15.0)	12.0 (7.0–15.0)	<0.001
NIHSS at first admission (IQR)	6.0 (2.0–14.0)	4.0 (1.0–10.0)	5.0 (2.0–12.0)	6.0 (2.0–14.0)	9.0 (3.0–17.0)	<0.001
Total cholesterol (mmol/L, IQR)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	<0.001
LDL-C (mmol/L, IQR)	2.6 (2.0–3.2)	2.5 (1.9–3.1)	2.5 (2.0–3.1)	2.6 (2.0–3.2)	2.6 (2.0–3.4)	<0.001
SBP (mmHg, IQR)	162 (145–181)	161 (143–181)	162 (145–181)	163 (145–182)	164 (146–182)	0.058
DBP (mmHg, IQR)	95 (84–105)	95 (83–105)	94 (83–105.0)	95 (85–106)	95 (84–105)	0.064
HbAlc (%, IQR)	5.6 (5.0–6.1)	5.5 (5.0–6.0)	5.5 (5.0–6.0)	5.6 (5.0–6.1)	5.6 (5.0–6.2)	<0.001
Fasting blood glucose (mmol/L, IQR)	5.9 (5.1–7.2)	5.7 (5.0–6.9)	5.8 (5.1–7.0)	5.9 (5.1–7.1)	6.1 (5.3–7.6)	<0.001
Infection, n (%)	3646 (25.1)	643 (20.0)	873 (21.7)	833 (22.9)	1297 (35.7)	<0.001
Functional disability, n (%)	5825 (40.1)	1134 (35.2)	1518 (37.6)	1425 (39.2)	1748 (48.1)	<0.001
Hematoma evacuation, n (%)	1712 (11.8)	268 (8.3)	402 (10.0)	400 (11.0)	642 (17.7)	<0.001
In-hospital mortality, n (%)	295 (2.0)	48 (1.5)	63 (1.6)	62 (1.7)	122 (3.4)	<0.001

Notes: Values are median (IQR) or number (%).

Abbreviations: CRP, indicates C-reactive protein; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbAlc, glycated hemoglobin and IQR, interquartile range.

Table 2 Logistics Regression Analyses of in-Hospital Outcomes

CRP (mg/L)	Events/Patients	Event Rate (%)	Crude		Adjusted		P for Trend
			OR (95% CI)	P	OR (95% CI)	P	
Functional disability							0.008
Q1 (CRP<1.00)	1134/3223	35.18	Ref.		Ref.		
Q2 (1.00≤CRP<3.41)	1518/4032	37.65	1.11(1.01,1.22)	0.030	1.01(0.90,1.13)	0.832	
Q3 (3.41≤CRP<8.50)	1425/3639	39.16	1.19(1.07,1.31)	0.001	0.99(0.88,1.11)	0.875	
Q4 (8.50≤CRP)	1748/3635	48.09	1.71(1.55,1.88)	<0.001	1.18(1.05,1.33)	0.004	
Hematoma evacuation							<0.001
Q1 (CRP<1.00)	268/3223	8.32	Ref.		Ref.		
Q2 (1.00≤CRP<3.41)	402/4032	9.97	1.22(1.04,1.44)	0.016	1.12(0.93,1.34)	0.233	
Q3 (3.41≤CRP<8.50)	400/3639	10.99	1.36(1.16,1.60)	<0.001	1.18(0.99,1.42)	0.071	
Q4 (8.50≤ CRP)	642/3635	17.66	2.37(2.03,2.75)	<0.001	1.73(1.45,2.05)	<0.001	
In-hospital mortality							0.096
Q1 (CRP<1.00)	48/3223	1.49	Ref.		Ref.		
Q2 (1.00≤CRP<3.41)	63/4032	1.56	1.05(0.72,1.53)	0.801	0.93(0.62,1.39)	0.712	
Q3 (3.41≤CRP<8.50)	62/3639	1.70	1.15(0.78,1.68)	0.481	0.90(0.59,1.36)	0.607	
Q4 (8.50≤CRP)	122/3635	3.36	2.30(1.64,3.22)	<0.001	1.31(0.90,1.92)	0.161	

Notes: Adjusted for age, male, diabetes, dyslipidemia, atrial fibrillation, NIHSS at first admission, total cholesterol, LDL-C, SBP, DBP, HbA1c, fasting blood glucose, infection.

Abbreviations: CRP, indicates C-reactive protein; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure and HbAlc, glycated hemoglobin.

intracranial hematoma (Q3 group: crude OR, 1.36, 95% CI 1.16–1.60, p < 0.001; Q4 group: crude OR, 2.37, 95% CI 2.03–2.75, p < 0.001). After adjustments, the Q4 group still had the higher risk (Q4 group: adjusted OR, 1.88, 95% CI 1.58–2.23, p < 0.001). However, compared with the Q1 group, only the Q4 group had a higher risk for in-hospital mortality (Q4 group: crude OR, 2.30, 95% CI 1.64–3.22, p < 0.001), while this association disappeared after adjustments.

In the RCS between CRP level and functional disability or hematoma evacuation, after adjusting for all potential confounders, the OR values showed a significant upward trend when the CRP level exceeded 2 mg/L. In the RCS between CRP and in-hospital mortality, the spline yielded a J-shaped curve showing a steady decrease in ORs with an increase in CRP up to approximately 2 mg/L, beyond which the curve rose (Figure 2).

Subgroup Analyses

In patients without infection during hospitalization, compared with the lowest CRP quartile group (Q1), both the Q3 and Q4 groups had a higher risk for functional disability (Q3 group: crude OR, 1.46, 95% CI 1.17–1.83, p < 0.001; Q4 group: crude OR, 2.59, 95% CI 2.10–3.21, p < 0.001). This association remained significant in the Q4 group after adjusting for confounding factors (Q4 group: adjusted OR, 2.16, 95% CI 1.71–2.73, p < 0.001). Similarly, compared with the Q1 group, both the Q3 and Q4 groups had a higher risk for hematoma evacuation (Q3 group: crude OR, 1.13, 95% CI 1.00–1.27, p = 0.049; Q4 group: crude OR, 1.47, 95% CI 1.31–1.66, p < 0.001). After adjustments, the Q4 group still had the higher risk (Q4 group: adjusted OR, 1.15, 95% CI 1.00–1.31, p = 0.049). The data showed no association between CRP levels and in-hospital mortality in patients without infection during hospitalization (Table 3).

Discussion

The results of the present study suggest that significantly increased CRP levels are associated with a higher risk of functional disability and hematoma evacuation in patients with ICH. Additionally, we observed a steady increase in the risk of functional disability and hematoma evacuation as CRP levels increased in the RCS analysis. In patients without infection during hospitalization, the risk of functional disability and hematoma evacuation remained high when CRP levels were high. However, the data showed no association between CRP levels and in-hospital mortality in patients with or without infection during hospitalization.

Based on the above results, we can conclude that regardless of whether patients with ICH have infectious complications, a significant increase in CRP is related to poor outcomes during hospitalization. Previous studies have shown that the addition of CRP concentration to the ICH score significantly increases the ability to predict 30-day mortality.[11] It is well known that CRP is an acute marker of inflammation, and its concentration increases in the circulation during inflammatory events.[3] For ICH patients, in addition to primary brain injury, secondary brain injury largely leads to poor outcome.[12] Secondary brain injury is typically attributed to inflammation, excitatory amino acids, and oxidative

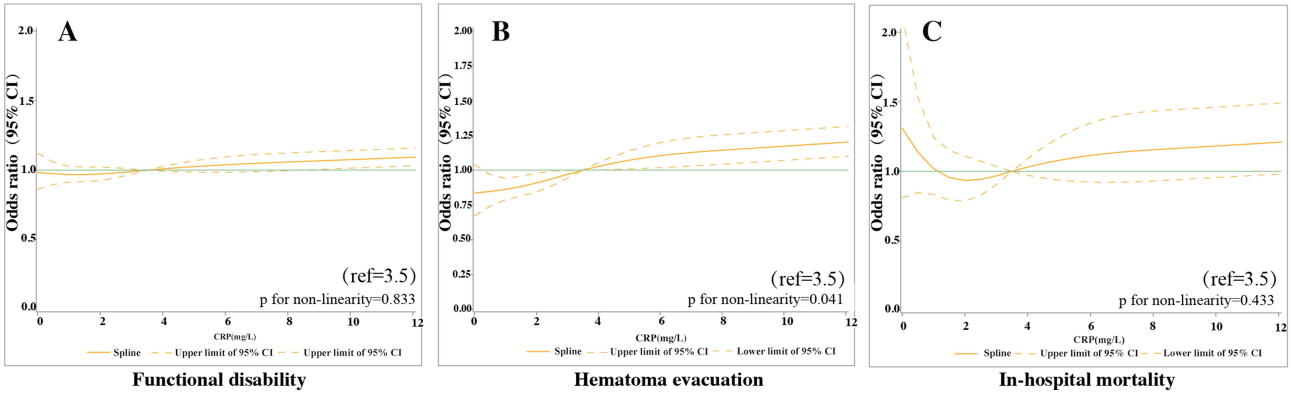


Figure 2 Restricted cubic splines to delineate the relationship between CRP and adjusted OR for (**A**) Functional disability, (**B**) Hematoma evacuation, and (**C**) In-hospital mortality. Adjusted for age, male, diabetes, dyslipidemia, atrial fibrillation, NIHSS at first admission, total cholesterol, LDL-C, SBP, DBP, HbA1c, fasting blood glucose, infection.

Abbreviations: CRP, indicates C-reactive protein; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure and HbAlc, glycated hemoglobin.

Table 3 Logistics Regression Analyses of in-Hospital Outcomes in Non-Infection Patients

CRP (mg/L)	Events/Patients	Event Rate (%)	Crude		Adjusted		P for Trend
			OR (95% CI)	P	OR (95% CI)	P	
Functional disability							0.151
Q1 (CRP<1.00)	731/2580	28.33	Ref.		Ref.		
Q2 (1.00≤CRP<3.41)	931/3159	29.47	1.06(0.94,1.19)	0.344	0.98(0.87,1.12)	0.814	
Q3 (3.41≤CRP<8.50)	864/2806	30.79	1.13(1.00,1.27)	0.049	0.91(0.80,1.04)	0.172	
Q4 (8.50≤ CRP)	861/2338	36.83	1.47(1.31,1.66)	<0.001	1.15(1.00,1.31)	0.049	
Hematoma evacuation							<0.001
Q1 (CRP<1.00)	134/2580	5.19	Ref.		Ref.		
Q2 (1.00≤CRP<3.41)	197/3159	6.24	1.21(0.97,1.52)	0.092	1.17(0.92,1.49)	0.1896	
Q3 (3.41≤CRP<8.50)	208/2806	7.41	1.46(1.17,1.83)	<0.001	1.23(0.97,1.57)	0.0892	
Q4 (8.50≤ CRP)	291/2338	12.45	2.59(2.10,3.21)	<0.001	2.16(1.71,2.73)	<0.001	
In-hospital mortality							0.783
Q1 (CRP<1.00)	29/2580	1.12	Ref.		Ref.		
Q2 (1.00≤CRP<3.41)	35/3159	1.11	0.99(0.60,1.62)	0.954	0.86(0.50,1.45)	0.565	
Q3 (3.41≤CRP<8.50)	33/2806	1.18	1.05(0.63,1.73)	0.858	0.79(0.46,1.35)	0.393	
Q4 (8.50≤CRP)	38/2338	1.63	1.45(0.89,2.36)	0.132	1.08(0.64,1.82)	0.773	

Notes: Adjusted for age, male, diabetes, dyslipidemia, atrial fibrillation, NIHSS at first admission, total cholesterol, LDL-C, SBP, DBP, HbA1c, fasting blood glucose.
Abbreviations: CRP, indicates C-reactive protein; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure and HbAlc, glycated hemoglobin.

stress.[13,14] Recent studies suggest that both systemic and local inflammation are involved in ICH.[15] After ICH occurs, the hematoma activates resident immune cells in the brain and recruits circulating immune cells to the lesion, releasing a large number of inflammatory factors into the circulation, thereby regulating CRP elevation. Along with systemic inflammation, CRP can directly participate in neuroinflammation and secondary brain injury by activating the complement cascade reactions and microglia, thereby exacerbating local inflammation. There is direct evidence that CRP levels are elevated in the brain tissue parenchyma and perihematomal regions after ICH in autopsy samples,[16] this may be another potential factor for CRP leading to poor outcomes. CRP participates in both systemic and local inflammation after ICH. Early elevation of CRP levels, which may reflect the degree of systemic and local inflammation caused by hematoma, further supports the active role of CRP in defining the extent of damage.[7]

As is well known, for patients with ICH, infection complicates the hospitalization process and is associated with poor functional outcomes.[17] In the neurointensive care unit (NICU), up to 70% of patients with ICH develop at least one complication, and 23–58% of patients may suffer from infectious complications.[8,18] In addition, infection causes inflammation and immune cells in the lesion release a large number of inflammatory factors. Hepatocytes produce CRP under the regulation of inflammatory factors (IL-1, IL-6, and TNF).[19] This process is similar to that of secondary brain injury after ICH, and the increase in CRP in patients with ICH may be caused by the ICH itself or the infection.

The present study suggests that, without infection, there is still an association between higher CRP levels and functional disability in patients with ICH. Furthermore, the data showed that when CRP was within the Q4 range (a significantly increased level), the OR values for functional disability in patients without infection were lower than those in the whole population, indicating that infection may further increase the risk of functional disability in the early stages of ICH based on the ICH itself. This is consistent with the conclusion of a cohort study of 103 patients with supratentorial hematoma, which stated that patients classified as having a poor condition (mRS > 2) at discharge had a higher incidence of infections.[20]

It is worth noting that, in contrast to functional disability, when CRP was within the Q4 range, although the OR values for hematoma evacuation increased in both non-infected patients and the whole population, it was higher in non-infected patients. Hematoma evacuation typically indicates that the larger hematoma has a more significant mass effect. The reason may be that, compared to infected patients, the significantly elevated CRP levels in non-infected patients are more likely to result from the brain hemorrhage itself, rather than from infection, potentially

indicating a larger hematoma or more intense inflammatory response associated with the ICH. However, since this study did not include continuous CRP monitoring, further research is needed to confirm whether elevated CRP levels in non-infected ICH patients are indeed associated with hematoma growth. Therefore, during the acute phase of ICH, if a significant increase in CRP is observed and infection is ruled out, clinicians should consider the possibility of worsening hematoma expansion and closely monitor these patients for early-stage deterioration.

The association between CRP and in-hospital mortality did not reach statistical significance. However, the RCS analysis indicated that around CRP = 2 mg/L, corresponding to the Q2 group, the odds ratio (OR) was relatively low. Although the 95% confidence interval still contains an adjusted OR of 1, we attempted to use this as a reference range (Table S1). The results suggest a potential trend indicating that a significant increase in CRP levels may be associated with higher in-hospital mortality.

This study has several limitations. First, in contrast to a randomized controlled design, our study had a retrospective design based on an observational cohort, which may have introduced a selection bias. Second, the CSCA database was not intended to include follow-up information; therefore, we were unable to evaluate patients' functional status after discharge. Third, the CSCA was designed to improve the quality of the diagnosis and treatment of cerebrovascular diseases in the neurology department. Patients admitted to neurosurgery or intensive care units may have more severe neurological impairment or a higher mortality risk, and may not be enrolled in the CSCA. This may have caused a selection bias. Fourth, the calculation methods for hematoma volume in different sub-centers of the CSCA (automatic software, semiautomatic software, or manually) are different; therefore, the hematoma volume information in this study cannot be collected. We analyzed the GCS score to reflect hematoma volume, and multivariate logistic regression analysis was used to adjust for confounding factors. Fifth, due to the large-scale, multicenter nature of this study, there was variability in the timing of CRP sample collection, with samples generally obtained on the second morning following admission, but the exact timing could vary by up to 12 hours. Additionally, our models were based solely on early CRP levels, and we did not monitor CRP changes over time. Both the timing variability and the lack of longitudinal CRP data represent limitations of the study. However, given the large sample size, we believe this variability is unlikely to have significantly affected the overall results. Sixth, the CSCA database does not include information on the precise location of hemorrhage (eg, lobar vs deep) or specific brain structures affected, which is an important variable influencing outcomes. This lack of data on hemorrhage location is another limitation of the study. Despite these limitations, we believe the findings provide valuable insights into the relationship between CRP levels and functional outcomes in patients with ICH.

Conclusion

This study revealed that significantly increased CRP levels were associated with a higher risk of early functional disability and hematoma evacuation in patients with ICH, regardless of the presence of infectious complications. While infections may exacerbate poor outcomes in patients with ICH, abnormally high CRP levels in the absence of infection should also prompt careful clinical evaluation.

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Disclosure

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