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Systemic C-Reactive Protein Predicts Cerebral Vasospasm and Delayed Cerebral Ischemia Following Aneurysmal Subarachnoid Hemorrhage: A Retrospective Observational Study

Ke Li[1], Dilaware Khan[1], Igor Fischer[1], Sajjad Muhammad[1-3]

■ BACKGROUND: **Aneurysmal subarachnoid hemorrhage (aSAH) is often complicated by cerebral vasospasm (CVS) and delayed cerebral ischemia (DCI), which significantly impact patient outcomes. The study aimed to investigate the predictive value of systemic serum biomarker levels for CVS and DCI following aSAH.**

■ METHODS: **We retrospectively analyzed data for 450 aSAH patients admitted to University Hospital Düsseldorf between January 2011 and October 2021. Serum biomarkers were measured on admission. The occurrence of CVS and DCI was assessed based on clinical and radiological criteria. Multivariate logistic regression analysis was performed to determine the independent association of serum biomarkers with CVS and DCI. We compared the predictive values of various models using the area under the receiver operating characteristic curve.**

■ RESULTS: **Of the 450 patients, 126 (28.0%) developed CVS, 123 (27.3%) developed DCI, and 62 (13.8%) developed co-occurring CVS and DCI. Patients with CVS, DCI, or both had significantly higher admission C-reactive protein (CRP) levels than those without these complications ($P < 0.001$). Elevated CRP levels were independently associated with an increased risk of CVS, DCI, and co-occurring CVS and DCI ($P < 0.05$). CRP demonstrated a higher predictive value for CVS (area under the curve [AUC]: 0.811) and co-occurring CVS and DCI (AUC: 0.802) compared to DCI alone (AUC: 0.690).**

■ CONCLUSIONS: **Our findings suggest that admission systemic CRP levels can serve as a more valuable predictor for developing CVS than DCI following aSAH. Incorporating CRP into clinical assessments may aid in risk stratification and early intervention strategies for patients at high risk of these complications.**

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) remains a devastating neurological event correlated with high morbidity and mortality rates.[1,2] Despite advances in neurocritical care, cerebral vasospasm (CVS) and delayed cerebral ischemia (DCI) continue to be regarded as significant

Key words
- aSAH
- Cerebral vasospasm
- CRP
- D-dimer
- Delayed cerebral ischemia
- Predictive value
- White blood cells

Abbreviations and Acronyms
AUC: Area under the curve
aSAH: Aneurysmal subarachnoid hemorrhage
CI: Confidence interval
CH: Chronic hydrocephalus
CVS: Cerebral vasospasm
CRP: C-reactive protein
CTA: Computed tomography angiography
DCI: Delayed cerebral ischemia
DSA: Digital subtraction angiography
GCS: Glasgow Coma Score
ICA: Internal carotid artery
IQR: Interquartile range
mFisher: Modified Fisher
mRS: Modified Rankin scale
OR: Odds ratio
WBCs: White blood cells
WFNS: World Federation of Neurosurgical Societies

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challenges in the management of patients with aSAH.[3] CVS, characterized by the narrowing of large cerebral arteries, typically manifests 3 to 14 days following the initial hemorrhage in approximately two-thirds of patients.[4,5] DCI, on the other hand, is a more complex phenomenon involving hypoperfusion and ischemia-driven neuronal injury, leading to neurological deterioration beyond the initial bleed.[3]

The early identification and prediction of CVS and DCI are crucial for implementing timely interventions to mitigate their impact on patient outcomes. In recent years, there has been growing interest in exploring biomarkers that may serve as predictors for these complications. Among these biomarkers, C-reactive protein (CRP), an acute-phase reactant synthesized by the liver in response to inflammatory stimuli, has emerged as a potential candidate.[6,7] CRP is a well-established marker of systemic inflammation and has been implicated in various pathological conditions, including cardiovascular diseases, infections, and inflammatory disorders.[8-10] In the context of aSAH, the role of CRP as a predictive biomarker for CVS and DCI has garnered increasing attention. Previous studies have suggested that elevated CRP levels may reflect the inflammatory response triggered by the initial hemorrhage and subsequent cerebral insults, thereby predisposing patients to the development of CVS and DCI.[11,12]

Despite these insights, the precise relationship between systemic CRP levels and the occurrence of CVS and DCI in patients with aSAH remains incompletely understood. Furthermore, there is limited data regarding the predictive value of CRP for these complications in the clinical setting. Therefore, the present retrospective observational study aims to investigate the association between systemic CRP levels measured on admission and the development of CVS and DCI in patients with aSAH. By elucidating the role of CRP as a potential prognostic marker, this study seeks to contribute to optimizing risk stratification and therapeutic decision-making in managing aSAH patients.

METHODS

Study Design and Participants

This retrospective observational study included patients diagnosed with aSAH admitted to University Hospital Düsseldorf between January 2011 and October 2021. Patients were identified through electronic medical records using relevant diagnostic codes. Inclusion criteria comprised adult patients (age $\geq$18 years) with confirmed aSAH based on clinical presentation, imaging findings (computed tomography angiography [CTA] or digital subtraction angiography [DSA]), and cerebrospinal fluid analysis consistent with subarachnoid hemorrhage. Exclusion criteria was that the laboratory examination had been significantly impacted by complications or significant infectious diseases. Finally, 450 patients aged 18 or older (21.0 to 93.0 years) were enrolled in the study. The study adhered to Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[13]

Data Collection

Demographic information (age, sex), clinical characteristics (World Federation of Neurosurgical Societies [WFNS] grade and Glasgow Coma Score [GCS]), laboratory results (serum CRP and D-dimer levels, complete blood count), radiological findings (modified Fisher [mFisher] grade, intracerebral hemorrhage, subdural hemorrhage, aneurysmal sizes, and locations), treatment modalities (surgical clipping or endovascular coiling of the aneurysm), and outcomes (6-month modified Rankin Scale [mRS], CVS, DCI, chronic hydrocephalus [CH], and seizures) were extracted from electronic medical records and outpatient follow-up. Serum laboratory test results levels were measured on admission within 24 hours post-aSAH.

Outcome Measures

The primary outcomes were the occurrence of CVS and DCI. CVS was defined as symptomatic or asymptomatic narrowing of cerebral arteries radiologically using transcranial Doppler ultrasound, DSA, or CTA. Transcranial Doppler ultrasound vasospasm was characterized by a mean flow velocity exceeding 120 cm/sec in the vessels. Angiographic vasospasm was identified as moderate to severe arterial constriction on CTA or DSA, determined by a neuroradiologist, excluding causes such as atherosclerosis, catheter-induced spasm, or vessel hypoplasia.[14,15] DCI was diagnosed clinically based on the onset of new focal neurological deficits or a decline in the GCS score attributed to cerebral ischemia within 6 weeks after aSAH, not detected on computed tomography or magnetic resonance imaging scans between 24 and 48 hours following early aneurysm occlusion, and not attributable to other causes.[15-17]

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical characteristics of the study population. Continuous variables were presented as mean $\pm$ standard deviation or median with interquartile range (IQR), as appropriate. Categorical variables were expressed as frequencies and percentages. The association between serum biomarker levels and the development of CVS and DCI was assessed using appropriate statistical tests (e.g., t-test, Mann-Whitney U test, and chi-square test). Multivariable logistic regression analysis was performed to adjust for potential confounders and determine the independent predictive value of parameters. The predictive value was performed using receiver operating characteristic curves. We performed a sensitivity analysis using the cutoff values of 1.05 mg/dL for CVS, 0.95 mg/dL for DCI, and 1.25 mg/dL for co-occurring CVS and DCI. Statistical significance was defined as $P < 0.05$. All statistical analyses were conducted using SPSS, version 25.0 (IBM Corp., Armonk, New York, USA) and R (version 4.1.2).

RESULTS

Baseline Characteristics

A total of 450 patients with aSAH were included in the study (Table 1). The median age of the patients was 55.0 years (IQR: 48.0–63.0), with the majority being female (67.8%). Hypertension was the most prevalent medical history among patients (69.3%). Upon admission, the median WFNS grade was 3 (IQR: 1–5), and the median GCS score was 12 (IQR: 3–15). Median admission serum biomarker levels were 0.6 mg/dL (IQR: 0.2–1.7) for CRP, 1.6 mg/L (IQR: 0.8–3.8) for D-dimer, 13.5 $\times$ 109/L (IQR: 10.7–16.7) for white blood cells (WBCs), and 240.0 $\times$ 10^9/L (IQR: 203.0–282.0) for platelets.

Table 1. Patients' Characteristics

Variables	Patients (n = 450)
Demographics	
Age, median (IQR), years	55.0 (48.0–63.0)
Female sex, n (%)	305 (67.8)
Medical history, n (%)	
Hypertension	312 (69.3)
Admission status, median (IQR)	
WFNS grade	3 (1–5)
GCS score	12 (3–15)
Admission serum biomarkers, median (IQR)	
CRP, (mg/dL)	0.6 (0.2–1.7)
D-Dimer, (mg/L)	1.6 (0.8–3.8)
WBCs, ($\times 10^9$/L)	13.5 (10.7–16.7)
Platelet, ($\times 10^9$/L)	240.0 (203.0–282.0)
Neuroradiological data	
mFisher score, median (IQR)	4 (3–4)
Intracerebral hemorrhage, n (%)	113 (25.1)
Subdural hemorrhage, n (%)	38 (8.4)
Aneurysmal locations, n (%)	
ACA/ACOM	186 (41.3)
MCA	108 (24.0)
PCOM	64 (14.2)
ICA	34 (7.6)
PC	58 (12.9)
Aneurysmal sizes, n (%)	
0–4.9 mm	129 (28.7)
5–6.9 mm	98 (21.8)
7–9.9 mm	74 (16.4)
10–19.9 mm	56 (12.4)
≥20 mm	16 (3.6)
Missing	77 (17.1)
Treatment status, n (%)	
Coil	159 (35.3)
Clip	256 (56.9)
No treatment	35 (7.8)
Neurological complications, n (%)	
CVS	126 (28.0)
DCI	123 (27.3)
Co-occurring CVS and DCI	62 (13.8)
CH	231 (51.3)
Seizures	61 (13.6)
Neurological functional outcomes	
mRS at 6 months, median (IQR)	3 (1–6)

IQR, interquartile range; WFNS, World Federation of Neurosurgical Societies; GCS, Glasgow Coma Score; CRP, C-reactive protein; WBCs, white blood cells; mFisher, modified Fisher; ACA, anterior cerebral artery; ACOM, anterior communicating artery; MCA, middle cerebral artery; PCOM, posterior communicating artery; ICA, internal carotid artery; PC, posterior circulation; CVS, cerebral vasospasm; DCI, delayed cerebral ischemia; CH, chronic hydrocephalus; mRS, modified Rankin Scale.

Neuroradiological data: The median mFisher score was 4 (IQR: 3–4). Intracerebral hemorrhage occurred in 25.1% of patients, while 8.4% had subdural hemorrhage. Aneurysmal locations varied, with the most common being anterior cerebral artery/anterior communicating artery aneurysms (41.3%), followed by middle cerebral artery (24.0%), posterior communicating artery (14.2%), internal carotid artery (ICA) (7.6%), and posterior circulation (12.9%). Aneurysm sizes were distributed as follows: 129 (28.7%) cases had sizes of 0–4.9 mm, 98 (21.8%) had sizes of 5–6.9 mm, 74 (16.4%) had sizes of 7–9.9 mm, 56 (12.4%) had sizes of 10–19.9 mm, and 16 (3.6%) had sizes ≥20 mm. Data from 77 (17.1%) cases were missing. Treatment status and neurological complications: The majority of patients received treatment, with 56.9% undergoing clipping and 35.3% undergoing coiling, while 7.8% received no treatment. Neurological complications included CVS in 28.0% of patients, DCI in 27.3%, co-occurring CVS and DCI in 13.8%, CH in 51.3%, and seizures in 13.6%. Neurological functional outcome: The median mRS score at 6 months was 3 (IQR: 1–6).

Stratification of aSAH Patients by CVS, DCI, and Co-occurring CVS and DCI

As shown in Table 2, 126 (28.0%) experienced CVS, while 324 (72.0%) did not. There were no significant differences in age between the CVS and no CVS groups (median age: 55.5 years vs. 55.0 years, $P = 0.943$), and the prevalence of female sex (69.0% vs. 67.3%, $P = 0.719$) and hypertension history (69.8% vs. 69.1%, $P = 0.884$) did not differ significantly between the 2 groups. Admission status and biomarkers: Upon admission, patients who experienced CVS had a significantly higher median WFNS grade than those who did not (median WFNS grade: 4 vs. 2, $P = 0.023$). Additionally, the median GCS score was significantly lower in the CVS group compared to the no CVS group (median GCS score: 10 vs. 13, $P = 0.034$). As shown in Table 2 and Figure 1, serum biomarker levels upon admission were significantly elevated in the CVS group compared to the no CVS group, including CRP (2.1 mg/dL vs. 0.4 mg/dL, $P < 0.001$), D-dimer (2.1 mg/L vs. 1.5 mg/L, $P = 0.016$), and WBC count (14.7×10^9/L vs. 13.0×10^9/L, $P < 0.001$). Neuroradiological data and treatment status: There were no significant differences in median mFisher scores between the CVS and no CVS groups (median mFisher score: 4 in both groups, $P = 0.139$). While the prevalence of intracerebral hemorrhage (31.0% vs. 22.8%, $P = 0.075$) and subdural

Table 2. Study Participants' Characteristics According to CVS Status and Comparison Between the 2 Subgroups

	Total Cohort (n = 450)			Subgroup Analysis (n = 317)		
Variables	**CVS (n = 126)**	**No CVS (n = 324)**	***P* Value**	**Low CRP Levels (n = 226)**	**High CRP Levels (n = 91)**	***P* Value**
Demographics						
Age, median (IQR), years	55.5 (49.0—61.3)	55.0 (47.0—64.0)	0.943	54.0 (47.0—62.0)	53.0 (45.0—62.0)	0.493
Female sex, n (%)	87 (69.0)	218 (67.3)	0.719	140 (61.9)	58 (63.7)	0.766
Medical history, n (%)						
Hypertension	88 (69.8)	224 (69.1)	0.884	156 (69.0)	64 (70.3)	0.820
Admission status, median (IQR)						
WFNS grade	4 (2—5)	2 (1—5)	**0.023**	2 (1—4)	1 (1—5)	0.749
GCS score	10 (3—15)	13 (3—15)	**0.034**	14 (6—15)	13 (4—15)	0.343
Admission serum biomarkers						
CRP, (mg/dL)	2.1 (0.8—4.3)	0.4 (0.2—0.9)	**<0.001**	0.3 (0.1—0.6)	2.6 (1.7—4.1)	**<0.001**
D-Dimer, (mg/L)	2.1 (1.0—4.5)	1.5 (0.8—3.7)	**0.016**	1.3 (0.7—3.0)	1.6 (0.9—3.8)	0.062
WBCs, ($\times 10^9$/L)	14.7 (11.9—18.4)	13.0 (10.1—16.2)	**<0.001**	12.1 (9.8—15.7)	14.7 (11.8—19.1)	**<0.001**
Platelet, ($\times 10^9$/L)	242.0 (205.5—285.0)	237.5 (202.0—279.0)	0.371	234.5 (203.8—275.8)	248.0 (213.0—299.0)	**0.035**
Neuroradiological data						
mFisher score, median (IQR)	4 (3—4)	4 (3—4)	0.139	4 (3—4)	1 (1—5)	0.236
Intracerebral hemorrhage, n (%)	39 (31.0)	74 (22.8)	0.075	0	0	—
Subdural hemorrhage, n (%)	10 (7.9)	28 (8.6)	0.809	0	0	—
Aneurysmal locations, n (%)			0.883			0.269
ACA/ACOM	52 (41.3)	134 (41.4)		113 (50.0)	34 (37.4)	
MCA	28 (22.2)	80 (24.7)		32 (14.2)	14 (15.4)	
PCOM	20 (15.9)	44 (13.6)		31 (13.7)	17 (18.7)	
ICA	8 (6.3)	26 (8.0)		18 (8.0)	7 (7.7)	
PC	18 (14.3)	40 (12.3)		32 (14.2)	19 (20.9)	
Aneurysmal sizes, n (%)			0.123			**0.003**
0—4.9 mm	30 (23.8)	99 (30.6)		78 (34.5)	22 (24.2)	
5—6.9 mm	25 (19.8)	73 (22.5)		59 (26.1)	20 (22.0)	
7—9.9 mm	23 (18.3)	51 (15.7)		34 (15.0)	18 (19.8)	
10—19.9 mm	21 (16.7)	35 (10.8)		16 (7.1)	20 (22.0)	
≥20 mm	8 (6.3)	8 (2.5)		4 (1.8)	0	
Missing	19 (15.1)	58 (17.9)		35 (15.5)	11 (12.1)	
Treatment status, n (%)			0.436			0.074
Coil	50 (39.7)	109 (33.6)		88 (38.9)	48 (52.7)	
Clip	68 (54.0)	188 (58.0)		122 (54.0)	39 (42.9)	
No treatment	8 (6.3)	27 (8.3)		16 (7.1)	4 (4.4)	

Bold marked values are statistically significantly different in two groups.

CVS, cerebral vasospasm; CRP, C-reactive protein; IQR, interquartile range; WFNS, World Federation of Neurosurgical Societies; GCS, Glasgow Coma Score; WBCs, white blood cells; mFisher, modified Fisher; ACA, anterior cerebral artery; ACOM, anterior communicating artery; MCA, middle cerebral artery; PCOM, posterior communicating artery; ICA, internal carotid artery; PC, posterior circulation; DCI, delayed cerebral ischemia; CH, chronic hydrocephalus; mRS, modified Rankin Scale.

Continues

Table 2. Continued

	Total Cohort (n = 450)			Subgroup Analysis (n = 317)		
Variables	**CVS (n = 126)**	**No CVS (n = 324)**	***P* Value**	**Low CRP Levels (n = 226)**	**High CRP Levels (n = 91)**	***P* Value**
Neurological complications, n (%)						
CVS	126 (100.0)	0	**<0.001**	28 (12.4)	56 (61.5)	**<0.001**
DCI	62 (49.2)	61 (18.8)	**<0.001**	31 (13.7)	36 (39.6)	**<0.001**
CH	87 (69.0)	144 (44.4)	**<0.001**	90 (39.8)	55 (60.4)	**0.001**
Seizures	21 (16.7)	40 (12.3)	0.229	31 (13.7)	13 (14.3)	0.895
Neurological functional outcome						
mRS at 6 months, median (IQR)	5 (2–6)	2 (1–5)	**<0.001**	2 (1–4)	3 (1–6)	**0.001**

Bold marked values are statistically significantly different in two groups.
CVS, cerebral vasospasm; CRP, C-reactive protein; IQR, interquartile range; WFNS, World Federation of Neurosurgical Societies; GCS, Glasgow Coma Score; WBCs, white blood cells; mFisher, modified Fisher; ACA, anterior cerebral artery; ACOM, anterior communicating artery; MCA, middle cerebral artery; PCOM, posterior communicating artery; ICA, internal carotid artery; PC, posterior circulation; DCI, delayed cerebral ischemia; CH, chronic hydrocephalus; mRS, modified Rankin Scale.

hemorrhage (7.9% vs. 8.6%, P = 0.809) did not differ significantly between the 2 groups, the distribution of aneurysmal locations (P = 0.883) and sizes (P = 0.123) showed no significant differences. Treatment modalities also did not differ significantly between the CVS and no CVS groups (P = 0.436). Neurological complications and functional outcome: Patients who experienced CVS had significantly higher rates of DCI (49.2% vs. 18.8%, P < 0.001) and CH (69.0% vs. 44.4%, P < 0.001) compared to those who did not experience CVS. However, the prevalence of seizures did not differ significantly between the 2 groups (16.7% vs. 12.3%, P = 0.229). Moreover, the mRS score at 6 months was significantly higher in the CVS group than the no CVS group (median mRS score: 5 vs. 2, P < 0.001), indicating a poorer neurological functional outcome among patients who experienced CVS.

As shown in Table 3, 123 (27.3%) developed DCI, while 327 (72.7%) did not. Patients who developed DCI had a median age of 58.0 years (IQR: 51.0–64.0), which was significantly higher than those who did not develop DCI (median age: 54.0 years, IQR: 48.0–63.0) (P = 0.049). There were no significant differences in female sex prevalence (69.1% vs. 67.3%, P = 0.712) or hypertension history (70.7% vs. 68.8%, P = 0.693) between the DCI and no DCI groups, respectively. Admission Status and Biomarkers: Patients who developed DCI had significantly higher median WFNS grades upon admission compared to those who did not (median WFNS grade: 5 vs. 2, P < 0.001). Similarly, the median GCS score was significantly lower in the DCI group compared to the no DCI group (median GCS score: 5 vs. 14, P < 0.001). As depicted in Table 3, serum biomarker levels upon admission were also significantly

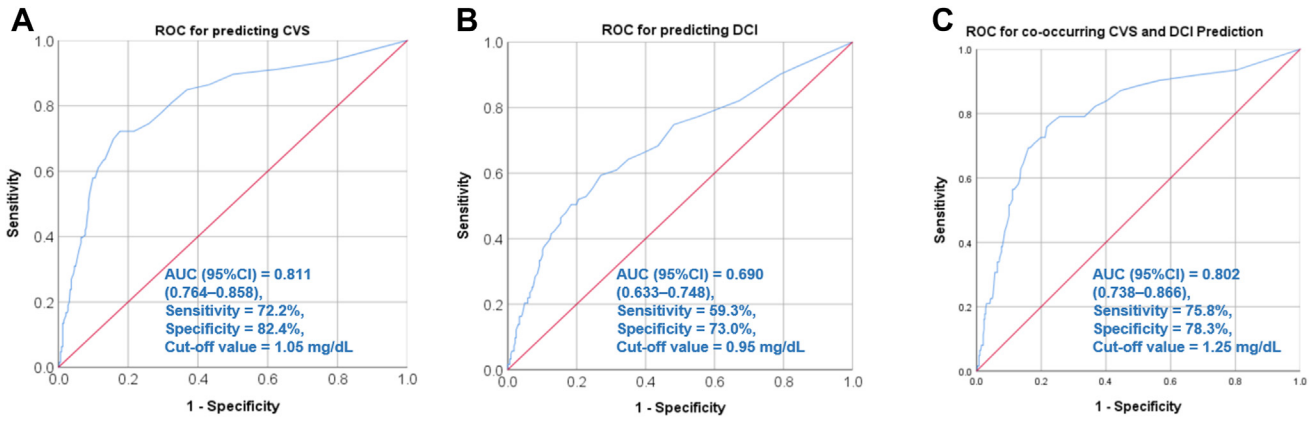

Figure 1. The ROC of admission CRP for CVS, DCI, and co-occurring CVS and DCI prediction. (**A**) ROC for predicting CVS; (**B**) ROC for predicting DCI; (**C**) ROC for predicting co-occurring CVS and DCI. ROC, receiver operating characteristic; CRP, C-reactive protein; CVS, cerebral vasospasm; DCI, delayed cerebral ischemia.

Table 3. Study Participants' Characteristics According to DCI Status and Comparison Between the 2 Subgroups

	Total Cohort (n = 450)			Subgroup Analysis (n = 317)		
Variables	**DCI (n = 123)**	**No DCI (n = 327)**	***P* Value**	**Low CRP Levels (n = 219)**	**High CRP Levels (n = 98)**	***P* Value**
Demographics						
Age, median (IQR), years	58.0 (51.0–64.0)	54.0 (48.0–63.0)	**0.049**	54.0 (47.0–62.0)	53.0 (46.0–62.0)	0.535
Female sex, n (%)	85 (69.1)	220 (67.3)	0.712	135 (61.6)	63 (64.3)	0.653
Medical history, n (%)						
Hypertension	87 (70.7)	225 (68.8)	0.693	150 (68.5)	70 (71.4)	0.600
Admission status, median (IQR)						
WFNS grade	5 (2–5)	2 (1–5)	**<0.001**	2 (1–4)	1 (1–5)	0.656
GCS score	5 (3–13)	14 (4–15)	**<0.001**	14 (6–15)	13 (6–15)	0.424
Admission serum biomarkers, median (IQR)						
CRP, (mg/dL)	1.6 (0.4–3.4)	0.4 (0.2–1.0)	**<0.001**	0.3 (0.1–0.5)	2.3 (1.6–4.0)	**<0.001**
D-dimer, (mg/L)	3.4 (1.4–6.5)	1.3 (0.7–3.0)	**<0.001**	1.3 (0.7–3.4)	1.6 (0.9–3.6)	0.094
WBCs, ($\times 10^9$/L)	14.8 (11.8–17.8)	13.0 (10.1–16.2)	**<0.001**	12.2 (9.8–15.8)	14.4 (11.7–19.0)	**<0.001**
Platelets, ($\times 10^9$/L)	240.0 (194.0–275.0)	240.0 (206.0–286.0)	0.173	237.0 (204.0–279.0)	244.5 (211.8–294.3)	0.136
Neuroradiological data						
mFisher score, median (IQR)	4 (3–4)	4 (3–4)	**0.001**	4 (3–4)	3 (3–4)	0.264
Intracerebral hemorrhage, n (%)	49 (39.8)	64 (19.6)	**<0.001**	0	0	–
Subdural hemorrhage, n (%)	16 (13.0)	22 (6.7)	**0.033**	0	0	–
Aneurysmal locations, n (%)			0.053			0.252
ACA/ACOM	42 (34.1)	144 (44.0)		109 (49.8)	38 (38.8)	
MCA	38 (30.9)	70 (21.4)		32 (14.6)	14 (14.3)	
PCOM	13 (10.6)	51 (15.6)		30 (13.7)	18 (18.4)	
ICA	9 (7.3)	25 (7.6)		18 (8.2)	7 (7.1)	
PC	21 (17.1)	37 (11.3)		30 (13.7)	21 (21.4)	
Aneurysmal sizes, n (%)			**<0.001**			**0.013**
0–4.9 mm	23 (18.7)	106 (32.4)		75 (34.2)	25 (25.5)	
5–6.9 mm	19 (15.4)	79 (24.2)		57 (26.0)	22 (22.4)	
7–9.9 mm	24 (19.5)	50 (15.3)		34 (15.5)	18 (18.4)	
10–19.9 mm	23 (18.7)	33 (10.1)		16 (7.3)	20 (20.4)	
≥20 mm	11 (8.9)	5 (1.5)		4 (1.8)	0	
Missing	23 (18.7)	54 (16.5)		33 (15.1)	13 (13.3)	
Treatment status, n (%)			**0.010**			**0.013**
Coil	32 (26.0)	127 (38.8)		82 (37.4)	54 (55.1)	
Clip	76 (61.8)	180 (55.0)		122 (55.7)	39 (39.8)	
No treatment	15 (12.2)	20 (6.1)		15 (6.8)	5 (5.1)	

Bold marked values are statistically significantly different in two groups.

DCI, delayed cerebral ischemia; CRP, C-reactive protein; IQR, interquartile range; WFNS, World Federation of Neurosurgical Societies; GCS, Glasgow Coma Score; WBCs, white blood cells; mFisher, modified Fisher; ACA, anterior cerebral artery; ACOM, anterior communicating artery; MCA, middle cerebral artery; PCOM, posterior communicating artery; ICA, internal carotid artery; PC, posterior circulation; CVS, cerebral vasospasm; CH, chronic hydrocephalus; mRS, modified Rankin Scale.

Continues

Table 3. Continued

Variables	Total Cohort (n = 450)			Subgroup Analysis (n = 317)		
	DCI (n = 123)	No DCI (n = 327)	*P* Value	Low CRP Levels (n = 219)	High CRP Levels (n = 98)	*P* Value
Neurological complications, n (%)						
CVS	62 (50.4)	64 (19.6)	**<0.001**	28 (12.8)	56 (57.1)	**<0.001**
DCI	123 (100.0)	0	**<0.001**	30 (13.7)	37 (37.8)	**<0.001**
CH	88 (71.5)	143 (43.7)	**<0.001**	88 (40.2)	57 (58.2)	**0.003**
Seizures	26 (21.1)	35 (10.7)	**0.004**	30 (13.7)	14 (14.3)	0.916
Neurological functional outcome						
mRS at 6 months, median (IQR)	6 (4–6)	2 (1–4)	**<0.001**	2 (1–4)	3 (1–6)	**0.006**

Bold marked values are statistically significantly different in two groups.

DCI, delayed cerebral ischemia; CRP, C-reactive protein; IQR, interquartile range; WFNS, World Federation of Neurosurgical Societies; GCS, Glasgow Coma Score; WBCs, white blood cells; mFisher, modified Fisher; ACA, anterior cerebral artery; ACOM, anterior communicating artery; MCA, middle cerebral artery; PCOM, posterior communicating artery; ICA, internal carotid artery; PC, posterior circulation; CVS, cerebral vasospasm; CH, chronic hydrocephalus; mRS, modified Rankin Scale.

different between the 2 groups, with higher median CRP (1.6 mg/dL vs. 0.4 mg/dL, $P < 0.001$), D-dimer (3.4 mg/L vs. 1.3 mg/L, $P < 0.001$), and WBC count (14.8 × 10^9/L vs. 13.0 × 10^9/L, $P < 0.001$) levels observed in the DCI group. Neuroradiological Data and Treatment Status: Median mFisher scores in DCI group were higher than those in no DCI group (median mFisher score: 4 vs. 4, mean mFisher score: 3.67 vs. 3.39, $P = 0.001$). However, intracerebral hemorrhage (39.8% vs. 19.6%, $P < 0.001$) and subdural hemorrhage (13.0% vs. 6.7%, $P = 0.033$) were more prevalent in the DCI group. Aneurysmal locations did not differ significantly between the 2 groups ($P = 0.053$). Aneurysm size also varied significantly ($P < 0.001$), with smaller aneurysms more prevalent in the DCI group. Treatment modalities differed between the DCI and no DCI groups ($P = 0.010$), with a higher proportion of patients in the DCI group undergoing clipping (61.8% vs. 55.0%) and a lower proportion receiving coiling (26.0% vs. 38.8%). Neurological complications and functional outcome: Patients who developed DCI experienced significantly higher rates of CVS (50.4% vs. 19.6%, $P < 0.001$), CH (71.5% vs. 43.7%, $P < 0.001$), and seizures (21.1% vs. 10.7%, $P = 0.004$) compared to those who did not develop DCI. Moreover, the median mRS score at 6 months was significantly higher in the DCI group compared to the no DCI group (median mRS score: 6 vs. 2, $P < 0.001$), indicating poorer neurological functional outcome among patients with DCI.

As shown in Table 4, patients with co-occurring CVS and DCI had significantly worse clinical status upon admission. The median WFNS grade was higher (4 vs. 2, $P = 0.003$), indicating more severe initial neurological impairment. Similarly, the median GCS score was lower in the co-occurring group (7 vs. 13, $P = 0.005$), reflecting more severe levels of consciousness impairment at presentation. Significant differences were observed in serum biomarkers between the 2 groups. The co-occurring group exhibited markedly higher levels of CRP (median 2.8 mg/dL vs. 0.5 mg/dL, $P < 0.001$), D-dimer (median 3.6 mg/L vs. 1.5 mg/L, $P < 0.001$), and WBC (median 15.0 × 10^9/L vs. 13.3 × 10^9/L, $P = 0.008$). Furthermore, intracerebral hemorrhage was significantly more common in the co-occurring group (43.5% vs. 22.2%, $P < 0.001$). Aneurysmal sizes were notably larger in the co-occurring group ($P = 0.001$). Moreover, all patients with co-occurring CVS and DCI had more common occurrences of CVS and DCI ($P < 0.001$). Additionally, CH was more prevalent in the co-occurring group (79.0% vs. 46.9%, $P < 0.001$). The functional outcome was significantly worse for patients with co-occurring CVS and DCI, as indicated by a higher 6-month mRS score (median 6 vs. 2, $P < 0.001$).

Multivariate Logistic Regression Analysis of Risk Factors for CVS, DCI, and Co-occurring CVS and DCI

As indicated in Table 5, admission CRP was an independent risk factor with CVS (odds ratio [OR] [95% confidence interval {CI}] 1.433 [1.245–1.649]; $P < 0.001$). Additionally, DCI emerged as an independent risk factor along with CVS (OR [95% CI] 2.258 [1.209–4.215]; $P = 0.011$). Similarly, as depicted in Table 6, on-admission CRP levels (OR [95% CI] 1.145 [1.008–1.299]; $P = 0.037$), mFisher score (OR [95% CI] 0.523 [0.307–0.891]; $P = 0.017$), mRS at 6 months (OR [95% CI] 1.781 [1.455–2.181]; $P < 0.001$), CVS (OR [95% CI] 2.414 [1.266–4.603]; $P = 0.007$), and CH (OR [95% CI] 2.275 [1.155–4.484]; $P = 0.018$) were independently associated with DCI. As described in Table 7, high on-admission CRP levels (OR [95% CI] 1.299 [1.143–1.477]; $P < 0.001$), CH (OR [95% CI] 2.988 [1.241–7.195]; $P = 0.015$), and mRS at 6 months (OR [95% CI] 1.633 [1.294–2.060]; $P < 0.001$) were independently associated with co-occurring CVS and DCI.

Predictive Value of CRP for CVS, DCI, and Co-occurring CVS and DCI Following aSAH

Using receiver operating characteristic curves, we evaluated the predictive value of CRP levels for CVS, DCI, and co-occurring CVS and DCI. The area under the curve (AUC) for CVS prediction was 0.811 (95% CI: 0.764–0.858; $P < 0.001$), with a sensitivity of 72.2%

Table 4. Study Participants' Characteristics According to Co-occurring CVS and DCI Status and Comparison Between the 2 Subgroups

	Total Cohort (n = 450)			Subgroup Analysis (n = 317)		
Variables	**Co-occurring CVS and DCI (n = 62)**	**No Co-occurring CVS and DCI (n = 388)**	***P* Value**	**Low CRP Levels (n = 236)**	**High CRP Levels (n = 81)**	***P* Value**
Demographics						
Age, median (IQR), years	58.0 (51.8—62.3)	55.0 (48.0—63.0)	0.197	54.0 (47.0—62.0)	53.0 (44.5—61.5)	0.471
Female sex, n (%)	42 (67.7)	263 (67.8)	0.995	147 (62.3)	51 (63.0)	0.914
Medical history, n (%)						
Hypertension	41 (66.1)	271 (69.8)	0.556	166 (70.3)	54 (66.7)	0.536
Admission status, median (IQR)						
WFNS grade	4 (2—5)	2 (1—5)	**0.003**	2 (1—4)	1 (1—5)	0.597
GCS score	7 (3—13)	13 (3—15)	**0.005**	14 (6—15)	13 (6—15)	0.539
Admission serum biomarkers, median (IQR)						
CRP, (mg/dL)	2.8 (1.3—4.8)	0.5 (0.2—1.1)	**<0.001**	0.3 (0.2—0.6)	2.8 (1.9—4.4)	**<0.001**
D-dimer, (mg/L)	3.6 (1.5—5.2)	1.5 (0.8—3.7)	**<0.001**	1.3 (0.7—3.1)	1.5 (0.9—3.7)	0.096
WBCs, ($\times 10^9$/L)	15.0 (12.2—18.1)	13.3 (10.5—16.5)	**0.008**	12.1 (9.8—15.6)	14.8 (12.1—19.3)	**<0.001**
Platelets, ($\times 10^9$/L)	240.0 (196.5—261.3)	239.5 (204.3—282.8)	0.300	236.5 (206.0—279.0)	248.0 (209.0—294.5)	0.163
Neuroradiological data						
mFisher score, median (IQR)	4 (3—4)	4 (3—4)	0.079	4 (3—4)	3 (3—4)	0.059
Intracerebral hemorrhage, n (%)	27 (43.5)	86 (22.2)	**<0.001**	0	0	—
Subdural hemorrhage, n (%)	6 (9.7)	32 (8.2)	0.707	0	0	—
Aneurysmal locations, n (%)			0.657			0.336
ACA/ACOM	23 (37.1)	163 (42.0)		116 (49.2)	31 (38.3)	
MCA	16 (25.8)	92 (23.7)		35 (14.8)	11 (13.6)	
PCOM	9 (14.5)	55 (14.2)		34 (14.4)	14 (17.3)	
ICA	3 (4.8)	31 (8.0)		18 (7.6)	7 (8.6)	
PC	11 (17.7)	47 (12.1)		33 (14.0)	18 (22.2)	
Aneurysmal sizes, n (%)			**0.001**			0.054
0—4.9 mm	10 (16.1)	119 (30.7)		80 (33.9)	20 (24.7)	
5—6.9 mm	10 (16.1)	88 (22.7)		61 (25.8)	18 (22.2)	
7—9.9 mm	13 (21.0)	61 (15.7)		36 (15.3)	16 (19.8)	
10—19.9 mm	11 (17.7)	45 (11.6)		20 (8.5)	16 (19.8)	
≥20 mm	8 (12.9)	8 (2.1)		4 (1.7)	0	
Missing	10 (16.1)	67 (17.3)		35 (14.8)	11 (13.6)	
Treatment status, n (%)			0.237			0.166
Coil	19 (30.6)	140 (36.1)		94 (39.8)	42 (51.9)	
Clip	35 (56.5)	221 (57.0)		126 (53.4)	35 (43.2)	

Bold marked values are statistically significantly different in two groups.

CVS, cerebral vasospasm; DCI, delayed cerebral ischemia; CRP, C-reactive protein; IQR, interquartile range; WFNS, World Federation of Neurosurgical Societies; GCS, Glasgow Coma Score; WBCs, white blood cells; mFisher, modified Fisher; ACA, anterior cerebral artery; ACOM, anterior communicating artery; MCA, middle cerebral artery; PCOM, posterior communicating artery; ICA, internal carotid artery; PC, posterior circulation; CH, chronic hydrocephalus; mRS, modified Rankin Scale.

Continues

Table 4. Continued

Variables	Total Cohort (n = 450)			Subgroup Analysis (n = 317)		
	Co-occurring CVS and DCI (n = 62)	No Co-occurring CVS and DCI (n = 388)	*P* Value	Low CRP Levels (n = 236)	High CRP Levels (n = 81)	*P* Value
No treatment	8 (12.9)	27 (7.0)		16 (6.8)	4 (4.9)	
Neurological complications, n (%)						
CVS	62 (100.0)	64 (16.5)	**<0.001**	31 (13.1)	53 (65.4)	**<0.001**
DCI	62 (100.0)	61 (15.7)	**<0.001**	32 (13.6)	35 (43.2)	**<0.001**
CVS and DCI	62 (100.0)	0	**<0.001**	9 (3.8)	25 (30.9)	**<0.001**
CH	49 (79.0)	182 (46.9)	**<0.001**	95 (40.3)	50 (61.7)	**0.001**
Seizures	12 (19.4)	49 (12.6)	0.151	32 (13.6)	12 (14.8)	0.778
Neurological functional outcome						
mRS at 6 months, median (IQR)	6 (4–6)	2 (1–5)	**<0.001**	2 (1–4)	4 (1–6)	**<0.001**

Bold marked values are statistically significantly different in two groups.
CVS, cerebral vasospasm; DCI, delayed cerebral ischemia; CRP, C-reactive protein; IQR, interquartile range; WFNS, World Federation of Neurosurgical Societies; GCS, Glasgow Coma Score; WBCs, white blood cells; mFisher, modified Fisher; ACA, anterior cerebral artery; ACOM, anterior communicating artery; MCA, middle cerebral artery; PCOM, posterior communicating artery; ICA, internal carotid artery; PC, posterior circulation; CH, chronic hydrocephalus; mRS, modified Rankin Scale.

Table 5. Multivariate Analysis of Variables Associated with CVS

Variables	OR (95% CI)	*P* Value
Admission status		
WFNS grade	0.827 (0.448–1.525)	0.542
GCS	0.990 (0.812–1.206)	0.918
Admission serum biomarkers		
CRP	1.433 (1.245–1.649)	**<0.001**
D-dimer	0.967 (0.917–1.021)	0.225
WBCs	1.012 (0.958–1.069)	0.674
Neurological complications		
DCI	2.258 (1.209–4.215)	**0.011**
CH	1.472 (0.807–2.687)	0.208
Neurological functional outcome		
mRS at 6 months	1.166 (0.983–1.383)	0.077

Bold marked values are statistically significantly different in two groups.
CVS, cerebral vasospasm; OR, odds ratio; CI, confidence interval; WFNS, World Federation of Neurosurgical Societies; GCS, Glasgow Coma Score; CRP, C-reactive protein; WBCs, white blood cells; DCI, delayed cerebral ischemia; CH, chronic hydrocephalus; mRS, modified Rankin Scale.

and specificity of 82.4%. The determined cut-off value for CVS prediction was 1.05 mg/dL (Figure 1A). Additionally, the AUC for DCI prediction was 0.690 (95% CI: 0.633–0.748; $P < 0.001$), with a sensitivity of 59.3% and specificity of 73.0%. The identified cut-off value for DCI prediction was 0.95 mg/dL (Figure 1B). Moreover, the AUC for co-occurring CVS and DCI prediction was 0.802 (95% CI: 0.738–0.866; $P < 0.001$), with a sensitivity of 75.8% and specificity of 78.3%. The proposed cut-off value for co-occurring CVS and DCI prediction was 1.25 mg/dL (Figure 1C). These findings suggest that admission serum CRP levels have a superior predictive value for CVS and co-occurring CVS and DCI compared to DCI after aSAH.

Subgroup and Sensitivity Analyses of the Associations Between CRP and CVS, DCI, as Well as co-occurring CVS and DCI, Following aSAH

We excluded patients with intracerebral and subdural hematomas or other significant focal hemorrhages from this analysis to ensure the homogeneity of the sample. We performed subgroup analyses using CRP cutoffs of 1.05 mg/dL for CVS, 0.95 mg/dL for DCI, and 1.25 mg/dL for co-occurring CVS and DCI. The incidences of CVS, DCI, and co-occurring CVS and DCI in patients with high levels of CRP were significantly higher than those with low levels of CRP ($P < 0.001$) (Tables 2–4). We performed sensitivity analyses, which consistently demonstrated a significant association between elevated CRP levels and the risk of CVS (OR [95% CI] 8.576 [4.631–15.881]; $P < 0.001$) and DCI (OR [95% CI] 3.007 [1.417–6.380]; $P = 0.004$), after multivariate logistic regression (Supplementary Tables 1 and 2). We further evaluated the

Table 6. Multivariate Analysis of Variables Associated with DCI

Variables	OR (95% CI)	*P* Value
Demographics		
Age	0.981 (0.958–1.004)	0.109
Admission status		
WFNS grade	1.175 (0.562–2.455)	0.668
GCS	1.086 (0.864–1.366)	0.480
Admission serum biomarkers		
CRP	1.145 (1.008–1.299)	**0.037**
D-dimer	1.010 (0.966–1.056)	0.658
WBCs	0.994 (0.938–1.054)	0.849
Neuroradiological data		
mFisher score	0.523 (0.307–0.891)	**0.017**
Intracerebral hemorrhage	1.587 (0.798–3.158)	0.188
Subdural hemorrhage	2.086 (0.723–6.018)	0.174
Aneurysmal sizes	1.091 (0.966–1.231)	0.161
Treatment status	1.641 (0.963–2.794)	0.068
Neurological complications		
CVS	2.414 (1.266–4.603)	**0.007**
CH	2.275 (1.155–4.484)	**0.018**
Seizures	1.866 (0.862–4.037)	0.113
Neurological functional outcome		
mRS at 6 months	1.781 (1.455–2.181)	**<0.001**

Bold marked values are statistically significantly different in two groups.
DCI, delayed cerebral ischemia; OR, odds ratio; CI, confidence interval; WFNS, World Federation of Neurosurgical Societies; GCS, Glasgow Coma Score; CRP, C-reactive protein; WBCs, white blood cells; mFisher, modified Fisher; CVS, cerebral vasospasm; CH, chronic hydrocephalus; mRS, modified Rankin Scale.

Table 7. Multivariate Analysis of Variables Associated with Co-occurring CVS and DCI Status

Variables	OR (95% CI)	*P* Value
Admission status		
WFNS grade	0.582 (0.241–1.402)	0.227
GCS	0.950 (0.726–1.242)	0.707
Admission serum biomarkers		
CRP	1.299 (1.143–1.477)	**<0.001**
D-dimer	1.006 (0.952–1.062)	0.842
WBCs	0.983 (0.911–1.061)	0.660
Neurological complications		
CH	2.988 (1.241–7.195)	**0.015**
Neurological functional outcome		
mRS at 6 months	1.633 (1.294–2.060)	**<0.001**

Bold marked values are statistically significantly different in two groups.
CVS, cerebral vasospasm; DCI, delayed cerebral ischemia; OR, odds ratio; CI, confidence interval; WFNS, World Federation of Neurosurgical Societies; GCS, Glasgow Coma Score; CRP, C-reactive protein; WBCs, white blood cells; CH, chronic hydrocephalus; mRS, modified Rankin Scale.

interaction between CRP levels and various variables on CVS, DCI, and co-occurring CVS and DCI (**Supplementary Tables 4-6**). Significant effect modification was observed with age (P for interaction = 0.006), sex (P for interaction = 0.045), and treatment status (P for interaction = 0.042) for CVS, and with treatment status for DCI (P for interaction = 0.016), and with aneurysmal locations (P for interaction = 0.023) and treatment status (P for interaction = 0.025) for co-occurring CVS and DCI. No other interactions between CRP and CVS, DCI, or co-occurring CVS and DCI were statistically significant.

DISCUSSION

Several predictive models have emerged in recent years to predict outcomes or modalities in patients with aSAH. Accurate prognosis prediction is crucial for tailoring appropriate clinical treatment strategies in these patients. Serum biomarkers such as CRP, D-dimer, WBCs, and platelets have gained attention as easily quantifiable indicators, warranting independent investigation for outcome prediction after aSAH.[18-20] Among the complications following aSAH, CVS and DCI are particularly critical, significantly impacting patient outcomes.[21] Our study aimed to explore the predictive value of CRP, D-dimer, WBCs, and platelets in patients with CVS and DCI after aSAH. Our findings underscored CRP's independent association with CVS, DCI, and co-occurring CVS and DCI, particularly as a valuable predictor for CVS after aSAH.

Our findings indicate a significant association between elevated systemic CRP levels and the development of CVS and DCI in patients with aSAH. This association persisted even after adjusting for confounding factors such as age, sex, comorbidities, aneurysm characteristics, and treatment modalities. These results suggest that CRP may be a valuable biomarker for identifying patients at increased risk of developing CVS and subsequent DCI following aSAH. The exact mechanisms underlying the association between CRP levels and CVS/DCI in aSAH patients remain fully elucidated. However, it is well established that inflammation plays a crucial role in the pathophysiology of CVS and subsequent ischemic complications.[22] CRP, functioning as an acute-phase reactant, indicates systemic inflammation and reflects its presence and extent in various pathologies. In aSAH, its elevation likely signifies the activation of inflammatory pathways contributing to vasospasm and ischemic injury.[23] Notably, interleukin-1 stimulates CRP production, and its correlation with the pathogenesis of CVS has been established.[24] Furthermore, CRP may influence CVS and DCI via mechanisms like inflammation, endothelial dysfunction, and altered blood flow dynamics. We hypothesized pathophysiological pathway linking CRP with CVS and DCI following aSAH. Systemic CRP levels rise in response to systemic inflammation caused by aSAH. Elevated CRP promotes

a pro-inflammatory state that leads to endothelial dysfunction. Endothelial dysfunction contributes to altered blood flow dynamics, increasing the risk of CVS. CVS can occur as a direct consequence of the inflammatory response and endothelial dysfunction. CVS contributes to DCI, but systemic inflammation and endothelial dysfunction may also directly lead to ischemia.[25] Studies by Fountas et al.[24] and Gaastra et al.[18] have emphasized the significance of CRP levels in predicting postoperative functional outcomes after aSAH, with higher levels strongly correlating with poorer outcomes. Additionally, Romero et al.[26] demonstrated that elevated admission serum CRP levels predict unfavorable clinical outcomes and increased occurrences of CVS and delayed ischemic neurological deficits. Our study corroborates these findings, confirming that admission serum CRP levels are indeed associated with CVS and DCI following aSAH, consistent with previous reports.

The investigation of D-dimer in the context of SAH began in 1995, when Fujii et al.[27] demonstrated that high admission serum D-dimer was associated with poor outcomes in SAH patients. Subsequent studies have further explored this relationship. For instance, Liu et al.[19] reported elevated serum D-dimer levels were significantly correlated with adverse outcomes, including DCI and seizures, in aSAH patients. Furthermore, Fukada et al.[28] found a significant correlation between high admission D-dimer levels and systemic complications such as nosocomial infections, serum sodium disorders, and cardiopulmonary complications. Admission D-dimer provides additional predictive value beyond conventional risk factors in predicting outcomes in aSAH patients. Our study observed significantly higher levels of on-admission D-dimer in CVS and DCI than those without these complications. However, our study showed that D-dimer did not serve as an independent CVS and DCI predictive factor following aSAH. This finding warrants further investigation to elucidate.

Furthermore, WBCs serve as indicators of systemic inflammation and are extensively studied for prognostic purposes in various diseases, including cancers and aSAH.[29,30] A study by Geraghty et al., using multivariate logistic analysis, identified admission WBC counts as an independent risk factor for CVS after aSAH.[31] Moreover, Hu et al. reported that elevated admission WBC counts could independently correlate with DCI after aSAH.[32] Our study observed significantly higher levels of admission WBC counts in CVS and DCI patients than those without complications after aSAH. However, multivariate analysis does not find on-admission WBC counts independently associated with CVS and DCI after aSAH, nor predictive of these complications, which needs further research.

Platelets are well-established as critical regulators of hemostasis and thrombus formation.[33] Their role in blood vessel function is crucial, with implications for conditions such as myocardial infarction, stroke, and venous thromboembolism.[33] Previous studies have highlighted the associations of platelets with CVS and DCI after aSAH.[34] However, we did not detect differences in on-admission platelet counts between patients with CVS and DCI after aSAH and those without these complications. This finding requires further investigation.

Moreover, in a previous study, nearly 50% of aSAH patients with CVS developed DCI.[21] In our study, 62 out of 126 CVS patients had co-occurring CVS and DCI. CRP levels were significantly higher in these patients compared to those without this co-occurrence, and elevated CRP levels were identified as an independent risk factor for the development of co-occurring CVS and DCI. Our investigation revealed that the specificity and sensitivity of on-admission CRP levels for predicting co-occurring CVS and DCI were 78.3% and 75.8%, respectively. These results suggest a high specificity and sensitivity of on-admission CRP levels in co-occurring CVS and DCI prediction, indicating its potential as a valuable predictor. Similarly, for CVS prediction, the specificity and sensitivity of on-admission CRP levels were 82.4% and 72.2%, respectively. For DCI prediction, the specificity and sensitivity of on-admission CRP levels were 73.0% and 59.3%, respectively. Although still significant, CRP levels demonstrated lower specificity and sensitivity for DCI prediction than CVS and co-occurring CVS and DCI prediction. Nonetheless, CRP levels exhibit a promising predictive value for identifying CVS after aSAH, aiding its diagnosis in clinical settings. Importantly, after excluding patients with intracerebral and subdural hematomas, we conducted subgroup and sensitivity analyses to evaluate the robustness of our findings, which consistently aligned with our initial results. Nevertheless, to achieve a more accurate prediction of CVS and DCI in the future, developing improved predictive models is imperative to enhance sensitivity and specificity. This may involve incorporating additional biomarkers or refining existing algorithms to better capture the complex dynamics underlying these neurological complications post-aSAH.

Furthermore, our study also adds to prior work and presents novel information. 1. Comprehensive multivariate analysis: While previous studies have explored the association between CRP and outcomes like vasospasm and DCI, the study employs a comprehensive multivariate analysis that controls for a wide range of potential confounders. By including variables such as WBCs, platelet count, D-Dimer levels, age, aneurysm size, type of treatment, and the presence of intracerebral or subdural hemorrhage components, we provide a more nuanced understanding of the independent role of CRP as a predictor. 2. Large and well-characterized cohort: Our study's cohort of over 450 patients is one of the larger samples studied in this context, providing sufficient statistical power to detect significant associations. This large, well-characterized population allows for a more robust evaluation of CRP as a predictive marker, potentially offering more generalizable findings than smaller or less diverse cohorts. 3. Exclusion of non-aSAH-related inflammatory causes: To reduce bias and enhance the specificity of our findings, we meticulously excluded patients with clear non-aSAH-related causes of systemic inflammation. This careful patient selection helps to isolate the effect of CRP related specifically to the pathophysiology of SAH, distinguishing our study from others that may not have addressed this confounding factor as rigorously. 4. Contribution to clinical practice: We believe that our findings have practical implications for clinical practice. If CRP is validated as a reliable early predictor, it could be integrated into clinical protocols to enhance the monitoring and management of patients with SAH, potentially improving outcomes through earlier intervention. This potential application underscores the novel clinical relevance of our work. In summary, while our study builds upon the existing body of literature, it adds significant value through its rigorous analysis,

large sample size, exclusion of confounding factors, and contributions to clinical practice. We are confident that these contributions offer new insights and enhance the understanding of CRP's role in predicting vasospasm and DCI following aSAH.

Some limitations exist in our study. Firstly, as a retrospective single-center study, our findings may be subject to biases from patient selection and treatment decisions. Hence, there is a need for prospective multicenter clinical trials to validate the conclusions. Secondly, including 87 cases lacking complete admission D-dimer data may have impacted our results. Thirdly, assessing neurological functional outcome relied on self-reporting rather than objective, blinded evaluations, potentially introducing subjectivity into our findings. Lastly, the underlying mechanisms remain incompletely understood despite uncovering associations between on-admission serum biomarkers and CVS and DCI after aSAH. Addressing these limitations through rigorous study designs and further mechanistic investigations will enhance our findings' robustness and clinical applicability.

CONCLUSIONS

Our study found higher on-admission CRP, D-dimer, and WBCs in patients with CVS, DCI, and co-occurring CVS and DCI than those without complications following aSAH. Notably, on-admission CRP levels were independently associated with CVS, DCI, and co-occurring CVS and DCI, with CRP showing a stronger predictive value for CVS and co-occurring CVS and DCI than for DCI. These findings have potential implications for clinical practice, providing clinicians with insights into assessing the risk of progression and developing tailored therapeutic strategies for aSAH patients.

ETHICS APPROVAL

Our study is in accordance with the guidelines of the Helsinki declaration and approved by the ethics committee of the medical faculty of the Heinrich-Heine-University (Reference Number: Studien-Nr.:2022—2007). The written informed was waived due to the retrospective study design.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Ke Li: Writing — original draft, Software, Methodology, Investigation, Conceptualization. **Dilaware Khan:** Writing — review & editing, Conceptualization. **Igor Fischer:** Writing — review & editing, Software, Formal analysis. **Sajjad Muhammad:** Writing — review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT in order to improve the language and readability. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Supplementary Table 1. Multivariate Analysis of Variables Associated with CRP Subgroups Dependent on CVS

Variables	OR (95% CI)	*P* Value
Admission serum biomarkers		
Platelet	1.006 (1.001—1.012)	**0.018**
WBCs	1.033 (0.971—1.100)	0.299
Neuroradiological data		
Aneurysmal sizes	1.009 (0.882—1.154)	0.899
Neurological complications		
CVS	8.576 (4.631—15.881)	**<0.001**
DCI	2.684 (1.271—5.668)	**0.010**
CH	1.450 (0.776—2.709)	0.244
Neurological functional outcome		
mRS at 6 months	1.031 (0.886—1.199)	0.694

Bold marked values are statistically significantly different in two groups.
CRP, C-reactive protein; CVS, cerebral vasospasm; OR, odds ratio; CI, confidence interval; WBCs, white blood cells; DCI, delayed cerebral ischemia; CH, chronic hydrocephalus; mRS, modified Rankin Scale.

Supplementary Table 2. Multivariate Analysis of Variables Associated with CRP Subgroups Dependent on DCI Status

Variables	OR (95% CI)	*P* Value
Admission serum biomarkers		
WBCs	1.048 (0.991—1.110)	0.103
Treatment status	0.487 (0.297—0.797)	**0.004**
Neurological complications		
CVS	6.857 (3.752—12.530)	**<0.001**
DCI	3.007 (1.417—6.380)	**0.004**
CH	1.192 (0.658—2.158)	0.562
Neurological functional outcome		
mRS at 6 months	0.986 (0.851—1.141)	0.847

Bold marked values are statistically significantly different in two groups.
CRP, C-reactive protein; DCI, delayed cerebral ischemia; OR, odds ratio; CI, confidence interval; WBCs, white blood cells; CVS, cerebral vasospasm; CH, chronic hydrocephalus; mRS, modified Rankin Scale.

Supplementary Table 3. Multivariate Analysis of Variables Associated with CRP Subgroups Dependent on Co-occurring CVS and DCI Status

Variables	OR (95% CI)	*P* Value
Admission serum biomarkers		
WBCs	1.075 (1.012—1.142)	**0.019**
Neurological complications		
CVS	11.814 (5.532—25.229)	**<0.001**
DCI	4.358 (1.656—11.467)	**0.003**
CVS and DCI	0.451 (0.121—1.681)	0.235
CH	1.239 (0.651—2.356)	0.514
Neurological functional outcome		
mRS at 6 months	1.015 (0.871—1.184)	0.846

Bold marked values are statistically significantly different in two groups.
CRP, C-reactive protein; CVS, cerebral vasospasm; DCI, delayed cerebral ischemia; OR, odds ratio; CI, confidence interval; WBCs, white blood cells; CH, chronic hydrocephalus; mRS, modified Rankin Scale.

Supplementary Table 4. Subgroup Analysis of Association Between CRP and CVS After aSAH

Subgroups	Number (%)	Low CRP Levels Event/Total	High CRP Levels Event/Total	OR (95% CI)	*P* for Interaction
All patients	317 (100.00)	28/226	56/91	11.31 (6.34—20.18)	
Age					**0.006**
<65	259 (81.70)	19/188	47/71	17.42 (8.80—34.49)	
≥65	58 (18.30)	9/38	9/20	2.64 (0.83—8.37)	
Sex					**0.045**
Male	119 (37.54)	9/86	25/33	26.74 (9.32—76.69)	
Female	198 (62.46)	19/140	31/58	7.31 (3.60—14.83)	
WFNS					0.983
1—2	188 (59.31)	21/137	51/51	1736497992.00 (0.00— Inf)	
3—5	129 (40.69)	7/89	5/40	1.67 (0.50—5.63)	
mFisher					0.998
0—2	36 (11.36)	28/28	8/8	1.00 (0.00—Inf)	
3—4	281 (88.64)	0/198	48/83	1171934343.18 (0.00— Inf)	
Hypertension					0.498
No	97 (30.60)	8/70	18/27	15.50 (5.23—45.98)	
Yes	220 (69.40)	20/156	38/64	9.94 (5.01—19.71)	
Aneurysmal locations					0.172
ACA/ACOM	147 (46.37)	15/113	20/34	9.33 (3.90—22.34)	
MCA	46 (14.51)	5/32	6/14	4.05 (0.97—16.84)	
PCOM	48 (15.14)	2/31	14/17	67.67 (10.13—452.18)	
ICA	25 (7.89)	2/18	4/7	10.67 (1.31—86.93)	
PC	51 (16.09)	4/32	12/19	12.00 (2.95—48.77)	
Aneurysmal sizes					0.836
0—4.9 mm	100 (31.55)	7/78	12/22	12.17 (3.88—38.18)	
5—6.9 mm	79 (24.92)	7/59	14/20	17.33 (5.02—59.89)	
7—9.9 mm	52 (16.40)	7/34	11/18	6.06 (1.72—21.38)	
10—19.9 mm	36 (11.36)	2/16	12/20	10.50 (1.86—59.27)	
≥20 mm	4 (1.26)	1/4	0/0	NA	
Missing	46 (14.51)	4/35	7/11	13.56 (2.71—67.88)	
CH					0.999
No	172 (54.26)	12/136	18/36	10.33 (4.28—24.96)	
Yes	145 (45.74)	16/90	38/55	10.34 (4.71—22.71)	
CVS and DCI					0.999
No	283 (89.27)	19/217	31/66	9.23 (4.70—18.12)	
Yes	34 (10.73)	9/9	25/25	1.00 (0.00—Inf)	
Treatment status					**0.042**
Coil	136 (42.90)	14/88	27/48	6.80 (3.03—15.23)	
Clip	161 (50.79)	13/122	25/39	14.97 (6.27—35.78)	
No treatment	20 (6.31)	1/16	4/4	4715490193.48 (0.00— Inf)	

Bold marked values are statistically significantly different in two groups.

CRP, C-reactive protein; CVS, cerebral vasospasm; aSAH, aneurysmal subarachnoid hemorrhage; OR, odds ratio; CI, confidence interval; WFNS, World Federation of Neurosurgical Societies; mFisher, modified Fisher; ACA, anterior cerebral artery; ACOM, anterior communicating artery; MCA, middle cerebral artery; PCOM, posterior communicating artery; ICA, internal carotid artery; PC, posterior circulation; CH, chronic hydrocephalus; DCI, delayed cerebral ischemia.

Supplementary Table 5. Subgroup Analysis of Association Between CRP and DCI After aSAH

Variables	Number (%)	Low CRP Levels Event/Total	High CRP Levels Event/Total	OR (95% CI)	*P* for Interaction
All patients	317 (100.00)	30/219	37/98	3.82 (2.18—6.70)	
Age					0.765
<65	259 (81.70)	23/182	28/77	3.95 (2.09—7.48)	
≥65	58 (18.30)	7/37	9/21	3.21 (0.97—10.60)	
Sex					0.666
Male	119 (37.54)	12/84	15/35	4.50 (1.82—11.14)	
Female	198 (62.46)	18/135	22/63	3.49 (1.70—7.15)	
WFNS					0.747
1—2	188 (59.31)	21/134	24/54	4.30 (2.12—8.76)	
3—5	129 (40.69)	9/85	13/44	3.54 (1.37—9.13)	
mFisher					0.129
0—2	36 (11.36)	9/28	3/8	1.27 (0.25—6.51)	
3—4	281 (88.64)	21/191	34/90	4.91 (2.64—9.16)	
Hypertension					0.220
No	97 (30.60)	8/69	13/28	6.61 (2.32—18.81)	
Yes	220 (69.40)	22/150	24/70	3.04 (1.55—5.93)	
Aneurysmal locations					0.189
ACA/ACOM	147 (46.37)	15/109	11/38	2.55 (1.05—6.20)	
MCA	46 (14.51)	7/32	5/14	1.98 (0.50—7.87)	
PCOM	48 (15.14)	1/30	7/18	18.45 (2.03—167.76)	
ICA	25 (7.89)	3/18	2/7	2.00 (0.26—15.62)	
PC	51 (16.09)	4/30	12/21	8.67 (2.22—33.83)	
Aneurysmal sizes					0.393
0—4.9 mm	100 (31.55)	6/75	7/25	4.47 (1.34—14.96)	
5—6.9 mm	79 (24.92)	4/57	8/22	7.57 (1.99—28.83)	
7—9.9 mm	52 (16.40)	6/34	9/18	4.67 (1.30—16.74)	
10—19.9 mm	36 (11.36)	6/16	9/20	1.36 (0.36—5.22)	
≥20 mm	4 (1.26)	2/4	0/0		
Missing	46 (14.51)	6/33	4/13	2.00 (0.46—8.72)	
CH					0.127
No	172 (54.26)	16/131	9/41	2.02 (0.82—5.00)	
Yes	145 (45.74)	14/88	28/57	5.10 (2.36—11.04)	
CVS and DCI					1.000
No	283 (89.27)	21/210	12/73	1.77 (0.82—3.81)	
Yes	34 (10.73)	9/9	25/25	1.00 (0.00—Inf)	

Continues

Supplementary Table 5. Continued

Variables	Number (%)	Low CRP Levels Event/Total	High CRP Levels Event/Total	OR (95% CI)	*P* for Interaction
Treatment status					**0.016**
Coil	136 (42.90)	3/82	20/54	15.49 (4.31—55.62)	
Clip	161 (50.79)	23/122	13/39	2.15 (0.96—4.82)	
No treatment	20 (6.31)	4/15	4/5	11.00 (0.93—130.32)	

Bold marked values are statistically significantly different in two groups.

CRP, C-reactive protein; DCI, delayed cerebral ischemia; aSAH, aneurysmal subarachnoid hemorrhage; OR, odds ratio; CI, confidence interval; WFNS, World Federation of Neurosurgical Societies; mFisher, modified Fisher; ACA, anterior cerebral artery; ACOM, anterior communicating artery; MCA, middle cerebral artery; PCOM, posterior communicating artery; ICA, internal carotid artery; PC, posterior circulation; CH, chronic hydrocephalus; CVS, cerebral vasospasm.

Supplementary Table 6. Subgroup Analysis of Association Between CRP and Co-occurring CVS and DCI After aSAH

Variables	Number (%)	Low CRP Levels Event/Total	High CRP Levels Event/Total	OR (95% CI)	P for Interaction
All patients	317 (100.00)	9/236	25/81	11.26 (4.98–25.47)	
Age					0.289
<65	259 (81.70)	6/195	20/64	14.32 (5.43–37.75)	
≥65	58 (18.30)	3/41	5/17	5.28 (1.10–25.41)	
Sex					0.321
Male	119 (37.54)	3/89	12/30	19.11 (4.89–74.71)	
Female	198 (62.46)	6/147	13/51	8.04 (2.87–22.55)	
WFNS					0.121
1–2	188 (59.31)	7/140	23/48	17.48 (6.78–45.10)	
3–5	129 (40.69)	2/96	2/33	3.03 (0.41–22.44)	
mFisher					0.987
0–2	36 (11.36)	9/28	3/8	1.27 (0.25–6.51)	
3–4	281 (88.64)	0/208	22/73	368,623,126.36 (0.00–Inf)	
Hypertension					0.774
No	97 (30.60)	4/70	10/27	9.71 (2.71–34.78)	
Yes	220 (69.40)	5/166	15/54	12.38 (4.24–36.14)	
Aneurysmal locations					**0.023**
ACA/ACOM	147 (46.37)	6/116	7/31	5.35 (1.65–17.34)	
MCA	46 (14.51)	2/35	2/11	3.67 (0.45–29.76)	
PCOM	48 (15.14)	0/34	6/14	640,901,571.97 (0.00–Inf)	
ICA	25 (7.89)	1/18	1/7	2.83 (0.15–52.74)	
PC	51 (16.09)	0/33	9/18	854,535,429.31 (0.00–Inf)	
CH					0.276
No	172 (54.26)	2/141	7/31	20.27 (3.97–103.47)	
Yes	145 (45.74)	7/95	18/50	7.07 (2.70–18.51)	
CVS					1.000
No	233 (73.50)	0/205	0/28	1.00 (0.00–Inf)	
Yes	84 (26.50)	9/31	25/53	2.18 (0.85–5.61)	
Treatment status					**0.025**
Coil	136 (42.90)	1/94	12/42	37.20 (4.64–298.09)	
Clip	161 (50.79)	7/126	9/35	5.88 (2.01–17.24)	
No treatment	20 (6.31)	1/16	4/4	4,715,490,229.71 (0.00– Inf)	
DCI					1.000
No	250 (78.86)	0/204	0/46	1.00 (0.00–Inf)	
Yes	67 (21.14)	9/32	25/35	6.39 (2.21–18.51)	
Aneurysmal sizes					0.841
0–4.9 mm	100 (31.55)	1/80	4/20	19.75 (2.07–188.55)	
5–6.9 mm	79 (24.92)	1/61	5/18	23.08 (2.48–214.35)	
7–9.9 mm	52 (16.40)	3/36	6/16	6.60 (1.39–31.28)	
10–19.9 mm	36 (11.36)	2/20	7/16	7.00 (1.20–40.82)	

Continues

Supplementary Table 6. Continued

Variables	Number (%)	Low CRP Levels Event/Total	High CRP Levels Event/Total	OR (95% CI)	P for Interaction
≥20 mm	4 (1.26)	1/4	0/0	NA	
Missing	46 (14.51)	1/35	3/11	12.75 (1.17—139.23)	

Bold marked values are statistically significantly different in two groups.

CRP, C-reactive protein; CVS, cerebral vasospasm; DCI, delayed cerebral ischemia; aSAH, aneurysmal subarachnoid hemorrhage; OR, odds ratio; CI, confidence interval; WFNS, World Federation of Neurosurgical Societies; mFisher, modified Fisher; ACA, anterior cerebral artery; ACOM, anterior communicating artery; MCA, middle cerebral artery; PCOM, posterior communicating artery; ICA, internal carotid artery; PC, posterior circulation; CH, chronic hydrocephalus.