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Platelets-to-serum Ca^{2+} ratio as a risk factor for postoperative cerebral vasospasm in surgically treated aneurysmal subarachnoid hemorrhage patients

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Abstract. – OBJECTIVE: Aneurysmal subarachnoid hemorrhage (aSAH) generally requires surgical intervention to secure the aneurysm(s). Cerebral vasospasm (CVS) is a common complication of aSAH that occurs before and after a clipping or coiling procedure. However, we have limited options for the prevention or early detection of CVS by far. Although some biomarkers were studied regarding the purpose, some of which are rather complicated and actually hard to obtain. We conducted this study to investigate the potential correlations between the platelets-to-serum Ca^{2+} ratio (P/C) and the occurrence of postoperative CVS in aSAH patients.

PATIENTS AND METHODS: We enrolled 262 patients in this retrospective study, clinical features and lab results were collected from an electronic medical record (EMR) system. The variables were consecutively analyzed in univariate and multivariate analyses; *p*-values < 0.05 were considered significant. The predictive values of several certain variables for CVS were further assessed through receiver operating characteristic (ROC) analysis.

RESULTS: The prevalence of CVS in our study was 33.6%. Patients suffering from CVS had significantly increased P/C levels compared to those who did not ($p = 0.045$). Multivariate logistic analysis revealed that P/C was independently associated with postoperative CVS ($p = 0.041$). ROC curves demonstrated prominent interactions between P/C and clinical rankings, in terms of predicting postoperative CVS in aSAH patients. At a cutoff value of 112.53, patients with higher P/C levels in the early stage of aSAH were more likely to develop symptomatic CVS after aneurysm occlusion ($p = 0.004$).

CONCLUSIONS: Among aSAH patients, a higher P/C at admission increases the risk of postoperative CVS events and, with easy access, it may serve as a novel predictor for the complication.

Key Words:
Aneurysmal subarachnoid hemorrhage, Cerebral vasospasm, Delayed cerebral ischemia, Platelets-to-serum calcium ratio, Cerebral vascular disease.

Introduction

Cerebral vascular diseases continue to pose major threats to modern health care, and spontaneous subarachnoid hemorrhage (SAH) is characterized by acute onset and a relatively high mortality/morbidity rate, as one dangerous category[1]. Intracranial aneurysms account for up to 80% of all SAH cases[2,3]; other predisposing conditions such as vascular malformation, inflammatory diseases, systemic coagulation dysfunction, and even leptospirosis, are occasionally observed. Patients with aneurysmal subarachnoid hemorrhage (aSAH) require immediate intensive care upon detection, and surgical treatment is usually warranted after the necessary evaluations are conducted. Maturing imaging technologies provide us with fast and dependable diagnoses of intracranial aneurysms, and in the meantime, we are making incredible progress in surgical treatment as well. However, postoperative complications of the disease can sometimes decisively affect the prognosis. To be more concise, cerebral vasospasm (CVS) has been, and will continue to significantly compromise the outcomes of patients with ruptured intracranial aneurysms despite effective aneurysmal securement by clipping or endovascular treatment (mainly coiling).

The occurrence of CVS usually leads to delayed cerebral ischemia (DCI). It is believed that symptomatic CVS happens roughly within a

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week after the rupture, in about one-third of the patients[4,5], with diversified manifestations including: changes in consciousness, linguistic dysfunction, limb weakness, and other location-specific ischemic symptoms. In most circumstances, doctors initially suspect CVS based on the worsening of the patient's general state, after which a computed tomography (CT) or a transcranial Doppler (TCD) is performed accordingly, to assess the severity. Nevertheless, admittedly, CVS progressed before we could diagnose it in many cases, which happens even in the most experienced neurological centers. CVS and DCI are rather difficult to predict due to their latent development, but can cause destructive consequences[6,7]. Therefore, an early prediction of CVS after aSAH will certainly aid in clinical practice. Unfortunately, so far, there are there no routinely acquired biomarkers or selective biomarkers that are strong enough or readily available, despite the remarkable efforts made regarding this matter.

CVS is a complicated condition with pathophysiological mechanisms that are not yet completely understood, the essence of which, conceivably, is a process of vessel constriction caused by various reasons. Since platelets and serum calcium are both crucial mediators in vascular activities[8-10], it seems reasonable to assume that they have potential influences on CVS, especially in the early stage. Meanwhile, the interactions between platelets and serum calcium in vascular incidents are also intricate and possibly contribute to CVS in some way[9,10]. Hence, we hypothesized that this combined indicator, P/C at admission, is potentially predictive of CVS in aSAH patients, despite the lack of previous reports. The aim of this study was to investigate the risk factors for postoperative CVS in surgically treated aSAH patients and to verify whether there is an association between P/C and CVS.

Patients and Methods

Population and Study Design

We enrolled 262 patients diagnosed with aSAH, all of whom received surgical intervention at our institution from January 2019 to December 2020 in this retrospective study. The inclusion criteria were as follows: (1) spontaneous SAH caused by rupture of intracranial aneurysm(s), confirmed by computed tomography angiography (CTA) or digital subtraction angiography (DSA); (2) clipping or endovascular procedure was performed; and (3) with routine blood tests on admission. The exclusion criteria were as follows: (1) vicious onset of aSAH leading to immediate death after even during admission; (2) a history of brain surgery; (3) regular or recent antiplatelet/anticoagulant drug administration; (4) stroke, brain tumor, or severe head trauma in the past; (5) other serious systemic diseases, such as autoimmune diseases, heart failure, respiratory conditions, uremia, or hematological disorders; (6) tumors outside the central nervous system; (7) other cerebrovascular malformation, such as Moyamoya disease; (8) aSAH in patients admitted for an unruptured aneurysm before elective operation; and (9) infectious diseases. All records used in the study were obtained from the official electronic medical record (EMR) system of our hospital, and no personal details that could expose the identities of the patients were involved.

Data on past illnesses were collected from straightforward recordings in medical paperwork. Determination of postoperative CVS was generally associated with indecipherable neurological deficits (sudden or gradual weakness in extremities, linguistic dysfunction, sopor, *etc*.) or visual ischemic/vasospasm changes on CT, CTA or TCD scans. We used the modified Fisher scale and Hunt-Hess scale to assess the severity of the hemorrhage; at least two, three whenever disputed, doctors participated to give a corresponding score. Blood test results at admission (*i.e.,* early stage of aSAH) were also acquired through the EMR system. P/C equals to platelets (10^9/L) divided by serum Ca^{2+} (mmol/L), W/C equals to white blood cells (WBCs, 10^9/L) divided by serum Ca^{2+} (mmol/L).

Patient Management

All patients were treated immediately upon arrival at the emergency room, and general management included monitoring of vital signs, supine position, oxygen inhalation, fluid supplementation and administration of brain-protecting agents. During hospitalization, *Nimodipine* was given routinely for each patient, intravenously in most cases, typically 2-3 times with a dosage of 10 mg/50 ml per day, in order to prevent or alleviate CVS. Notably, the use of *Nimodipine* was not relevant to any clinical trials but its use is a standard treatment in our institution, in compliance with the Chinese domestic guidelines for aSAH. To investigate the peculiarities of aneurysms, CTA and/or DSA were performed, accordingly. Surgical operations were performed by experi-

enced doctors after necessary preparations. The choice between clipping or coiling was made after assessing the benefits and risks, based on the patients' clinical conditions, aneurysmal features, and preferences when appropriate. The patients were discharged only after their conditions had been stabilized.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics R27.0.1.0 (IBM Corporation, Armonk, NY, USA) and MedCalc v20.009 (MedCalc Software Ltd, Ostend, Belgium). Categorical variables were expressed as counts (percentage) and analyzed with the Pearson χ^2 test or Fisher's exact test depending on the characteristics of the data[11]. Continuous variables are shown as the mean ± standard deviation when normally distributed, otherwise, the median alongside with quartile range (Q_1, Q_3), and analyzed by 2-tailed *t*-test and Mann-Whitney U test, respectively[12]. We considered *p*-values < 0.05 for all results as statistically significant. Demographics and baseline characteristics were compared between patients with and without postoperative CVS in univariate analysis. The variables, mainly those significant in the univariate analysis, were selected for a backward stepwise logistic regression to be performed[13]. After the optimal model was achieved, significant variables were included in the formula to generate receiver operating characteristic (ROC) curves to evaluate the predictive powers of these factors for postoperative CVS, and the areas under curves (AUCs) were compared through a nonparametric approach[14,15].

Results

Demographics and Clinical Baseline Characteristics

A total of 262 patients were included in the study, each of whom received surgical treatment and 88 (33.6%) had postoperative CVS, which was generally symptomatic. According to the presence of CVS, baseline characteristics were compared between the two groups (Table I). Patients in the CVS group tended to be elder (61.50 ± 10.74 years *vs.* 56.65 ± 12.03 years), while 100 (38.2%) of the total population was male, but there was no evidence of a significant difference in sex. Clinical grading scores, both modified Fisher scale and Hunt-Hess scale exhibited significantly higher among patients who experienced CVS after surgery ($p < 0.001$). As for major medical history, we found only diabetes statistically differed between the groups (12/88 [13.6%] *vs.* 10/174 [5.7%], $p = 0.030$). Surgery methodology and location of aneurysmal lesions were not relevant to CVS occurrence in this study. The time between aSAH onset to surgery and size of the (responsible) aneurysm also showed significant differences in the univariate analysis. Sustained lumbar cistern drainage procedures were more aggressively performed in the CVS group.

Lab Results

In comparison of the lab results, the two groups had undifferentiated serum Ca^{2+} levels (2.28 [2.15, 2.34] *vs.* 2.25 [2.17, 2.31] mmol/L, $p = 0.485$), while these data in the general study population were 2.25 [2.17, 2.32]. The three key indicators we chose were serum calcium, WBC and platelets. To avoid repetition and confusion, we calculated the ratios of serum Ca^{2+} with platelets and WBCs, for further analysis. P/C and W/C levels were both significantly higher ($p = 0.045$, 0.015) in the CVS group. Moreover, red blood cells (RBCs), hematocrit (HCT), and hemoglobin (Hb) did not show statistical differences between the groups.

Logistic Regression

Significant variables from the univariate analysis were fed into a multivariate logistic regression model. Additionally, due to the importance of hypertension in the clinical course of aSAH and CVS, as well as its essential role in vascular pathophysiological conditions, we also involved it in the regression regardless of its poor significance in the univariate analysis. Interestingly, sustained lumbar cistern drainage treatment manifested a positive correlation with CVS but was excluded as an evident anomaly, which we will elaborate in the Discussion section.

A backward stepwise logistic regression revealed associations of age, modified Fisher scale, Hunt-Hess scale and P/C with higher CVS risks (Table II).

ROC Analysis

The cutoff value of P/C for potential CVS prediction was 112.53, determined at a Youden index of 0.163, so P/C was converted into a binary variable to make up two groups (P/C: higher and lower), after which the patient characteristics

Table I. Demographics and baseline characteristics of aSAH patients according to the occurrence of postoperative CVS.

		CVS- (n =174)	CVS+ (n =88)	*p*-values
Demographics				
Age	58.28 ± 11.82	56.65 ± 12.03	61.50 ± 10.74	0.002*
Male	100 (38.2%)	61 (35.1%)	39 (44.3%)	0.145
Clinical grading				
mFisher scale				< 0.001*
1	150 (57.3%)	121 (69.5%)	29 (33.0%)	
2	10 (3.8%)	4 (2.3%)	6 (6.8%)	
3	80 (30.5%)	41 (23.6%)	39 (44.3%)	
4	22 (8.4%)	8 (4.6%)	14 (15.9%)	
Hunt-Hess scale				< 0.001*
I	152 (58.0%)	118 (67.8%)	34 (38.6%)	
II	36 (13.7%)	26 (14.9%)	10 (11.4%)	
III	49 (18.7%)	23 (13.2%)	26 (29.5%)	
IV	22 (8.4%)	6 (3.4%)	16 (18.2%)	
V	3 (1.1%)	1 (0.6%)	2 (2.3%)	
Major medical history				
Hypertension	127 (48.5%)	79 (45.4%)	48 (54.5%)	0.162
Diabetes	22 (8.4%)	10 (5.7%)	12 (13.6%)	0.030*
Smoking history	17 (6.5%)	12 (6.9%)	5 (5.7%)	0.706
Surgery				
Surgery method				0.136
Clipping	69 (26.3%)	39 (22.4%)	30 (34.1%)	
Endovascular treatment	187 (71.4%)	130 (74.7%)	57 (64.8%)	
Mixed	3 (1.1%)	3 (1.7%)	0 (0.0%)	
Failure attempt	3 (1.1%)	2 (1.1%)	1 (1.1%)	
Time between aSAH onset and surgery				< 0.001*
< 24h	38 (14.5%)	12 (6.9%)	26 (29.5%)	
24-48h	59 (22.5%)	44 (25.3%)	15 (17.0%)	
> 48h	165 (63.0%)	118 (67.8%)	47 (53.4%)	
Sustained lumbar cistern drainage	15 (5.7%)	4 (2.3%)	11 (12.5%)	< 0.001*
Aneurysm features				
Site (responsible)				0.656
AcoA	84 (32.1%)	52 (29.9%)	32 (36.4%)	
MCA	49 (18.7%)	31 (17.8%)	18 (20.5%)	
ICA	84 (32.1%)	61(35.1%)	23(26.1%)	
ACA	9 (3.4%)	6 (3.4%)	3 (3.4%)	
APC	36 (13.7%)	24 (13.8%)	12 (13.6%)	
Size				0.023*
< 0.5 cm	176 (67.2%)	126 (72.4%)	50 (56.8%)	
0.5-1.5 cm	81 (30.9%)	44 (25.3%)	37 (42.0%)	
1.5-2.5 cm	3 (1.1%)	2 (1.1%)	1 (1.1%)	
> 2.5 cm	2 (0.8%)	2 (1.1%)	0 (0.0%)	
Multiple aneurysms	54 (20.6%)	38 (21.8%)	16 (18.2%)	0.489
Second-time rupture	5 (1.9%)	1 (0.6%)	4 (4.5%)	0.045*
Admission blood tests				
Ca^{2+}, mmol/L	2.25 (2.17, 2.32)	2.25 (2.17, 2.31)	2.28 (2.15, 2.34)	0.485
Plt, 10^9/L	211 (178.5, 249)	206.5 (176.5,245)	223 (186, 263)	0.036*
P/C	93.48 (77.92,112.80)	91.92 (77.78, 109.34)	99.11(81.02, 118.36)	0.045*
WBCs, 10^9/L	10.20 (8.46, 13.02)	10.09 (7.92, 12.64)	10.81 (8.97, 13.91)	0.013*
W/C	4.58 (3.74, 5.70)	4.42 (3.60, 5.59)	4.68 (4.03, 6.29)	0.015*
HCT, %	41.39 ± 4.17	41.18 ± 4.19	41.79 ± 4.13	0.266
RBC, 10^{12}/L	4.58 ± 0.48	4.55 ± 0.47	4.63 ± 0.48	0.206
Hb, g/L	139.38 ± 15.31	138.36 ± 15.57	141.39 ± 14.65	0.131

Patients were divided into two groups by the presence of postoperative CVS. Univariate analyses showed significant differences of age, modified Fisher scale, Hunt-Hess scale, diabetes, time between aSAH onset and surgery, sustained lumbar cistern drainage, aneurysmal size, second-time rupture of aneurysm, Plt, WBCs, P/C and W/C between groups. Values are showed as n (%), mean ± standard deviation, median with quartile range (Q1, Q3). *Significant results ($p < 0.05$). aSAH: Aneurysmal subarachnoid hemorrhage; CVS: Cerebral vasospasm; mFisher: modified Fisher; AcoA: Anterior communicating artery; MCA: Middle cerebral artery; ICA: Internal carotid artery; ACA: Anterior cerebral artery; APC: Arteries of posterior circulation; Plt: Platelets; WBCs: White blood cells; P/C: Platelets-to-serum Ca^{2+} ratio; W/C: White blood cells-to-serum Ca^{2+} ratio; HCT: Hematocrit; RBCs: Red blood cells; Hb: Hemoglobin.

Table II. Multivariate logistic analysis of risk factors for postoperative CVS in aSAH patients.

	b	SE(b)	Wald	*p*-values	OR	95% CI of OR
Age	0.034	0.014	6.066	0.014	1.034	1.007-1.062
mFisher scale	0.327	0.151	4.715	0.030	1.387	1.032-1.863
Hunt-Hess scale	0.437	0.150	8.499	0.004	1.548	1.154-2.077
Admission P/C	0.012	0.006	4.156	0.041	1.012	1.000-1.024
Constant	-4.257	1.104	14.863	–	–	–

A backward stepwise logistic regression was performed to generate this final model. The candidate pool consists of significant variables from univariate analysis (except lumbar cistern drainage was excluded) and hypertension. Four factors: age, modified Fisher scale, Hunt-Hess scale and admission P/C were identified to be independent risk factors for postoperative CVS in aSAH patients ($p < 0.05$). CVS: Cerebral vasospasm; aSAH: Aneurysmal subarachnoid hemorrhage; mFisher: modified Fisher; P/C: Platelets-to-serum Ca^{2+} ratio; OR: Odds ratio; CI: Confidence interval.

were compared (Table III). Patients with higher P/C levels at admission had more CVS events after surgical treatment (32/67 [47.8%] *vs.* 56/195 [28.7%], $p = 0.004$). The medians of P/C were 125.69 and 85.84, respectively, in the two groups. There was no evidence to distinguish the two groups by the modified Fisher scale or Hunt-Hess scale. Admission P/C had an AUC of 0.576, acting as a solo early indicator for CVS (Figure 1). The AUCs increased significantly after P/C was combined with the modified Fisher scale ($Z = 3.651$, $p < 0.001$) and ($Z = 3.905$, $p < 0.001$)/or Hunt-Hess scale ($Z = 3.253$, $p = 0.001$).

Discussion

In our study, we recognized that an increased P/C at admission was associated with postoperative CVS in aSAH patients who underwent surgical treatment, which could be simply calculated from routine blood tests in the early stage. The CVS prevalence in our study was 33.6% (88/262), consistent with previous reports[4,16]. Early prediction and diagnosis of CVS are essential for aSAH patients, especially for those in poor condition, so we might use P/C to identify patients who are more vulnerable to CVS. P/C is an independent risk factor for postoperative CVS in aSAH patients according to our findings, which probably suggests that P/C may reflect subtle and non-quantifiable, also abstruse changes in the pathophysiology of SAH. These changes may have further influenced the patient's general state, leading to different Hunt-Hess levels.

There have been some previous reports[8,17] noting routine blood markers function as CVS predictors, such as the mean platelet volume (MPV) and neutrophil-to-albumin ratio (NAR). To our knowledge, our report is the first to demonstrate P/C as a risk factor for postoperative CVS in aSAH patients. It may be practical and promising to use P/C for the early prediction of CVS.

Both platelets and serum calcium play important roles in coagulation homeostasis and vascular function, and there are possible explanations for the significance of P/C in CVS incidents. Morotti et al[9] reported that a lower serum Ca^{2+} level at admission was associated with greater intracranial hemorrhage volumes as well as hematoma expansion, possibly due to calcium's role in platelet function and the coagulation cascade. As a widely used lipophilic dihydropyridine calcium-channel blocker against CVS, *Nimodipine* can cross the blood-brain barrier (BBB) and prevent the influx of extracellular calcium into vascular smooth muscle, while the selectivity for the cerebral vasculature may come from its greater dependence on extracellular calcium for smooth muscle contraction[18]. Given the complexity of calcium regulation, hypocalcemia could also lead to vasoconstriction through its influence on vascular reactivity, thus, the risks of hypertension and (second-time) rupture of aneurysms also increase[19]. As we know, platelets act as critical mediators of hemostasis, inflammation, and vascular tone[20]. Upon exposure to the subarachnoid space, platelets become activated, and above all, platelets can initiate blood vessel constriction *via* the release of vasoconstricting factors[10]. Among many vasoconstricting factors, two of them, thromboxane A2 (*TXA2*) and platelet-derived growth factor-β (*PDGF-β*), are critical in platelet-induced CVS in aSAH patients[10,21]. An elevated *PDGF-β* level after aSAH and its causal correlation with CVS and DCI were reported[22]. The idea of platelets as a major contributor to CVS following SAH was also supported in animal models[23]. In

Table III. Demographics and baseline characteristics of aSAH patients of higher and lower P/C upon admission.

	Higher P/C (≥ 112.53, n=67)	Lower P/C (< 112.53, n=195)	*p*-values
CVS events	32 (47.8%)	56 (28.7%)	0.004*
Demographics			
Age	56.54 ± 12.65	58.88 ± 11.49	0.163
Male	26 (38.8%)	74 (37.9%)	0.901
Clinical grading			
mFisher scale			0.650
1	41 (61.2%)	109 (55.9%)	
2	2 (3.0%)	8 (4.1%)	
3	17 (25.4%)	63 (32.3%)	
4	7 (10.4%)	15 (7.7%)	
Hunt-Hess scale			0.055
I	36 (53.7%)	116 (59.5%)	
II	5 (7.5%)	31 (15.9%)	
III	15 (22.4%)	34 (17.4%)	
IV	9 (13.4%)	13 (6.7%)	
V	2 (3.0%)	1 (0.5%)	
Major medical history			
Hypertension	36 (53.7%)	91 (46.7%)	0.318
Diabetes	9 (13.4%)	13 (6.7%)	0.085
Smoking history	2 (3.0%)	15 (7.7%)	0.253
Surgery			
Surgery method			0.647
Clipping	20 (29.9%)	49 (25.1%)	
Endovascular treatment	46 (68.7%)	141 (72.3%)	
Mixed	0 (0.0%)	3 (1.5%)	
Failure attempt	1 (1.5%)	2 (1.0%)	
Time between aSAH onset and surgery			0.937
< 24h	10 (14.9%)	28 (14.4%)	
24-48h	16 (23.9%)	43 (22.1%)	
> 48h	41 (61.2%)	124 (63.6%)	
Sustained lumbar cistern drainage	7 (10.4%)	8 (4.1%)	0.068
Aneurysm features			
Site (responsible)			0.300
AcoA	28 (41.8%)	56 (28.7%)	
MCA	9 (13.4%)	40 (20.5%)	
ICA	19 (28.4%)	65 (33.3%)	
ACA	3 (4.5%)	6 (3.1%)	
APC	8 (11.9%)	28 (14.4%)	
Size			0.703
< 0.5 cm	44 (65.7%)	132 (67.7%)	
1.0-1.5 cm	21 (31.3%)	60 (30.8%)	
1.5-2.5 cm	1 (1.5%)	2 (1.0%)	
> 2.5 cm	1 (1.5%)	1 (0.5%)	
Multiple aneurysms	11 (16.4%)	43 (22.1%)	0.325
Second-time rupture	2 (3.0%)	3 (1.5%)	0.605
Admission blood tests			
Ca^{2+}, mmol/L	2.24 (2.17, 2.32)	2.25 (2.16, 2.32)	0.986
WBCs, 10^9/L	11.85 (9.23, 14.61)	9.87 (8.19, 12.21)	0.002*
Plt,10^9/L	284 (262, 313)	193 (161, 216)	< 0.001*
W/C	5.05 (4.10, 6.32)	4.37 (3.70, 5.48)	0.003*
P/C	125.69 (117.72, 135.02)	85.84 (72.69, 96.93)	–
HCT, %	41.50 ± 4.26	41.35 ± 4.15	0.800
RBCs, 10^{12}/L	4.62 ± 0.50	4.56 ± 0.46	0.423
Hb, g/L	139.81 ± 15.66	139.23 ± 15.22	0.791

With a cutoff value of 112.53, patients were divided into the higher and lower P/C groups and then compared. The occurrence of CVS differed significantly between groups. Values are showed as n (%), mean ± standard deviation, median with quartile range (Q1,Q3). *Significant results ($p < 0.05$). aSAH: Aneurysmal subarachnoid hemorrhage; CVS: Cerebral vasospasm; mFisher: modified Fisher; AcoA: Anterior communicating artery; MCA: Middle cerebral artery; ICA: Internal carotid artery; ACA: Anterior cerebral artery; APC: Arteries of posterior circulation; WBCs: White blood cells; Plt: Platelets; W/C: White blood cells-to-serum Ca^{2+} ratio; P/C: Platelets-to-serum Ca^{2+} ratio; HCT: Hematocrit; RBCs: Red blood cells; Hb: Hemoglobin.

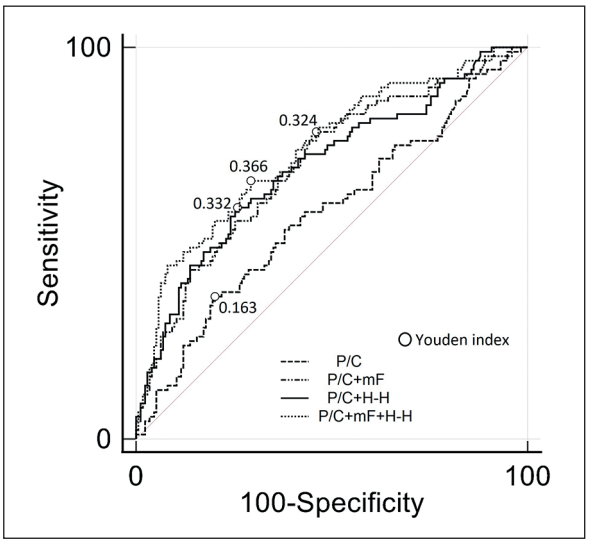

Figure 1. The ROC analysis comparing admission P/C, P/C + mF, P/C + H-H, and P/C + H-H + mF regarding the early prediction of CVS in aSAH patients showed the AUCs of which are 0.576 (95% CI: 0.513-0.636), 0.700 (95% CI: 0.641-0.755), 0.696 (95% CI: 0.637-0.751), 0.738 (95% CI: 0.680-0.790), respectively. The logistic formula we acquired in Table II was used to combine these factors. When combined, the AUCs were comparable and the predictive powers were significantly increased after P/C was combined with mF ($Z = 3.651$, $p < 0.001$), H-H ($Z = 3.253$, $p = 0.001$), mF and H-H together ($Z = 3.905$, $p < 0.001$). ROC: Receiver operating characteristic; P/C: Platelets-to-serum Ca^{2+} ratio; mF: Modified Fisher scale; H-H: Hunt-Hess scale; CVS: Cerebral vasospasm; aSAH: Aneurysmal subarachnoid hemorrhage; AUC: Area under curve; CI: Confidence interval.

addition, studies have shown that microvessel constriction and formation of clots began within seconds after SAH ictus, and platelet aggregates were observed within the most constricted small cerebral arteries, leading to a striking correlation between platelet aggregates/clots and microvessel constriction[24]. In brief, platelets take active parts in CVS through both large artery spasm and microvessel constriction. Activities including promoting blood clotting *via* self-aggregation, interacting with endothelial and immune cells, and participating in inflammation (through the release of chemokines and cytokines) make platelets a key mediator in CVS events. Another important pathological factor triggered after aSAH is hypercoagulability which leads to aggregation and microthrombi formation in cerebral arteries[10,21,25]. Both experimental and human studies[21,26] revealed an early aggregation of platelets soon after aneurysm rupture. Although coagulation is immediately activated following aneurysm rupture to stop the bleeding, the hypercoagulable state does not end when the bleeding ceases[21]. In the days following aneurysm securement, aSAH patients remain hypercoagulable, and platelet reactivity is increased in aSAH patients with CVS damage compared to those without[27,28]. Deposition of platelet aggregates/microthrombi within the microvasculature reduces cerebral blood flow furthermore and consequently they potentiate each other to more deleterious ischemic effects resulting in poorer outcomes.

Inducing and propagating inflammation, leukocytes also seem to influence CVS after aSAH and, interestingly, promote a hypercoagulable state[21]. Normally, blood within the subarachnoid space triggers several response mechanisms after aSAH, including the removal of RBCs. Specific cell adhesion molecules are rapidly expressed on the luminal endothelial cell surface[29]. This process allows circulating macrophages and neutrophils to enter the subarachnoid space, and extravasated blood is phagocytosed by infiltrating macrophages[30]. As a result, phagocytosis of RBCs and subsequent death of the infiltrated leukocytes in cerebrospinal fluid (CSF) then initiate the release of a plethora of toxic molecules[31] including endothelins, oxygen free radicals, and hemoglobin/heme (and by-products), thereby potentiating pro-inflammatory pathways and endothelial cell-mediated thrombosis. The latter incident can further create a positive feedforward loop continually activating platelets, leading to microthrombi formation[32]. In response to platelet activation, several molecules, including Ca^{2+} from dense granules of platelets, are released to participate in the overlap between inflammation and thrombosis by a yet unknown mechanism. We believe these interactions will intensify CVS symptoms in aSAH patients after surgical treatment. Specific mechanisms for P/C's impact on CVS still need to be explored more deeply to be conclusive.

On the other hand, platelets have endogenous inhibitory mechanisms, whose augmentation may have therapeutic potential. Prostacyclin and nitric oxide (*NO)*, which are platelet inhibitors and vasodilators, were promising in recent clinical studies[33,34]. The same clinical trials even suggested that the risk of new bleeds for antiplatelet therapies after aSAH is minimal and can be ignored compared to the benefits for reducing CVS and DCI events.

We also found that elderly patients were more likely to have CVS after clipping or coiling of the aneurysms, but this matter is still in dispute, with some authors suggesting a higher risk of CVS in younger patients[16].

In the univariate analysis we performed, it could be inferred that timely treatment reduces CVS risk, which is supported by a study of over 8000 aSAH cases[16]. This brought us to one more paradox in the treatment of aSAH that early-stage aSAH is often linked with an increased intracranial pressure (ICP) which seems to be merited but also creates obstacles for the operation, especially clipping. Poor exposure can make the procedure very tricky and endanger the efficacy of the procedure; however, this disadvantage is inevitable even for extremely skilled neurosurgeons.

Sustained lumbar cistern drainage was a risk factor for CVS in primary models but was excluded. Only 5.7% (15/262) of patients were given this treatment, meanwhile, separated lumbar punctures were also performed in some patients, but they were not included because the procedures, effects, and infection risks were completely different. There were 2 cases of external ventricular drainage from the frontal horn of the lateral ventricle, and the decisions were based on malicious hydrocephalus conditions after aSAH, which changed the levels of consciousness substantially and were potentially life-threatening. Although hydrocephalus is a common complication after SAH, existing in 3.6% to 46.7% of patients[35-38], it is still challenging to determine the proper time for intervention. Elective operations after stabilization are recommended in most such cases, but a resolute decision of external ventricular drainage should be expected if the patient's condition is deteriorating before and after aneurysmal surgery. However, many aSAH patients with acute (0-3 days after onset) hydrocephalus changes on CT scans improved after only conservative treatment. The relationship between CVS and hydrocephalus after aSAH is not clear. In practice, we maximally drained 20-30 ml of CSF at one lumbar puncture, a small portion (3-4 ml) of which was sent for testing, and the rest was slowly drained for treatment purposes. However, sustained lumbar cistern drainage was used for continuous elimination of hemic CSF, which is believed to be hazardous for cerebral vessels and leads to CVS, normally 200-300 ml per day for balance of the system. We intended to perform sustained lumbar cistern drainage only on patients with poor general conditions or considerable amounts of SAH, possibly with a hematoma, based on experience. In other words, it was used only among individuals with high modified Fisher scale or Hunt-Hess scale scores, and as studied, these were the same patients with CVS in all likelihood. Therefore, sustained lumbar cistern drainage was generally performed for CVS patients, and it was no wonder that it was a "risk factor" for CVS. To choose repeated, separate lumbar punctures or sustained lumbar cistern drainage, if needed, we must include several factors regarding cost-effectiveness (sustained drainage systems are usually more expensive) and the patient's willingness to make the decision, however, the doctor's preference is sometimes considered. Regardless, either of them is invasive, but the intention of aggressive drainage of CSF in CVS prevention is preferred for some clinicians, often neurosurgeons. Is the benefit enticing enough in consideration of all the risks? We still expect large-sample trials on this matter.

In our study, there were three more hemodynamic parameters: RBCs, HCT, and Hb, and we did not observe significant differences of them between the two groups. However, the rheology of circulation is another important factor in the pathophysiological process of CVS, speaking of which, we have to bring up one more topic--the "3H" treatment. It stands for hypervolemic, hypertensive and hemodilution. The fact is, traditional 3H treatment is now drastically challenged[39]. The "hypertensive" seems to be the only one remaining as an effective treatment by increasing the cerebral blood flow[40-42], while "hypervolemic" and "hemodilution" are questioned more and more for their side effects[42-45]. The latest version of Chinese guideline for aSAH management recommended a strategy of keeping the balance of blood volume, and only induce hypertensive conditions in patients highly suspect of CVS.

There are also some limitations of our study. First, the sample we used is relatively small and from a single center. Second, we chose the Hunt-Hess scale and the modified Fisher scale to evaluate the patients because access to the system was guaranteed, while the World Federation of Neurosurgical Societies (WFNS) grade is also a popular choice that we did not include. Next, we arbitrarily selected the laboratory parameters of interest that may have the potential to represent the principal pathophysiological process of aSAH: platelets, WBCs, serum Ca^{2+}, RBCs, HCT, and Hb. Furthermore, since we also have a sufficient number of patients with unruptured intracranial aneurysms, we may conduct further studies to identify the difference between these patients and aSAH patients regarding CVS.

Conclusions

The study indicates that aSAH patients with higher P/C levels at admission are more likely to have CVS after being surgically treated. More aggressive anti-CVS treatment options can be suggested for these patients for their vulnerability. With easy access, P/C has the potential to serve as an early predictor for postoperative CVS in aSAH patients. Further research on a large-sample basis is needed to confirm the finding and the mechanisms involved are also to be studied.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Ethics Statement

The study was approved by the Ethics Committee of The First Affiliated Hospital of Dalian Medical University. All patients who were treated provided written informed consent signed by a legal representative of the family or an assigned member of the family members. No clinical trials or experimental medications/treatment were involved. No personal patient information was disclosed.

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Data Availability

The data used in this study can be provided by the corresponding author upon reasonable request.

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