Aus der Klinik für Neurochirurgie der Heinrich-Heine-Universität Düsseldorf

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CLR (C-Reactive Protein to Lymphocyte Ratio) Served as a Promising Predictive Biomarker for Cerebral Vasospasm in Aneurysmal Subarachnoid Hemorrhage (aSAH): A Retrospective Cohort Study

Dissertation

zur Erlangung des Grades eines Doktors der Medizin

Der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

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2024

Als Inauguraldissertation gedruckt mit Genehmigung der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

gez.:

Dekan: Prof. Dr. med. Nikolaj Klöcker

Erstgutachter/in: PD Dr. med. Sajjad Muhammad

Zweitgutachter/in: Univ.-Prof. Dr. Julian Caspers

Parts of this work have been published:

Li, K., Khan, D., Fischer, I., Hänggi, D., Cornelius, J.F., & Muhammad, S. (2024). CLR (C-Reactive Protein to Lymphocyte Ratio) Served as a Promising Predictive Biomarker for Cerebral Vasospasm in Aneurysmal Subarachnoid Hemorrhage (aSAH): A Retrospective Cohort Study. *J. Clin. Med.*, 13, 940.

Zusammenfassung

Unsere Studie zielt in erster Linie darauf ab, den Zusammenhang zwischen dem Verhältnis von C-reaktivem Protein zu Lymphozyten- (CLR) und dem neurologischen Funktionsergebnis und den Komplikationen nach einer aSAB zu untersuchen. Wir haben Serum-Biomarker inklusive weißer Blutkörperchen (WBC), Thrombozyten, Neutrophile, Lymphozyten und Monozytenzählungen sowie Serum-C-reaktives Protein (CRP) innerhalb von 24 Stunden nach der Notaufnahme quantifiziert. Die Berechnung des CLR erfolgte durch Division des CRP durch die Lymphozytenzahl. Das funktionelle Ergebnis wurde anhand der modifizierten Rankin-Skala (mRS) nach 6 Monaten nach der aSAB-Aufnahme bewertet. Neurologische Komplikationen, einschließlich zerebraler Vasospasmen (CVS), verzögerter zerebraler Ischämie (DCI), chronischer Hydrozephalus (CH) und Krampfanfälle, wurden anhand von Symptomen und radiologischer Bildgebung untersucht. Multivariate logistische Regressionsmodelle wurden verwendet, um die unabhängigen Faktoren zu bewerten Receiver-operative-Kurven (ROC) wurden verwendet, um den Vorhersagewert zu bewerten. Unsere Ergebnisse zeigten, dass aSAB-Patienten mit CVS höhere CLR-Werte aufwiesen als Patienten ohne CVS. Es wurde festgestellt, dass die CLR bei der Aufnahme unabhängig mit der CVS nach aSAB assoziiert ist. Darüber hinaus hatte die CLR bei der Aufnahme einen günstigen prädikativen Wert für ein CVS nach aSAB auf. Ein Aufnahme-CLR von 0.757 $mg \times 10^{-6}$ wurde als optimaler Grenzwert identifiziert, um zwischen CVS- und Nicht-CVS-Fällen zu unterscheiden. Zusammenfassend lässt sich sagen, dass die CLR bei der Aufnahme ein leicht quantifizierbarer Laborparameter ist, der ein CVS nach aSAB effizient vorhersagt.

Summary

Our study primarily aims to investigate the associations of C-reactive protein to lymphocyte ratio (CLR) with neurological functional outcome and complications following aSAH. We obtained admission serum biomarkers including white blood cell (WBC), platelet, neutrophil, lymphocyte, and monocyte counts, and serum C-reactive protein (CRP) levels within 24 hours at the emergency unit. Calculations of CLR involved dividing the CRP by the lymphocyte count. Functional outcome was assessed using the 6-month modified Rankin Scale (mRS) after aSAH admission. Neurological complications, including cerebral vasospasm (CVS), delayed cerebral ischemia (DCI), chronic hydrocephalus (CH), and seizures, were evaluated through symptoms, signs, and imaging examinations. Multivariate logistic regression models were used to assess the independent factors, and receiver operating characteristic (ROC) curves were employed to evaluate the predictive value. Our findings showed that aSAH patients with CVS displayed higher CLR values than patients without CVS. Admission CLR was found to be independently associated with CVS after aSAH. Additionally, admission CLR performed favorable predictive value for CVS following aSAH. An admission CLR of 0.757 mg$\times 10^{-6}$ was identified as the optimal cutoff threshold to distinguish between CVS and non-CVS cases. In conclusion, admission CLR is an easily quantifiable laboratory parameter that efficiently predicts CVS after aSAH.

List of abbreviations

SAH	subarachnoid hemorrhage
aSAH	aneurysmal subarachnoid hemorrhage
USA	United States of America
CT	computed tomography
DSA	digital subtraction angiography
DCI	delayed cerebral ischemia
MCA	middle cerebral artery
mRS	modified Rankin Scale
CVS	cerebral vasospasm
NO	nitric oxide
CTA	computed tomography angiography
TCD	transcranial Doppler ultrasonography
cEEG	continuous electroencephalography
CSF	cerebrospinal fluid
EVD	external ventricular drain
ICU	intensive care unit
CH	chronic hydrocephalus
IL-6	interleukin-6
TNF	tumor necrosis factor
CRP	C-reactive protein
NLR	neutrophil to lymphocyte ratio
AUC	area under the curve
SAHIT	Subarachnoid Hemmorhage International Trialists
WPR	white blood cell to platelet ratio
CLR	C-reactive protein to lymphocyte ratio
WBC	white blood cell
GOS	Glasgow outcome scale
IL-1	interleukin-1
DIND	delayed ischemic neurological deficits
PLR	platelet to lymphocyte ratio
CAR	C-reactive protein to albumin ratio

NAR	neutrophil to albumin ratio
PAR	platelet to albumin ratio
MLR	monocyte to lymphocyte ratio

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1. Introduction

The subject has been approved by the ethics committe (Studien-Nr.: 2022-2007).

"When healthy individuals suddenly experience head pains, become speechless, and breathe with stertor, they typically succumb within seven days." Hippocrates described the symptoms of subarachnoid hemorrhage (SAH) about 2400 years ago[1-3].

1.1 Aneurysmal Subarachnoid Hemorrhage (aSAH)

1.1.1 Epidemiological Characteristics

Aneurysmal subarachnoid hemorrhage (aSAH) arises from the rupture of intracranial aneurysms, resulting in arterial blood filling the subarachnoid space and causing high mortality and disability compared to all other stroke subtypes [4]. Approximately 85% of aSAH cases stem from intracranial aneurysm rupture, with 10% attributed to perimesencephalic hemorrhage of unknown etiology, and the remaining 5% associated with rare congenital and acquired lesions of cerebral arteries and systemic disorders such as sickle cell disease, coagulopathies, tumors, and cocaine abuse [5]. The incidence of aSAH was reported as 9 per 100,000 people annually in the United States of America (USA), with 600,000 cases globally [5]. The premature mortality rate for aSAH was approximately 40%, with almost 10-20% of cases resulting in death before receiving medical attention or during transportation, imposing a significant economic and social burden on patients, families, and national healthcare systems [6]. The average age of presentation for aSAH patients was around 50 years [7]. Furthermore, well-known risk factors for aSAH include hypertension, cigarette smoking, female gender, a history of familial intracranial aneurysms, and hereditary connective tissue diseases [8].

1.1.2 Diagnosis and Therapy

Although the clinical symptoms of aSAH may vary in severity, few neurosurgeons would be unaware that a middle-aged woman could suddenly present with the typical dramatic symptoms of headache, loss of consciousness, nausea, vomiting, and neck stiffness [3]. During the initial days, computed tomography (CT) without contrast enhancement is the primary diagnostic choice for patients suspected of having aSAH,

as it can detect subarachnoid blood in over 95% of cases [3, 9, 10]. However, as the blood ages and becomes isointense with brain tissue, CT may fail to detect SAH in patients presenting several days after onset despite suggestive headache symptoms. Evidence of red blood cells or xanthochromia via lumbar puncture becomes most effective for diagnosing SAH in these cases [11]. Furthermore, initial angiography should be followed by digital subtraction angiography (DSA) to enhance the sensitivity of detecting initially undetected aneurysms or to better select aneurysms for endovascular coiling or surgical clipping [12-14]. Dural arteriovenous fistula, arteriovenous malformation, and distal vasculopathy, which can cause SAH, may also be more effectively detected via DSA than CT imaging [4].

To date, endovascular coiling and neurosurgical clipping remain the primary treatment methods for bleeding ruptured aneurysms [15]. The International Subarachnoid Aneurysm Trial revealed that patients with aSAH treated with endovascular coiling had a better clinical prognosis than those treated with surgical clipping at one year [16, 17]. Another randomized trial, the Barrow Ruptured Aneurysm Trial, compared SAH patients treated with clips versus coils to treat aneurysms in posterior circulation and found that a poor outcome was more prevalent in the surgical clipping group compared to the endovascular coiling group at one year [18]. Furthermore, evidence supported that coiling was associated with a lower occurrence rate of delayed cerebral ischemia (DCI) [19]. With advancements in endovascular techniques and recent data from randomized clinical trials, most ruptured aneurysms could be effectively treated with endovascular coiling. Surgical clipping might be preferred in select cases, such as patients with complex broad based intracranial aneurysms and ruptured middle cerebral artery (MCA) aneurysms with massive hematoma and mass effects requiring evacuation. However, in such cases, some surgeons preferred coiling the aneurysm followed by immediate craniectomy for decompression [20]. Several new endovascular aneurysm treatment techniques have emerged, including flow diverter devices and expandable intravascular flow disruption devices. However, caution should be exercised when using flow-diverted and stent-assisted techniques because dual antiplatelet therapy is necessary to prevent stent or flow-diverted device thrombosis, which poses a bleeding risk [21, 22]. Therefore, patients should be evaluated by a multidisciplinary team experienced in endovascular techniques and surgical clipping to determine the most appropriate treatment plan for each patient [20].

1.1.3 Neurological Functional Outcome

The functional outcome following aSAH is assessed using the modified Rankin Scale (mRS) score, designed to quantify disability in aSAH patients and track changes over time to evaluate recovery and the extent of ongoing disability [23]. The mRS score ranges from 0 to 6, indicating varying levels of disability: 0 signifies no symptoms; 1 denotes no significant disability, despite symptoms, able to perform all usual duties and activities; 2 indicates slight disability, unable to perform all previous activities but able to look after own affairs without assistance; 3 reflects moderate disability, requires some help, but able to walk without assistance; 4 represents moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 equals to severe disability, bedridden, incontinent, and requires constant nursing care and attention; 6 means dead [24, 25]. A higher mRS score indicates unfavorable recovery in aSAH patients [23, 24]. Functional outcome is dichotomized into good (mRS Scores 0-2) and poor (mRS Scores 3-6) categories [26].

1.1.4 Neurological Complications

Cerebral vasospasm (CVS), DCI, hydrocephalus, and seizures are life-threatening neurological complications following aSAH [27-32]. Approximately 70% of aSAH patients developed CVS between 3 and 14 days after the initial rupture [33]. The severity and duration of CVS were associated with the thickness, density, location, and persistence of the SAH [34, 35]. The potential mechanisms of CVS formation remain unclear. However, the most significant one likely involves the release of hemoglobin and erythrocytes, leading to oxidative stress, inflammation, and endothelial injury, which activate calcium channels in smooth muscle cells, elevated expression of endothelin-1, and reduce levels of nitric oxide (NO) [36, 37]. About 50% of patients with CVS developed DCI, which was associated with unfavorable neurological functional outcome [38]. Previous studies reported DCI occurrence rates of 33% before 1994 and 29% between 1994 and 2009 in SAH patients [38]. Patients treated with calcium channel antagonists showed a lower incidence of DCI compared to those who did not receive such drugs [33]. Furthermore, endovascular coiling for aSAH treatment was associated with a lower CVS and DCI incidence than surgical clipping [30].

Diagnosing CVS and DCI remains challenging, particularly for SAH patients in critical conditions [39]. CVS can be asymptomatic, and not all cases are related to DCI [40]. Similarly, DCI can be asymptomatic, mainly when cerebral ischemia is observed in imaging scans without corresponding clinical symptoms [41]. Firstly, DSA has traditionally been the gold standard for diagnosing CVS but is increasingly being replaced by computed tomography angiography (CTA) due to its noninvasive nature [42, 43]. Previous studies have reported an accuracy degree and negative predictive value for DSA and CTA in diagnosing CVS ranging from 87.0% to 97.5% and 95.0% to 99.5%, respectively [44]. Secondly, transcranial Doppler ultrasound (TCD) is still utilized for diagnosing CVS, with a sensitivity of 95% for severe CVS, albeit requiring a trained technician or experienced user [45]. However, TCD is limited in assessing only a small number of large arteries and patients without thick temporal bones. False positives and negatives may occur due to increased blood pressure and severe artery narrowing caused by low blood flow [46]. Thirdly, continuous electroencephalography (cEEG) represents another potential modality that could be utilized to detect impending DCI. While promising, the cEEG approach is resource-intensive and necessitates anepileptologist specially trained in grading records for DCI risk [4, 47]. Lastly, invasive brain-tissue monitoring equipment, including brain tissue oxygen monitoring, brain microdialysis, invasive thermal diffusion flowmetry, and noninvasive methods such as near-infrared spectroscopy, are employed to detect DCI in SAH patients [48-50]. Treatment principles for CVS and DCI aim to maintain an oxygen- and glucose-rich blood supply to the brain and normalize physiological variables as much as possible [6]. Clinical trials mainly target CVS, and drugs addressing microthromboembolism and providing neuroprotective effects are also utilized in DCI treatment [51-67].

Hydrocephalus is one of the most common complications in patients with aSAH [4, 31]. When the blood from a ruptured intracranial aneurysm enters the subarachnoid space, intracranial pressure significantly increases due to the limited and non-expandable nature of the subarachnoid space, potentially disrupting cerebrospinal fluid (CSF) circulation and leading to hydrocephalus formation. Hydrocephalus indicates external ventricular drain (EVD) placement and CSF diversion [68, 69]. EVD is widely employed for the treatment of acute hydrocephalus. Managing the EVD after postoperative aneurysm treatment is crucial. EVD duration is correlated with the length of stay in the intensive care unit (ICU) and the prognosis of aSAH

patients. Previous studies have indicated that intermittently opening and closing the EVD can help reduce drain malfunction and ventriculostomy-associated infections [4, 70, 71]. However, some studies suggest that once the aneurysm has been treated, the EVD should remain continuously open and draining by default [72, 73]. Draining CSF continuously may help reduce red blood cells and breakdown products, contributing to neuroinflammation [4]. The diagnosis of chronic hydrocephalus (CH) relies on radiographic ventricular enlargement without clinical symptoms or signs of significantly increased intracranial pressure [74, 75]. Ventriculoperitoneal shunting is the primary method for placing a permanent shunt catheter in patients requiring permanent CSF diversion [76, 77]. Despite the unclear etiology of CH, ventriculoperitoneal shunting remains the most effective treatment for symptomatic CH. Previous studies have reported CH incidence rates between 6.0% and 48.0% following ventriculoperitoneal shunt placement for SAH treatment [20, 78, 79]. Therefore, strictly postoperative follow-up is essential when SAH patients have treatments with ventriculoperitoneal shunt.

Diagnosing seizures after hospitalization for aSAH remains challenging, particularly for patients in a coma or with mental disability. The most common method to confirm suspicions of seizures is through cEEG [80]. When seizures occur and are detected by cEEG, treatment depends on physicians' clinical judgment. There is no evidence supporting the notion that treating seizures after SAH improves outcomes. However, it is essential to keep patients with seizures in the ICU because seizures in SAH may cause more severe neurological damage. Once seizures are under control, it is recommended to maintain or cautiously reduce the dose of anticonvulsant drugs to decrease the risk of seizure recurrence during the resolution phase [81]. We should note that the decision to continue anticonvulsants in patients with isolated seizure-like episodes on presentation is controversial. Non-epileptic convulsions are common during syncope. A previous study found no relationship between seizure-like episodes and the risk of developing seizures [82]. Therefore, in patients who experience only isolated epileptic seizures, it is reasonable to delay the use of anticonvulsant medications in the absence of associated features of abnormal movements.

1.2 Predictive Values of Biomarkers in aSAH

Accurately predicting neurological outcome and complications remains a significant challenge. A study identified several risk factors related to CVS and DCI, including

the volume, location, persistence over time, and density of the subarachnoid blood clot [35]. Unfavorable clinical status and loss of consciousness upon admission increased the risk of DCI [6]. Additionally, substantial evidence indicated that smoking enhanced the risk of DCI, while moderate evidence confirmed that diabetes mellitus, systemic inflammatory response syndrome, hyperglycemia, and hydrocephalus also increased the risk [83]. Biomarkers in CSF, such as endothelin-1 and interleukin-6 (IL-6), and serum biomarkers, including tumor necrosis factor (TNF), IL-6, S100β, vascular endothelial growth factor, selectins, and adhesion molecules, have been associated with DCI after aSAH [6, 84]. In addition, peripheral blood biomarkers serve as a hot topic for the outcomes and complications prediction in patients with aSAH. Among them, peripheral white blood cells, including neutrophils, lymphocytes, and monocytes, indicate of pro-inflammatory and immunosuppressed states, serum D-dimer, and serum C-reactive protein (CRP) may impact aSAH. As shown in Table 1, Giede-Jeppe et al. (2019) demonstrated that serum neutrophil to lymphocyte ratio (NLR), with an area under the curve (AUC) of 0.612 and a cut-off of 7.05, serves as an independent parameter associated with unfavorable functional outcome at 3 months following aSAH [26]. According to Liu et al. (2017), their findings revealed that serum D-dimer levels, with an AUC of 0.86, a sensitivity of 82.09%, and a specificity of 78.43%, serve as a robust independent prognostic factor for predicting poor neurological functional outcome at 6 months following aSAH [85]. Furthermore, Gaastra et al. (2021) demonstrated that the inclusion of serum CRP as a predictor in the Subarachnoid Hemorrhage International Trialists (SAHIT) model significantly enhanced the model's performance, resulting in an improved AUC of 0.846 ($p = 0.01$). This showed CRP's role as an independent predictor of poor outcome at 6 months following aSAH [86]. Moreover, Zhang et al. (2023) revealed that serum white blood cell to platelet ratio (WPR) levels upon admission, with an AUC of 0.804 and a cut-off of 5.26, emerged as a novel and promising serum marker for identifying the risk of DCI and predicting poor prognosis at 90 days following aSAH [87]. Recently, Zhang et al. (2023) employed 221 participants and demonstrated that serum C-reactive protein to lymphocyte ratio (CLR), a novel predictive biomarker with an AUC of 0.840 and a cut-off value of 10.81, could serve as a feasible biomarker for predicting the clinical prognosis of patients with aSAH, particularly in identifying those at risk of poor outcome at

discharge (mRS > 2) [88]. However, the predictive value of admission CLR levels for neurological complications, including CVS, DCI, and CH, remains unclear.

Table 1: Predictive values of biomarkers in aSAH.

Author (year)	Sample size	Biomarkers	Predictive values	Predictive model	Main findings
Giede-Jeppe et al. (2019) [26]	319	Serum NLR	AUC=0.612, cut-off=7.05	Unfavorable functional outcome at 3 months (mRS 3-6)	NLR represents an independent parameter associated with unfavorable functional outcome after aSAH.
Liu et al. (2017) [85]	146	Serum CRP, D-dimer, WBC	CRP, AUC=0.69, Sensitivity=70.45%, Specificy=65.69%; D-dimer, AUC=0.86, Sensitivity=82.09%, Specificy=78.43%; WBC, AUC=0.61, Sensitivity=50.00%, Specificy=76.47%	Poor neurological functional outcome at 6 months (GOS 1-2)	D-dimer levels are a good independent prognostic factor for poor outcomes after aSAH.
Gaastra et al. (2021) [86]	1017	Serum CRP	Addition of CRP to the predictors of the full SAHIT model improved model performance (AUC=0.846, p=0.01)	Poor outcome at 6 months (mRS 3-6)	CRP is an independent predictor of outcome after aSAH.
Zhang et al. (2023) [87]	447	Serum WPR	AUC=0.804, cut-off=5.26	DCI and poor outcome at 90-day (mRS 3-6)	WPR level at admission is a novel serum marker for DCI and the poor prognosis after aSAH.
Zhang et al. (2023) [88]	221	Serum CLR	AUC=0.840, cut-off=10.81	Poor outcome at discharge (mRS>2)	CLR value can be considered as a feasible biomarker to predict the clinical

	prognosis of patients with aSAH.

aSAH = anurysmal subarachnoid hemorrhage; NLR = neutrophil to lymphocyte ratio; AUC = area under the curve; mRS = modified Rankin Scale; CRP = C-reactive protein; WBC = white blood cell; GOS = Glasgow outcome scale; SAHIT = Subarachnoid Hemmorhage International Trialists; WPR = white blood cell to platelet ratio; DCI = delayed cerebral ischemia; CLR = C-reactive protein to lymphocyte ratio.

1.3 Aims of Thesis

Due to the predictive value of admission CLR levels for neurological complications remains unclear, the aims of the thesis included: 1. Investigating the association between CLR levels and neurological functional outcome and complications: Explore the relationship between CLR levels and neurological functional outcome and the occurrence of neurological complications in patients with aSAH; 2. Assessing the predictive value of CLR for CVS: Evaluate the potential of CLR as a predictive biomarker for identifying patients at risk of developing CVS following aSAH, comparing its performance with established clinical and laboratory predictors; 3. Validating CLR as a prognostic indicator for clinical outcomes in aSAH: Determining the prognostic significance of CLR in predicting adverse outcomes such as DCI, CH, and poor functional recovery following aSAH, assessing its utility as a predictive tool in clinical practice; 4. Exploring potential clinical applications and implications of CLR measurement: Investigate the feasibility and practicality of incorporating CLR measurement into routine clinical practice for risk stratification, early detection, and management optimization of CVS in patients with aSAH; 5. Contributing to evidence-based decision-making in aSAH management: Generate evidence to support the integration of CLR assessment into existing clinical algorithms for monitoring and managing CVS in aSAH patients, aiming to improve patient outcomes and reduce morbidity and mortality associated with this complication.

2. Publication

Journal of *Clinical Medicine*

MDPI

Article

CLR (C-Reactive Protein to Lymphocyte Ratio) Served as a Promising Predictive Biomarker for Cerebral Vasospasm in Aneurysmal Subarachnoid Hemorrhage (aSAH): A Retrospective Cohort Study

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Abstract: Background: Subarachnoid hemorrhage is a devastating disease. Even after state-of-the-art treatment patients suffer from complications, including cerebral vasospasm (CVS), delayed cerebral ischemia (DCI), and chronic hydrocephalus (CH) following aneurysmal subarachnoid hemorrhage (aSAH). The aim of our study is to identify the predictive value of the C-reactive protein to lymphocyte ratio (CLR) for neurological functional outcome and complications after aSAH. **Methods**: We retrospectively analyzed a total of 166 aSAH patients who met the inclusion criteria enrolled in our study. Multivariate logistic regression analyses were performed to evaluate the independent risk factors. The predictive value of different models was compared by calculating the areas under the receiver operating characteristic (ROC) curve. **Results**: On-admission levels of CLR in patients with poor outcomes (6 months mRS 3–6), CVS, DCI, and CH were significantly higher than those in patients with good outcomes (6 months mRS 0–2), non-CVS, non-DCI, and non-CH. Multivariate logistic regression analysis revealed that admission CLR was independently associated with CVS (OR [95% CI] 2.116 [1.507–2.971]; $p < 0.001$), and DCI (OR [95% CI] 1.594 [1.220–2.084]; $p = 0.001$). In ROC analysis, the area under the curve (AUC) of CLR for poor outcomes (6 months mRS 3–6), CVS, DCI, and CH prediction were (AUC [95% CI] 0.639 [0.555–0.724]; $p = 0.002$), (AUC [95% CI] 0.834 [0.767–0.901]; $p < 0.001$), (AUC [95% CI] 0.679 [0.581–0.777]; $p < 0.001$), and (AUC [95% CI] 0.628 [0.543–0.713]; $p = 0.005$) revealing that admission CLR had a favorable predictive value for CVS after aSAH. The sensitivity and specificity of admission CLR for CVS prediction were 77.1% and 75.4%. On-admission CLR of 0.757 mg $\times 10^{-6}$ was identified as the best cutoff threshold to discriminate between CVS and non-CVS (CVS: CLR < 0.757 mg $\times 10^{-6}$ 11/100 [11.0%] vs. CLR $\geq$ 0.757 mg $\times 10^{-6}$ 37/66 [56.1%]; $p < 0.001$). **Conclusions**: High levels of on-admission CLR serve as an independent risk factor for CVS and DCI after aSAH. Admission CLR is an easy-to-quantify laboratory parameter that efficiently predicts the CVS after aSAH, which can provide some guidance for clinicians to evaluate for possible progression and treatment strategies in patients with aSAH.

Keywords: C-reactive protein to lymphocyte ratio; CLR; C-reactive protein; lymphocyte; NLR; PLR; MLR; mRS; cerebral vasospasm; delayed cerebral ischemia; chronic hydrocephalus; predictive value

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Citation: Li, K.; Khan, D.; Fischer, I.; Hänggi, D.; Cornelius, J.F.; Muhammad, S. CLR (C-Reactive Protein to Lymphocyte Ratio) Served as a Promising Predictive Biomarker for Cerebral Vasospasm in Aneurysmal Subarachnoid Hemorrhage (aSAH): A Retrospective Cohort Study. *J. Clin. Med.* **2024**, *13*, 940. https://doi.org/10.3390/jcm13040940

Academic Editors: Tihamér Molnár and Péter Csécsei

Received: 22 December 2023
Revised: 30 January 2024
Accepted: 4 February 2024
Published: 6 February 2024

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1. Introduction

Subarachnoid hemorrhage (SAH) is a serious stroke subtype that is mainly caused by ruptured aneurysms and has high mortality and disability [1]. Around 85% of aneurysmal SAH (aSAH) emerges through the rupture of intracranial aneurysms [2]. The incidence of aSAH was reported as 9/100,000 people per year in the USA, and 600,000 cases per year

globally [2]. The premature mortality rate of aSAH was approximately 40% and patients in almost 10–20% of cases died before acquiring medical attention or during transportation [3]. Cerebral vasospasm (CVS), delayed cerebral ischemia (DCI), and chronic hydrocephalus (CH) are life-threatening complications in patients with aSAH [4]. CVS has been defined as the narrowing of large cerebral arteries usually occurring 3–14 d after SAH in almost 70% of patients [5]. CVS is one of the major causes of morbidity and mortality after aSAH in patients surviving from initial aneurysmal rupture. CVS can be diagnosed through transcranial Doppler ultrasonography (TCD), digital subtraction angiography (DSA), or computed tomography angiography (CTA)/perfusion (CTP) [6]. For survivors of aSAH, DCI serves as an important modifiable prognostic factor and occurs mostly on the fourth day or later. CVS was usually considered to be the cause of DCI [7]. However, cortical spreading ischemia, microcirculatory constriction, and/or thrombosis have also been shown to contribute to DCI formation [3]. Furthermore, hitherto, the etiology of the occurrence of CH after aSAH is still unclear. The diagnosis of CH depends on radiographic enlargement of the ventricles in the absence of clinical symptoms and signs of dramatically increasing intracranial pressure [8]. Ventriculoperitoneal shunting is the most common method of placing a permanent shunt catheter for patients requiring permanent CSF diversion [9]. CVS, DCI, and CH cause high morbidity and mortality after aSAH. An accurate prediction of clinical functional outcome and complications is essential to the possible progression and the choices of treatment strategies.

A previous study stated that high levels of neutrophil to lymphocyte ratio (NLR) might serve as an independent predictive factor associated with an unfavorable functional outcome after aSAH [10]. Platelet to lymphocyte ratio (PLR) was reported to weakly associate with the mortality in hospital after aSAH [11]. Little research focused on the correlation between monocyte to lymphocyte ratio (MLR) and the outcome after aSAH. Furthermore, elevated admission serum C-reactive protein (CRP) levels were correlated with poor outcome in patients with aSAH [12]. Similarly, a high count of platelets in patients with aSAH was associated with the elevated occurrence of DCI after aSAH [13]. Recently, Zhang et al. employed a novel biomarker named C-reactive protein to lymphocyte ratio (CLR) and demonstrated that admission CLR value serves as a feasible biomarker to predict the clinical prognosis of patients with aSAH [14]. However, the predictive value of the admission CLR value for neurological complications including CVS, DCI, and CH is still not clear. Hence, the purpose of the present study is to identify the predictive value of admission CLR, NLR, PLR, and MLR values in neurological functional outcome and complications after aSAH.

2. Methods

2.1. Study Design

We retrospectively analyzed 662 patients with SAH, who had been hospitalized within 48 h and underwent laboratory examination in the Department of Neurosurgery of the Medical Faculty and University Hospital Düsseldorf from January 2011 to October 2021 and were diagnosed with a computed tomography (CT) scan. The clinical data including patient demographics (e.g., age, sex) and medical history (e.g., hypertension, diabetes, etc.) from these patients were collected via medical records and/or outpatient follow-up. The inclusion criteria for enrollment were as follows: (1) age above 18 years, (2) hospitalized within 48 h in the emergency unit, (3) detected SAH by CT scan, and the diagnosis of the aSAH was achieved by CTA or DSA. The study exclusion criteria were as follows: (1) no aneurysms detected by CTA or DSA, (2) patients without complete clinical data and laboratory examination, (3) having complications with infection, immune dysfunction, blood system diseases, organ function damage, or major infectious diseases, which had significantly influenced the laboratory examination. Forty-six patients were excluded because in them SAH was not caused by aSAH, consisting of 30 cases with perimesencephalic/nonaneurysmal and 16 cases that were unclear. Furthermore, 140 patients were diagnosed with diabetes, 10 cases took the platelet inhibitor, six cases had the vitamin K/Xa

antagonist, three cases took the vitamin K/Xa antagonist and platelet inhibitor together, two cases were diagnosed with acute renal dysfunction, one case with renal dysfunction and pancreatitis, one case with renal function failure, one case with acute renal and liver failure, one case with chronic renal dysfunction, and one case with infection that could have significantly influenced the peripheral serum biomarkers; 284 cases with no data on the admission lymphocyte count were excluded. Finally, 166 patients aged above 18 years (ranging from 21.00 to 84.00 years) met the inclusion criteria and were enrolled in our study (Figure 1). The strict inclusion/exclusion criteria and the use of standardized data collection procedures minimized the impact of selection bias and information bias. All 166 patients had complete data. The study was reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines.

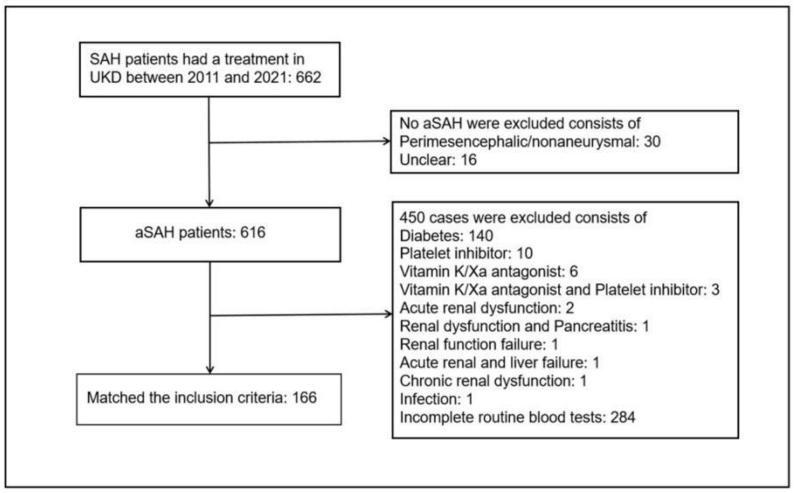

Figure 1. Flowchart of patient enrollment.

2.2. Clinical Data Collection and Neurological Complication Evaluation

We followed our standardized diagnostic and treatment charts as previously described [15]. SAH was detected by a CT scan. CTA and DSA were employed for further evaluation of neuroradiological data such as modified Fisher (mFisher) Grading Scale, intracerebral hemorrhage, subdural hemorrhage, and aneurysmal locations and sizes. The admission status was measured by the World Federation of Neurosurgical Societies (WFNS) grade, Glasgow Coma Score (GCS). The treatment methods (coiling or clipping) were dependent on an interdisciplinary approach. Our treatment protocol at the neurological intensive care unit (NICU) included hourly neurological monitoring, continuous invasive blood pressure and body temperature measurements, daily TCD, and the application of nimodipine for 21 days starting from the day of admission. CTA and CTP were performed for confirmation upon suspicion of CVS. The diagnostic criteria for CVS included symptomatic vasospasm (secondary clinical decline with new neurological deficits) or radiological vasospasm (diagnosed with digital subtraction angiography, with transcranial Doppler (TCD) and with CT perfusion (CTP) studies). All patients underwent daily TCD and CT perfusion on day 1, 4, 7, 10, and 14 on a routine basis. On any suspicion of CVS, the patients received DSA to confirm CVS and to treat CVS with intraarterial nimodipine. Symptomatic vasospasm was defined as the development of new focal neurological signs, deterioration in level of consciousness, or both, when the cause was felt to be ischemia attributable to vasospasm after other possible causes of worsening (for example, hydrocephalus, seizures, metabolic derangement, infection, or oversedation) had been excluded. Angiographic

vasospasm was defined as moderate-to-severe arterial narrowing on DSA not attributable to atherosclerosis, catheter-induced spasm, or vessel hypoplasia, as determined by a neuroradiologist. TCD vasospasm was defined as a mean flow velocity in any vessel >120 cm/s. CTP vasospasm diagnosed with the patients showing significant perfusion deficits with a mean transient time ≥5 s in CTP and DSA excluded the perfusion deficits caused by occlusion of the blood vessels (such as by clots) with/without a new focal neurological deficit within 3 days to 2 weeks after SAH [12,15,16]. Furthermore, as previously mentioned, DCI was defined as combining the presence of cerebral infarction on a CT or MR scan of the brain within 6 weeks after SAH, or the latest CT or magnetic resonance imaging (MRI) scan made before death within 6 weeks, or proven at autopsy, not present on the CT or MRI scan between 24 and 48 h after early aneurysm occlusion, and not attributable to other causes such as surgical clipping or endovascular treatment with the occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least two points on the Glasgow Coma Scale (either on the total score or on one of its components [eye, motor on either side, verbal]). This should last for at least 1 h, should not be apparent immediately after aneurysm occlusion and cannot be attributed to other causes employing clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies [17]. Hydrocephalus was diagnosed by the following standards: (1) Evans index > 0.3 (the ratio of the greatest distance between bilateral anterior horns of the lateral ventricles and the greatest internal distance of the skull); and (2) enlargement of the anterior horns of the lateral ventricles, temporal horns, and the third ventricle accompanied with periventricular cerebral edema [18]. CH was defined by hydrocephalus that occurred postoperatively for 2 weeks. Seizures were mainly diagnosed by clinical symptoms, signs, and outpatient follow-up. Neurological functional outcome was measured by modified Rankin Scale (mRS) after admission at 6 months collected from outpatients at follow-up. Functional outcome was dichotomized into good (mRS Score 0–2) and poor (mRS Score 3–6) [10].

2.3. Admission Serum Biomarker Collection

The quantitative variables including the admission WBC, platelet, neutrophil, lymphocyte, and monocyte count, and the levels of CRP were obtained from routine blood tests and comprehensive biochemical tests within 24 h at the hospital emergency unit. Calculations of CLR, NLR, PLR, and MLR used the ratio by the level of CRP, and the neutrophil, platelet, and monocyte count dividing the lymphocyte count.

2.4. Statistical Analysis

All statistical analyses were performed using SPSS, version 25.0 (IBM Corp., Armonk, New York, NY, USA). We employed the Kolmogorov–Smirnov test to test the normality of the variables. The normally distributed variables were defined as the mean ± standard deviation (SD) and the non-normally distributed variables as the median and interquartile range (IQR). The categorical variables were defined as numbers and percentages. Univariate analysis was performed by dividing the cohort into two groups according to the dependent variables. We employed the independent Student t-test and Mann–Whitney U test to compare the differences between the two groups of normally distributed and non-normally distributed variables, respectively. Differences in the categorical variables were compared using the Chi-square test or Fisher exact test. The associations between the risk factors and CVS and DCI were performed using multivariate logistic regression models, which were presented by the calculations of the odds ratio (OR) and 95% confidence interval (CI). Only statistically significant variables with a $p < 0.005$ in univariate analysis were included in the multivariate logistic regression. The independent risk factors were evaluated by multivariate logistic regression [19]. The receiver operating characteristic (ROC) curves were used to evaluate the predictive value [11]. $p < 0.05$ was considered to be a statistically significant difference.

3. Results

3.1. Baseline Characteristics

The baseline characteristics of 166 aSAH patients are shown in Table 1. The mean age of the cohort was 55.58 (SD, 12.22) years ranging from 21.00 to 84.00 years. A total of 114 (68.7%) patients were females. A total of 117 (70.5%) patients were diagnosed with hypertension. The median admission WFNS grade was 2 (IQR, 1–5) and the median GCS score was 13 (IQR, 4–15). Additionally, the median of CRP, WBC, platelet, neutrophil, lymphocyte, monocyte, CLR, NLR, PLR, and MLR in the cohort were 0.50 (IQR, 0.20–1.40) mg/dL, 13.35 (IQR, 10.58–15.90) $\times$ 10^9/L, 230.50 (IQR, 196.75–278.25) $\times$ 10^9/L, 11.17 (IQR, 8.52–14.00) $\times$ 10^9/L, 1.05 (IQR, 0.74–1.60) $\times$ 10^9/L, 0.78 (IQR, 0.50–1.00) $\times$ 10^9/L, 0.50 (IQR, 0.17–1.56) mg $\times$ 10^{-6}, 11.00 (IQR, 6.24–16.74), 218.87 (IQR, 143.57–323.11), and 0.63 (IQR, 0.43–0.90), respectively. Furthermore, neuroradiological data in our study included on-admission mFisher scores, intracerebral and subdural hemorrhage status, and aneurysmal locations and sizes. The median of the mFisher score was 4 (IQR, 3–4). There were 37 (22.3%) aSAH patients with intracerebral hemorrhage and 14 (8.4%) patients with subdural hemorrhage. The locations of aneurysms displayed different distributions: 77 (46.4%) cases with anterior cerebral arteries (ACA) and/or anterior communicating artery (ACOM), 38 (22.9%) cases with middle cerebral artery (MCA), 19 (11.4%) cases with posterior communicating artery (PCOM), and nine (5.4%) and 23 (13.9%) cases with internal carotid artery (ICA) and posterior circulation (PC), respectively. The sizes of aneurysms also showed different distributions: 49 (29.5%) cases with 0–4.9 mm, 46 (27.7%) cases with 5–6.9 mm, 21 (12.7%) cases with 7–9.9 mm, 19 (11.4%) cases with 10–19.9 mm, and six (3.6%) cases with $\geq$20 mm. The data of 25 (15.1%) cases were missing. Endovascular coiling was performed in 46 (27.7%) cases and surgical clipping was performed in 114 (68.7%) cases. Six (3.6%) cases had no treatment. There were 48 (28.9%) aSAH patients diagnosed with CVS, 53 (31.9%) cases with DCI, 88 (53.0%) cases with CH, and 23 (13.9%) cases with seizures in the cohort, respectively. The median of 6 months mRS (represented the neurological functional outcome) was 3 (IQR, 1–5).

Table 1. Patient characteristics.

Variables	Patients (n = 166)
Demographics	
Age, mean (SD), y	55.58 ± 12.22
Female sex, n (%)	114 (68.7)
Medical history, n (%)	
Hypertension	117 (70.5)
Admission status, median (IQR)	
WFNS grade	2 (1–5)
GCS score	13 (4–15)
Admission serum biomarkers, median (IQR)	
CRP, (mg/dL)	0.50 (0.20–1.40)
WBC, ($\times 10^9$/L)	13.35 (10.58–15.90)
Platelet, ($\times 10^9$/L)	230.50 (196.75–278.25)
Neutrophil, ($\times 10^9$/L)	11.17 (8.52–14.00)
Lymphocyte, ($\times 10^9$/L)	1.05 (0.74–1.60)
Monocyte, ($\times 10^9$/L)	0.78 (0.50–1.00)
CLR, (mg $\times$ 10^{-6})	0.50 (0.17–1.56)
NLR	11.00 (6.24–16.74)
PLR	218.87 (143.57–323.11)
MLR	0.63 (0.43–0.90)
Neuroradiological data	
mFisher score, median (IQR)	4 (3–4)
Intracerebral hemorrhage, n (%)	37 (22.3)
Subdural hemorrhage, n (%)	14 (8.4)
Aneurysmal locations, n (%)	
ACA/ACOM	77 (46.4)
MCA	38 (22.9)
PCOM	19 (11.4)
ICA	9 (5.4)

Table 1. *Cont.*

Variables	Patients (*n* = 166)
PC	23 (13.9)
Aneurysmal sizes, *n* (%)	
0–4.9 mm	49 (29.5)
5–6.9 mm	46 (27.7)
7–9.9 mm	21 (12.7)
10–19.9 mm	19 (11.4)
≥20 mm	6 (3.6)
Missing	25 (15.1)
Treatment status, *n* (%)	
Coil	46 (27.7)
Clip	114 (68.7)
No treatment	6 (3.6)
Neurological complications, *n* (%)	
CVS	48 (28.9)
DCI	53 (31.9)
CH	88 (53.0)
Seizures	23 (13.9)
Neurological functional outcome	
6 months mRS, median (IQR)	3 (1–5)

SD: standard deviation, IQR: interquartile range, WFNS: World Federation of Neurosurgical Societies, GCS: Glasgow Coma Score, CRP: C-reactive protein, mg/dL: milligram/deciliter, mg/L: milligram/liter, WBC: white blood cell, $\times 10^9$/L $\times 10^9$/Liter, CLR: C-reactive protein to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, 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.

3.2. Univariate Analysis on CVS, mRS (Good 0–2 vs. Poor 3–6), DCI, and CH after aSAH

As shown in Table 2, the included 166 aSAH patients were categorized by CVS. Univariate analysis revealed that the on-admission serum levels of CRP (median [IQR] CRP 1.95 [0.80–3.10] mg/dL vs. 0.30 [0.18–0.80] mg/dL; $p < 0.001$), WBC (median [IQR] WBC 14.05 [11.68–18.33] $\times$ 10^9/L vs. 12.60 [10.10–15.70] $\times$ 10^9/L; $p = 0.040$), neutrophil (median [IQR] neutrophil 11.95 [10.05–15.95] $\times$ 10^9/L vs. 10.49 [7.88–13.49] $\times$ 10^9/L; $p = 0.007$), and CLR (median [IQR] CLR 1.83 [0.77–4.46] mg $\times$ 10^{-6} vs. 0.30 [0.12–0.76] mg $\times$ 10^{-6}; $p < 0.001$), NLR (median [IQR] NLR 12.90 [9.80–20.59] vs. 8.74 [5.54–15.97]; $p = 0.001$), PLR (median [IQR] PLR 262.08 [189.38–397.88] vs. 215.88 [135.60–294.97]; $p = 0.012$), and MLR (median [IQR] MLR 0.74 [0.59–1.11] vs. 0.58 [0.39–0.77]; $p = 0.001$) in patients with CVS were significantly higher than those in patients without CVS. The admission lymphocyte count (median [IQR] lymphocyte 0.93 [0.60–1.32] $\times$ 10^9/L vs. 1.17 [0.80–1.62] $\times$ 10^9/L; $p = 0.010$) in patients with CVS was significantly less than that in patients without CVS. The patients without CVS had favorable admission status, meaning a lower WFNS grade (median [IQR] WFNS grade 2 [1–5] vs. 3 [2–5]; $p = 0.018$) and higher GCS score (median [IQR] GCS score 14 [5–15] vs. 11 [3–14]; $p = 0.016$) than those in patients with CVS. The patients without CVS had better neurological functional outcome (median [IQR] 6 months mRS 2 [1–5] vs. 5 [2–6]; $p < 0.001$) and less incidence of neurological complications including DCI (number [%] DCI 26 [22.0%] vs. 27 [56.3%]; $p < 0.001$), CH (number [%] CH 53 [44.9%] vs. 35 [72.9%]; $p = 0.001$), and seizures (number [%] seizures 12 [10.2%] vs. 11 [22.9%]; $p = 0.031$) than those in patients with CVS. Similarly, admission serum levels of CLR in patients with poor outcome (6 months mRS 3–6) (median [IQR] CLR 0.77 [0.20–2.74] mg $\times$ 10^{-6} vs. 0.34 [0.13–0.83] mg $\times$ 10^{-6}; $p = 0.002$; Supplemental Table S1), DCI (median [IQR] CLR 1.34 [0.21–3.60] mg $\times$ 10^{-6} vs. 0.43 [0.13–0.84] mg $\times$ 10^{-6}; $p < 0.001$; Supplemental Table S2), and CH (median [IQR] CLR 0.75 [0.21–1.98] mg $\times$ 10^{-6} vs. 0.33 [0.13–0.95] mg $\times$ 10^{-6}; $p = 0.004$; Supplemental Table S3) were significantly higher than those in patients with good outcome (6 months mRS 0–2), non-DCI, and non-CH. Admission serum levels of NLR in patients with poor outcome (6 months mRS 3–6) (median [IQR] NLR 12.75 [7.11–19.17] vs. 8.74 [5.32–13.32]; $p = 0.001$; Supplemental Table S1), DCI (median [IQR] NLR 12.76 [8.14–22.39] vs. 9.33 [5.90–15.85]; $p = 0.012$; Supplemental Table S2), and CH (median [IQR] NLR 12.90 [8.63–19.17] vs. 8.46 [4.83–13.05]; $p < 0.001$; Supplemental Table S3) were significantly

higher than those in patients with good outcome (6 months mRS 0–2), non-DCI, and non-CH. Admission serum levels of MLR in patients with poor outcome (6 months mRS 3–6) (median [IQR] MLR 0.70 [0.51–1.12] vs. 0.55 [0.39–0.74]; $p = 0.001$; Supplemental Table S1), DCI (median [IQR] MLR 0.69 [0.56–1.32] vs. 0.58 [0.42–0.81]; $p = 0.010$; Supplemental Table S2), and CH (median [IQR] MLR 0.69 [0.47–1.08] vs. 0.56 [0.39–0.74]; $p = 0.007$; Supplemental Table S3) were significantly higher than those in patients with good outcome (6 months mRS 0–2), non-DCI, and non-CH. Admission serum levels of PLR in patients with CH (median [IQR] PLR 240.17 [163.58–352.87] vs. 198.43 [132.50–296.56]; $p = 0.041$; Supplemental Table S3) were significantly higher than those in patients with non-CH.

Table 2. Univariate analysis on CVS after aSAH.

Variables	CVS ($n = 48$)	Non-CVS ($n = 118$)	p Value
Demographics			
Age, mean (SD), y	57.60 ± 10.40	54.75 ± 12.83	0.174
Female sex, *n* (%)	33 (68.8)	81 (68.6)	0.989
Medical history, *n* (%)			
Hypertension	37 (77.1)	80 (67.8)	0.234
Admission status, median (IQR)			
WFNS grade	3 (2–5)	2 (1–5)	0.018 *
GCS score	11 (3–14)	14 (5–15)	0.016 *
Admission serum biomarkers, median (IQR)			
CRP, (mg/dL)	1.95 (0.80–3.10)	0.30 (0.18–0.80)	<0.001 *
WBC, ($\times 10^9$/L)	14.05 (11.68–18.33)	12.60 (10.10–15.70)	0.040 *
Platelet, ($\times 10^9$/L)	237.00 (194.25–284.50)	226.00 (199.25–274.25)	0.781
Neutrophil, ($\times 10^9$/L)	11.95 (10.05–15.95)	10.49 (7.88–13.49)	0.007 *
Lymphocyte, ($\times 10^9$/L)	0.93 (0.60–1.32)	1.17 (0.80–1.62)	0.010 *
Monocyte, ($\times 10^9$/L)	0.80 (0.52–1.18)	0.73 (0.50–1.00)	0.404
CLR, (mg $\times 10^{-6}$)	1.83 (0.77–4.46)	0.30 (0.12–0.76)	<0.001 *
NLR	12.90 (9.80–20.59)	8.74 (5.54–15.97)	0.001 *
PLR	262.08 (189.38–397.88)	215.88 (135.60–294.97)	0.012 *
MLR	0.74 (0.59–1.11)	0.58 (0.39–0.77)	0.001 *
Neuroradiological data			
mFisher score, median (IQR)	4 (3–4) 3.56 ± 0.65	4 (3–4) 3.43 ± 0.63	0.151
Intracerebral hemorrhage, *n* (%)	12 (25.0)	25 (21.2)	0.592
Subdural hemorrhage, *n* (%)	3 (6.3)	11 (9.3)	0.736
Aneurysmal locations, *n* (%)			0.248
ACA/ACOM	19 (39.6)	58 (49.2)	
MCA	9 (18.8)	29 (24.6)	
PCOM	9 (18.8)	10 (8.5)	
ICA	2 (4.2)	7 (5.9)	
PC	9 (18.8)	14 (11.9)	
Aneurysmal sizes, *n* (%)			0.282
0–4.9 mm	13 (27.1)	36 (30.5)	
5–6.9 mm	11 (22.9)	35 (29.7)	
7–9.9 mm	4 (8.3)	17 (14.4)	
10–19.9 mm	9 (18.8)	10 (8.5)	
≥20 mm	3 (6.3)	3 (2.5)	
Missing	8 (16.7)	17 (14.4)	
Treatment status, *n* (%)			0.903
Coil	14 (29.2)	32 (27.1)	
Clip	32 (66.7)	82 (69.5)	
No treatment	2 (4.2)	4 (3.4)	
Neurological complications, *n* (%)			
DCI	27 (56.3)	26 (22.0)	<0.001 *
CH	35 (72.9)	53 (44.9)	0.001 *
Seizures	11 (22.9)	12 (10.2)	0.031 *
Neurological functional outcome			
6 months mRS, median (IQR)	5 (2–6)	2 (1–5)	<0.001 *

CVS: cerebral vasospasm, aSAH: aneurysmal subarachnoid hemorrhage, SD: standard deviation, IQR: interquartile range, WFNS: World Federation of Neurosurgical Societies, GCS: Glasgow Coma Score, CRP C-reactive protein, mg/dL: milligram/deciliter, mg/L: milligram/liter, WBC: white blood cell, $\times 10^9$/L $\times 10^9$/Liter, CLR: C-reactive protein to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, 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, * $p < 0.05$ are considered significant.

3.3. Multivariate Logistic Analysis of Risk Factors for Poor Outcome (6 Months mRS 3–6), CVS, DCI, and CH

Due to admission CLR being dependent on the levels of CRP, we only included the CLR in the multivariate logistic analysis. Neurological functional outcome and complications were excluded in the multivariate logistic analysis of variables associated with CVS, DCI, and CH. As shown in Table 3, multivariate logistic regression analysis revealed that the on-admission CLR was independently associated with CVS (OR [95% CI] 2.116 [1.507–2.971]; $p < 0.001$). However, NLR (OR [95% CI] 1.007 [0.946–1.072]; $p = 0.830$), and MLR (OR [95% CI] 0.843 [0.372–1.909]; $p = 0.682$) were not independently associated with the occurrence of CVS. Similarly, multivariate logistic regression analysis demonstrated that on-admission CLR was independently associated with DCI (OR [95% CI] 1.594 [1.220–2.084]; $p = 0.001$; Supplemental Table S5) after aSAH. However, high levels of on-admission CLR were not an independent risk factor for poor outcome (6 months mRS 3–6) (OR [95% CI] 1.474 [0.997–2.177]; $p = 0.052$; Supplemental Table S4) and CH (OR [95% CI] 0.957 [0.843–1.087]; $p = 0.501$; Supplemental Table S6) after aSAH.

Table 3. Multivariate logistic regression analysis of variables associated with CVS after aSAH.

Variables	CVS (n = 48)		
	OR	95% CI	p Value
CLR	2.116	1.507–2.971	<0.001 *
NLR	1.007	0.946–1.072	0.830
MLR	0.843	0.372–1.909	0.682

CVS: cerebral vasospasm, aSAH: aneurysmal subarachnoid hemorrhage, OR: odds ratio, CI: confidence interval, CLR: C-reactive protein to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, * $p < 0.05$ are considered significant.

3.4. Predictive Value of CLR for CVS, DCI, Poor Outcome (6 Months mRS 3–6), and CH after aSAH

The ROC curves were performed to clarify the predictive value of admission CLR, NLR, PLR, MLR, CRP, WBC, platelet, neutrophil, lymphocyte, and monocyte in CVS, DCI, CH, and poor outcome (6 months mRS 3–6) after aSAH. The area under the curve (AUC) of admission CLR for the predicted of CVS, poor outcome (6 months mRS 3–6), DCI, and CH were (AUC [95% CI] 0.834 [0.767–0.901]; $p < 0.001$; Figure 2; Table 4), (AUC [95% CI] 0.639 [0.555–0.724]; $p = 0.002$; Supplemental Figure S1; Supplemental Table S7), (AUC [95% CI] 0.679 [0.581–0.777]; $p < 0.001$; Supplemental Figure S2; Supplemental Table S8), and (AUC [95% CI] 0.628 [0.543–0.713]; $p = 0.005$; Supplemental Figure S3; Supplemental Table S9), respectively. The AUC of admission NLR for the predicted of CVS, poor outcome (6 months mRS 3–6), DCI, and CH were (AUC [95% CI] 0.665 [0.577–0.752]; $p = 0.001$; Figure 2; Table 4), (AUC [95% CI] 0.644 [0.560–0.728]; $p = 0.001$; Supplemental Figure S1; Supplemental Table S7), (AUC [95% CI] 0.621 [0.528–0.714]; $p = 0.012$; Supplemental Figure S2; Supplemental Table S8), and (AUC [95% CI] 0.681 [0.601–0.762]; $p < 0.001$; Supplemental Figure S3; Supplemental Table S9), respectively. The AUC of admission PLR for the predicted of CVS, poor outcome (6 months mRS 3–6), DCI, and CH were (AUC [95% CI] 0.624 [0.531–0.718]; $p = 0.012$; Figure 2; Table 4), (AUC [95% CI] 0.582 [0.495–0.668]; $p = 0.069$; Supplemental Figure S1; Supplemental Table S7), (AUC [95% CI] 0.545 [0.448–0.642]; $p = 0.350$; Supplemental Figure S2; Supplemental Table S8), and (AUC [95% CI] 0.592 [0.505–0.679]; $p = 0.041$; Supplemental Figure S3; Supplemental Table S9), respectively. The AUC of admission MLR for the predicted of CVS, poor outcome (6 months mRS 3–6), DCI, and CH were (AUC [95% CI] 0.659 [0.571–0.748]; $p = 0.001$; Figure 2; Table 4), (AUC [95% CI] 0.654 [0.571–0.737]; $p = 0.001$; Supplemental Figure S1; Supplemental Table S7), (AUC [95% CI] 0.624 [0.533–0.715]; $p = 0.010$; Supplemental Figure S2; Supplemental Table S8), and (AUC [95% CI] 0.622 [0.537–0.707]; $p = 0.007$; Supplemental Figure S3; Supplemental Table S9), respectively. The results revealed that admission CLR had a favorable predictive value for CVS after aSAH. The sensitivity and specificity of admission CLR for CVS prediction were 77.1% and 75.4% (Table 4).

An admission CLR of 0.757 mg × 10^{-6} was identified as the best cutoff threshold to discriminate between CVS and non-CVS (CVS: CLR < 0.757 mg × 10^{-6} 11/100 [11.0%] vs. CLR ≥ 0.757 mg × 10^{-6} 37/66 [56.1%]; $p < 0.001$) (Table 5). The incidence of DCI (DCI: CLR < 0.757 mg × 10^{-6} 20/100 [20.0%] vs. CLR ≥ 0.757 mg × 10^{-6} 33/66 [50.0%]; $p < 0.001$) and CH (CH: CLR < 0.757 mg × 10^{-6} 45/100 [45.0%] vs. CLR ≥ 0.757 mg × 10^{-6} 43/66 [65.2%]; $p = 0.011$) in patients with CLR < 0.757 mg × 10^{-6} were significantly lower than those in patients with CLR ≥ 0.757 mg × 10^{-6}. The outcome (median [IQR] 6 months mRS 2 [1–5] vs. 4 [1–6]; $p = 0.003$) in patients with CLR < 0.757 mg × 10^{-6} was better than that in patients with CLR ≥ 0.757 mg × 10^{-6}.

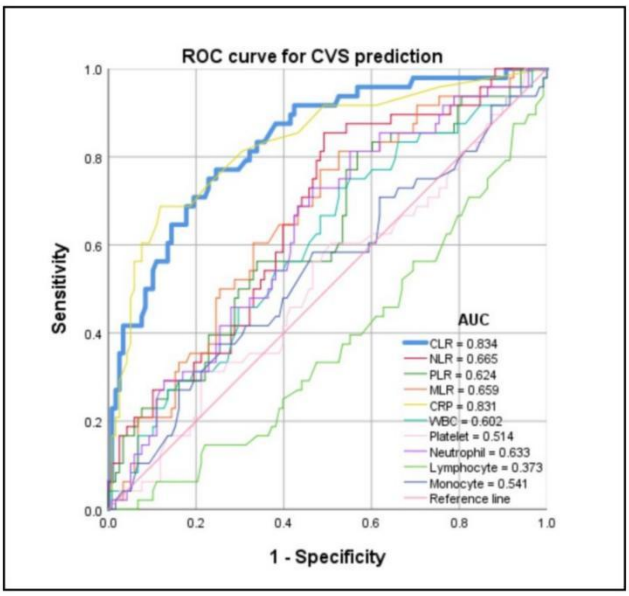

Figure 2. Predictive value of each admission serum biomarkers for the cerebral vasospasm (CVS) using receiver operating characteristics (ROC) curve.

Table 4. Comparison of the predictive value of different admission serum biomarkers associated with CVS.

Predictive Biomarkers	AUC	95% CI	Sensitivity (%)	Specificity (%)	Cut-Off Value	*p* Value
CLR	0.834	0.767–0.901	77.1	75.4	0.757 mg × 10^{-6}	<0.001 *
NLR	0.665	0.577–0.752	85.4	50.8	8.775	0.001 *
PLR	0.624	0.531–0.718	81.3	43.2	177.312	0.012 *
MLR	0.659	0.571–0.748	77.1	51.7	0.584	0.001 *
CRP	0.831	0.758–0.903	68.8	88.1	1.150 mg/dL	<0.001 *
WBC	0.602	0.508–0.697	72.9	47.5	12.050 × 10^9/L	0.040 *
Platelet	0.514	0.416–0.612	31.3	78.8	280.500 × 10^9/L	0.781
Neutrophil	0.633	0.542–0.723	72.9	53.4	10.840 × 10^9/L	0.007 *
Lymphocyte	0.373	0.280–0.465	100	0	–	0.010 *
Monocyte	0.541	0.442–0.641	37.5	74.6	0.980 × 10^9/L	0.405

CVS: cerebral vasospasm, AUC: area under the curve, CI: confidence interval, CLR: C-reactive protein to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, CRP: C-reactive protein, WBC: white blood cell, * $p < 0.05$ are considered significant.

Table 5. Neurological complications and functional outcome categorized by the identified CLR threshold (0.757 mg × 10^{-6}).

Variables	CLR		*p* Value
	<0.757 mg × 10^{-6} (*n* = 100)	≥0.757 mg × 10^{-6} (*n* = 66)	
Neurological complications, *n* (%)			
CVS	11 (11.0)	37 (56.1)	<0.001 *
DCI	20 (20.0)	33 (50.0)	<0.001 *
CH	45 (45.0)	43 (65.2)	0.011 *
Seizures	14 (14.0)	9 (13.6)	0.947
Neurological functional outcome			
6 months mRS, median (IQR)	2 (1–5)	4 (1–6)	0.003 *

CLR: C-reactive protein to lymphocyte ratio, CVS: cerebral vasospasm, DCI: delayed cerebral ischemia, CH: chronic hydrocephalus, IQR: interquartile range, mRS: modified Rankin Scale, * $p < 0.05$ are considered significant.

4. Discussion

Accurate prognosis prediction for aSAH patients is necessary for determining the choices of clinical treatment strategies. The admission WBC, platelet, neutrophil, lymphocyte, and monocyte counts, and the levels of CRP are easy-to-quantify parameters and have promising predictive value for the outcome prediction after aSAH. In addition, CVS, DCI, and CH are the most critical post-aSAH complications, which are significantly associated with the outcome of aSAH. However, the predictive value of CLR for neurological outcome and complications was rarely investigated in patients with aSAH. In our study, we investigated admission CLR for the prediction of neurological functional outcome and complications after aSAH and found that high admission CLR was an independent risk factor for CVS and DCI after aSAH. The AUC of admission CLR for the predicted poor outcome (6 months mRS 3–6), CVS, DCI, and CH were 0.639, 0.834, 0.679, and 0.628, revealing that admission CLR had a favorable predictive value for CVS after aSAH. The sensitivity and specificity of admission CLR for CVS prediction were 77.1% and 75.4%. An admission CLR of 0.757 mg × 10^{-6} was identified as the best cutoff threshold to discriminate between CVS and non-CVS.

Elevated CLR was equal to high levels of CRP and relevant low serum levels of lymphocyte. CRP was identified in the 1930s and has been reported as an acute phase plasma protein and a response for the acute phase, which is synthesized in hepatocytes and induced by cytokines, particularly interleukin-6 (IL-6), which activates the complement system contributing to natural immunity and released into the blood [13,20,21]. CRP can rise 1000-fold within a few hours after the onset of stimuli such as infection, tissue necrosis, trauma, cancer, or various inflammatory diseases. The level of CRP rises to a peak 48 h after the initial stimulus and falls to baseline levels within 7–12 days when the inflammatory stimulus has disappeared [22,23]. CRP is also stimulated by interleukin-1 (IL-1), which is correlated with the pathogenesis of CVS [22,24,25]. According to the description of Fountas et al., elevated CRP levels in serum and cerebrospinal fluid (CSF) after angiographic vasospasm occurred in patients with aSAH, and higher CRP level measurements were strongly correlated with worse clinical outcomes in their cohort [22]. Additionally, Gaastra et al. confirmed that on-admission CRP levels are an independent predictive factor for the postoperative functional outcome after aSAH and high levels of on-admission CRP are closely correlated to poor functional outcomes after aSAH [20]. Romero et al. clarified that high serum CRP predicts unfavorable clinical outcomes and the occurrence of CVS and delayed ischemic neurological deficits (DIND) [26]. Meanwhile, when the central nervous system is stimulated, the immune system is activated, releasing large numbers of lymphocytes to reduce the damage to brain tissue through antigen recognition, cell activation, and immunocide [27]. Frösen et al. histologically compared 42 ruptured aneurysms with 24 unruptured aneurysms and found that lymphocytes were actively involved in the inflammatory cascade in the aneurysmal vessel wall [28]. When an aneurysm ruptures, lymphocytes are overconsumed, leading to a decrease in lymphocyte count, which is also

considered to be associated with worsening brain injury and poor clinical outcomes [27]. In our study, the level of CLR in patients with poor outcome (6 months mRS 3–6) after aSAH was significantly higher than that in patients with good outcome (6 months mRS 0–2). CLR is a novel inflammatory biomarker and has been employed to serve as one of the most effective prognostic markers for pancreatic and rectal cancer surgery, tumor, and strangulated abdominal hernia (intestinal ischemia) [29–32]. Fan et al. found that CLR displayed higher predicted accuracy of poor prognosis compared to the combination of NLR, platelet to lymphocyte ratio (PLR), C-reactive protein to albumin ratio (CAR), neutrophil to albumin ratio (NAR), and platelet to albumin ratio (PAR) in patients with pancreatic cancer [30]. Recently, Zhang et al. first demonstrated that admission CLR serves as a valuable serum biomarker to predict the clinical prognosis of patients with aSAH [14]. In this study, increased admission levels of CLR were related to increased risk of poor outcome, which is consistent with the previously reported findings. Additionally, we first revealed that increased admission levels of CLR were associated with a high risk of occurrence of CVS, DCI, and CH. Higher AUC of CLR compared with CRP, WBC, neutrophil, and lymphocyte was observed to predict the occurrence of CVS in patients with aSAH. In addition, we first confirmed that admission CLR was independently associated with the occurrence of CVS and DCI after aSAH. Admission CLR had a favorable predictive value for CVS compared with poor outcome (6 months mRS 3–6) and DCI. High levels of CLR were associated with the poor prognosis of patients with aSAH and might be mediated by the elevated occurrence of CVS.

In addition, WBC represents the systemic inflammation status of humans and is widely investigated to predict the prognosis of diseases, such as cancers and aSAH [33,34]. Mahta et al. revealed that WBC count in the early course of SAH may have prognostic values in predicting DCI and functional outcome [35]. Furthermore, Geraghty et al. demonstrated that the WBC count within 24 h of admission was an independent risk factor for CVS after aSAH [35]. Similarly, Hu et al. reported that elevated WBC count within 24 h of admission could predict DCI occurrence between 4 and 30 days after aSAH [36]. In our study, the on-admission WBC count in patients with poor outcome (6 months mRS 3–6), CVS, and CH was significantly higher compared with patients with good outcome (6 months mRS 0–2), non-CVS and non-CH after aSAH. However, in our study, on-admission WBC count was not independently associated with poor outcome (6 months mRS 3–6) and the occurrence of CVS, DCI, and CH after aSAH. Furthermore, platelets are widely recognized as the major cells regulating hemostasis and thrombus formation. The influence of platelets on blood vessels has been attributed to their main role in thrombus formation, mediating myocardial infarction, stroke, and venous thromboembolism [37]. Wang et al. and Zhang et al. confirmed that platelets were correlated with the CVS and DCI after aSAH [13,38]. However, in our study, no significant differences in on-admission platelet count were observed in patients with poor outcome (6 months mRS 3–6), CVS, DCI, and CH compared to those with good outcome (6 months mRS 0–2), non-CVS, non-DCI, and non-CH after aSAH. The associations between on-admission WBC and platelet count and neurological functional outcome and complications after aSAH need to be further elucidated.

Additionally, an accurate prediction of clinical functional outcome and complications in patients with aSAH is still a challenge today. Admission CRP was widely employed to investigate the outcome and complications prediction, while admission CLR was rarely reported previously. We were the first to evaluate the predictive value of admission CLR for neurological functional outcome and complications after aSAH and found that the sensitivity of admission CLR in predicting CVS was higher than that compared with admission CRP (CLR [77.1%] vs. CRP [68.8%]). The sensitivity (CLR [77.1%] vs. CRP [68.8%]) and specificity (CLR [75.4%] vs. CRP [88.1%]) of CLR for CVS predicted were performed at relatively equal levels compared with admission CRP. We can combine the admission CLR and CRP to improve the sensitivity and specificity of CVS prediction. Moreover, in multivariate logistic regression analysis, admission CLR was an independent risk factor of CVS compared with admission NLR and MLR. Admission CLR displayed a better specificity for the

prediction of CVS compared with admission NLR, PLR, and MLR. Our results supported the possibility of admission CLR being a promising predictive biomarker, which could provide some guidance for clinical work. Up to now, there is an abundance of lab parameters/ratios predicting outcome or DCI. We recruited C-reactive protein to lymphocyte ratio (CLR), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and monocyte to lymphocyte ratio (MLR) in our research and found that these lab parameters/ratios improve the predictive value of CVS (CLR AUC = 0.834 vs. CRP AUC = 0.831; NLR AUC = 0.665 vs. neutrophil AUC = 0.633; PLR AUC = 0.624 vs. platelet AUC = 0.514; MLR AUC = 0.659 vs. monocyte AUC = 0.541; Figure 2; Table 4), DCI (CLR AUC = 0.679 vs. CRP AUC = 0.674; NLR AUC = 0.621 vs. neutrophil AUC = 0.599; PLR AUC = 0.545 vs. platelet AUC = 0.428; MLR AUC = 0.624 vs. monocyte AUC = 0.564; Supplemental Figure S2; Supplemental Table S8), CH (CLR AUC = 0.628 vs. CRP AUC = 0.593; NLR AUC = 0.681 vs. neutrophil AUC = 0.685; PLR AUC = 0.592 vs. platelet AUC = 0.425; MLR AUC = 0.622 vs. monocyte AUC = 0.553; Supplemental Figure S3; Supplemental Table S9), and poor outcome (6 months mRS 3–6) (CLR AUC = 0.639 vs. CRP AUC = 0.610; NLR AUC = 0.644 vs. neutrophil AUC = 0.610; PLR AUC = 0.582 vs. platelet AUC = 0.461; MLR AUC = 0.654 vs. monocyte AUC = 0.565; Supplemental Figure S1; Supplemental Table S7). In the future, more and more novel and accurate predictive biomarkers will be developed to predict the prognosis and complications in patients with aSAH.

Our study was explorative in nature. The explorative approach was deliberately chosen due to the complex and multifactorial nature of CVS in aSAH. This condition is influenced by a range of biological and physiological factors, making it challenging to hypothesize the impact of specific biomarkers a priori. We aimed to comprehensively investigate the potential of CLR as a predictive biomarker, considering its previously demonstrated relevance in inflammatory and vascular conditions. Selection of parameters: The parameters analyzed in this study, including some less common ones, were carefully chosen based on their potential relevance to the pathophysiology of CVS. Each parameter was selected based on a thorough review of existing literature and our clinical experience in managing aSAH patients. We believe that examining these parameters, in conjunction with CLR, provided a more robust understanding of the biomarker's predictive capabilities. Hypothesis development: While our approach was explorative, it was not without direction. The hypothesis that CLR could serve as a predictive biomarker for CVS in aSAH was based on preliminary data and existing research indicating the role of inflammation and immune response in the pathogenesis of CVS. The additional parameters were included to investigate the specificity and sensitivity of CLR in this context and to explore potential mechanisms that might underlie its predictive value. Statistical analysis: To ensure the rigor of our explorative approach, we employed robust statistical methods. These included the use of multivariate analyses to control for potential confounders and to isolate the specific impact of CLR on the risk of CVS. In conclusion, the explorative nature of our study was a deliberate and considered choice, aimed at thoroughly investigating CLR's potential as a predictive biomarker in aSAH. The parameters analyzed were selected based on their relevance to the disease's pathophysiology and the hypothesis was grounded in existing scientific evidence. We believe our findings contribute valuable insights into the role of CLR in aSAH and pave the way for further hypothesis-driven research in this area.

Due to the complex nature of the disease, every non-invasive predictive marker may add its diagnostic value providing in this case an easy-to-quantify ratio to improve the predictive value of current diagnostics for post hemorrhagic complications. Risk stratification: The primary value of CLR in this context is its ability to stratify patients based on their risk of developing CVS. Clinicians can prioritize monitoring and interventions for the patients who are most likely to benefit from them. Tailoring clinical monitoring: For patients with a high CLR, indicating a higher risk of CVS, clinicians can intensify monitoring protocols including more frequent neurological assessments, more frequent monitoring of hemodynamic parameters, and earlier or more frequent imaging tests to detect vasospasm before causing clinical deterioration. Early intervention and preventive strategies: Stratifying

a patient's risk can guide the initiation of preventive measures. For instance, clinicians might be more vigilant about implementing strategies like hemodynamic augmentation or prophylactic use of nimodipine in patients with elevated CLR. Customizing treatment plans: The CLR value can help in deciding the aggressiveness of therapeutic interventions. Clinicians might choose earlier endovascular treatments for vasospasm (like angioplasty or intra-arterial nimodipine therapy) rather than waiting for clinical deterioration in patients with high CLR. Patient counseling and resource allocation: Understanding the risk of CVS can assist in patient and family counseling regarding prognosis and potential complications. It also helps in the optimal allocation of healthcare resources, such as ICU and specialized care for those who need it most. Research and clinical trials: The identification of CLR as a predictive biomarker opens directions for further research, including clinical trials to test targeted interventions for patients identified as high-risk based on the levels of CLR. In conclusion, the addition of CLR as a predictive biomarker for CVS in aSAH patients is not just about adding another test; it is about providing a practical, cost-effective tool for better patient stratification and management. It helps to guide clinical decisions from monitoring to intervention and has the potential to significantly improve patient outcomes.

5. Limitations

Admittedly, some limitations exist in our research. First, our study was a retrospective and single-center study making it susceptible to bias arising from patient and treatment choices. Therefore, prospective multi-center clinical trials on the associations of CLR with neurological functional outcome and complications after aSAH need to be set up. Second, the aSAH patients diagnosed with the diseases influenced by the peripheral serum biomarkers were excluded. It is still not clear whether the CLR has a predictive value for the prognosis and the occurrence of neurological complications in patients with admission systemic metabolic diseases. The development of new predictive biomarkers and models for patients with admission systemic metabolic diseases is essential. Third, due to 284 cases not having complete routine blood tests, our results strongly recommend that clinicians should complete routine blood and comprehensive biochemical tests within 24 h at the hospital emergency unit for every aSAH patient. Fourth, out of 662 patients, only 166 patients included making it susceptible to sampling bias. Last but not least, though we reported the associations of on-admission serum biomarkers with neurological functional outcome and complications after aSAH, the potential mechanisms are still not fully understood.

6. Conclusions

In summary, admission serum levels of CLR in patients with CVS, poor outcome (6 months mRS 3–6), DCI, and CH were significantly higher than those in patients with good outcome (6 months mRS 0–2), non-CVS, non-DCI, and non-CH. The on-admission high levels of CLR served as an independent risk factor for CVS and DCI. Admission CLR is an easy-to-quantify laboratory parameter that efficiently predicts the CVS after aSAH, which could provide some guidance for clinicians to evaluate for possible progression and treatment strategies in patients with aSAH.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm13040940/s1, STROBE checklist; Table S1. Univariate analysis on outcome (6 months mRS) after aSAH. Table S2. Univariate analysis on DCI after aSAH. Table S3. Univariate analysis on CH after aSAH. Table S4. Multivariate logistic regression analysis of variables associated with poor outcome (6 months mRS 3–6). Table S5. Multivariate logistic regression analysis of variables associated with DCI after aSAH. Table S6. Multivariate logistic regression analysis of variables associated with CH after aSAH. Table S7. Comparison of predictive value of different admission serum biomarkers associated with poor outcome (6 months mRS 3–6). Table S8 Comparison of predictive value of different admission serum biomarkers associated with DCI. Table S9 Comparison of predictive value of different admission serum biomarkers associated with CH. Figure S1. Predictive value of each admission serum biomarkers for poor outcome (6 months mRS 3–6) using receiver operating characteristics (ROC) curve. Figure S2. Predictive value of each

admission serum biomarkers for delayed cerebral ischemia (DCI) using receiver operating characteristics (ROC) curve. Figure S3. Predictive value of each admission serum biomarkers for chronic hydrocephalus (CH) using receiver operating characteristics (ROC) curve.

Author Contributions: Formal analysis, I.F.; Funding acquisition, S.M.; Investigation, K.L.; Methodology, K.L.; Project administration, S.M.; Resources, S.M.; Software, I.F.; Supervision, D.K. and S.M.; Writing—original draft, K.L. and D.K.; Writing—review & editing, D.H., J.F.C. and S.M. All authors have read and agreed to the published version of the manuscript.

Funding: We are thankful for the financial support from Research commission of medical Faculty, Heinrich-Heine University Düsseldorf to S. Muhammad, Open access funding provided by University of Helsinki.

Institutional Review Board Statement: 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, 25 September 2022).

Informed Consent Statement: Written informed consent was waived due to the retrospective study design.

Data Availability Statement: Available upon reasonable request.

Acknowledgments: We thank Peter Zech and Boris Schmidt for reading the manuscript.

Conflicts of Interest: The authors declare no competing interests.

Abbreviations

SAH: subarachnoid hemorrhage, aSAH: aneurysmal subarachnoid hemorrhage, CVS: cerebral vasospasm, DCI: delayed cerebral ischemia, CH: chronic hydrocephalus, TCD: transcranial Doppler ultrasonography, DSA: digital subtraction angiography, CTA: computed tomography angiography, CTP: computed tomography perfusion, WBC: white blood cell, NLR neutrophil to lymphocyte ratio, CRP: C-reactive protein, CLR: C-reactive protein to lymphocyte ratio, CT: computed tomography, STROBE: Strengthening the Reporting of Observational Studies in Epidemiology, mFisher: modified Fisher, WFNS: World Federation of Neurosurgical Societies, GCS: Glasgow Coma Score, NICU: Neurological Intensive Care Unit, MRI magnetic resonance imaging, mRS: modified Rankin Scale, PLR: platelet to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, SD standard deviation, IQR: interquartile range, OR: odds ratio, CI: confidence interval, ROC: receiver operating characteristic, ACA anterior cerebral artery, ACOM: anterior communicating artery, MCA: middle cerebral artery, PCOM: posterior communicating artery, ICA: internal carotid artery, PC: posterior circulation, mg/d:L milligram/deciliter, mg/L milligram/liter, $\times 10^9$/L $\times 10^9$/Liter, AUC: area under the curve, IL-6: interleukin-6, IL-1: interleukin-1, CSF: cerebrospinal fluid, DIND: delayed ischemic neurological deficits; PLR: platelet to lymphocyte ratio, CAR C-reactive protein to albumin ratio, NAR: neutrophil to albumin ratio, PAR: platelet to albumin ratio.

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3. Discussion

Our study explored admission CLR for predicting neurological functional outcome and complications after aSAH. We discovered high admission CLR was an independent risk factor for CVS and DCI after aSAH. The AUC of admission CLR for predicting poor outcome (6 months mRS 3-6), CVS, DCI, and CH were 0.639, 0.834, 0.679, and 0.628, respectively, indicating that admission CLR had a favorable predictive value for CVS after aSAH. The sensitivity and specificity of admission CLR for CVS prediction were 77.1% and 75.4%, respectively. An admission CLR of 0.757 $mg \times 10^{-6}$ was identified as the best cutoff threshold to discriminate between CVS and non-CVS. Numerous predictive models have been developed to predict outcomes/modalities in aSAH patients. Accurate prognosis prediction for aSAH patients is imperative for determining clinical treatment strategies. Admission white blood cell (WBC), platelet, neutrophil, lymphocyte, monocyte counts, and CRP levels are easily quantifiable parameters and show promising predictive value for outcome prediction after aSAH. Additionally, CVS, DCI, and CH are critical post-aSAH complications significantly associated with aSAH outcome. However, the predictive value of CLR for neurological outcome and complications in aSAH patients has yet to be investigated.

Multiple inflammatory mechanisms are directly involved in the pathogenesis of CVS. CRP, identified in the 1930s, is recognized as an acute-phase plasma protein and a response marker for the acute phase. It is synthesized in hepatocytes and induced by cytokines, particularly IL-6, which activates the complement system, contributing to natural immunity, and is released into the blood [89-92]. CRP levels can rise to 1,000-fold within a few hours following stimuli such as infection, tissue necrosis, trauma, cancer, or various inflammatory diseases. The level of CRP peaks 48 hours after the initial stimulus and returns to baseline levels within 7-12 days once the inflammatory stimulus has disappeared [93, 94]. CRP serves as a sensitive inflammatory marker, which is also stimulated by interleukin-1 (IL-1), which is correlated with the pathogenesis of CVS [92, 95]. Elevated CRP levels in serum and CSF after angiographic vasospasm have been observed in patients with aSAH, and higher CRP levels are strongly correlated with worse clinical outcomes [92]. The occurrence of CVS after aSAH might be caused by the inflammatory effects mediated by CRP. In brief, CRP levels increase in response to systemic inflammation triggered by aSAH.

This elevation promotes a pro-inflammatory state, leading to endothelial dysfunction. The resulting endothelial dysfunction disrupts blood flow dynamics, heightening the risk of CVS. Vasospasm can directly result from the inflammatory response and endothelial dysfunction [96]. Additionally, Gaastra et al. confirmed that on-admission CRP levels served as an independent predictive factor for postoperative functional outcome after aSAH, closely correlated with poor functional outcome [86]. Romero et al. clarified that high serum CRP predicted unfavorable clinical outcomes and the occurrence of CVS and delayed ischemic neurological deficits (DIND) [97]. Meanwhile, when the central nervous system is stimulated, the immune system is activated, releasing large numbers of lymphocytes to reduce brain tissue damage through antigen recognition, cell activation, and immunocide [98]. Frösen et al. compared histologically 42 ruptured aneurysms with 24 unruptured aneurysms and found that lymphocytes were actively involved in the inflammatory cascade in the aneurysmal vessel wall [99]. When an aneurysm ruptures, lymphocytes are overconsumed, leading to a decrease in lymphocyte count, which is also associated with worsening brain injury and poor clinical outcomes [98]. Interestingly, in our study, the admission lymphocyte count in patients with poor outcome (6 months mRS 3-6), CVS, and CH was lower than in patients with good outcome (6 months mRS 0-2), non-CVS, and non-CH. CLR is a novel inflammatory biomarker and has been employed as one of the most compelling prognostic markers for pancreatic and rectal cancer surgery, tumors, and strangulated abdominal hernia (intestinal ischemia) [100–103]. Fan et al. found that CLR displayed higher predicted accuracy of poor prognosis compared to the combination of NLR, platelet to lymphocyte ratio (PLR), C-reactive protein to albumin ratio (CAR), neutrophil to albumin ratio (NAR), and platelet to albumin ratio (PAR) in patients with pancreatic cancer [101]. Zhang et al. recently first demonstrated that admission CLR is a valuable serum biomarker to predict the clinical prognosis of patients with aSAH [88]. In this study, the level of CLR in patients with poor outcome (6 months mRS 3-6) after aSAH was significantly higher than in patients with good outcome (6 months mRS 0-2). Increased admission levels of CLR were related to increased risk for poor prognosis, which was consistent with the previously reported findings. Additionally, we first revealed that increased admission levels of CLR were associated with a high risk of the occurrence of CVS, DCI, and CH. Higher AUC of CLR compared to CRP, WBC, neutrophil, and lymphocyte count was observed to predict the occurrence of CVS in patients with

aSAH. In addition, we confirmed that admission CLR was independently associated with the occurrence of CVS and DCI after aSAH. Admission CLR had a favorable predictive value for CVS compared to poor outcome (6 months mRS 3-6), DCI, and CH. Furthermore, we verified that CVS and DCI were strongly associated with the poor outcome (6 months mRS 3-6) of patients with aSAH. High levels of CLR were associated with the poor prognosis of patients with aSAH, which might be mediated by the elevated occurrence of CVS and DCI. Though we found the favorable predictive value of CLR for CVS after aSAH, the mechanisms are still not fully understood, and further research is needed.

Furthermore, white blood cells indicate systemic inflammation in humans and are extensively studied for their predictive value in diseases such as cancers and aSAH [104, 105]. In a study by Geraghty et al., multivariate logistic analysis confirmed that the WBC count within 24 hours of admission was an independent risk factor for CVS after aSAH [106]. Similarly, Hu et al. reported that an elevated WBC count within 24 hours of admission could independently predict DCI occurrence between 4 and 30 days after aSAH [107]. In our study, the on-admission WBC count in patients with poor outcome (6 months mRS 3-6), CVS, and CH was significantly higher compared to patients with good outcome (6 months mRS 0-2), non-CVS, and non-CH after aSAH. Additionally, in our study, on-admission neutrophil count in patients with poor outcome (6 months mRS 3-6), CVS, DCI, and CH was higher than that in patients with good outcome (6 months mRS 0-2), non-CVS, non-DCI, and non-CH. However, admission monocyte count did not show significant differences. On-admission WBC and neutrophil counts were not independently associated with poor outcome (6 months mRS 3-6) and the occurrence of CVS, DCI, and CH after aSAH, requiring further investigation.

Meanwhile, platelets are widely acknowledged as the primary cells regulating hemostasis and thrombus formation. Their influence on blood vessels stems from their pivotal role in thrombus formation, which mediates conditions such as myocardial infarction, stroke, and venous thromboembolism [108]. Zhang et al. and Wang et al. confirmed the correlation between platelets, CVS, and DCI after aSAH [87, 109]. However, in our study, no significant differences in on-admission platelet count were observed in patients with poor outcome (6 months mRS 3-6), CVS, DCI, and CH compared to those with good outcome (6 months mRS 0-2), non-CVS, non-DCI, and non-CH after aSAH. Further investigation is needed to elucidate the associations

between on-admission platelet count, neurological functional outcome, and complications after aSAH.

To our knowledge, many novel predictive models and algorithms are being developed to accurately predict outcomes and the occurrence of complications after aSAH. Various biomarkers have been developed, including NLR, D-dimer, CRP, WBC, and WPR [26, 85-87]. In our study, we employed admission CLR, NLR, PLR, and monocyte to lymphocyte ratio (MLR) for the first time to predict poor outcome (6 months mRS 3-6), CVS, DCI, and CH. We found that the AUC of admission CLR for predicting poor outcome (6 months mRS 3-6), CVS, DCI, and CH were 0.639, 0.834, 0.679, and 0.628, respectively. Moreover, the AUC of NLR, PLR, and MLR for CVS prediction were 0.665, 0.624, and 0.659, respectively. It demonstrated that on-admission CLR had a higher predictive value for CVS after aSAH than admission NLR, PLR, and MLR. The sensitivity and specificity of admission CLR for CVS prediction were 77.1% and 75.4%, respectively. An admission CLR of 0.757 $mg \times 10^{-6}$ was identified as the best cutoff threshold to discriminate between CVS and non-CVS, which could be utilized for diagnosing CVS in clinical practice.

Furthermore, our study has certain limitations. Firstly, it was retrospective and single-center, rendering it susceptible to patient and treatment selection bias. Hence, prospective multi-center clinical trials are needed to investigate the associations of CLR with neurological functional outcome and complications following aSAH. Secondly, aSAH patients with diseases influenced by peripheral serum biomarkers were excluded. Consequently, it remains unclear whether CLR holds predictive value for prognosis and the occurrence of neurological complications in patients admitted with systemic metabolic diseases. Developing new predictive biomarkers and models for such patients is imperative. Thirdly, due to 284 cases lacking complete routine blood tests, our results strongly advocate that clinicians conduct routine blood and comprehensive biochemical tests within 24 hours of hospital admission or in the emergency unit for every aSAH patient. Fourthly, only 166 patients were included out of 662, potentially introducing sampling bias. Fifthly, there is a lack of methodological diversity given the purely statistical work on retrospectively collected data. More novel statistical methods and algorithms should be employed in our study. We can conduct additional subgroup and sensitivity analyses as necessary to ensure sample homogeneity and minimize potential bias in further research. Lastly, while we have reported associations between on-admission serum biomarkers and neurological

functional outcome and complications after aSAH, a comprehensive understanding of the underlying mechanisms is still required.

In summary, serum levels of CLR upon admission were found to be significantly higher in patients with CVS, poor outcome (6 months mRS 3-6), DCI, and CH compared to those with non-CVS, good outcome (6 months mRS 0-2), non-DCI, and non-CH. Elevated CLR levels upon admission emerged as an independent risk factor for CVS and DCI following aSAH. Admission CLR serves as an easily quantifiable laboratory parameter that effectively predicts CVS after aSAH, potentially guiding clinicians in assessing progression and determining treatment strategies for patients with aSAH [110].

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5. Appendix

5.1 Declaration of author contributions

Title: CLR (C-Reactive Protein to Lymphocyte Ratio) Served as a Promising Predictive Biomarker for Cerebral Vasospasm in Aneurysmal Subarachnoid Hemorrhage (aSAH): A Retrospective Cohort Study.

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Formal analysis, Igor Fischer; Funding acquisition, Sajjad Muhammad; Investigation, Ke Li; Methodology, Ke Li; Project administration, Sajjad Muhammad; Resources, Sajjad Muhammad; Software, Igor Fischer; Supervision, Dilaware Khan and Sajjad Muhammad; Writing – original draft, Ke Li and Dilaware Khan; Writing – review & editing, Daniel Hänggi, Jan Cornelius and Sajjad Muhammad.

5.2 List of Figures

5.3 List of Tables

5.4 Acknowledgments

First of all, I appreciate PD Dr. med. Sajjad Muhammad gave me the opportunity start scientific research and pursue my doctoral degree. I am very grateful for the time and patience he took to guide me through my entire process. Without his help, I would not have an achievement right now.

Thanks, Prof. Dr. med. Jan Frederick Cornelius, for giving me the chance and guidance to complete my MD thesis at the Department of Neurosurgery. I am also very thankful to my co-supervisor, Prof. Dr. Majeed Rana, for his scientific guidance and support.

Thanks to Xinwei Zhao, Igor Fischer, Lilian Oberschachtsiek, Dilaware Khan in Germany, and Prof. Dr. Chongjian Wang in China for the help in my project. In addition, thanks to all my former and current lab colleagues Ann-Christin Nickel, Michael Hewera, Serdar Alpdogan, Renfei Du, Rui Zhang, Xuanchen Li, Huakang Zhou, Baolong Zheng, and Jinliang You for the precious time working together and their help.

I want to express my gratitude to my close friends, including Dr. med. Peter Zech, Boris Schmidt, Irina Schmidt, Volker Scheidt, Claudia Scheidt, Dennis Scheidt, Jesper, and Jorg, for their training, which gave me a lot of energy and confidence. I especially want to thank Dr. med. Peter Zech for teaching me many relevant things. His attitude toward study has had a profound influence on me. Our friendships will never fade.

Lastly, I thank my family, teachers, and friends in China for their love and support in achieving my goals. My biggest regret is that I could not stay with them for these years, and I will spend the rest of my life to be with them.