Research article

Dynamic changes of platelets before and after surgery predict the prognosis of patients with aneurysmal subarachnoid hemorrhage

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ABSTRACT

Objective: This investigation explored the association between postoperative/preoperative platelet ratio (PPR) and the incidence of unfavorable outcomes within 90 days in individuals with aneurysmal subarachnoid hemorrhage (aSAH).
Methods: This investigation, utilizing data from 2015 to 2022, concentrated on patients diagnosed with aSAH, categorizing them into four groups based on PPR quartiles. The association between PPR levels and clinical outcomes—comprising in-hospital complications, mortality, and modified Rankin Scale (mRS) scores at discharge and 90 days after that—was evaluated through logistic regression analyses. To explore potential non-linear associations between PPR levels and outcomes, restricted cubic spline (RCS) regression was applied. Further, mediation analysis was performed to elucidate the role of in-hospital complications in modulating the impact of PPR levels on 90-day outcomes.
Results: This study analyzed data from 948 patients. Upon adjustment for confounding variables, it was observed that patients in the higher quartiles showed reduced incidences of anemia, hypoproteinemia, and pneumonia, alongside a decreased frequency of unfavorable outcomes within a 90-day follow-up period. The RCS analysis indicated a linear association of PPR with pneumonia, hypoproteinemia, and adverse 90-day outcomes (p for nonlinear = 0.61, 0.52, and 0.96, respectively). Moreover, the association of PPR with anemia was found to be nonlinear (p for nonlinear = 0.01). Mediation analysis further indicated that anemia and pneumonia significantly influenced the association between PPR and unfavorable outcomes at 90 days, accounting for 15.49 % and 27.61 % of the effect, respectively.

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Conclusions: This study establishes a significant correlation between decreased PPR levels and 90-day adverse outcomes following aSAH, potentially relating to pneumonia and anemia.

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) represents a form of diffuse subarachnoid hemorrhage, which arises from the rupture of intracranial aneurysms. It is the primary cause of spontaneous subarachnoid hemorrhage [1]. Despite recent advancements in treatment, the mortality and morbidity rates among aSAH patients remain high. Startlingly, the mortality rate can rise to 45 % within 30 days. Moreover, survivors often experience severe disabilities, and almost half of the patients fail to regain normal neurological functioning [2]. Extensive research has demonstrated that inflammation and post-stroke immunosuppression are pivotal in precipitating infections, which, in turn, lead to adverse outcomes in a spectrum of cerebrovascular disorders. These include ischemic stroke, intracerebral hemorrhage, and aSAH [3].

Platelets, typically acknowledged as the cellular agents of thrombus formation, constitute a noteworthy portion of the immune system. They are critical in regulating and stimulating tissue damage and inflammatory responses [4]. In recent decades, numerous studies have underscored the role of platelets in the pathogenesis of various diseases, including non-small cell lung cancer, diabetes, and atherosclerosis [5–7]. However, the present comprehension of the correlation between the platelet system and adverse consequences in aSAH patients remains a topic of contention [8–10].

Substantial variation in platelet counts exists among individuals of different genders, ages, and races [11]. Additionally, predicting the prognosis of aSAH patients based solely on their preoperative platelet count can be difficult owing to the dynamic progression of the disease. Consequently, the postoperative/preoperative platelet ratio (PPR) emerges as a valuable prognostic indicator for patients with aSAH, offering a comprehensive assessment of platelet fluctuations pre- and post-surgery.

This study aimed to investigate the relationship between PPR and various clinical outcomes in aSAH patients by categorizing PPR into four distinct quartile-based groups. Furthermore, mediation analysis was conducted to elucidate the clinical pathways leading to adverse outcomes. This approach may unveil novel targets for future therapeutic interventions.

2. Materials and methods

2.1. Patient selection and eligibility criteria

The core data for this study were derived from the LongTEAM (Long-term Prognosis of Emergency Aneurysmal Subarachnoid Hemorrhage) project. Informed consent was appropriately obtained from all participants, or surrogate consent was secured through legal procedures when necessary. Complete registration details for this study are publicly accessible on the ClinicalTrials.gov website under the registration number NCT04785976. Informed consent, or surrogate consent when appropriate, was secured for all participants involved in the study.

This study employed a retrospective analysis to thoroughly examine the records of patients with aSAH treated at Beijing Tiantan Hospital between 2015 and 2022. The patient selection process adhered strictly to predefined criteria, which included the following: (1) age 18 years or older; (2) admission through emergency services; (3) diagnosis and initiation of treatment within 72 h of aneurysm rupture; (4) confirmed diagnosis of a single aneurysm; (5) underwent either surgical clipping or endovascular embolization; and (6) availability of comprehensive clinical records, laboratory results, and pathological data.

Concurrently, patients were deemed ineligible for inclusion in the study if they met any of the following exclusion criteria: (1) a history of subarachnoid hemorrhage; (2) the presence of hematologic or systemic diseases; (3) a history of neurosurgical procedures for any reason; (4) pre-existing functional disabilities due to previous illnesses; or (5) prior interventions at other medical institutions, including but not limited to ventricular drainage, lumbar puncture, angiography, intubation, or mechanical ventilation, before admission.

2.2. Data collection

The baseline characteristics of the patients were as follows: (1) Demographic information: including age, gender, and other essential details; (2) Medical history: encompassing hypertension, diabetes, hyperlipidemia, cardiovascular diseases, and other relevant health conditions; (3) Behavioral risk factors: including smoking, alcohol consumption, and other lifestyle habits potentially impacting health; (4) Aneurysm characteristics: detailed descriptions of the aneurysm's location, size, and other critical attributes; (5) Early-onset seizures; (6) Clinical status: assessed using the World Federation of Neurosurgical Societies (WFNS) grading system to evaluate the overall clinical condition of the patients; (7) Imaging scores: based on preoperative cranial CT findings, employing tools such as the modified Fisher score (mFS), Graeb score, and the Subarachnoid Hemorrhage Early Brain Edema Score (SEBES), along with an assessment for the presence of acute hydrocephalus; (8) Laboratory results: with a particular focus on preoperative lymphocyte count and PPR, defined as the ratio of postoperative to preoperative platelet counts, reflecting dynamic changes in platelet levels; (9) In-hospital complications: comprehensive documentation of all complications, including delayed cerebral ischemia (DCI), cardiovascular events, intracranial infections, stress ulcer bleeding, anemia, urinary tract infections, hypoproteinemia, pneumonia, and deep

vein thrombosis (DVT). Detailed diagnostic criteria are given in Table 1S; and (10) treatment types such as surgical clipping and endovascular coiling.

Additionally, this study specifically highlights that peripheral blood laboratory tests were conducted both 72 hours before surgery and 24 h postoperatively to obtain comprehensive data on platelet counts and other hematological parameters.

2.3. Study outcome

At 90 days post-discharge, this study systematically collected the mRS scores for each patient through telephone or outpatient visits. The primary focus of the study was to assess the long-term prognosis following discharge, categorizing outcomes into two groups: favorable prognosis (mRS score less than 3) and unfavorable outcomes (mRS score equal to or greater than 3). Additionally, the study included several secondary outcome measures, such as the incidence of various complications during hospitalization, in-hospital mortality, and adverse outcomes at discharge.

2.4. Statistical analysis

In this study, the patient cohort was evenly divided into four subgroups based on the quartiles of PPR values. Categorical variables were described using percentages, while continuous variables were reported as mean with standard deviation for normally distributed data or as median with interquartile range (IQR) for non-normally distributed data. A one-way analysis of variance (ANOVA) was initially employed to explore differences in baseline characteristics among the subgroups. Upon identifying significant differences, post-hoc analyses were conducted using Bonferroni correction to ensure the accuracy and reliability of the results.

We constructed logistic regression models to examine the association between PPR levels and in-hospital complications, mortality, and outcomes. Results were expressed as adjusted odds ratios (ORs) with 95 % confidence intervals (CIs), with the lowest PPR quartile (Q1) serving as the reference group.

We further developed two multivariable logistic regression models: Model 1 was adjusted for gender, age, and treatment modality; Model 2 included additional covariates such as SEBES score 3–4, WFNS grade 4–5, and hyperlipidemia, based on Model 1. A logistic regression model incorporating RCS was applied to capture the nonlinear relationship between PPR levels and the risk of adverse outcomes, adjusting for potential confounders as in Model 2. This analysis used PPR's lowest quartile (Q1) as the baseline, with three spline knots positioned at the 10th, 50th, and 90th percentiles of the PPR distribution to elucidate the complex relationship fully.

To identify which in-hospital complications mediated the relationship between PPR and adverse 90-day outcomes, we performed a mediation analysis using the "mediation" package in R software. This analysis accounted for covariate adjustments and assessed the robustness of indirect, direct, and total effects through 1000 bootstrap samples. The specific regression pathways evaluated included the total effect of PPR on adverse 90-day outcomes (path C), the direct effect of PPR after controlling for mediators (path C′), the effect

Table 1
Baseline information.

Characteristics	Total	PPR level				
		Q1 (<0.85)	Q2 (0.85–0.93)	Q3 (0.93–1.01)	Q4 (≥1.01)	p
No. of patients	948	237	237	237	237	
Age, years, mean ± SD	54.64 ± 11.23	53.89 ± 12.02	54.38 ± 10.79	54.92 ± 10.91	55.35 ± 11.18	0.520
Female, n (%)	556 (58.6)	150 (63.3)	135 (57.0)	134 (56.5)	137 (57.8)	0.409
Hypertension, n (%)	561 (59.1)	134 (56.5)	135 (57.0)	141 (59.5)	151 (63.7)	0.363
Hyperlipidemia, n (%)	75 (7.9)	18 (7.6)	10 (4.2)	16 (6.8)	31 (13.1)	0.004
Diabetes mellitus, n (%)	84 (8.8)	17 (7.2)	19 (8.0)	24 (10.1)	24 (10.1)	0.575
Heart disease, n (%)	181 (19.0)	48 (20.3)	41 (17.3)	46 (19.4)	46 (19.4)	0.866
Current smoking, n (%)	250 (26.3)	56 (23.6)	66 (27.8)	61 (25.7)	67 (28.3)	0.643
Current drinking, n (%)	192 (20.2)	36 (15.2)	50 (21.1)	47 (19.8)	59 (24.9)	0.070
Posterior circulation, n (%)	101 (10.6)	16 (6.8)	25 (10.5)	32 (13.5)	28 (11.8)	0.105
Maximum diameter of aneurysm[b], mean ± SD	6.67 ± 5.54	6.92 ± 4.93	6.47 ± 3.85	6.64 ± 5.69	6.64 ± 7.37	0.884
Early seizures, n (%)	57 (6.0)	18 (7.6)	9 (3.8)	12 (5.1)	18 (7.6)	0.209
WFNS grade 4–5, n (%)	200 (21.0)	71 (30.0)	51 (21.5)	38 (16.0)	40 (16.9)	0.001
mFS grade 3–4, n (%)	720 (75.9)	188 (79.3)	172 (72.6)	176 (74.3)	184 (77.6)	0.296
Graeb score 5–12, n (%)	76 (8.0)	29 (12.2)	16 (6.8)	16 (6.8)	15 (6.3)	0.053
SEBES score 3–4, n (%)	447 (47.1)	141 (59.5)	108 (45.6)	102 (43.0)	96 (40.5)	<0.001
Acute hydrocephalus, n (%)	382 (40.2)	103 (43.5)	89 (37.6)	90 (38.0)	100 (42.2)	0.455
Lymphocytes[a], median (IQR)	0.960 (0.693–1.350)	1.040 (0.765–1.485)	0.940 (0.685–1.330)	0.960 (0.650–1.375)	0.900 (0.645–1.300)	0.160
Treatment modality						0.001
Surgical clipping, n (%)	499 (52.6)	148 (62.4)	129 (54.4)	113 (47.7)	109 (46.0)	
Endovascular coiling, n (%)	449 (47.3)	89 (37.6)	108 (45.6)	124 (52.3)	128 (54.0)	

Abbreviations: WFNS, world federation of neurological societies; mFS, modified Fisher; SEBES, subarachnoid hemorrhage early brain edema score.
Notes:
[a] unit of measurement: 10^9/L.
[b] Unit of measurement: mm.

of PPR on in-hospital complications (path A), the effect of in-hospital complications on adverse 90-day outcomes (path B) **(shown in Fig. 1)**. Furthermore, the indirect effect was calculated through Pathway A*B, which was employed to analyze the indirect impact of PPR on 90-day adverse outcomes, with in-hospital complications serving as the mediator. Finally, the proportion of the total effect mediated by in-hospital complications was quantified to determine the magnitude of the mediation effect.

A sensitivity analysis excluded patients with a history of antiplatelet or anticoagulant use. Logistic regression models (specifically Model 1 and Model 2) were utilized to explore the potential associations between baseline PPR levels and the occurrence of in-hospital complications, mortality, and outcomes. To gain a more comprehensive understanding of these relationships, we also conducted subgroup analyses to identify whether there were interactions between PPR levels and specific variables such as age, gender, smoking status, history of hypertension, WFNS grade, and treatment modality. These analyses mainly focused on the interactions with pneumonia, anemia, and 90-day adverse outcomes. Through this approach, we aim to determine whether the impact of PPR levels on clinical prognosis varies across different patient subgroups. To determine the optimal PPR range for clinical application, the threshold-moving technique, based on the Youden index, was employed to sequentially calculate PPR thresholds for significant outcomes, along with their corresponding Area Under the Curve (AUC) values. This approach maximizes sensitivity (actual positive rate) while minimizing the false positive rate.

3. Results

3.1. Baseline characteristic

This study included 948 participants, with each PPR quartile group (Q1 to Q4) comprising 237 patients diagnosed with aSAH. Among the study participants, 556 were female, accounting for 58.6 % of the total cohort. The mean age of the patients was 54.64 years. The median PPR value was 0.93, with an IQR of 0.85–1.01. Notably, patients in the higher PPR quartiles exhibited higher WFNS grades 4–5 and SEBES scores 3–4 compared to those in the lower PPR quartiles. However, these patients had a relatively lower proportion of undergoing surgical clipping. Additionally, a higher prevalence of hyperlipidemia was observed among patients in the highest PPR quartile **(shown in Table 1)**.

3.2. Correlation of PPR with clinical outcomes

After adjusting for age, sex, and treatment modality, higher PPR levels were significantly associated with a reduced incidence of various adverse outcomes. Further adjustments for related risk factors (Model 2) revealed that compared to the Q1 group, higher PPR levels (Q2, Q3, Q4) were linked to a lower risk of anemia (adjusted OR = 0.66, p = 0.045; OR = 0.57, p = 0.008; OR = 0.60, p = 0.016). Additionally, patients in the Q3 and Q4 groups had a reduced risk of hypoproteinemia (OR = 0.64, p = 0.034; OR = 0.57, p = 0.009), while those in Q4 demonstrated a lower risk of pneumonia (OR = 0.53, p = 0.004) and a decreased likelihood of a 90-day unfavorable outcome (OR = 0.56, p = 0.033) **(shown in Table 2)**.

The RCS models demonstrated that PPR was positively and linearly correlated with pneumonia, hypoproteinemia, and 90-day adverse outcomes, with no evidence of nonlinearity (p for nonlinear = 0.61, 0.52, and 0.96, respectively) **(shown in Fig. 2A–C and D)**. However, the association of PPR with anemia was nonlinear (p for nonlinear value = 0.01) **(shown in Fig. 2B)**.
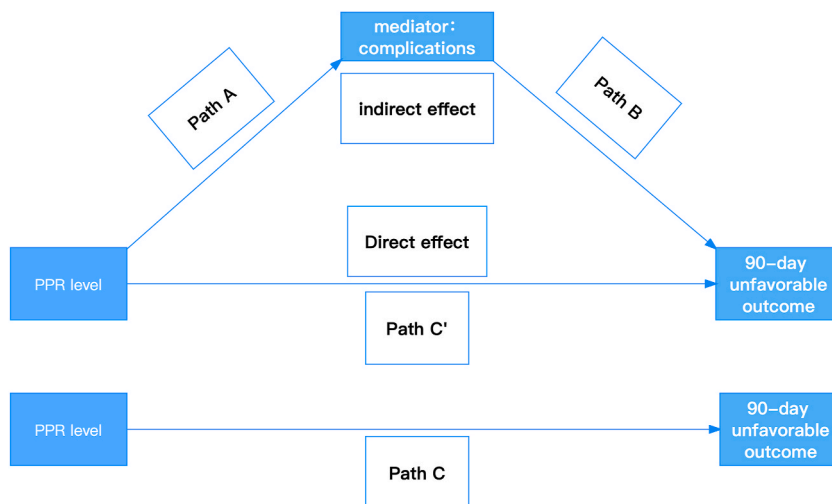
Fig. 1. Schematic diagram of the mediation effect analysis. Path C indicates the total effect; path C′ indicates the direct effect. The indirect effect is estimated as multiplying paths A and B (path A*B). The mediated proportion is calculated as indirect effect/(indirect effect + direct effect) × 100 %.

Table 2
Adjusted odds ratios of in-hospital complications and functional outcomes according to baseline PPR levels.

| Variables	PPR level	No.	Model 1			Model 2	
			Events, n (%)	Adjusted OR (95 % CI)	p	Adjusted OR (95 % CI)	p
Cardiac event	Q1	237	89 (37.6)	1 (reference)	–	1 (reference)	–
	Q2	237	88 (37.1)	0.92 (0.63–1.35)	0.678	1.01 (0.69–1.49)	0.965
	Q3	237	88 (37.1)	0.88 (0.60–1.28)	0.498	0.97 (0.66–1.44)	0.896
	Q4	237	103 (43.5)	1.13 (0.77–1.65)	0.523	1.24 (0.84–1.83)	0.271
DCI	Q1	237	74 (31.2)	1 (reference)	–	1 (reference)	–
	Q2	237	64 (27.0)	0.83 (0.55–1.24)	0.359	0.88 (0.58–1.32)	0.523
	Q3	237	64 (27.0)	0.85 (0.57–1.27)	0.424	0.94 (0.62–1.41)	0.751
	Q4	237	58 (24.5)	0.74 (0.49–1.12)	0.160	0.83 (0.54–1.26)	0.373
Intracranial infection	Q1	237	29 (12.2)	1 (reference)	–	1 (reference)	–
	Q2	237	32 (13.5)	1.25 (0.71–2.20)	0.442	1.28 (0.72–2.27)	0.399
	Q3	237	20 (8.4)	0.80 (0.42–1.48)	0.481	0.81 (0.42–1.53)	0.518
	Q4	237	31 (13.1)	1.46 (0.82–2.59)	0.199	1.47 (0.82–2.65)	0.195
Stress ulcer bleeding	Q1	237	50 (21.1)	1 (reference)	–	1 (reference)	–
	Q2	237	45 (19.0)	0.84 (0.53–1.32)	0.440	0.93 (0.58–1.49)	0.772
	Q3	237	57 (24.1)	1.09 (0.70–1.69)	0.707	1.32 (0.84–2.09)	0.230
	Q4	237	63 (26.6)	1.23 (0.80–1.90)	0.354	1.49 (0.95–2.36)	0.081
Urinary tract infection	Q1	237	8 (3.4)	1 (reference)	–	1 (reference)	–
	Q2	237	5 (2.1)	0.56 (0.16–1.72)	0.316	0.57 (0.17–1.76)	0.332
	Q3	237	6 (2.5)	0.63 (0.20–1.86)	0.402	0.66 (0.21–1.98)	0.460
	Q4	237	8 (3.4)	0.81 (0.29–2.29)	0.691	0.88 (0.31–2.51)	0.803
Anemia	Q1	237	110 (46.4)	1 (reference)	–	1 (reference)	–
	Q2	237	81 (34.2)	0.65 (0.44–0.96)	0.030	0.66 (0.44–0.99)	0.045
	Q3	237	67 (28.3)	0.52 (0.34–0.77)	0.001	0.57 (0.38–0.86)	0.008
	Q4	237	70 (29.5)	0.54 (0.36–0.81)	0.003	0.60 (0.39–0.91)	0.016
Hypoproteinemia	Q1	237	110 (46.4)	1 (reference)	–	1 (reference)	–
	Q2	237	97 (40.9)	0.82 (0.56–1.21)	0.321	0.93 (0.62–1.39)	0.723
	Q3	237	74 (31.2)	0.54 (0.36–0.80)	0.002	0.64 (0.42–0.97)	0.034
	Q4	237	69 (29.1)	0.49 (0.32–0.72)	<0.001	0.57 (0.38–0.87)	0.009
Pneumonia	Q1	237	101 (42.6)	1 (reference)	–	1 (reference)	–
	Q2	237	80 (33.8)	0.65 (0.44–0.96)	0.029	0.73 (0.49–1.10)	0.132
	Q3	237	77 (32.5)	0.60 (0.41–0.89)	0.011	0.75 (0.50–1.13)	0.168
	Q4	237	62 (26.2)	0.44 (0.29–0.65)	<0.001	0.53 (0.35–0.81)	0.004
DVT	Q1	237	96 (40.5)	1 (reference)	–	1 (reference)	–
	Q2	237	74 (31.2)	0.65 (0.44–0.97)	0.038	0.68 (0.45–1.02)	0.066
	Q3	237	74 (31.2)	0.64 (0.43–0.96)	0.033	0.70 (0.47–1.06)	0.093
	Q4	237	84 (35.4)	0.78 (0.52–1.16)	0.215	0.84 (0.56–1.27)	0.406
Lipid metabolism disorder	Q1	237	54 (22.8)	1 (reference)	–	1 (reference)	–
	Q2	237	63 (26.6)	1.16 (0.76–1.77)	0.503	1.11 (0.73–1.71)	0.625
	Q3	237	69 (29.1)	1.26 (0.83–1.92)	0.286	1.20 (0.79–1.84)	0.399
	Q4	237	77 (32.5)	1.46 (0.97–2.22)	0.073	1.43 (0.94–2.19)	0.094
Mortality at discharge	Q1	237	4 (1.7)	1 (reference)	–	1 (reference)	–
	Q2	237	2 (0.8)	0.49 (0.07–2.58)	0.421	0.76 (0.10–4.23)	0.759
	Q3	237	2 (0.8)	0.50 (0.07–2.65)	0.435	0.96 (0.12–5.55)	0.966
	Q4	237	2 (0.8)	0.51 (0.07–2.69)	0.444	0.92 (0.12–5.19)	0.924
Unfavorable outcome at discharge	Q1	237	112 (47.3)	1 (reference)	–	1 (reference)	–
	Q2	237	93 (39.2)	0.71 (0.49–1.04)	0.079	0.86 (0.55–1.33)	0.490
	Q3	237	86 (36.3)	0.63 (0.42–0.92)	0.017	0.86 (0.56–1.34)	0.515
	Q4	237	84 (35.4)	0.60 (0.40–0.88)	0.009	0.82 (0.53–1.28)	0.386
90-day unfavorable outcome	Q1	237	64 (27.0)	1 (reference)	–	1 (reference)	–
	Q2	237	45 (19.0)	0.61 (0.39–0.96)	0.033	0.70 (0.42–1.16)	0.172
	Q3	237	38 (16.0)	0.49 (0.30–0.78)	0.003	0.69 (0.41–1.16)	0.168
	Q4	237	34 (14.3)	0.42 (0.26–0.68)	<0.001	0.56 (0.32–0.95)	0.033

Abbreviations: DCI: delayed cerebral ischemia; DVT: deep vein thrombosis.
Model 1: adjusted for age, sex, and treatment modality.
Model 2: adjusted for Model 1+WFNS grade 4–5+SEBES score 3–4+Hyperlipidemia.

3.3. Mediation effects of in-hospital complications on the association between PPR and 90-day unfavorable outcomes

The mediation analysis results indicated that anemia significantly mediated the relationship between PPR and 90-day adverse outcomes, accounting for 15.49 % of the mediated effect, with statistical significance (p = 0.018). However, the direct effect of PPR on adverse outcomes did not reach statistical significance (p = 0.096). Additionally, pneumonia was identified as a critical mediator in this association, showing a highly significant contribution to the indirect effect (p < 0.001) and holding substantial importance in the total effect (p = 0.020). The complete mediation proportion of pneumonia was calculated to be 27.61 %, which was also statistically significant (p = 0.002). It is noteworthy that the study did not find any other potential mediators, including cardiac events, DCI, intracranial infection, stress ulcer bleeding, hypoproteinemia, DVT, lipid metabolism disorders, and urinary tract infections, to
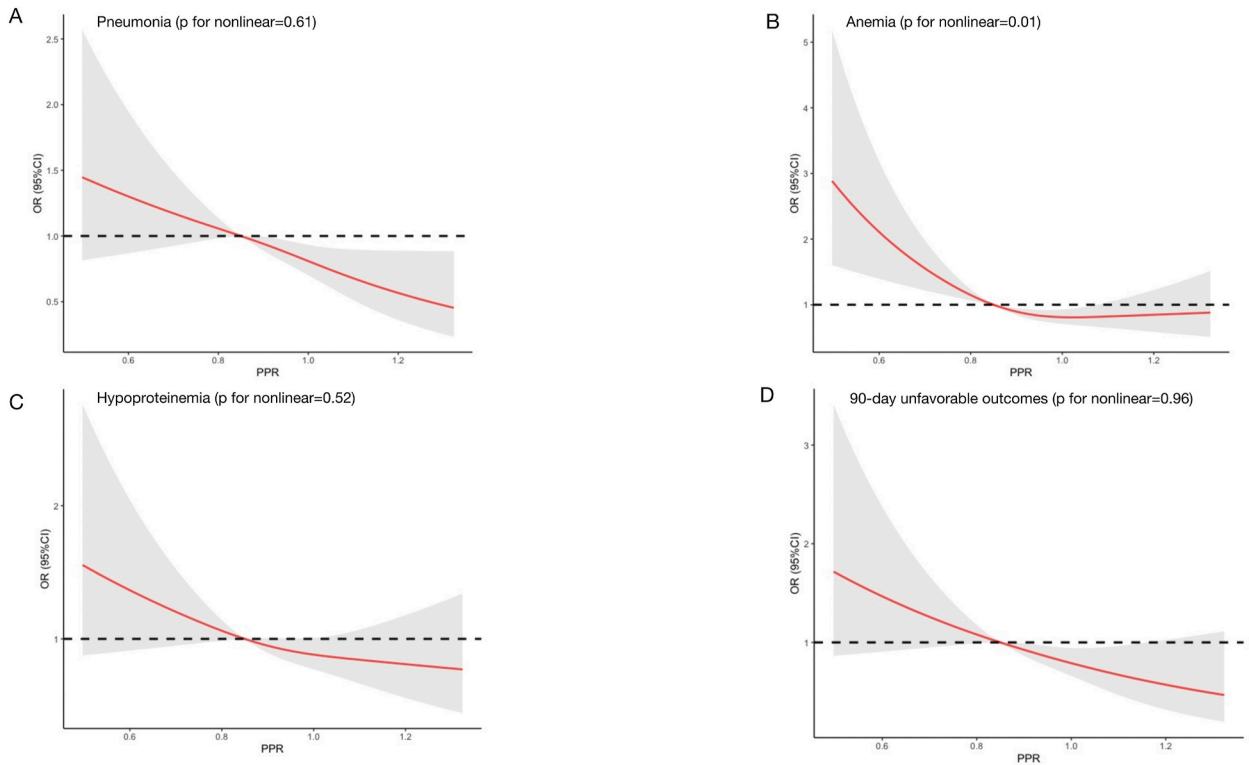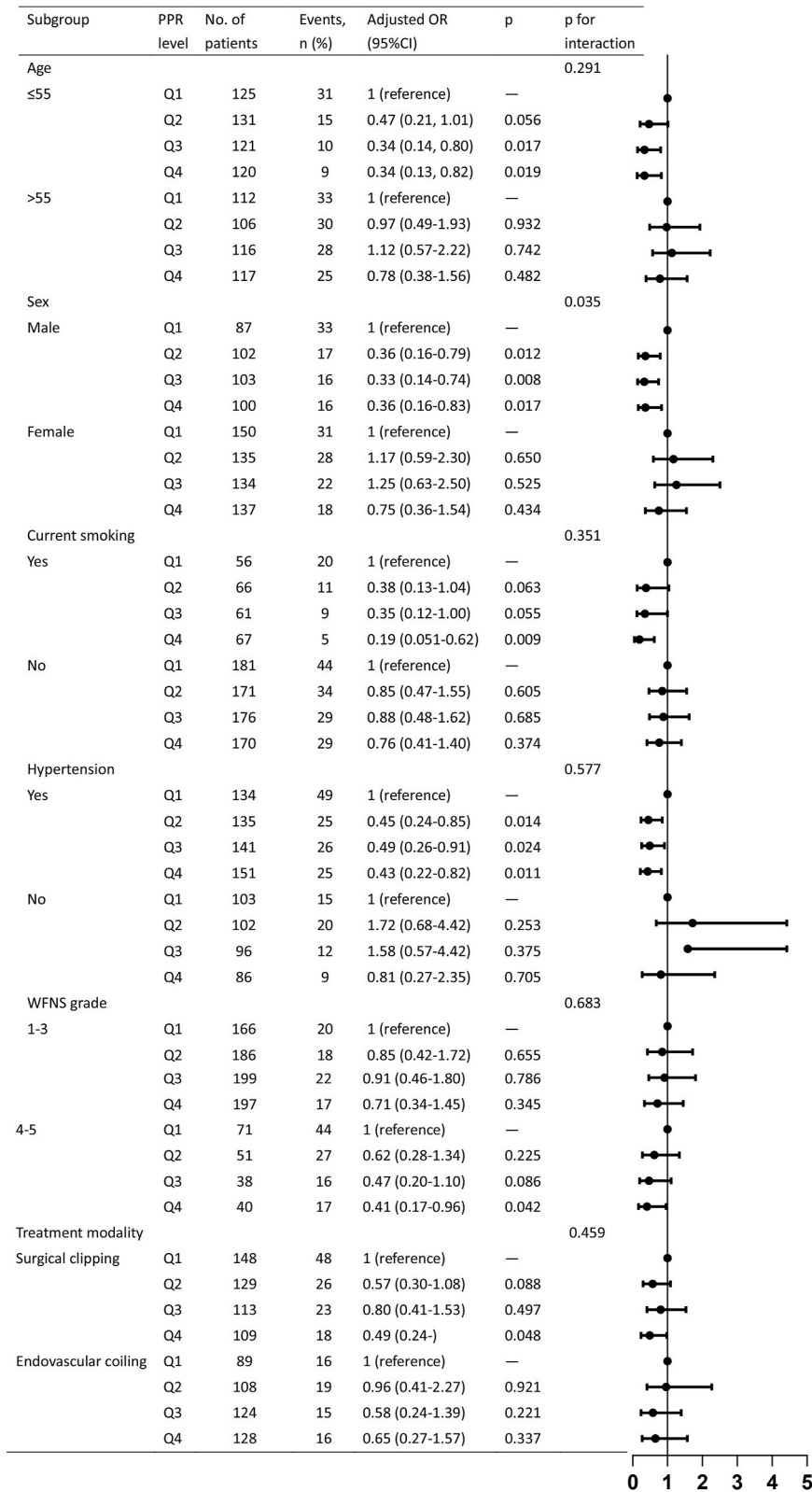
Fig. 2. Adjusted odds ratios for (A) pneumonia, (B) anemia, (C) hypoproteinemia, and (D) 90-day adverse outcomes in relation to baseline PPR levels. The first quartile (Q1) served as the reference category. Odds ratios were derived using logistic regression with a restricted cubic spline model incorporating three knots (located at the 10th, 50th, and 90th percentiles) for baseline PPR levels, with adjustments made for relevant covariates.

Table 3
The mediation effects of in-hospital complications on the associations of PPR level with 90-day unfavorable outcome.

Outcomes	Mediator	Indirect effects (95 % CI)	Direct effects (95 % CI)	Total effects (95 % CI)	Mediated proportion (%)	P value
90-day unfavorable outcome	Cardiac event	0.01 (0.00, 0.02)	−0.25 (−0.48, −0.07)**	−0.24 (−0.47, −0.06)**	2.90	0.276
	DCI	−0.01 (−0.07, 0.03)	−0.20 (−0.42, −0.03)*	−0.21 (−0.43, −0.04)**	5.50	0.630
	Intracranial infection	0.00 (−0.01, 0.01)	−0.23 (−0.47, −0.06)**	−0.23 (−0.47, −0.06)**	0.12	0.914
	Stress ulcer bleeding	0.01 (−0.02, 0.03)	−0.25 (−0.49, −0.06)**	−0.24 (−0.48, −0.06)**	3.27	0.412
	Urinary tract infection	0.00 (−0.01, 0.01)	−0.24 (−0.47, −0.06)**	−0.24 (−0.47, −0.06)**	0	0.908
	Anemia	−0.03 (−0.07, 0.00)*	−0.18 (−0.39, −0.01)*	−0.21 (−0.43, −0.05)**	15.49	0.018
	Hypoproteinemia	−0.01 (−0.04, 0.00)	−0.22 (−0.45, −0.04)**	−0.23 (−0.46, −0.06)	5.61	0.144
	Pneumonia	−0.06 (−0.11, −0.02)***	−0.15 (−0.37, 0.02)	−0.20 (−0.45, −0.03)*	27.61	0.020
	DVT	0.00 (−0.03, 0.02)	−0.23 (−0.45, −0.05)**	−0.22 (−0.45, −0.05)**	0.66	0.800
	Lipid metabolism disorder	0.01 (0.00, 0.02)	−0.25 (−0.49, −0.07)	−0.25 (−0.48, −0.07)	3.68	0.094

Abbreviations: DCI: delayed cerebral ischemia; MCVT: muscular calf vein thrombosis; DVT: deep vein thrombosis.

Subgroup	PPR level	No. of patients	Events, n (%)	Adjusted OR (95%CI)	p	p for interaction
Age						0.291
≤55	Q1	125	31	1 (reference)	—	
	Q2	131	15	0.47 (0.21, 1.01)	0.056	
	Q3	121	10	0.34 (0.14, 0.80)	0.017	
	Q4	120	9	0.34 (0.13, 0.82)	0.019	
>55	Q1	112	33	1 (reference)	—	
	Q2	106	30	0.97 (0.49-1.93)	0.932	
	Q3	116	28	1.12 (0.57-2.22)	0.742	
	Q4	117	25	0.78 (0.38-1.56)	0.482	
Sex						0.035
Male	Q1	87	33	1 (reference)	—	
	Q2	102	17	0.36 (0.16-0.79)	0.012	
	Q3	103	16	0.33 (0.14-0.74)	0.008	
	Q4	100	16	0.36 (0.16-0.83)	0.017	
Female	Q1	150	31	1 (reference)	—	
	Q2	135	28	1.17 (0.59-2.30)	0.650	
	Q3	134	22	1.25 (0.63-2.50)	0.525	
	Q4	137	18	0.75 (0.36-1.54)	0.434	
Current smoking						0.351
Yes	Q1	56	20	1 (reference)	—	
	Q2	66	11	0.38 (0.13-1.04)	0.063	
	Q3	61	9	0.35 (0.12-1.00)	0.055	
	Q4	67	5	0.19 (0.051-0.62)	0.009	
No	Q1	181	44	1 (reference)	—	
	Q2	171	34	0.85 (0.47-1.55)	0.605	
	Q3	176	29	0.88 (0.48-1.62)	0.685	
	Q4	170	29	0.76 (0.41-1.40)	0.374	
Hypertension						0.577
Yes	Q1	134	49	1 (reference)	—	
	Q2	135	25	0.45 (0.24-0.85)	0.014	
	Q3	141	26	0.49 (0.26-0.91)	0.024	
	Q4	151	25	0.43 (0.22-0.82)	0.011	
No	Q1	103	15	1 (reference)	—	
	Q2	102	20	1.72 (0.68-4.42)	0.253	
	Q3	96	12	1.58 (0.57-4.42)	0.375	
	Q4	86	9	0.81 (0.27-2.35)	0.705	
WFNS grade						0.683
1-3	Q1	166	20	1 (reference)	—	
	Q2	186	18	0.85 (0.42-1.72)	0.655	
	Q3	199	22	0.91 (0.46-1.80)	0.786	
	Q4	197	17	0.71 (0.34-1.45)	0.345	
4-5	Q1	71	44	1 (reference)	—	
	Q2	51	27	0.62 (0.28-1.34)	0.225	
	Q3	38	16	0.47 (0.20-1.10)	0.086	
	Q4	40	17	0.41 (0.17-0.96)	0.042	
Treatment modality						0.459
Surgical clipping	Q1	148	48	1 (reference)	—	
	Q2	129	26	0.57 (0.30-1.08)	0.088	
	Q3	113	23	0.80 (0.41-1.53)	0.497	
	Q4	109	18	0.49 (0.24-)	0.048	
Endovascular coiling	Q1	89	16	1 (reference)	—	
	Q2	108	19	0.96 (0.41-2.27)	0.921	
	Q3	124	15	0.58 (0.24-1.39)	0.221	
	Q4	128	16	0.65 (0.27-1.57)	0.337	

0 1 2 3 4 5

Fig. 3. Subgroup analysis of the relationship between PPR categories and 90-day outcomes. Abbreviations: WFNS, World Federation of Neurological Societies.

effectively mediate the association between PPR and 90-day outcomes, as the p-values for these analyses were all greater than 0.05, indicating a lack of statistical significance(**shown in** Table 3).

3.4. Sensitivity analysis

This study further conducted a sensitivity analysis to evaluate the robustness of Model 2. The results demonstrated that patients in the higher PPR quartiles (Q3 and Q4) exhibited significantly reduced risks of anemia and hypoproteinemia. Specifically, the risk of anemia in the Q3 group was reduced, with an OR of 0.54 (95 % CI: 0.35–0.82), achieving statistical significance (p = 0.004). Similarly, the risk of anemia in the Q4 group was also significantly lower, with an OR of 0.59 (95 % CI: 0.38–0.89) and a p-value of 0.013. Regarding hypoproteinemia, the Q3 group had a reduced risk, with an OR of 0.62 (95 % CI: 0.41–0.94), p = 0.026, while the Q4 group showed a significant decrease in risk, with an OR of 0.56 (95 % CI: 0.37–0.86), p = 0.008. Moreover, it is noteworthy that patients in the highest PPR quartile (Q4) not only had a lower incidence of pneumonia (OR = 0.48, 95 % CI: 0.31–0.74, p < 0.001) but also demonstrated a lower rate of adverse 90-day outcomes (OR = 0.52, 95 % CI: 0.30–0.91, p = 0.022), suggesting that higher PPR levels may be associated with better clinical outcomes **(shown in** Table 2S**)**.

3.5. Subgroup analysis

After fully adjusting for all potential confounding factors in the model, an in-depth subgroup analysis was conducted. The results revealed a significant interaction between PPR and patient gender concerning 90-day adverse outcomes. The association between elevated PPR levels and the likelihood of these outcomes was notably stronger in male patients than female patients (p for interaction = 0.035)**(shown in** Fig. 3, Tables 3S and 4S**)**.

3.6. Association of pneumonia with hospital length of stay and total charges

Patients who developed pneumonia had significantly prolonged hospital stays (14.0 [10.0–19.0] vs 11.0 [8.0–14.8] , p < 0.001) and faced higher hospital costs (137550 [94805–191631] vs 100619 [72908–153487], p < 0.001) compared to those without pneumonia **(shown in** Fig. 4A and B**)**.

3.7. Association of anemia with hospital length of stay and total charges

Patients with anemia had significantly longer hospital stays compared to those without anemia (14.0 [10.0–18.8] vs 11.0 [8.0–15.0], p < 0.001) **(shown in** Fig. 5A**)**. There was no significant difference in total hospital costs between the two groups (116152 [80520–167253] vs 113484 [76759–168505], p < 0.280) **(shown in** Fig. 5B**)**.

3.8. Cutoff values of PPR in a 90-day unfavorable outcome

This study employed the threshold-moving technique to determine the optimal cutoff value of the PPR for predicting 90-day adverse outcomes. The calculated cutoff value was 0.232. To visually present this analysis, we displayed the cutoff value and its corresponding AUC, sensitivity, and specificity in Fig. 6. Specifically, the AUC was 0.590, with a sensitivity of 0.232 and a specificity of 0.919.

4. Discussion

This study delineates the complex relationship between the PPR level and the occurrence of 90-day adverse outcomes in patients with aSAH. Our findings illuminate the significant predictive value of PPR levels in forecasting adverse outcomes post-aSAH, with higher quartiles of PPR showing a consistent association with a diminished incidence of clinical complications such as anemia, hypoproteinemia, and pneumonia, in addition to a decreased frequency of adverse outcomes within a 90-day follow-up. Our analysis indicates that the relationship between PPR and specific complications like anemia deviates from linearity, suggesting a more complex
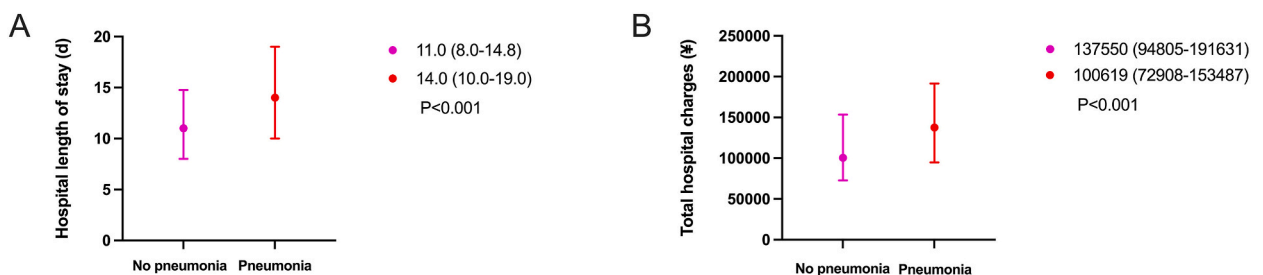

Fig. 4. (A) Association between length of stay and pneumonia. (B) Association between total hospital charges and pneumonia.
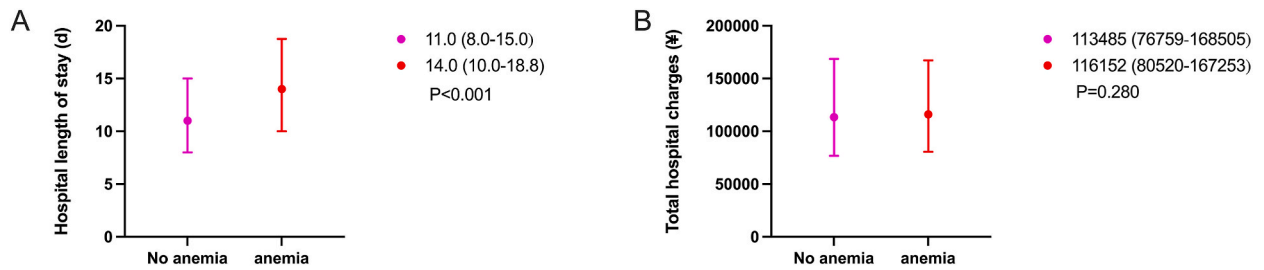
Fig. 5. (A) Association between length of stay and anemia. (B) Association between total hospital charges and anemia.
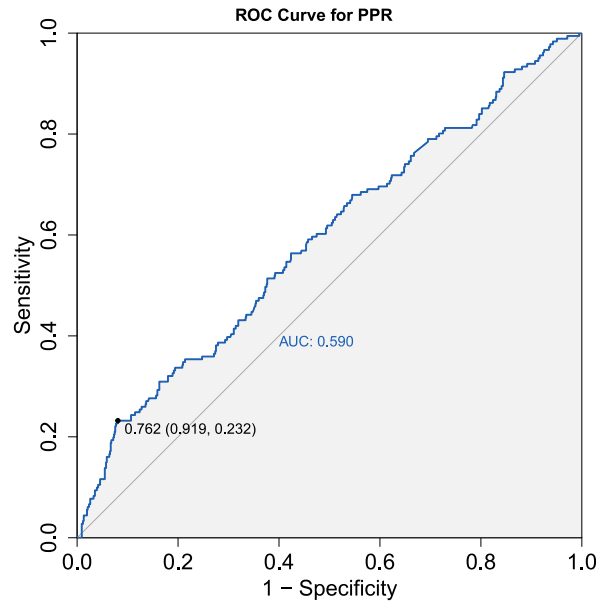

Fig. 6. This ROC curve represents the diagnostic performance of PPR in predicting a 90-day unfavorable outcome. The AUC indicates the overall ability of the PPR to discriminate between patients with and without the unfavorable outcome. On the ROC curve, the cut-off value of PPR, along with its sensitivity and specificity, are marked.

interaction than previously appreciated. Furthermore, through mediation analysis, the significant roles of anemia and pneumonia were unveiled not merely as complications but as mediators in the pathway leading to 90-day adverse outcomes, offering a novel perspective on patient management strategies.

In current research, there remains considerable debate and discussion regarding the role of platelets in the development of complications and the prediction of outcomes in patients with aSAH. Previous studies have focused on the impact of platelet activation markers and mean platelet volume in patients with aSAH, suggesting a potential association between elevated platelet-related indices and the occurrence of DCI within the first three months post-aSAH, as well as unfavorable functional outcomes [8,10,12]. This may be attributed to the role of platelets in microthrombosis formation, vasospasm, microvascular constriction, and inflammation following aSAH [13]. However, our findings indicate that lower levels of the PPR are associated with adverse outcomes within 90 days, mediated through in-hospital pneumonia and anemia. These observations align with a study from 2013, which reported a correlation between lower levels of coated platelets and an increased one-month mortality rate in patients with aSAH [14]. Despite these insights, inconsistencies in research findings persist, highlighting the complexity of understanding the role of platelets in the aftermath of aSAH in terms of complications and prognosis. This underscores the need for further research to unravel the precise mechanisms of these complex interactions.

Several factors were believed to contribute to the discrepancy between the findings of this study and those of previous studies. Firstly, there is variation in the study populations' demographics and the number of participants enrolled; notably, our cohort encompasses a larger sample size relative to previous studies. Second, the platelet parameters examined in each study may be influenced by different factors additionally, whether the influence of confounding factors on the outcome has been considered, such as admission grade, age, gender, etc. Patients with high-grade aSAH are more likely to experience unfavorable outcomes. It is essential to adjust for potential confounders appropriately.

Beyond their primary role in hemostasis, recent studies have uncovered that platelets also play a critical role in host defense and immune processes [15]. Platelets are essential in the innate immune response to infection and inflammation, acting as both

autonomous effectors and co-conductors of antimicrobial defense [16,17]. Clinically, thrombocytopenia is frequently considered an ominous indicator in the context of severe infections. Notably, the contemporary consensus definition of sepsis now integrates the Sepsis-Associated Organ Dysfunction Assessment (SOFA) score, which enumerates platelet count among its essential criteria [18]. Multiple studies have demonstrated that low platelet counts increase the risk and severity of pneumonia. For instance, a study conducted in 2020 focusing on acute type A aortic dissection revealed a significant statistical association between reduced platelet levels, as indicated by peripheral blood laboratory tests, and the incidence of pneumonia following surgery [19]. Additionally, in cases of COVID-19(COVID-19), a notable feature observed is that severe patients often present with thrombocytopenia [20]. Our findings suggest that patients with heightened PPR levels exhibit a decreased propensity for developing postoperative pneumonia, likely reflecting an augmented immune capability.

In preceding research, it was established that in-hospital complications, notably DCI and pneumonia, significantly contribute to adverse outcomes in patients with aSAH. According to numerous studies, pneumonia is closely correlated with unfavorable outcomes in patients with aSAH [21]. Furthermore, our results indicated that patients with pneumonia had a lengthier hospital stay and more expensive hospital charges when compared to those without pneumonia. It is encouraging to note that a substantial body of research has been dedicated to preventing and managing postoperative pneumonia. Preoperative examination of white blood cells, neutrophils, lactate dehydrogenase, and other laboratory factors have been proven to indicate postoperative pneumonia [22,23]. However, such research has not given weightage to the significant differences in laboratory indicators between gender, age, and race. Additionally, the development of aSAH is a dynamic process. Thus, the PPR is considered more appropriate for individualized prediction of postoperative pneumonia in aSAH patients compared to laboratory factors measured at a particular time before the operation.

A large-scale observational study conducted in 2022 robustly confirmed the prevalence of anemia as a common complication in patients with aSAH, noting that up to four-fifths of patients experienced anemia during their hospitalization [24]. The existing literature shows that anemia has a detrimental effect on the overall prognosis of aSAH patients [25]. Our findings also reveal that patients suffering from anemia endured more extended hospitalizations than those without anemia. Why does PPR partially affect the prognosis through anemia? The application of RCS analysis within our study has elucidated that, across a delineated spectrum, an augmentation in PPR levels is significantly associated with a reduced incidence of anemia. This observed correlation is potentially attributable to variations in intracranial hemorrhage volume. Given that the quintessential role of platelets encompasses promoting hemostasis and facilitating the coagulation cascade, individuals presenting with diminished PPR might experience an exacerbated extent of intracranial bleeding, subsequently culminating in anemia.

The association between alterations in platelet counts and prognosis and in-hospital complications is elucidated for the first time. Furthermore, the importance of inflammatory biomarkers in aSAH is further emphasized. As a routine component of peripheral blood laboratory tests, platelet count has the distinct advantage of being widely accessible across different levels of healthcare facilities. Its low cost and ease of use make it an especially attractive marker. Furthermore, exploring individualized pharmacological strategies based on platelet levels may hold significant promise in future research and warrants further investigation.

5. Limitation

Our study has several limitations. Primarily, as a single-center, retrospective analysis, the generalizability of our findings requires validation through more rigorous prospective, multicenter studies with larger sample sizes. Such studies are necessary to more accurately establish the significance of PPR in the prognostic assessment of patients with aSAH. Second, we did not collect data on daily platelet counts during hospitalization, necessitating further research to elucidate the role of platelets in aSAH. Thirdly, it is essential to note that our analysis was strictly limited to a cohort of patients with a single intracranial aneurysm. Consequently, the applicability of our findings to patients with multiple intracranial aneurysms remains uncertain and warrants further investigation to clarify and explore this aspect. Thus, the applicability of our findings to patients with multiple intracranial aneurysms needs further exploration. Lastly, whether patients had preoperative infections remains unclear, which may impact our findings. Further investigation is needed in this aspect.

6. Conclusion

Our study reveals a significant association between decreased PPR levels in patients with aSAH and adverse outcomes within 90 days, with anemia and pneumonia identified as key mediating factors in this relationship. These findings hold crucial clinical value and may provide valuable guidance for optimizing treatment and management strategies for aSAH patients.

Data availability statement

The data supporting this study are not deposited in a publicly accessible repository but can be obtained from the corresponding author upon reasonable request.

Funding

Ethics statement

This study received approval from the Institutional Review Board of Beijing Tiantan Hospital (Approval No. KY 2021-008-01, issued on January 20, 2021). All participants or their authorized representatives provided informed consent for clinical analysis. All analyses complied with the Declaration of Helsinki and local ethical standards.

CRediT authorship contribution statement

Yunfan Zhou: Writing – original draft, Methodology. **Ke Wang:** Writing – original draft, Formal analysis. **Runting Li:** Resources. **Fa Lin:** Resources, Methodology. **Yu Chen:** Resources, Methodology. **Jun Yang:** Software, Methodology. **Heze Han:** Resources. **Tu Li:** Software. **Yitong Jia:** Software. **Kexin Yuan:** Resources, Methodology. **Haibin Zhang:** Software. **Ruinan Li:** Resources. **Zhipeng Li:** Resources. **Cunyang Li:** Data curation. **Yahui Zhao:** Software. **Qiang Hao:** Methodology. **Xiaolin Chen:** Writing – review & editing, Conceptualization. **Yuanli Zhao:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37706.

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