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Association of Hemoglobin Decrement During Hospitalization with Prognosis of Aneurysmal Subarachnoid Hemorrhage and Mediation Effects of Cerebral Infarction and Pneumonia

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Background: Hemoglobin decrement is a common complication after aneurysmal subarachnoid hemorrhage (aSAH) and is associated with poor outcome. However, the mediating variables on the causal pathway between hemoglobin decrement and poor outcome in aSAH are not clear.

Methods: This is a single-center retrospective observational study containing all consecutive patients with aSAH admitted to our hospital between January 1, 2019, and June 30, 2022. Hemoglobin decrement was defined as the hemoglobin at admission minus the minimum hemoglobin during hospitalization. Calculation of cutoff value using ROC curve Youden index. The main exposure of interest was a hemoglobin decrement greater than the cutoff value. The primary outcome was poor outcome at 3 months (mRS 4–6).

Results: A total of 480 patients with aSAH were included in the study, 414 (71.1%) had a favorable and 66 (28.9%) had a poor outcome at 3 months. The cut-off value for calculating the degree of hemoglobin decrease using the ROC curve was 12.5 g/l. Hemoglobin decrement greater than the cutoff value was significantly associated with pneumonia (OR 3.12; 95% CI 1.78–5.57; $p < 0.001$), cerebral infarction (OR 3.06; 95% CI 1.80–5.30; $p < 0.001$), and poor prognosis (OR 2.88; 95% CI 1.44–5.92; $p = 0.003$) at 3 months. The mediation effect was significant for both pneumonia and cerebral infarction, with the average causal mediation effect (ACME) were 0.04 (95% CI 0.02–0.08; $p < 0.05$) and 0.05 (95% CI 0.02–0.08; $p < 0.001$), respectively.

Conclusion: Hemoglobin decrement during hospitalization was significantly associated with poor prognosis after aSAH, and the increased risk of cerebral infarction and pneumonia might mediate this effect. Avoiding hemoglobin decrement greater than 12.5g/l may improve the prognosis of patients with aSAH.

Keywords: aneurysmal subarachnoid hemorrhage, hemoglobin decrement, cerebral infarction, pneumonia

Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a serious cerebrovascular accident that kills more than 30% of patients and leaves neurological deficits in approximately 25% of survivors.[1] Anemia is a common complication after SAH, and studies have reported that about half of patients may develop anemia during hospitalization.[2] In addition, patients with post-SAH anemia are more likely to have delayed cerebral ischemia (DCI) and a poor outcome.[3–6]

Previous studies have reported that lower mean hemoglobin during the acute phase of aSAH is a predictor of vasospasm and poor neurological prognosis at discharge.[7] However, studies on whether to transfuse blood to correct anemia after aSAH are now at an impasse.[8] A small RCT on the feasibility of correcting anemia after aSAH showed that blood transfusion did not significantly reduce the incidence of cerebral infarction.[9] Recently, Asghar et al reported that in patients with SAH, independently of any hemoglobin values, greater hemoglobin decrement during hospitalization was associated with DCI and poor prognosis.[10] Therefore, we speculate that the factor contributing to the poor prognosis of SAH may be the process of hemoglobin decrement, rather than anemia caused by a drop in hemoglobin.

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In addition, pneumonia, a common extracranial complication after aSAH, affects the prognosis of aSAH and is prevalent in anemic patients as well.[11–13] However, few studies have reported a correlation between pneumonia, anemia, and aSAH.

Traditional causal analysis is a blind box effect, we know that decreased hemoglobin may affect the prognosis of aSAH, but we do not know how this effect occurs. Causal mediation analysis can effectively overcome this shortcoming by identifying intermediate variables (or mediators) that exist in the causal pathway between cause and effect.[14,15] In this study, we sought to explore the association between minimum hemoglobin and hemoglobin decrement with poor prognosis in SAH, as well as, using mediation analyses, to explore the mediating factors by which hemoglobin decrement jeopardizes the prognosis of SAH.

Materials and Methods

Patients

This is a single-center retrospective observational study containing all consecutive patients with aSAH admitted to our hospital between January 1, 2019, and June 30, 2022. Exclusion criteria included traumatic SAH, non-aneurysmal SAH, onset of more than 72 hours, death or discharge within 72 hours of onset, conservative treatment of aneurysms, missing data, and loss to follow-up. This study was approved by the Ethics Committee of the hospital.

Management Protocol

Treatment of aSAH patients at our center was according to the standard policy. Early treatment of aneurysms by endovascular coiling or microsurgical clipping. The treatment team consists of experienced neurosurgeons and neurointerventionalists, and surgical plan was decided by the treatment team together with the patients, depending on the patient's condition. When both options are available, endovascular coiling was preferred. Patients with hypertension receive antihypertensive treatment to maintain systolic blood pressure less than 180 mmHg. Treatment with intravenous nimodipine for anti-vasospasm is routinely used in the acute phase and then switched to oral nimodipine. External ventricular drainage is given in acute hydrocephalus. In patients with persistent hydrocephalus, the external cerebrospinal fluid (CSF) drain was replaced by a permanent ventriculoperitoneal shunt.[16]

Clinic Definition

Clinical grade was assessed with the World Federation of Neurosurgical Societies (WFNS) at admission.[17] The radiographic severity of aSAH was assessed based on the first computed tomography (CT) after onset by two experienced neurosurgeons (Che and Jiang) using the modified Fisher scale (mFisher). Delayed cerebral ischemia (DCI) was defined as a worsening of the Glasgow Coma Score by greater than or equal to 2 points or the development of new focal neurological symptoms after exclusion of any other underlying cause being determined.[18] Cerebral infarction was defined as a new infarction on CT or magnetic resonance imaging (MRI) 48 hours after onset.[19] Proven pneumonia had a confirmed change in diagnosis on at least one image of the chest x-ray or CT. Hydrocephalus was defined as persistent hydrocephalus requiring ventriculoperitoneal shunt surgery.

Outcome Assessment

Patient outcomes were assessed using the Modified Rankin Score (mRS) at 3 months.[20] An outcome of mRS 0–3 was considered a favourable prognosis, and mRS 4–6 was considered a poor prognosis at 3 months after onset. Follow-up data were obtained from follow-up transcripts completed by specialized neurosurgeons.

Data Collection and Laboratory Analyses

Data collected from the electronic medical record system included demographic information (age, gender, singleness status), disease history (hypertension, diabetes mellitus, anticoagulation and antiplant therapy, chronic obstructive pulmonary disease, prior stroke, smoking, drinking), neurological status on admission (WFNS), radiographic severity (mFisher), surgical approach (coiling or clipping), complications during hospitalization (DCI, cerebral infarction,

pneumonia, epilepsy, hydrocephalus, gastrointestinal bleeding, deep vein thrombosis), admission hemoglobin concentration (g/L), minimum hemoglobin concentration. Minimum hemoglobin was defined as the lowest value recorded in the electronic medical record system. Hemoglobin decrement was expressed as the hemoglobin concentration on admission minus the minimum hemoglobin concentration, and if the result is negative, it was expressed as 0.

Statistical Analysis

Student's *t* test or the MannWhitney *U*-test were used as appropriate in continuous variables, $\chi 2$ test was used in categorical variables. The receiver operating characteristic (ROC) curve for the effect of hemoglobin decrement on the poor outcome was established, and the cut-off value was calculated using Youden index. Exploring the association between hemoglobin decrement greater than the cut-off value and complications during hospitalization, the association between complications and prognosis at 3 months was performed with multivariate logistic regression analysis adjusted for age, gender, WFNS, mFisher, and surgical approach. Only variables whose univariate analyses suggested statistical significance were included in the multivariate analyses. The analysis of the effect of minimum hemoglobin on prognosis suffered from Simpson's paradox[21] and was adjusted by the addition of hemoglobin decrement to the multivariate analysis.

Causal mediation analyses (CMA) can explore the direct effect of the treatment on the outcome which reported as average direct effect (ADE), the indirect effect which reported as average causal mediation effect (ACME), and the total effect.[14] In our study, we used hemoglobin decrement as a treatment variable and DCI, cerebral infarction, epilepsy, hydrocephalus, pneumonia as mediator variables to explore the possible mediators and corresponding mediating effects present between hemoglobin decrement and poor prognosis. Causal mediation analyses were performed using methods proposed by previous scholars.[14] All statistical analyses were performed using the R package (version 4.3.0), and $p < 0.05$ was considered statistically significant.

Result

Demographic Data and Baseline Characteristics

A total of 651 patients with aSAH were admitted during the study period, of whom 480 met the criteria for inclusion in the study. Flow diagram of study patient inclusion and exclusion was shown in Figure 1. Of all the included cases, 414 (71.1%) had a favorable and 66 (28.9%) had a poor outcome at 3 months. Demographic data and baseline characteristics are displayed in Table 1. Compared with patients with a favorable outcome, those with a poor outcome were older (62 vs 56 yr; $P = 0.001$), had poorer neurological function on admission (29% and 20% for WFNS grades 4 and 5, respectively, $P < 0.001$), had larger hemorrhages (32% and 35% for mFisher grades 3 and 4, respectively, $P < 0.001$), and had a higher incidence of DCI, cerebral infarction, epilepsy, and pneumonia. Patients undergoing clipping have a higher rate of poor prognosis compared to coiling procedures. In addition, the poor prognosis group had lower minimum hemoglobin and greater hemoglobin decrement. However, gender, hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), prior stroke, anticoagulation or antiplatelet therapy, smoking, drinking, and singleness status, admission hemoglobin, postoperative gastrointestinal bleeding (GIB), and deep vein thrombosis (VTE) were not significantly different between two groups.

Simpson's Paradox of Minimum Hemoglobin Affecting Prognosis of aSAH

Univariate analysis suggested that the minimum hemoglobin was significantly lower in the poor prognosis group than in the favourable prognosis group (109g/l vs 123g/l, $p < 0.001$). However, multivariate logistic regression analysis revealed that the odds ratio (OR) of the minimum hemoglobin affecting prognosis was lower than 1 (OR 0.96; 95% CI 0.94, 0.98; $p < 0.001$). This is apparently a Simpson's paradox. Subsequently, further multivariate logistic regression adjusted by hemoglobin decrement found that there was no statistical difference between the minimum hemoglobin and poor prognosis. This suggests that the lurking variable in this Simpson's paradox is hemoglobin decrement (Table 2).

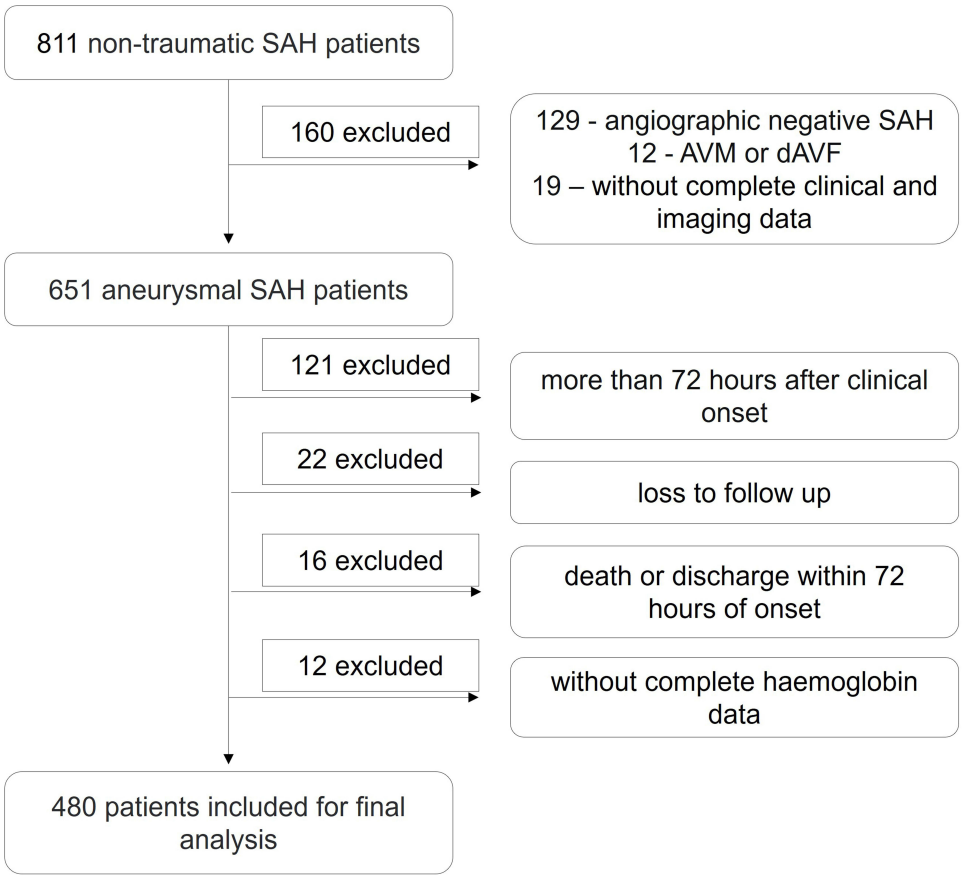

Figure 1 Flow diagram for patient exclusion.
Abbreviation: SAH, subarachnoid hemorrhage.

ROC Curve of Hemoglobin Decrement Affecting Prognosis of aSAH

The ROC curve demonstrated good accuracy for predicting the poor-outcome of aSAH patients, with an unadjusted area under the curve (AUC) of 0.78 (95% CI: 0.72–0.85). Using the Youden index, the cutoff value is calculated as 12.5g/l (specificity: 0.67, sensitivity: 0.77) (Figure 2).

Univariate and Multivariate Analysis of Hemoglobin Decrement Affecting Complications During Hospitalization

A hemoglobin decrement greater than the cut-off value (12.5g/l) on univariate analysis increased the incidence of DCI, cerebral infarction, and pneumonia, with no statistically different between epilepsy, GIB, hydrocephalus, and VTE. Further multivariate logistic regression analyses adjusted by age, gender, WFNF, mFisher, and surgery approach suggested that a hemoglobin decrement greater than 12.5g/l increased the risk of pneumonia (OR 2.21; 95% CI 1.22, 4.06; p = 0.009) and cerebral infarction (OR 2.16; 95% CI 1.22, 3.85; p = 0.008) and with no statistically different between DCI (Table 3).

Multivariate Logistic Regression Analysis of Complications Affecting Prognosis of aSAH

Multivariate logistic regression analysis adjusted for age, gender, WFNF, mFisher, and surgery approach suggested that among the complications during hospitalization, DCI (OR 7.44; 95% CI 3.76–15.4; P < 0.001), cerebral infarction (OR 18.5; 95% CI 8.24–45.0; p < 0.001), pneumonia (OR 9.64; 95% CI 4.74–20.2; p < 0.001) and hemoglobin decrement greater than 12.5g/l (OR 2.88; 95% CI 1.44–5.92; p = 0.003) were significantly associated with poor prognosis at 3 months (Table 4).

Table 1 Demographic Data and Baseline Characteristics

Variables	Favorable Outcome (mRS 0–3) (n = 414)	Poor Outcome (mRS 4–6) (n = 66)	P-Value
Age, Median (Q1, Q3)	55.5 (50, 64)	61.5 (53.25, 68.75)	0.001
Gender, n (%)			0.448
Female	278 (67)	48 (73)	
Male	136 (33)	18 (27)	
Hypertension, n (%)			0.125
No	264 (64)	35 (53)	
Yes	150 (36)	31 (47)	
Diabetes mellitus, n (%)			0.05
No	392 (95)	58 (88)	
Yes	22 (5)	8 (12)	
Anticoagulation or antiplatelet therapy, n (%)			0.248
No	409 (99)	64 (97)	
Yes	5 (1)	2 (3)	
COPD, n (%)			1
No	410 (99)	66 (100)	
Yes	4 (1)	0 (0)	
Prior stroke, n (%)			0.174
No	399 (96)	61 (92)	
Yes	15 (4)	5 (8)	
Smoking, n (%)			0.306
No	318 (77)	55 (83)	
Yes	96 (23)	11 (17)	
Drinking, n (%)			1
No	344 (83)	55 (83)	
Yes	70 (17)	11 (17)	
Single, n (%)			0.056
No	370 (89)	53 (80)	
Yes	44 (11)	13 (20)	
WFNS, n (%)			< 0.001
1	157 (38)	5 (8)	
2	215 (52)	29 (44)	
3	6 (1)	0 (0)	
4	33 (8)	19 (29)	
5	3 (1)	13 (20)	
mFisher, n (%)			< 0.001
0	18 (4)	0 (0)	
1	248 (60)	16 (24)	
2	46 (11)	6 (9)	
3	80 (19)	21 (32)	
4	22 (5)	23 (35)	
Surgery approach, n (%)			0.016
Coiling	347 (84)	46 (70)	
Clipping	67 (16)	20 (30)	
DCI, n (%)			< 0.001
No	341 (82)	24 (36)	
Yes	73 (18)	42 (64)	
Cerebral infarction, n (%)			< 0.001
No	376 (91)	29 (44)	
Yes	38 (9)	37 (56)	

(*Continued*)

Table 1 (Continued).

Variables	Favorable Outcome (mRS 0–3) (n = 414)	Poor Outcome (mRS 4–6) (n = 66)	P-Value
GIB, n (%)			1
No	401 (97)	64 (97)	
Yes	13 (3)	2 (3)	
Epilepsy, n (%)			0.036
No	408 (99)	62 (94)	
Yes	6 (1)	4 (6)	
Pneumonia, n (%)			< 0.001
No	379 (92)	24 (36)	
Yes	35 (8)	42 (64)	
Hydrocephalus, n (%)			0.008
No	411 (99)	62 (94)	
Yes	3 (1)	4 (6)	
VTE, n (%)			0.123
No	387 (93)	58 (88)	
Yes	27 (7)	8 (12)	
Admission Hemoglobin (g/L), Median (Q1, Q3)	131 (121, 142)	132.5 (126.25, 142)	0.082
Minimum Hemoglobin (g/L), Mean (SD)	123.95 (16.26)	109.7 (21.46)	< 0.001
Hemoglobin decrement (g/L), Median (Q1, Q3)	7 (0, 16)	24.5 (13.25, 36)	< 0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; WFNS, the World Federation of Neurosurgical Societies; GIB, gastrointestinal bleeding; DCI, delayed cerebral ischemia; VTE, venous thrombosis embolism.

Table 2 Multivariate Regression Analysis of Minimum Hemoglobin Affecting Prognosis

Characteristic	Model a			Model b		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Minimum hemoglobin	0.96	0.94, 0.98	<0.001	0.99	0.97, 1.02	0.6

Notes: Model a: adjusted for age, gender, mFisher, WFNS, and surgery approach. Model b: adjusted for age, gender, mFisher, WFNS, surgery approach, and hemoglobin decrement.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval.

Causal Mediation Analysis

Mediators between hemoglobin decrement and poor prognosis after aSAH were identified using CMA. The indirect effect was significant when pneumonia and cerebral infarction were used as mediator variable. When the mediator variable was cerebral infarction, the total effect was 0.11 (95% CI 0.04–0.17; $p < 0.05$), the ACME was 0.05 (95% CI 0.02–0.08; $p < 0.001$), the ADE was 0.06 (95% CI 0.003–0.12; $p < 0.05$), and the proportion of total effect via mediation was 47% (95% CI 21%–93%; $p < 0.05$) (Figure 3A). When the mediator variable was pneumonia, the total effect was 0.12 (95% CI 0.06–0.08; $p < 0.001$), the ACME was 0.04 (95% CI 0.02–0.08; $p < 0.05$), the ADE was 0.07 (95% CI 0.02–0.13; $p < 0.05$), and the proportion of total effect via mediation was 39% (95% CI 15%–74%; $p < 0.05$) (Figure 3B). We conclude that a hemoglobin decrement greater than the cutoff value affects the prognosis of aSAH partly mediated through increasing the risk of cerebral infarction and pneumonia.

Discussion

Our study reveals that hemoglobin decrement during hospitalization is significantly associated with poor outcome after 3 months in patients with aneurysm subarachnoid hemorrhage (aSAH). Using causal mediation analyses, we found that

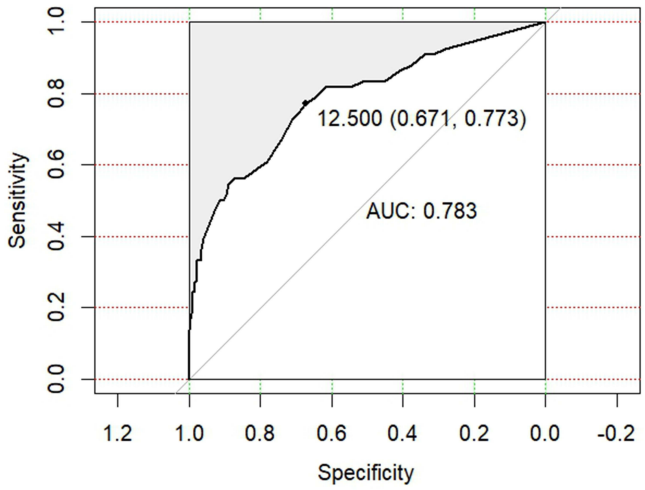

Figure 2 ROC curve of hemoglobin decrement affecting prognosis in aSAH. The unadjusted AUC for this ROC curve was 0.78 (95% CI: 0.72–0.85). Using the Youden index, the cutoff value is calculated as 12.5g/l (specificity: 0.67, sensitivity: 0.77).
Abbreviations: aSAH, aneurysmal subarachnoid hemorrhage; ROC, receiver operating characteristic; AUC, area under the curve.

hemoglobin decrement affects the prognosis of patients with aSAH possibly mediated by an increased risk of pneumonia and cerebral infarction. Our study found for the first time that pneumonia and cerebral infarction were important mediating variables for the prognostic impact of hemoglobin decrement in aSAH.

There is much evidence that anemia is a common complication after SAH, and studies have reported that about half of patients may develop anemia during hospitalization.[2] In addition, patients with post-SAH anemia are more likely to

Table 3 Univariate and Multivariate Analysis of Hemoglobin Decrement Affecting Complications During Hospitalization

Characteristic	Non-Hemoglobin Decrement More Than 12.5g/l (n = 293)	Hemoglobin Decrement More Than 12.5g/l (n = 187)	p-Value	Adjusted OR	95% CI	p-Value
DCI, n (%)	58 (20)	57 (30)	0.01	0.99	0.61, 1.60	>0.9
Cerebral infarction, n (%)	27 (9)	48 (26)	< 0.001	2.16	1.22, 3.85	0.008
Pneumonia, n (%)	23 (8)	54 (29)	< 0.001	2.21	1.22, 4.06	0.009
Epilepsy, n (%)	5 (2)	5 (3)	0.522	-	-	-
Hydrocephalus, n (%)	5 (2)	2 (1)	0.711	-	-	-
GIB, n (%)	7 (2)	8 (4)	0.373	-	-	-
VTE, n (%)	17 (6)	18 (10)	0.164	-	-	-

Notes: Adjusted by age, gender, WFNS, mFisher, and surgery approach.
Abbreviations: OR, odds ratio; CI, confidence interval; DCI, delayed cerebral ischemia; GIB, gastrointestinal bleeding; VTE, venous thrombosis embolism.

Table 4 Multivariate Logistic Regression Analysis of Complications During Hospitalization Affecting Prognosis

Characteristic	Adjusted OR	95% CI	p-Value
DCI	7.44	3.76, 15.4	<0.001
Cerebral infarction	18.5	8.24, 45.0	<0.001
Epilepsy	3.00	0.50, 14.8	0.2
Pneumonia	9.64	4.74, 20.2	<0.001
Hydrocephalus	2.18	0.35, 13.4	0.4
Hemoglobin decrement greater than 12.5g/l	2.88	1.44, 5.92	0.003

Notes: Adjusted for age, gender, mFisher, WFNS, and surgery approach.
Abbreviations: OR, Odds Ratio; CI, Confidence Interval; DCI, delayed cerebral ischemia.

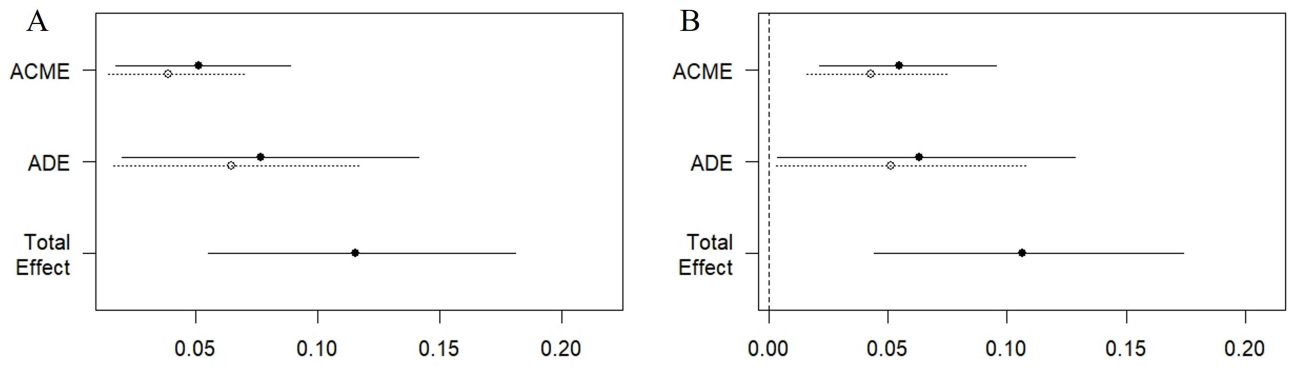

Figure 3 Causal mediation analysis for cerebral infarction and pneumonia. The solid line represents that the hemoglobin decrement exceeded the cut-off value (12.5g/l), and the dashed line represents that the hemoglobin decrement did not exceed the cut-off value. (**A**) Causal mediation analysis for cerebral infarction: shows cerebral infarction as a mediating variable. (**B**) Causal mediation analysis for pneumonia: shows pneumonia as a mediating variable.
Abbreviations: ACME, average indirect effect; ADE, average direct effect.

have delayed cerebral ischemia (DCI) and a poor outcome.[6,22–24] Our previous studies have similarly shown that the mean postoperative hemoglobin concentration is significantly associated with vasospasm, with the lowest risk of vasospasm occurring at 11–12 g/dl.[23] In addition, studies have shown that low mean hemoglobin in the acute phase of aSAH may induce vasospasm and is a predictor of poor prognosis at discharge.[7] In the current study, we similarly found that the minimum hemoglobin concentration was lower and the extent of hemoglobin decrement was more pronounced in the poor prognosis group. These results are in general agreement with the conclusions drawn from previous studies.

However, studies on whether to transfuse blood to correct anemia after aSAH are now at an impasse.[8] A previous small RCT aimed at assessing the safety and feasibility of correcting low hemoglobin concentrations by transfusion within 3 days of aSAH onset showed that no significant differences in new-onset cerebral infarcts and DCI between the treatment and control groups.[9] Subsequently, a secondary analysis of the above findings using propensity score matching similarly found no difference in mortality between the two groups.[3] However, we encountered Simpson's paradox in our study of the association between minimum hemoglobin and poor prognosis. Even though univariate analysis suggested that the mean value of minimum hemoglobin was significantly lower in the poor prognosis group than in the good prognosis group, the OR on multivariate regression analysis was lower than 1. Fortunately, we seem to have found the devil's variable (lurking variable) that triggered this Simpson's paradox. Further adjusted by the addition of hemoglobin decrement revealed no statistical difference between minimum hemoglobin and poor prognosis. We suspect that the reason why transfusion therapy does not improve the prognosis of patients with SAH may be that the factor affecting the prognosis of SAH may be hemoglobin decrement rather than anemia due to the drop in hemoglobin.

Further, we used causal mediation analysis to preliminarily explore the possible mechanisms by which decreased hemoglobin affects the prognosis of aSAH. DCI and its associated cerebral infarction are the most common complications affecting the prognosis of patients with aSAH.[18] Many studies have shown that anemia is significantly associated with DCI after aSAH. In our study, hemoglobin decrement greater than the cutoff value (12.5g/l) was significantly associated with cerebral infarction, and its mediating effect (indirect effect) through cerebral infarction affecting the poor prognosis of aSAH was approximately 46.5%.

Patients with aSAH are at high risk of developing pneumonia. It has been shown that 13–37% of the patients with aSAH develop postoperative lung infections.[25] China Stroke Statistics 2019 shows that the leading comorbidity in Chinese stroke patients was pneumonia (29.7% for SAH).[26] Pneumonia after aSAH has been reported in the literature to be significantly associated with poor prognosis.[27] In addition, anemia, particularly hemoglobin level is less than 10 mg/dl, may significantly increase the risk of death in studies of hospitalized patients with community-acquired pneumonia.[11] However, there are few studies in which anemia affects the prognosis of aSAH involving pneumonia. Our study confirms that hemoglobin decrement greater than the cutoff value (12.5g/l) may significantly increase the risk of pneumonia and that its mediating effect through pneumonia affects the prognosis of SAH by approximately 38.5%.

There are some limitations to our study. First, the study was a single-center study and, therefore, there was an unavoidable selection bias, which was further exacerbated by the exclusion of cases with an onset of more than 72 hours from the study. Secondly, this is a retrospective study and some confounding factors that may affect the prognosis, such as use of postoperative antiplatelet agents, blood transfusions, and causes of hemoglobin drop, were not included in the study. Third, because CT and MRI have different sensitivities in identifying acute cerebral infarction, CT may result in some patients with asymptomatic cerebral infarction being missed. In addition, hemoglobin values were collected in a retrospective electronic case system, the minimum hemoglobin in our study may not be the true lowest hemoglobin. More prospective studies are needed in the future.

Conclusion

In summary, a hemoglobin decrement during hospitalization may be associated with a poor prognosis in patients with aSAH, and this association may be due to the fact that hemoglobin decrement may increase the risk of pneumonia and cerebral infarction.

Ethics Statement

This study protocol was reviewed and approved by the Research Ethics Committee (REC) of Chongqing Medical University First Affiliated Hospital (K2023-648) with the 1964 helsinki declaration and its later amendments or comparable ethical standards. In accordance with the guidelines established by the REC, the requirement for patient consent to review medical records has been waived for this study. This waiver is justified on the grounds that the study is retrospective, relying solely on the analysis of existing medical records to derive insights that are deemed beneficial for improving patient care and advancing medical knowledge. In addition, the nature of the data being reviewed is such that it will be analyzed in an aggregate manner, ensuring that individual patient identities remain anonymous and are not directly linked to the research findings. The confidentiality and privacy of patient data are of utmost importance in our research. All data obtained from medical records will be handled with the highest ethical standards and in compliance with relevant regulations. Specifically, we commit to the following: First, all patient information will be anonymized prior to analysis. Identifying information will be removed to ensure that individuals cannot be identified in any reports or publications resulting from this research. Second, access to the data will be restricted to authorized research personnel only. All team members will undergo training regarding data privacy and confidentiality. Third, appropriate data security measures, including secure storage and encrypted transmission of data, will be implemented to protect against unauthorized access or breaches of confidentiality. Finally, this research will be conducted in accordance with applicable laws and ethical guidelines governing the use of medical data, including adherence to the principles of the Declaration of Helsinki. We are committed to upholding the trust placed in us by patients and the community, and we will ensure that all patient data is treated with the utmost respect and confidentiality throughout the duration of this study.

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Disclosure

The authors declared that they have no competing interests.

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