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Neutrophil-to-albumin ratio as a predictor of mortality in patients with intracerebral hemorrhage: a multicenter retrospective cohort study

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Abstract

Background Intracerebral hemorrhage (ICH) is associated with a poor prognosis. The association between the neutrophil-to-albumin ratio (NAR) with mortality in patients with ICH remains underexplored. This study investigated the relationship between the NAR and mortality in patients with ICH.

Methods A multicenter retrospective observational cohort study was conducted from January 2010 to June 2019. Participants were divided into four groups according to NAR quartiles at admission. Univariable and multivariable logistic regression analyses were used to evaluate the relationship between NAR and 90-day mortality. The predictive power of NAR was compared with neutrophil count and albumin levels using receiver operating characteristic (ROC) curve analysis.

Results Patients in the highest NAR quartile had significantly greater odds of 90-day mortality (adjusted OR 1.74, 95% CI 1.27–2.39, $p < 0.001$) compared to those in the lowest quartile. The area under the curve (AUC) for NAR was 0.68, demonstrating superior discriminative ability compared to neutrophil count (AUC 0.64) and albumin (AUC 0.60). These findings were consistent across various subgroups, with multivariate analysis confirming the independent predictive value of NAR for mortality in patients with ICH.

Conclusions Elevated NAR was independently associated with increased mortality in patients with ICH. NAR is a promising inflammatory marker that could aid in early risk assessment and guide management strategies for patients with ICH.

Keywords Intracerebral hemorrhage, Neutrophil-to-albumin ratio, Mortality

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Introduction

Intracerebral hemorrhage (ICH) is one of the most devastating forms of stroke [1, 2], with high morbidity and mortality rates and over 2 million deaths worldwide each year [3, 4]. Hence, identifying reliable biomarkers for the early detection of mortality risk is crucial for enhancing clinical decision-making and optimizing patient management.

The neutrophil-to-albumin ratio (NAR) has recently emerged as a potential biomarker reflecting systemic inflammation and nutritional status, both of which are considered crucial determinants of outcomes in critically ill patients [5]. Neutrophils, as one of the first responders to tissue injury, play a key role in the inflammatory cascade following ICH. Upon hemorrhagic injury to the brain, neutrophils are activated and migrate to the site of injury, where they release pro-inflammatory cytokines and enzymes, contributing to secondary brain damage and further exacerbating the injury. This dysregulated neutrophil activation is thought to worsen the inflammatory response, leading to increased neuronal damage, blood-brain barrier disruption, and ultimately poor outcomes in ICH patients [6, 7].

Albumin, a major plasma protein synthesized in the liver, serves as a marker of both nutritional status and systemic inflammation. Low serum albumin levels (hypoalbuminemia) are common in critically ill patients and are associated with poorer clinical outcomes, including higher mortality rates. Hypoalbuminemia reflects a complex interplay between inflammation, impaired hepatic function, and inadequate nutrition, all of which contribute to the prognosis of critically ill patients. Given that albumin levels often decrease in response to systemic inflammation, its role as an inflammatory marker should not be overlooked [8].

The NAR integrates two critical aspects—immune response and nutritional status—offering a potentially valuable metric for assessing disease severity and predicting patient prognosis. Higher NAR values may indicate a heightened inflammatory response combined with inadequate nutrition, both of which are associated with worse clinical outcomes. Previous studies have highlighted the role of inflammatory markers, such as neutrophil count and hypoalbuminemia, in predicting mortality across various diseases, including cardiovascular and neurological disorders [9, 10]. However, the relationship between NAR and mortality in patients with ICH remains underexplored. Understanding this relationship may offer valuable insights into risk stratification and personalized therapeutic strategies for patients with ICH. The purpose of our study was to determine whether the NAR was associated with prognosis in patients with ICH.

Methods

Study design and data source

A multicenter retrospective cohort study was conducted between January 2009 and June 2019, involving Sichuan University West China Hospital and People's Hospital of Longquanyi District Chengdu. The departments of information from each participating hospital assisted in retrieving hospitalization data via their respective electronic health record systems. The institutional review boards of all participating centers approved the study, and informed consent was waived due to its observational nature. Patients were treated in accordance with established guidelines.

Patient selection

For the present analysis, we included patients who met the following criteria: [1] age > 18 years; [2] diagnosis of acute spontaneous ICH; [3] availability of baseline non-contrast CT (NCCT) images and serum neutrophils and albumin measurements; [4] availability of 90-day mortality data.

Exclusion criteria included: [1] primary intraventricular hemorrhage; [2] other types of ICH (e.g., trauma, tumor, cerebral aneurysm, vascular malformation, hemorrhagic transformation of acute ischemic stroke); [3] were lost to follow-up or had missing outcome data; [4] patients who had undergone surgical treatment (e.g., craniotomy or hematoma aspiration).

Clinical data collection and image analysis

The clinical and demographic data, including age, sex, admission systolic blood pressure (SBP), diastolic blood pressure (DBP), Glasgow Coma Scale (GCS) score, modified Rankin Scale (mRS) score, duration of hospital stay, history of hypertension, and history of diabetes, as well as risk factors such as smoking and alcohol use, were prospectively collected. At 24 h after hospitalization, 5 ml of venous blood was collected. All blood samples, including measurements of leukocyte count, neutrophil count, lymphocyte count, and albumin levels, were collected from each patient at admission in EDTA tubes (for plasma) or vacutainer tubes (for serum). Cell counts were measured using an auto-analyzer, and all biochemical parameters were analyzed using an automatic biochemical analyzer. Our primary exposure variable was the neutrophil-to-albumin ratio (NAR), which was calculated by dividing the neutrophil count by the albumin level. Furthermore, Youden's Index was employed to determine the optimal cutoff value for NAR. The primary outcome of interest was all-cause mortality within 90 days of admission.

Statistical analysis

Data analysis was performed using the R software (version 4.3.3). Categorical variables were expressed as count

(percentage), and continuous variables were presented as mean (± standard deviation [SD]) or median (interquartile range [IQR]). Comparisons were evaluated through the Mann-Whitney U-test, Student t-test, or Chi-square test as appropriate. To evaluate the potential impact of missing data, we conducted a sensitivity analysis comparing the baseline characteristics of included patients (i.e., those with complete NAR and mortality data) and excluded patients (i.e., those missing either NAR or mortality information). The baseline variables analyzed included age, sex, GCS score, and other relevant clinical factors.For multivariate analysis, variables with a p-value < 0.10 in univariate analysis, as well as those previously identified as predictors of poor outcomes, were included. A multivariable logistic regression model was then applied to identify independent risk factors and prognostic indicators, with results reported as odds ratios (ORs) and 95% confidence intervals (CIs).

To assess the robustness of our variable selection strategy, we further performed a sensitivity analysis using a forward-backward stepwise selection approach, guided by Akaike's Information Criterion (AIC). This method allowed for both the inclusion and exclusion of variables throughout the model-building process. The same candidate predictors as those used in the forward-only stepwise selection were entered into the model. The selection process was implemented using the *stepAIC()* function from the MASS package in R (version 4.3.3).

The relationship between NAR levels and 90-day mortality was visualized using a restricted cubic spline (RCS). Odds ratios (ORs) and 95% confidence intervals (95% CI) were estimated using logistic regression models for both univariable and multivariable analyses. Characteristics that influenced the results ($p < 0.10$) were incorporated into a multivariable logistic regression model. When factors remained statistically significant, they were considered independently associated.

To evaluate the discriminatory ability of NAR for the primary outcome of 90-day mortality, receiver operating characteristic (ROC) curve analysis was performed based on baseline NAR values measured at admission. The area under the curve (AUC) was used to quantify predictive performance, with higher AUC values indicating better discrimination.

To further assess the relative importance of each variable in predicting 90-day mortality, a Random Forest model was employed using the same set of covariates included in the multivariate logistic regression. Variable importance was evaluated based on the mean decrease in Gini impurity. This approach aimed to validate the predictive value of the neutrophil-to-albumin ratio (NAR) within a non-linear ensemble framework.

Subgroup analysis was conducted to determine whether the association between NAR and long-term mortality varied across different subgroups, and interaction p-values were calculated.

To further evaluate the relationship between NAR levels and 90-day mortality, violin plots were generated to visualize the distribution of NAR across patients who survived and those who did not. The violin plot included kernel density estimates to show the data distribution, overlaid with boxplots to highlight the median, interquartile range, and overall range of NAR levels in each group ("No" and "Yes" for 90-day mortality).

Results

Baseline characteristics of the cohort

A total of 7013 patients with ICH were included in the study Exclusion criteria consisted of 1 pediatric patient, 1967 patients who lacked neutrophil-to-albumin ratio, and 1696 patients who lacked death records. After applying these exclusions, the final analysis included 3350 patients. (Figure S1). The baseline characteristics of the cohort, categorized into four NAR quartiles: Q1 (< 0.15), Q2 (0.15–0.21), Q3 (0.21–0.30), and Q4 (> 0.30). The mean age was 57.91 years (SD = 14.71), with 33.0% of the cohort being female. Significant differences were observed across quartiles in age ($p < 0.001$), systolic blood pressure (SBP, $p < 0.001$), and Glasgow Coma Scale (GCS) scores ($p < 0.001$). Patients in Q4 had lower GCS scores (mean 8.35, SD = 4.10), larger hematomas (mean size 30.16 cm^3, SD = 29.68), and higher SBP (mean 163.96 mmHg, SD = 36.53) compared to Q1. (Table 1)

Sensitivity analysis

To assess the potential impact of missing data, we conducted a sensitivity analysis comparing the baseline characteristics of included patients (those with complete NAR and mortality data) and excluded patients (those missing either NAR or mortality information). We found that there were no statistically significant differences between the two groups in terms of age, sex, smoking status, or other key clinical variables (all p-values > 0.05). (Table S1) These results suggest that the missing data were likely missing at random (MAR), and that the risk of systematic selection bias due to data exclusion was minimal.

In addition, the forward-backward stepwise selection procedure produced an identical final model to that obtained through forward-only stepwise selection. The selected covariates, corresponding regression coefficients, and odds ratios remained unchanged. Model performance was also consistent, with an AUC of 0.812 in both models. Importantly, the association between the neutrophil-to-albumin ratio (NAR) and 90-day mortality remained statistically significant ($p < 0.001$). These findings reinforce the stability and robustness of our modeling approach.(Table S2).

Table 1 Baseline characteristics of the patients

Characteristics	ALL	NAR quartile				*P*	Miss value (*n*, %)
	Overall (*n* = 3350)	< 0.15 (*n* = 838)	0.15–0.21 (*n* = 837)	0.21–0.30 (*n* = 837)	> 0.30 (*n* = 838)		
Demographics							
Age, years, mean (SD)	57.91 (14.71)	58.65 (14.78)	57.80 (14.51)	59.19 (14.93)	56.01 (14.45)	< 0.001	0(0.00)
Female, n (%)	1107 (33.0)	296 (35.3)	266 (31.8)	265 (31.7)	280 (33.4)	0.341	0(0.00)
Smoking, n (%)						0.447	0(0.00)
Never	2283 (68.1)	562 (67.1)	557 (66.5)	587 (70.1)	577 (68.9)		
Current	889 (26.5)	224 (26.7)	230 (27.5)	215 (25.7)	220 (26.3)		
Ever	178 (5.3)	52 (6.2)	50 (6.0)	35 (4.2)	41 (4.9)		
Alcohol, n (%)	1040 (31.0)	252 (30.1)	274 (32.7)	258 (30.8)	256 (30.5)	0.658	0(0.00)
Medical history, n (%)							0(0.00)
Hypertension	2396 (71.5)	549 (65.5)	613 (73.2)	612 (73.1)	622 (74.2)	< 0.001	
Diabetes	341 (10.2)	96 (11.5)	73 (8.7)	85 (10.2)	87 (10.4)	0.324	
SBP, mmHg, mean (SD)	162.00 (32.45)	156.71 (29.48)	161.99 (30.12)	165.36 (32.55)	163.96 (36.53)	< 0.001	25(0.7)
Hematoma characteristics							
Intraventricular hematoma, n (%)	807 (24.1)	143 (17.1)	187 (22.3)	227 (27.1)	250 (29.8)	< 0.001	0(0.00)
Size of hematoma, cm, mean (SD)	23.73 (27.27)	15.68 (19.89)	22.23 (28.36)	26.58 (27.70)	30.16 (29.68)	< 0.001	415(12.4)
Infratentorial hematoma, n (%)	622 (18.6)	105 (12.5)	164 (19.6)	174 (20.8)	179 (21.4)	< 0.001	0(0.00)
GCS score, mean (SD)	10.81 (4.12)	13.19 (2.98)	11.58 (3.72)	10.11 (3.95)	8.35 (4.10)	< 0.001	0(0.00)
Laboratory tests, mean (SD)							
Neutrophil count, 10^9/L	8.84 (4.35)	4.43 (1.26)	7.15 (1.17)	9.56 (1.66)	14.22 (4.28)	< 0.001	0(0.00)
White blood cell count, 10^9/L	10.78 (10.38)	6.42 (4.51)	8.77 (1.48)	11.13 (1.89)	16.81 (18.60)	< 0.001	0(0.00)
Blood glucose, mmol/L	7.68 (3.31)	6.49 (2.57)	7.25 (2.72)	8.14 (3.08)	8.84 (4.14)	< 0.001	58(1.7)
Albumin, g/L	37.97 (5.90)	39.40 (4.79)	38.92 (5.09)	37.92 (5.79)	35.63 (6.97)	< 0.001	0(0.00)
C-reactive protein, mg/L	82.11 (88.49)	47.10 (70.95)	68.43 (82.60)	85.21 (86.89)	103.52 (94.43)	< 0.001	2760(82.4)
D-dimer, μg/L	3.69 (9.13)	1.88 (3.98)	2.67 (4.97)	4.48 (13.90)	5.02 (8.54)	< 0.001	1924(57.4)
Platelet, 10^9/L	156.02 (71.17)	149.44 (61.30)	153.79 (63.96)	154.60 (66.60)	166.27 (88.52)	< 0.001	0(0.00)
Lymphocyte count, 10^9/L	1.08 (0.72)	1.26 (0.63)	1.07 (0.78)	0.94 (0.53)	1.04 (0.85)	< 0.001	0(0.00)

SBP: systolic blood pressure; GCS: Glasgow Coma Scale

Table 2 Associations between NAR levels and mortality in patients with ICH

	NAR levels	Events/Total, *n* (%)	Unadjusted OR	*P*	Adjusted OR	*P*
Continuous	per SD	790/3350(23.6%)	1.93(1.76–2.10)	< 0.001	1.37(1.24–1.51)	< 0.001
Best cutoff	< 0.217	237/1722(13.8%)	1 [Reference]		1 [Reference]	
	> 0.217	553/1628(34%)	3.22(2.72–3.83)	< 0.001	1.58(1.28–1.95)	< 0.001
Quartile	Q1 (< 0.15)	96/838(11.5%)	1 [Reference]		1 [Reference]	
	Q2 (0.15–0.21)	131/837(15.7%)	1.43(1.08–1.90)	0.012	0.83(0.59–1.16)	0.280
	Q3 (0.21–0.30)	220/837(26.3%)	2.76(2.12–3.58)	< 0.001	1.19(0.87–1.63)	0.285
	Q4 (> 0.30)	343/838(40.9%)	5.36(4.16–6.90)	< 0.001	1.74(1.27–2.39)	0.001

The model was adjusted for age, Glasgow Coma Scale score, hematoma location, hematoma volume, and intraventricular hematoma

Association between NAR and mortality

A total of 790 patients (23.6%) died within 90 days. The association between NAR levels and 90-day mortality, higher NAR quartiles were associated with increased mortality risk, with Q4 showing some adjusted odds ratio (OR) of 1.74 (95% CI 1.27–2.39, $p = 0.001$) compared to Q1. The best NAR cutoff was 0.217; patients above this threshold had an adjusted OR of 1.58 (95% CI 1.28–1.95, $p < 0.001$) for 90-day mortality. (Table 2) Restricted cubic spline analysis (Fig. 1) demonstrated a linear increase in mortality risk with higher NAR levels.

ROC analysis showed that NAR had an AUC of 0.68 for predicting 90-day mortality. In comparison to other biomarkers, NAR outperformed Neutrophil-to-Lymphocyte Ratio (NLR) with an AUC of 0.66, while Neutrophil Count showed an AUC of 0.65. Albumin and Platelet-to-Lymphocyte Ratio (PLR) demonstrated lower AUC values, with AUCs of 0.60 and 0.51, respectively. These results suggest that NAR was the most effective biomarker among the ones tested in predicting 90-day mortality. (Fig. 2) The multivariable logistic regression model yielded an AUC of 0.812 (95% CI: 0.795–0.829), indicating strong discriminatory ability.The random forest

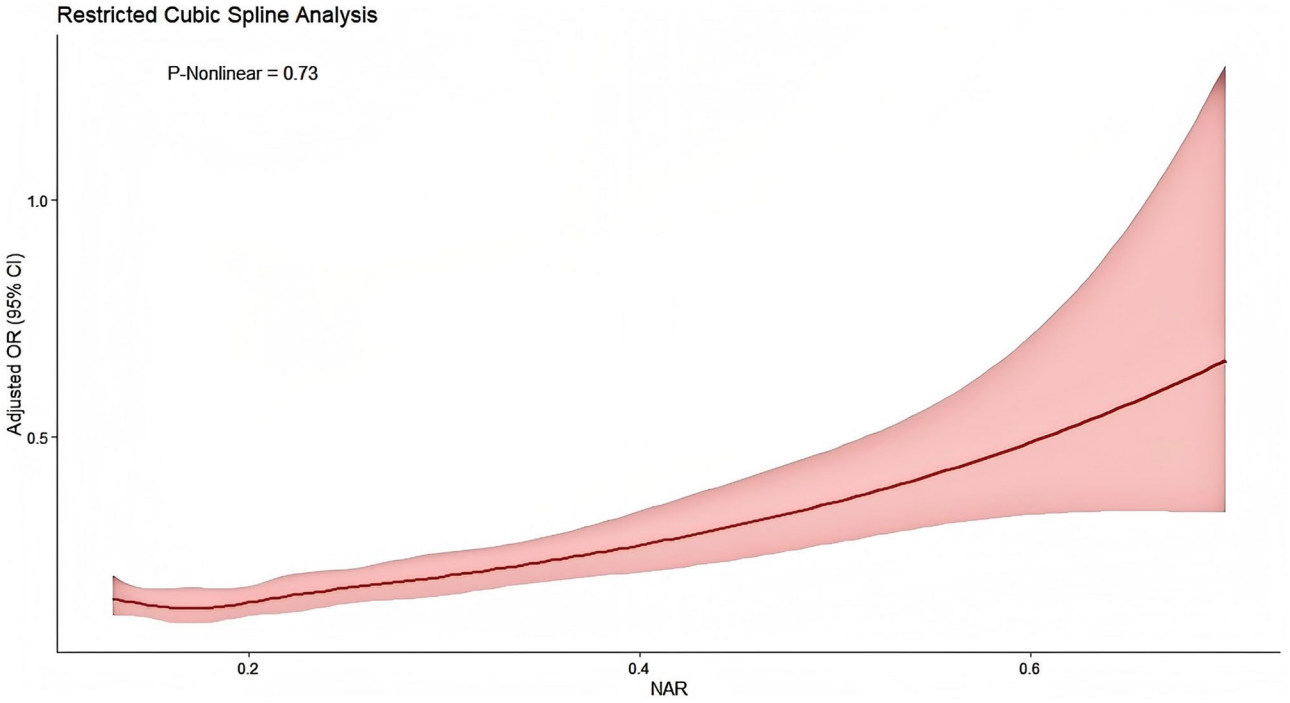

Fig. 1 The Restricted Cubic Spline Depicting the Odds Ratio of NAR Associated with Mortality among Patients with Intracerebral Hemorrhage. Abbreviations: NAR: Neutrophil-to-albumin ratio. (The x-axis represents NAR, while the y-axis depicts the hazard ratio of mortality. The model was adjusted for age, Glasgow Coma Scale score, hematoma location, hematoma volume, and intraventricular hematoma, with the FAR second quartile serving as the reference. Red indicates 95% CIs. OR: odds ratio)

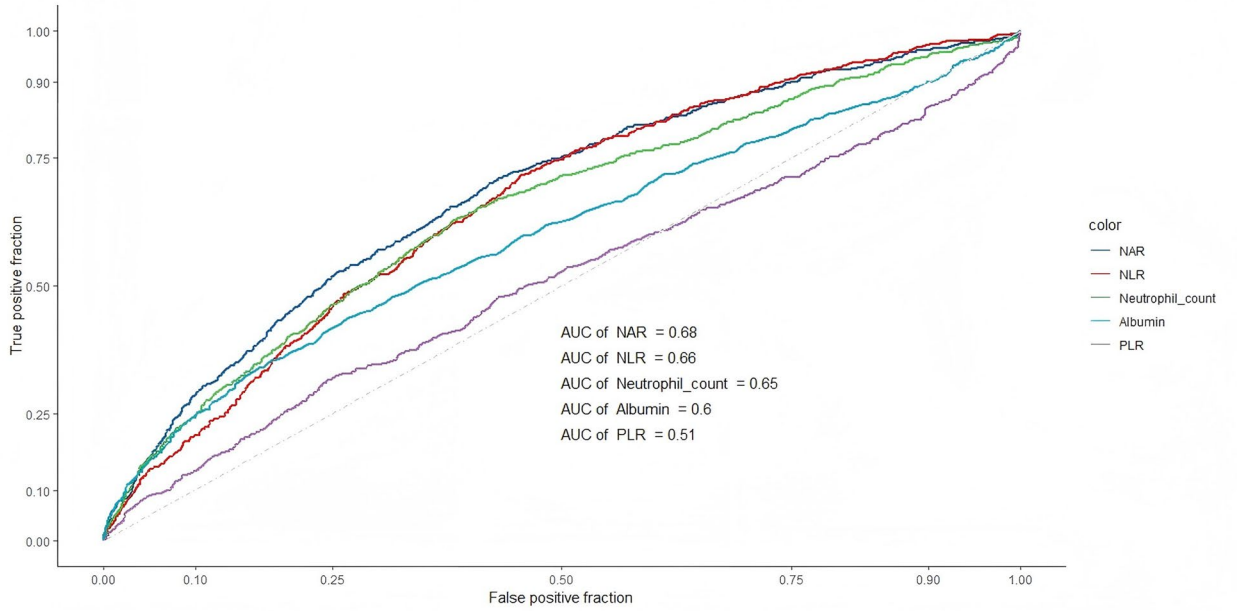

Fig. 2 The Receiver Operating Characteristic Curves Illustrating the Predictive Value of the NAR for Mortality. Abbreviations: NAR: Neutrophil-to-albumin ratio, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio

model demonstrated comparable performance, with an AUC of 0.803 (95% CI: 0.771–0.835). (Table 3). Additionally, the Random Forest model identified NAR as one of the most important predictors, indicating its robustness and potential clinical utility across different modeling approaches (Figure S4).

The violin plot illustrates the distribution of NAR levels stratified by 90-day mortality status. Patients in the

Table 3 Discriminatory performance of the logistic regression and random forest models for predicting mortality

Model	AUC (95% CI)
Random Forest Model	0.803 (0.771–0.835)
Multivariate logistic regression Model	0.812 (0.795–0.829)

mortality group ("Yes") had significantly higher median NAR levels compared to those in the survival group ("No"). The kernel density estimates indicate a broader and more pronounced peak in the mortality group, reflecting a skew towards higher NAR levels. The overlaid box plots further highlight significant differences in medians and interquartile ranges between the two groups, with the mortality group displaying a greater spread of elevated NAR values ($p < 0.001$). These visualized results underscore the strong association between elevated NAR levels and higher 90-day mortality risk (Figure S2).

Subgroup analyses revealed consistent associations between elevated NAR levels and higher 90-day mortality across patient characteristics, including age, sex, and comorbidities such as hypertension and diabetes. This association was particularly strong among patients with intraventricular hemorrhages and larger hematomas (Figure S3).

The multivariable logistic regression model yielded an AUC of 0.812 (95% CI: 0.795–0.829), indicating strong discriminatory ability. The random forest model demonstrated comparable performance, with an AUC of 0.803 (95% CI: 0.771–0.835). (Table 3). Additionally, the Random Forest model identified NAR as one of the most important predictors, indicating its robustness and potential clinical utility across different modeling approaches (Figure S4).

Multivariable logistic regression identified several significant predictors of 90-day mortality: age (adjusted OR 1.02, 95% CI 1.02–1.03, $p < 0.001$), infratentorial hematoma (adjusted OR 1.41, 95% CI 1.23–1.60, $p < 0.001$), intraventricular hematoma (adjusted OR 1.13, 95% CI 1.01–1.28, $p = 0.038$), hematoma size (adjusted OR 1.00 per cm^3, 95% CI 1.00–1.01, $p < 0.001$), and GCS score (adjusted OR 0.84, 95% CI 0.83–0.86, $p < 0.001$). Elevated NAR was a significant independent predictor, with an adjusted OR of 1.37 per standard deviation increase (95% CI 1.24–1.51, $p < 0.001$). (Table S3)

Discussion

The results of this study indicate a significant association between the neutrophil-to-albumin ratio (NAR) and mortality in patients with ICH, higher NAR values were associated with increased mortality, suggesting that NAR may be a useful prognostic indicator for predicting outcomes in ICH.

Previous studies have confirmed the association between Platelet-to-Lymphocyte Ratio (PLR) and Neutrophil-to-Lymphocyte Ratio (NLR) with mortality in patients with ICH [11–15]. For instance, Yuan et al. [14] found that there was a non-linear relationship between Platelet-to-Lymphocyte Ratio and 90-day mortality for patients with ICH, while Li et al. [15] demonstrated that Neutrophil-to-Lymphocyte Ratio was linked to increase in-hospital mortality. Unlike these studies that focused solely on inflammatory markers, our study has three major strengths. Firstly, our study evaluated multiple biomarkers and determined that NAR demonstrated the greatest predictive ability for mortality in ICH patients, as reflected by its superior AUC. Secondly, NAR is a comprehensive marker that integrates both inflammatory and nutritional status, making it a better indicator for assessing disease severity and overall systemic condition. Finally, our study is a multicenter investigation involving multiple hospitals and a large sample size, which helps capture a diverse patient population, providing greater statistical power and enhancing the robustness and generalizability of our findings.

A high NAR likely reflects stronger inflammation and poor nutritional status in ICH patients. Neutrophils, as early responders in inflammation, may indicate substantial immune stress [6], while low albumin levels are often indicative of malnutrition and systemic inflammation [16, 17], both linked to poor outcomes in critically ill patients. NAR, as a composite index, may better reflect ICH severity than neutrophil count or albumin alone, as it integrates both factors, capturing the complexity of the patient's systemic status. Clinicians can use NAR early in the course of ICH to help predict prognosis and support decision-making.

In addition to traditional biomarkers like NAR, machine learning (ML) models have been gaining increasing attention in clinical neurology for predicting outcomes in patients with intracerebral hemorrhage (ICH).A recent systematic review and meta-analysis highlighted the growing potential of ML algorithms, especially in predicting poor outcomes in patients with aneurysmal subarachnoid hemorrhage (aSAH). The study demonstrated that ML algorithms, particularly XGBoost and CatBoost, exhibited significant diagnostic performance, with a pooled sensitivity of 0.88 and an AUC of 0.82. These findings suggest that ML algorithms have a considerable advantage in predictive accuracy compared to traditional methods [18]. This suggests that combining machine learning (ML) models with biomarkers like NAR could enhance the ability to predict outcomes in patients with ICH. Future research could explore the integration of NAR with ML models to achieve more accurate and robust predictions, offering a promising approach for

improving clinical decision-making by providing both simplicity and predictive precision.

Our study has several limitations. Firstly, it is a retrospective study, which may introduce selection bias. Secondly, we had no access to the specific causes of death of the survivors, limiting our ability to explore the relationship between inflammation and specific disease risks, such as cardiovascular diseases or cancer. Thirdly, although we adjusted for multiple confounding variables, we acknowledge that unmeasured confounders such as surgical interventions or medication use may have affected patient outcomes. Lastly, the absence of dynamic NAR measurements means that only baseline values were assessed. Dynamic monitoring of NAR could provide more insight, as long-term NAR levels might indicate a persistent, chronic inflammatory condition.

Conclusion

In conclusion, our study indicated that a high level of NAR was associated with increased mortality in patients with ICH, providing crucial information for early risk assessment in clinical practice. NAR may be a useful marker for early risk assessment and treatment optimization. Future studies should validate these findings and assess how to incorporate NAR into clinical practice.

Abbreviations

AUC	Area Under the Curve
DBP	Diastolic Blood Pressure
GCS	Glasgow Coma Scale
ICH	Intracerebral Hemorrhage
NAR	Neutrophil-to-Albumin Ratio
NLR	Neutrophil-to-Lymphocyte Ratio
PLR	Platelet-to-Lymphocyte Ratio
ROC	Receiver Operating Characteristic
SBP	Systolic Blood Pressure

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04220-6.

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

Y.Z. developed the study concept and J.W. and Y.Z. conducted the statistical analysis. J.W. and S.Z. wrote the main manuscript text, and X.Y., X.C., H.L., F.Y., Y.A., and X.L. prepared Figs. 1 and 2. Y.L. and S.L. contributed to the study design and data interpretation. All authors reviewed and critically revised the manuscript for important intellectual content. All authors reviewed the final manuscript.

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Data availability

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the following ethics committees: Medical Ethics Committee of Sichuan University. (Approval No. 2021－624) Ethics Committee of the First People's Hospital of Longquanyi District, Chengdu (Approval No. AF-AK-2022010). This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Consent for publication

Not applicable. The requirement for informed consent was waived by the ethics committees in accordance with China's Regulations on Ethical Review of Biomedical Research Involving Humans (2016).

Competing interests

The authors declare no competing interests.

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