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Identifying Key Inflammatory Markers of Mortality in Acute Ischemic Stroke Using Logistic Regression Analysis

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Abstract

Aim: This study evaluates the prognostic significance of inflammatory markers in predicting in-hospital mortality among acute ischemic stroke (AIS) patients and constructs a logistic regression model to identify the most relevant predictors.

Materials and Methods: A retrospective analysis was conducted on 259 AIS patients. Laboratory findings were analyzed to compare survivors and non-survivors. To address potential multicollinearity, a correlation matrix and variance inflation factor analysis were applied to identify the most relevant inflammatory markers for logistic regression.

Results: Non-survivors exhibited significantly higher levels of C-reactive protein (CRP), CRP/albumin ratio (CAR), white blood cell count, neutrophil count, neutrophil/lymphocyte ratio, and platelet/lymphocyte ratio, while lymphocyte and albumin levels were lower. Univariable analysis identified albumin and CAR as key predictors, with albumin significantly associated with increased mortality risk [odds ratio (OR): 1.16, 95% confidence interval (CI): 1.081-1.253, $p<0.001$], whereas CAR was associated with reduced mortality (OR: 0.729, 95% CI: 0.589-0.902, $p=0.004$). However, in the final multivariable model, only albumin remained statistically significant (OR: 1.137, 95% CI: 1.043-1.240, $p=0.03$), suggesting its independent prognostic value.

Conclusion: Careful selection of variables for inclusion in the logistic regression model is crucial, as not all variables may exert a significant influence on survival or mortality outcomes. Albumin emerged as an independent predictor of in-hospital mortality in AIS patients, while other inflammatory markers lost significance in multivariable logistic regression analysis. This underscores the potential role of albumin in early risk stratification and prognosis.

Keywords: Acute ischemic stroke, emergency department, markers of inflammation, logistic regression analysis, accurate modeling, prognosis

Introduction

Acute ischemic stroke (AIS), accounting for approximately 87% of all stroke cases, is a critical medical emergency caused by the abrupt cessation of blood flow to a specific area of the brain, leading to neurological deficits (1). Mortality in AIS is influenced by various risk factors, including age, sex; comorbidities such as diabetes, hypertension, atrial fibrillation, and coronary artery disease; metabolic factors like high systolic blood pressure, elevated low-density lipoprotein and cholesterol levels, renal dysfunction, high body mass index; and the timing of interventions such as tissue plasminogen activator administration and endovascular thrombectomy (2-4). Despite these well-established prognostic factors, our study specifically aimed to assess the independent prognostic value of inflammatory markers, which are readily available at emergency department (ED) admission, and objectively measurable. This approach allows for a focused analysis of laboratory-based markers without the variability associated with clinical scoring systems.

The role of inflammation in AIS has gained growing attention due to its emerging significance in stroke outcomes. Inflammation exacerbates stroke severity by promoting secondary brain injury through mechanisms such as endothelial dysfunction, increased blood-brain barrier permeability, and the activation of pro-inflammatory cytokines (5,6). This process ultimately worsens patient outcomes by leading to cerebral edema, increased intracranial pressure, and further ischemic damage. For instance,

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elevated levels of markers such as C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and interleukin-6 have been linked to poor prognoses in AIS patients (7-10). Despite its recognized importance, studies specifically examining the prognostic value of inflammatory markers measured at the time of emergency admission remain limited. Therefore, identifying reliable inflammatory biomarkers is crucial for timely risk stratification in AIS patients.

Given this context, the present study focuses on evaluating the predictive value of inflammatory markers measured during ED admission in patients with AIS. Determining which biomarkers most effectively predict mortality could guide early risk stratification and improve patient management. To achieve this, we employed binary logistic regression, a statistical method commonly used for modeling binary outcomes such as survival or death (11). The accurate construction of logistic regression models is crucial for ensuring reliable predictions. Proper variable selection is essential because including irrelevant or highly correlated predictors may lead to misleading results. For instance, Yang et al. (12) highlighted the importance of appropriate variable selection in improving logistic regression model accuracy when predicting heart failure risk factors. Similarly, Bélanger et al. (13) demonstrated that selecting clinically significant variables enhanced prediction accuracy in models assessing Alzheimer's disease risk. These examples underscore the direct relationship between variable selection and the predictive power of a logistic regression model.

Additionally, addressing multicollinearity where predictors are highly correlated is vital for maintaining stable coefficient estimates and ensuring the statistical reliability of the model. As Algamal and Hammood (14) emphasized, failure to manage multicollinearity can compromise the validity of logistic regression results by inflating standard errors and producing unstable coefficients.

Thus, this study aims to identify key inflammatory markers associated with in-hospital mortality in AIS patients and construct a robust logistic regression model to evaluate their prognostic value. By focusing on both clinical relevance and statistical robustness, we aim to contribute to more effective risk stratification strategies and improve early clinical decision making in the ED setting.

Materials and Methods

Study Design and Patient Selection

This study was initiated with the approval of Niğde Ömer Halisdemir University Non-Interventional Clinical Research Ethics Committee (decision number: 2024/123, date: 12.12.2024). This retrospective study included 259 patients admitted to the ED of Niğde Training and Research Hospital between October 1, 2021, and October 1, 2023, with a confirmed diagnosis of AIS. Patient identification was performed through a systematic review of hospital electronic medical records using the International Classification of Diseases codes related to AIS. Medical records were reviewed to verify diagnoses through clinical findings supported by radiological findings such as brain computed tomography and diffusion magnetic resonance imaging. Patients aged 18 years and older with a definitive AIS diagnosis were eligible for inclusion. Inclusion criteria required accessible hospital records, hospitalization with an AIS diagnosis, and complete laboratory data. Severe chronic diseases, including terminal cancer, end-stage renal failure, and advanced liver failure, were excluded because they can trigger persistent systemic inflammation, potentially influencing inflammatory indices NLR, [CRP/albumin ratio (CAR), platelet/lymphocyte ratio (PLR), and neutrophil/platelet ratio (NPR)] and obscure the relationship between stroke-related inflammation and mortality outcomes. Additionally, patients with hemorrhagic stroke, acute trauma, or incomplete hospital records were excluded.

Operational Definitions

The following formulas were used to calculate the inflammatory indices:

NLR: Neutrophil count (10^3/μL)/Lymphocyte count (10^3/μL)

CAR: C-reactive protein (mg/dL)/Albumin (g/dL)

PLR: Platelet count (10^3/μL)/Lymphocyte count (10^3/μL)

NPR: Neutrophil count (10^3/μL)/Platelet count (10^3/μL)

Statistical Analysis

The Shapiro-Wilk test was applied to determine the normality of the data distribution, revealing that all quantitative data exhibited a non-parametric distribution. Descriptive statistics are expressed as medians (interquartile range: 25-75 percentiles) for continuous quantitative variables, while categorical variables are presented as frequencies and percentages. Pearson's chi-square test or Fisher's exact test was used to compare categorical variables. The Mann-Whitney U test was applied for comparisons of non-parametric continuous variables. Binary logistic regression analysis was conducted using the enter method to evaluate factors affecting mortality. Correlation analysis using Spearman's rho test was performed to detect multicollinearity among variables. Variables showing a high degree of correlation were reviewed, and one was excluded to avoid redundancy, ensuring that only the most representative variable was included in the logistic regression model. Both univariable and multivariable

logistic regression analyses were conducted to identify the most predictive inflammatory markers for mortality. All data were recorded using Microsoft Excel (2010, Redmond, WA, USA), and statistical analyses were performed using IBM SPSS Statistics Version 27 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p<0.05$.

Testing the Multicollinearity Problem for Logistic Regression Analysis

To detect multicollinearity, attention should be paid to highly correlated pairs of variables in the correlation matrix. Typically, a correlation coefficient of 0.7 or above indicates a multicollinearity problem (15). Furthermore, a variation inflation factor (VIF) of >10 indicates a high probability of multicollinearity, and it is recommended to exclude variables with high VIF values from the model (16). In this context, if two variables showed a correlation coefficient of $|r| > 0.7$, or VIF value > 10, indicating a high degree of collinearity, the variable with less clinical relevance or weaker association with the outcome, based on previous literature, was excluded to improve model stability and interpretability.

Results

The relationships between demographic, clinical, and laboratory characteristics and mortality in patients with AIS are presented in Table 1. In total, 259 patients were included in this study (Table 1). The median age of the patients was 75 years (67-82); it was 75 years (66-80) in survivors and 83 years (71-90) in deceased patients, and this difference was statistically significant (p=0.001). Male patients constituted 58.7% of the entire group, 60.5% of the survivors, and 47.2% of the deceased patients (p=0.186). In laboratory data, white blood cell (WBC) count was significantly higher in the deceased group, with a median of 8.50 (6.81-10.49) in survivors and 9.86 (7.75-12.07) in deceased patients (p=0.025). Similarly, the neutrophil count was significantly higher in the deceased median: 7.67 (4.63-10.14). In survivors, it was 5.34 (4.30-6.98) (p=0.005). In terms of lymphocyte count, the median was 1.38 (1.01-1.69) in the deceased and 1.79 (1.25-2.55) in the survivors, and this difference was significant (p=0.004). The median albumin level was 42 g/L (a range of: 39-44) among the survivors and 38 g/L (a range of: 34-41) among the deceased group, showing a significant difference (p<0.001). CRP values were significantly higher in the deceased group (median: 11.90, 2.67-68.07) compared to the survivors (median: 3.40, 1.70-9.40) (p=0.002). Among the inflammatory indices, NLR was higher in the deceased group median: 5.52 (2.67-11.44) and in the survivors median: 2.92 (1.82-5.39) (p=0.001). Similarly, PLR and CAR were significantly higher in the deceased group (p=0.004 and p=0.001, respectively). The length of hospital stay was longer in patients who died 10 days (5-22.25) vs. 5 days (3-9), p<0.001. There was no significant difference between the groups in terms of NPR values (p=0.557).

Variable Selection and Multicollinearity Management

Accordingly, the correlation analysis revealed high correlations between WBC and neutrophils (r=0.846, p<0.001; VIF for WBC: 1.760, VIF for neutrophil: 8.245), CRP and CAR (r=0.997, p<0.001;

Table 1. Association of demographic, clinical and laboratory characteristics with mortality in patients with acute ischemic stroke

Parameters	Mortality		p value
	Yes n=36	No n=223	
Age	83 (71-90)	75 (66-80)	<0.001
Sex, n (%) Male Female	 17 (47.2) 19 (52.8)	 135 (60.5) 88 (39.5)	0.186
Length of hospitalization (days)	10 (5-22.25)	5 (3-9)	<0.001
WBC (x10^3/µL)	9.86 (7.75-12.07)	8.50 (6.81-10.49)	0.025
CRP (mg/dL)	11.90 (2.67-68.07)	3.40 (1.70-9.40)	0.002
Neutrophils (x10^3/µL)	7.67 (4.63-10.14)	5.34 (4.30-6.98)	0.005
Platelets (x10^3/mL)	340 (258-452)	289 (190-426)	0.066
Lymphocytes (x10^3/µL)	1.38 (1.01-1.69)	1.79 (1.25-2.55)	0.004
Albumin (mg/dL)	38 (34-41)	42 (39-44)	<0.001
NLR	5.52 (2.67-11.44)	2.92 (1.82-5.39)	0.001
CAR	0.33 (0.07-1.75)	0.08 (0.40-0.22)	0.001
PLR	240.54 (136.32-380.75)	159.42 (96.05-267.61)	0.004
NPR	0.209 (0.014-0.035)	0.0194 (0.012-0.032)	0.557

Continuous data are presented as median (interquartile range: 25-75). WBC: White blood cell, CRP: C-reactive protein, NLR: Neutrophil/lymphocyte ratio, CAR: C-reactive protein/albumin ratio, PLR: Platelet/lymphocyte ratio, NPR: Neutrophil/platelet ratio

VIF for CAR: 28.956, VIF for CRP: 27.618), neutrophil count and NLR (r=0.720, p<0.001; VIF for neutrophil: 8.245, VIF for NLR: 7.253), and neutrophils and NPR (r=0.773, p<0.001; VIF for neutrophil: 8.245, VIF for NPR: 6.071), raising the possibility of multicollinearity. Based on the correlation matrix and VIF values, it was deemed appropriate to include neutrophils as a more direct marker of inflammation, CAR as a more comprehensive inflammatory marker, and NLR as a comparative marker. In addition, albumin, which has a statistically significant effect on mortality and does not exhibit multicollinearity, was included in the model. Finally, PLR, which is a more clinically relevant marker than NPR, was included in the model. Consequently, neutrophils, CAR, NLR, PLR, and albumin were preferred in the proposed model (VIF values: 3.200, 1.414, 4.651, 2.031, and 1.288, respectively).

Univariable and Multivariable Modeling

The results of binary logistic regression analysis of the five parameters included in the model are presented in Table 2. In the univariable model, each unit increase in neutrophil count and CAR, NLR, and PLR levels increased the risk of mortality and decreased the probability of survival. In contrast, an increase in albumin levels has a decreasing effect on mortality risk and an increasing effect on survival probability.

In the multivariable model, albumin level was the only variable significantly associated with mortality risk, while other factors, including neutrophil count, CAR, NLR, and PLR, showed no statistically significant impact. Given its strong association with mortality, albumin emerged as the most critical factor contributing to survival. Model fit analysis revealed a -2 log likelihood value of 184.353 and a Nagelkerke R^2 value of 0.163, indicating that the variables in the final model explained 16.3% of the variance in mortality risk (Table 2).

Discussion

This study evaluated the association between inflammatory markers measured at emergency admission and in-hospital mortality among patients with AIS using a binary logistic regression model. The results highlight the prognostic value of albumin and CAR in predicting mortality risk. Univariable analysis indicated that elevated neutrophil count, CAR, NLR, and PLR were associated with an increased mortality risk, whereas higher albumin levels were protective. However, in the multivariable model, only albumin retained statistical significance, underscoring its critical role in patient survival.

The protective effect of albumin aligns with its established anti-inflammatory and neuroprotective properties (17,18). Its inverse association with mortality risk supports its role as a negative acute phase reactant. Hypoalbuminemia may reflect a heightened inflammatory response and compromised nutritional status, which are both associated with adverse AIS outcomes (19). The prominence of albumin as a strong independent predictor in multiple analyses emphasizes that it is a potential biomarker for in-hospital mortality risk. This may make an important contribution to clinical practice and suggests that routine monitoring of albumin levels may play a role in the management of serious diseases, particularly stroke. This finding corroborates previous research demonstrating that lower albumin levels predict worse survival across various acute medical conditions. Although CAR emerged as a strong mortality indicator in the univariable model, its statistical significance was diminished in the multivariable analysis. This outcome likely reflects its inherent correlation with albumin, which is a key component of the CAR calculation. Similarly, while NLR and PLR were significant predictors in univariable analysis, their effects weakened after adjustment, suggesting multicollinearity as a contributing factor.

Systemic inflammation plays a significant role in stroke severity, influencing both acute and long-term outcomes. Elevated levels of inflammatory markers have been linked to worse functional recovery and increased mortality following both ischemic and hemorrhagic strokes (20,21). Numerous studies in the literature highlight the prognostic value of these inflammatory indices in AIS, although their applicability may vary depending on the

Table 2. Logistic regression model

Variable	Univariable model		Multivariable model*	
	OR (95% CI)	p value	OR (95% CI)	p value
Neutrophil	0.900 (0.833-0.973)	**0.008**	0.974 (0.837-1.133)	0.729
CAR	0.729 (0.589-0.902)	**0.004**	0.965 (0.751-1.240)	0.780
NLR	0.920 (0.873-0.970)	**0.002**	0.920 (0.858-1.100)	0.646
PLR	0.998 (0.996-0.999)	**0.007**	0.999 (0.996-1.001)	0.291
Albumin	1.164 (1.081-1.253)	**<0.001**	1137 (1.043-1.240)	**0.003**

Model summary: Nagelkerke R square: 0.163, Hosmer and Lemeshow test, the chi-square: 3.614, sig. (p): 0.890 CAR: C-reactive protein/albumin ratio, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, CI: Confidence interval, OR: Odds ratio CI: Confidence interval

patient population and study context (22-24). For instance, several investigations have found that elevated NLR levels are associated with poorer functional outcomes and higher mortality rates in AIS patients (9,10). However, unlike these studies, the present research found, albumin to be the only significant independent predictor of mortality in multivariable analysis, despite the initial significance of markers like CAR and NLR. Again, this finding underlines the importance of considering albumin not merely as part of CAR but as an independent indicator of prognosis. Vo et al. (25) reported that elevated WBC levels in patients with acute ischaemic stroke increased the risk of death and new vascular events after adjustment for infection. The present study also found that WBC and neutrophil counts were significantly higher in deceased patients, which is consistent with the role of systemic inflammation in stroke severity. While these markers were excluded owing to multicollinearity, their significance underscores the need for future studies exploring more comprehensive inflammatory profiles.

Furthermore, a statistically significant effect of advanced age on mortality was observed, which was hypothesized to be primarily attributable to frailty and diminished physiological reserves associated with senescence. Although the sex differences were not statistically significant, subsequent investigations in larger cohorts may elucidate potential gender-related disparities. Additionally, in a study by Labán-Seminario et al. (26), prolonged hospitalization in patients with ischemic stroke was associated with increased mortality. In our study, the duration of hospitalization was longer in patients who died. This is probably due to the severity of the disease at baseline and complications that arise during treatment.

Finally, future research should include larger multicenter cohorts and dynamic monitoring of inflammatory markers to capture their temporal evolution. Studying the interactions between albumin and other biomarkers may provide a more comprehensive understanding of the risk of inflammation-induced mortality in AIS.

Study Limitations

This study has several limitations. The most significant limitation is that, although various clinical and demographic factors influence AIS mortality, this study specifically focused on laboratory-based inflammatory markers to assess their independent prognostic value. While data on age, sex, and length of hospital stay were available, they were not included in the final multivariable regression model. This decision was made to maintain the focus on inflammatory indices and avoid potential collinearity or distort the impact of inflammatory parameters, which could have affected the generalizability of the findings.

Another important limitation was the lack of stroke severity scores, such as the National Institutes of Health Stroke Scale and modified Rankin Scale, which are widely used prognostic indicators. As these scores were not systematically recorded for all patients, their inclusion in the model could have introduced selection bias and affected the validity of the results. Additionally, inflammatory markers were measured only at hospital admission, making it impossible to assess the changes over time.

The single-center nature of this study may also limit the generalizability of the findings to broader populations. Finally, as this was an observational study, it does not allow for definitive conclusions regarding causality. Future research should integrate both inflammatory biomarkers and clinical severity scores to develop a more comprehensive prognostic model for AIS mortality.

Conclusion

This study highlights albumin level as an independent predictor of in-hospital mortality in patients with AIS. While inflammatory indices such as CAR, NLR, and PLR offer valuable initial insights, the consistent significance of albumin underscores its clinical utility for risk stratification. Routine albumin assessment in emergency settings can facilitate early risk evaluation and guide treatment strategies in patients with AIS.

Ethics

Ethics Committee Approval: This study was initiated with the approval of Niğde Ömer Halisdemir University Non-Interventional Clinical Research Ethics Committee (decision number: 2024/123, date: 12.12.2024).

Informed Consent: This retrospective study included 259 patients admitted.

Footnotes

Authorship Contributions

Concept: A.V., Design: A.V., Data Collection or Processing: A.V. M.O.C., Analysis or Interpretation: A.V. M.O.C., Literature Search: A.V. M.O.C., Writing: A.V. M.O.C.

Conflict of Interest: The authors declare that they have no conflict of interest.

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