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Original Article

Decreased albumin to INR ratio is a prognostic marker of 30-day mortality in neonatal sepsis: a retrospective study

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Abstract

Introduction: Neonatal sepsis is a leading cause of neonatal mortality. This study aims to assess the clinical significance of the serum albumin (ALB) to international normalized ratio (INR) ratio (AIR) as a predictor for 30-day mortality in neonates with sepsis.

Methodology: Neonates diagnosed with sepsis between January 2019 and December 2022 were included. Admission data were collected, enabling the categorization of neonates into survival and non-survival groups. Logistic regression analyses and receiver operating characteristic (ROC) curves, were employed.

Results: A total of 195 neonates with sepsis were analyzed. The non-survival group exhibited significantly lower AIR compared to the survival group. Multivariate analysis identified low AIR as an independent risk factor (hazard ratio [HR]: 9.091, $p < 0.001$), achieving an area under the curve (AUC) of 0.746 for AIR. The sensitivity and specificity of AIR were 79.31% and 66.87%, respectively.

Conclusions: AIR serves as a cost-effective and easily obtainable marker in neonatal sepsis research. It emerges as an independent predictor of adverse outcomes in neonatal sepsis, demonstrating good predictive capabilities.

Key words: Albumin; international normalized ratio; mortality; neonatal sepsis; prognosis.

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Introduction

Neonatal sepsis is a critical infectious condition caused by pathogenic bacteria entering the bloodstream of infants within the first four weeks of life [1]. The clinical presentation of neonatal sepsis is nonspecific and frequently involves multiple organ dysfunctions, which can lead to mortality [2]. Current treatments include antibiotic therapy and supportive care designed to alleviating symptoms and improving the condition of affected infants [3]. Nonetheless, due to the immaturity and compromised immune function in neonates, high mortality rates persist despite these interventions [4]. Consequently, there is a pressing need for more rational and effective treatment strategies to mitigate mortality risks [5]. Additionally, the diagnostic challenges associated with nonspecific symptoms, prolonged blood culture times, and low positivity rates have spurred extensive research into early and reliable biomarkers for neonatal sepsis diagnosis and prognosis. Promising markers under investigation include antithrombin III, cytokine profiles, as well as the C-reactive protein-to-albumin ratio (CAR) [6-12].

Serum albumin (ALB), as an important nutrient in the body, is closely related to inflammatory response. Some studies have suggested that the serum albumin level is negatively correlated with the severity of sepsis [13,14]. International normalized ratio (INR) is routinely used to evaluate the coagulation status of patients for adjusting therapy. Coagulation dysfunction is one of the important pathological mechanisms of neonatal sepsis, and almost all patients with sepsis have coagulation abnormalities [15]. INR /albumin ratio has been reported to be associated with prognosis of patients with sepsis, upper gastrointestinal bleeding, and liver cirrhosis [16-18]. However, the value of this ratio in neonates, particularly in the context of cirrhosis and upper gastrointestinal bleeding, remains uncertain and has not been previously mentioned. Given the significance of INR in assessing coagulation disorders and its alterations in the setting of liver failure, which are pertinent to sepsis, we postulate that the ALB to International Normalized Ratio (INR) ratio (AIR) could be a crucial prognostic marker for predicting 30-day mortality in neonates with sepsis. To our knowledge, no

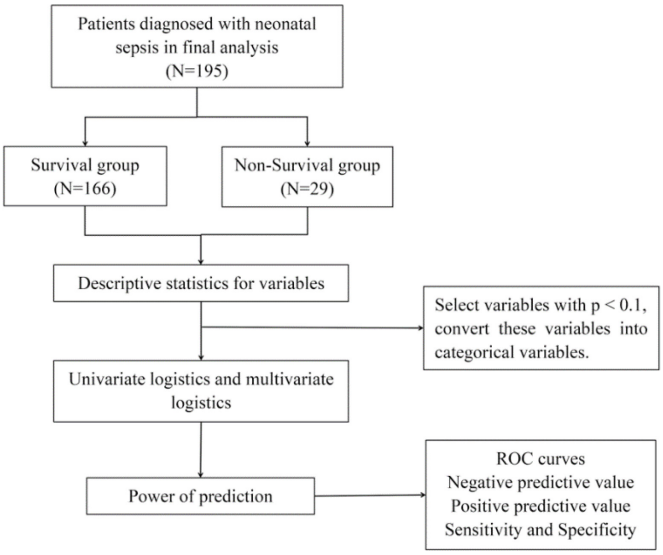
relevant studies have been conducted to evaluate the correlation between AIR and neonatal sepsis. In addition, no additional testing and cost are needed, as AIR is a cheap and easy-to-obtain marker, which was based on the routine measurement. Therefore, the aim of this study was to explore the association between AIR and the 30-day mortality in neonatal sepsis and provide guidance in clinical evaluation, prognosis and treatment of neonatal sepsis.

Methodology

Patients

This retrospective study encompassed hospitalized newborns diagnosed with neonatal sepsis between January 2019 and December 2022. Inclusion criteria adhered to the International Consensus on Pediatric Sepsis, which defines neonatal sepsis as a systemic inflammatory response syndrome with either suspected or confirmed infection [19]: 1) infants displaying sepsis signs with positive blood culture results or DNA evidence of pathogenic bacteria in the blood; 2) infants presenting sepsis symptoms and meeting two of the screening criteria—abnormal C-reactive protein (CRP), total white blood cell, platelet, neutrophil, or an immature neutrophil/total neutrophil ratio exceeding 0.2. Non-sepsis status was assigned when both blood cultures and sepsis screening tests yielded negative results. Following application of inclusion criteria and exclusion of cases with unknown medical histories, population received protein or blood product treatments or incomplete laboratory examinations, 195 infants with neonatal sepsis were included (Figure 1). Ethical approval for the study was granted by the local hospital's Ethics Committee, and the study was conducted in compliance with the guidelines of the Declaration of Helsinki (2023-007).

Figure 1. Analytical flow for identifying risk factors of 30-day mortality in neonatal sepsis.



Data collection

Patients' clinical data, including gender, age, gestational age, weight, 5-minute and 10-minute Apgar scores, were collected from our hospital's electronic medical record system. Upon admission, venous blood samples were collected from the patients and sent to the laboratory for testing. Routine complete blood count (including white blood cell count (WBC), platelet count (PLT), neutrophil count and lymphocyte count) was measured using an automatic hematology analyzer (Mindray BC-7500CS); Coagulation tests, which included prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and international normalized ratio (INR), were measured by an automatic coagulation analyzer (Mindray EXC810); Albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea (UREA), and creatinine (CREA), C-reactive protein (CRP) and other biochemical indicators were measured using an automatic biochemical analyzer (Germany Roche cobas8000). AIR was calculated using the formula ALB/INR. Patients were followed for 30 days to evaluate survival. Data on mortality were obtained from medical records or by telephone.

Statistical analysis

Data were analyzed using SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk method was employed to assess the normality of the data. For measurement data that followed a normal distribution, the mean ± standard deviation was reported, whereas for non-normal distributions, the median was used, and measurement data were expressed as cases and percentages. Baseline data between the two groups were compared using the T-test, Chi-square test, and Mann-Whitney U test. Independent risk factors for mortality were identified through logistic regression analyses. The predictive value of AIR for neonatal sepsis was evaluated using receiver operating characteristics curves (ROC). The optimal cutoff values were assessed using the Youden index. Statistical significance was set at $p < 0.05$.

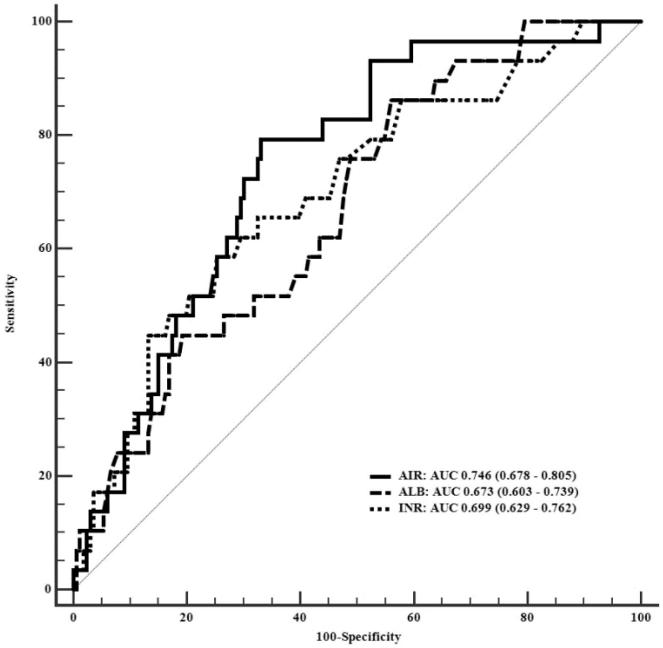
Results

Baseline characteristics

The study encompassed a total of 195 neonates diagnosed with neonatal sepsis, among which 29

(14.9%) died. The neonates were categorized into two groups: the survival group (n = 166) and the non-survival group (n = 29). Of the 195 cases, 123 were male, with 17 deaths, and 72 were female, with 12 deaths. There were no significant differences in gender, age, gestational age, body weight, and Apgar scores between the two groups (all $p > 0.05$). Similarly, there were no significant disparities in laboratory test indices such as CRP, WBC, neutrophil, lymphocyte, ALT, AST, CREA, APTT, and TT between the groups (all $p > 0.05$). In contrast, several clinical parameters were significantly different between the non-survival and survival groups. Specifically, PLT (181.38 × 10/L vs. 265.81 × 10/L) and UREA (2.91 mmol/L vs. 1.38 mmol/L) were significantly lower in the non-survival group compared to the survival group (all $p < 0.05$). Conversely, ALB (31.2 g/L vs. 33.4 g/L), PT (17.4 s vs. 13.7 s), and INR (1.51 vs. 1.18) were significantly higher in the non-survival group compared to the survival group (all $p < 0.05$). Additionally, AIR was also significantly lower in the non-survival group compared to the survival group (20.424 vs. 28.273) ($p < 0.001$) (Table 1). Furthermore, in the survival group, the incidence rates of respiratory distress syndrome, hyperbilirubinemia, purulent meningitis, and pneumonia did not significantly differ from those in the non-survival group (all $p > 0.05$) (Table 1).

Figure 2. Area under the curves (AUC) of factors for predicting mortality.



ALB: albumin; INR: international normalized ratio; AIR: ALB/INR.

Table 1. Characteristics of patients.

General	Total (n = 195)	Survivor (n = 166)	Nonsurvivor (n = 29)	*p*
Gender (male/female), n	123/72	106/60	17/12	0.521
Median age (range), day	3 (1, 28)	3 (1, 27)	5 (1, 28)	0.407
Gestational age at birth (weeks)	38.0 (28.0, 41.0)	38.5 (29.0, 41.0)	38.0 (27, 41)	0.671
Weight (g)	3000 (1100, 3800)	3050 (1090, 3860)	2625 (1088, 3510)	0.351
Apgar score (1 min)	10 (5, 10)	10 (5, 10)	9 (4.5, 10)	0.570
Apgar score (5 min)	10 (8, 10)	10 (8, 10)	10 (9, 10)	0.299
Respiratory distress syndrome, n	41/154	34/132	7/22	0.816
Hyperbilirubinemia, n	37/158	31/135	6/23	0.642
Purulent meningitis, n	47/148	41/125	6/23	0.254
Pneumonia, n	59/136	49/117	10/19	0.410
Culture positive, n (%)	56 (28.7)	50 (30.1)	6 (20.1)	0.070
CRP (mg/L)	8.9 (0.1, 103.8)	7.85 (0.1, 96.4)	20.6 (0.1, 152.3)	0.187
WBC ($\times 10^9$/L)	11.48 (3.77, 25.88)	11.63 (4.14, 25.04)	10.52 (2.47, 26.18)	0.930
Lymphocyte ($\times 10^9$/L)	3.74 ± 2.16	3.66 ± 1.80	4.23 ± 3.62	0.309
Neutrophil ($\times 10^9$/L)	6.01 (1.77, 18.23)	6.01 (1.91, 18.39)	6.87 (1.36, 17.98)	0.656
Hemoglobin (g/L)	148 (95.5, 189)	149 (99.0, 190.6)	133 (91.5, 182.0)	0.066
Platelet ($\times 10^9$/L)	253.26 ± 130.44	265.81 ± 128.97	181.38 ± 116.54	0.001
ALT (U/L)	10 (3.00, 62.50)	10 (3.0, 44.0)	14 (3.0, 580.8)	0.001
AST (U/L)	39 (15.0, 268.6)	37 (14.1, 191.4)	48 (15.8, 1791.2)	0.003
UREA (mmol/L)	3.8 (1.52, 11.08)	3.55 (1.38, 9.82)	5.25 (2.91, 18.42)	< 0.001
CREA (μmol/L)	45.5 (18.2, 110.0)	44 (18.8, 98.0)	55.5 (14.7, 145.3)	0.050
PT (s)	14 (10.8, 25.3)	13.7 (10.8, 23.0)	17.4 (11.6, 31.3)	< 0.001
INR	1.21 (0.93, 2.22)	1.18 (0.93, 2.01)	1.51 (1.00, 2.89)	< 0.001
APTT (s)	52.8 (33.8, 111.3)	52.5 (33.9, 110.6)	57.6 (32.9, 112.3)	0.259
TT (s)	18.6 (15.2, 30.9)	18.5 (15.2, 27.8)	19.4 (15.2, 54.2)	0.001
ALB (g/L)	33.0 (25.3, 39.8)	33.4 (25.5, 40.1)	31.2 (21.4 to 36.6)	0.001
AIR	26.618 (12.456, 38.260)	28.273 (13.222, 38.764)	20.424 (10.095, 30.701)	< 0.001

ALB: Albumin; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AIR: serum albumin to international normalized ratio (INR) ratio; AST: aspartate aminotransferase; CRP: C-reactive protein; CREA: creatinine; INR: international normalized ratio; PLT: platelet; PT: prothrombin time; TT: thrombin time; UREA: urea nitrogen.; WBC: white blood cell

Table 2. Analysis of in-hospital death.

Variables	Univariate analyses			Multivariate analyses		
	HR	95% CI	*p*	HR	95% CI	*p*
Culture positive	2.695	0.891- 8.130	0.076			
Hemoglobin ≤ 133 g/L	2.855	1.279 - 6.377	0.011	3.236	1.280 - 8.197	0.013
Platelet ≤ 244 × 10^9/L	4.762	1.925 -11.778	< 0.001			
AST > 41 U/L	2.014	0.850 - 4.769	0.111			
ALT > 32 U/L	5.775	2.163 - 15.415	0.001			
UREA > 2.9 mmol/L	13.378	1.771- 101.045	0.001	8.044	1.018-63.538	0.048
CREA > 71 μmol/L	3.291	1.394 - 7.768	0.009			
PT > 16.6s	4.613	2.029 - 10.490	< 0.001			
INR > 1.45	4.183	1.846 - 9.474	0.001			
TT > 18.35	2.786	1.129 - 6.876	0.026			
ALB ≤ 33.9 g/L	4.904	1.635 - 14.724	0.002			
AIR ≤ 24.712	7.736	2.978 - 20.101	< 0.001	9.091	3.106 - 26.316	< 0.001

ALB: albumin; ALT: alanine aminotransferase; AIR: serum albumin to international normalized ratio (INR) ratio; AST: aspartate aminotransferase; CI: Confidence interval; CREA:creatinine; HR: hazard ratio; INR: international normalized ratio; PT: prothrombin time; TT: thrombin time; UREA: urea nitrogen.; Bold values indicate statistical significance ($p < 0.05$).

Low AIR as an independent predictor of 30-day mortality

Univariate and multivariate logistic regression analyses revealed that AIR was an independent and significant predictor of 30-day mortality. We initially selected variables with a $p < 0.1$ in Table 1 and converted them into categorical variables for univariate logistic analysis. Variables with a $p < 0.05$ in the univariate logistic analysis were included in the multivariate logistic analysis (Figure 1). Even after adjusting for confounding variables such as hemoglobin, ALT, AST, PT, INR, and ALB, the significant association between AIR and 30-day mortality was maintained. This finding is detailed in Table 2.

Clinical value of AIR in prediction of 30-day mortality in neonatal sepsis

ROC was established to assess the ability of AIR to predict neonatal sepsis mortality. Results showed that the area under the ROC curve (AUC) of AIR for predicting the 30-day mortality of neonatal sepsis was 0.746 (95% CI 0.678-0.805), better than that of ALB and INR. In addition, the best cut-off value 24.7 was selected, the sensitivity was 79.31% and the specificity was 66.87% (Figure 2, Table 3).

Discussion

Neonatal sepsis is a widespread and severe condition in neonatal intensive care units, significantly contributing to the escalating global medical burden [20]. A systematic review reveals that the incidence of neonatal sepsis is notably high, with 2842 cases per 100,000 live births, and the mortality rate stands at a significant 17.6% [21]. Our study corroborates these findings, with 58.6% of deceased neonates being male and 41.4% female, reporting a mortality rate of 14.8%.

Albumin is a vital nutrient that helps maintain plasma osmotic pressure and serves as a carrier for substances in blood circulation [22]. It also mitigates inflammatory damage by modulating the inflammatory response and immune repair through anti-oxidative stress, binding and transporting inflammatory substances, and mediators [23]. Early-stage sepsis with low serum albumin suggests poor nutritional status and a heightened risk of severe infection. As sepsis progresses, the release of numerous inflammatory cytokines damages vascular endothelial cells, enhances vascular permeability, and leads to intravascular albumin leakage, significantly reducing serum albumin levels [24]. During sepsis, a low serum albumin concentration signifies increased vascular leakage. Conversely, diminished albumin levels can lower plasma colloid osmotic pressure, leading to fluid imbalances and a reduced effective circulating blood volume [25]. This can precipitate multiple organ dysfunction, posing a life-threatening risk to patients. Recent studies have shown that an elevated Fibrinogen-to-Albumin Ratio is associated with the severity of neonatal sepsis [26], while another study indicates that decreased albumin levels are related to the risk of developing neonatal sepsis [27]. These findings are

Table 3. The diagnostic efficacy of AIR, ALB and INR in neonatal sepsis.

Indicator	AUC	Cut-off	Sensitivity (%)	Specificity (%)	PPV	NPV
AIR	0.746	24.7	79.31	66.87	29.5	94.9
ALB	0.673	33.9	86.21	43.98	21.2	94.8
INR	0.699	1.45	58.62	74.70	28.8	91.2

ALB: albumin; AIR: serum albumin to international normalized ratio (INR) ratio; INR: international normalized ratio; NPV: negative predictive value; PPV: positive predictive value.

consistent with our study, in which the non-survival group exhibited lower albumin levels upon admission, indicative of a poorer nutritional status, as albumin is a well-established marker of nutritional health. The change in albumin correlated with the extent of inflammatory damage, thereby forecasting a poor prognosis.

Abnormal coagulation function is prevalent among neonatal sepsis patients, varying from minor coagulation index abnormalities to the life-threatening condition of disseminated intravascular coagulation (DIC) [15,28]. Sepsis-induced coagulopathy, often termed consumptive coagulopathy, occurs when pathogenic bacteria invade the bloodstream, triggering a systemic inflammatory response that damages endothelial cells. This results in increased production and release of pro-coagulants, consuming substantial platelets and coagulation factors [29]. Decreased FVII and FIX activity effectively predicts sepsis mortality [30]. Recent studies have shown that higher INR values are associated with 30-day mortality in patients with sepsis or septic shock [31]. Another study indicates that INR combined with IL-6 and NT-proBNP can serve as potential predictors of 28-day mortality in critically ill patients with sepsis or septic shock [32]. These findings support our study, where the non-survival group exhibited significantly higher INR levels, suggesting a poorer prognosis. AIR reflects patients' nutrition, inflammation, and coagulation status. By combining these two critical indicators, AIR offers a more nuanced understanding of neonatal sepsis progression, sensitively capturing subtle patient changes.

A study highlighted that a higher INR to albumin ratio (PTAR) correlated with 90-day mortality in critically cirrhotic patients [17]. Recently, PTAR has been utilized for sepsis risk stratification, demonstrating moderate discriminatory power for predicting in-hospital and 90-day mortality [16]. PTAR was also found to be associated with the severity of upper gastrointestinal bleeding [18]. However, the predictive capacity of AIR for neonatal sepsis mortality remains uncertain.

In our study, univariate analysis identified culture positivity, PLT, UREA, CREA, PT, INR, TT, AIR, and ALB as risk factors for neonatal sepsis mortality. This implies that liver, kidney, and hematological dysfunctions may be linked to mortality during sepsis progression. Multivariate analysis confirmed AIR as an independent risk factor for neonatal sepsis mortality. Moreover, the AUC for AIR in predicting 30-day mortality from neonatal sepsis was 0.746, surpassing that of ALB and INR. This suggests that combining multiple indicators could enhance prognostic value in clinical practice.

This study's limitations include a small sample size and its monocentric design, which may introduce bias and restrict the generalizability of the findings. Considering the significance of neonatal sepsis, further validation is imperative. Future research should involve multicenter studies with larger sample sizes to confirm our results.

Conclusions

AIR serves as a dependable indicator for assessing the prognosis of neonatal sepsis patients. Lower AIR levels are associated with increased 30-day mortality in neonatal sepsis, signaling a poorer prognosis. Clinicians should monitor disease progression and initiate aggressive treatment when AIR falls below the optimal cut-off value to mitigate adverse outcomes. Furthermore, using AIR as a marker eliminates the need for additional testing and reduces cost, as it is an inexpensive and easy-to-obtain measurement based on routine procedures.

Availability of data and materials

The datasets are available from the corresponding author on reasonable request.

Ethics statement

The study was performed to conform with the Declaration of Helsinki and was approved by the local ethics committee of the hospital (2023-007).

Authors Contributions

W L and J-K C designed the study. All the authors contributed to the generation, collection, assembly, analysis and/or interpretation of data. X-W T wrote the manuscript, All the authors revised the manuscript. All the authors have read manuscript and approved the final manuscript.

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Conflict of interests

No conflict of interests is declared.

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