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Association between red cell distribution width-to-albumin ratio and short-term mortality in patients with sepsis-associated delirium: a retrospective study from the MIMIC-IV database

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Abstract

Background Sepsis-associated delirium (SAD) is a common and severe acute neuropsychiatric manifestation in patients with sepsis, which is associated with increased mortality and lasting cognitive deficits. The red cell distribution width to albumin ratio (RAR) has been recognized as a robust prognostic indicator for adverse outcomes across various diseases. This study aims to investigate the relationship between RAR and short-term mortality in patients with SAD after admission to the intensive care unit (ICU).

Methods This retrospective cohort study leveraged the MIMIC-IV 3.1 database to analyze the primary outcome of all-cause mortality within 30 days of ICU admission for patients with SAD. According to the receiver operating characteristic(ROC) curve to determine the optimal cut-off point of RAR, SAD patients were divided into low RAR group (RAR < 5.85) and high RAR group (RAR ≧ 5.85). To mitigate potential confounding factors, a 1:1 propensity score matching (PSM) method was implemented. The relationship between RAR and short-term mortality was further assessed using multivariate Cox proportional hazards regression models and Kaplan–Meier (KM) survival curve analyses.

Results The study included 4021 patients with SAD. After PSM, 1063 score-matched pairs of patients were generated. Cox proportional hazards models were adjusted for potential confounders, Patients with elevated RAR (≥ 5.85) exhibited a significantly higher 30-day mortality rate compared to those with a lower RAR (< 5.85), with a hazard ratio (HR) of 1.53 (95% CI: 1.35–1.75, $P < 0.001$). Propensity scores matching analysis corroborated these results, consistently indicating a higher mortality rate in the high RAR group, with an HR of 1.39 (95% CI: 1.19–1.61, $P < 0.001$).

Conclusions An Elevated RAR upon ICU admission was independently associated with an increased risk of short-term mortality in patients with SAD.

Keywords Red cell distribution width, Albumin, Sepsis, Delirium, Short-term mortality

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Background

Sepsis-associated delirium (SAD) is a prevalent acute neuropsychiatric complication in patients with sepsis, characterized by a decline in cognitive function and concentration [1]. SAD is associated with increased mortality, persistent cognitive deficits, and prolonged hospital stay [2]. The pathophysiology of SAD is complex and involves neuroinflammation, impaired cerebral blood flow, and neurotransmitter imbalances [3]. Currently, there are no effective treatments to reduce mortality among patients with SAD. Thus, the accurate prediction of prognosis for patients with SAD in a timely manner and the initiation of prompt and effective clinical interventions are crucial.

Red cell distribution width (RDW), a measure of red blood cell size variability, is associated with inflammation and oxidative stress [4, 5]. Emerging evidence indicates that RDW can serve as a predictive marker of cardiovascular disease-related morbidity and mortality [6]. In parallel, serum albumin, an indicator of nutritional status and inflammation, has been linked to sepsis prognosis [7, 8]. The Red Cell Distribution Width to Albumin Ratio (RAR), which compares the erythrocyte distribution width and albumin levels, may provide a more complete picture of a patient's nutritional and inflammatory conditions [9]. Early research indicated that a high RAR could correlate with adverse outcomes in several clinical scenarios [10, 11]. According to recent studies, albumin and RDW can be used to predict mortality in patients with septic encephalopathy [12]. RAR integrates RDW (a marker of acute inflammation/oxidative stress) and albumin (a marker of chronic metabolic defects), two pathways that are independently associated in SAD pathogenesis but rarely combined in existing biomarkers [13]. Unlike SOFA/ SAPS-II, RAR can directly link IL-6-mediated inhibition of erythropoiesis to vascular endothelial dysfunction exacerbated by hypoalbuminemia, providing a unified model for the pathophysiology of SAD [14, 15]. By utilizing routine assays (RDW and albumin), RAR eliminates the need for specialized testing.

Nevertheless, the relationship between RAR and short-term mortality in individuals with SAD remains largely unknown.

This study aimed to determine the link between RAR and the 30-day mortality rate among patients with SAD following intensive care unit (ICU) admission, potentially guiding the creation of new treatment strategies and prognostic models.

Methods

Data source

This retrospective cohort study utilized the Medical Information Mart for Intensive Care-IV3.1 (MIMIC-IV3.1) database, which is a publicly accessible database. The database collates clinical data from patients admitted to the Beth Israel Deaconess Medical Center (BIDMC), a teaching hospital affiliated with Harvard Medical School in the USA, between 2008 and 2019 [16].

Ethical considerations and data privacy

The MIMIC-IV database, which de-identifies patient records, has been approved by the institutional ethics review boards of both MIT and the Beth Israel Deaconess Medical Center and is exempt from the requirement for informed consent. The information of all patients was anonymized prior to extraction and data analysis, thereby waiving the requirement for individual patient consent. Lifeng Ni was authorized to access the database after successfully completing online training and assessments, as evidenced by certification number 65,512,516. This study adhered to the principles outlined in the Declaration of Helsinki.

Definition of sepsis-associated delirium (SAD)

SAD was defined as sepsis accompanied by delirium. The diagnostic criteria for sepsis were based on the Sepsis 3.0 definition, which includes a suspected infection and a Sequential Organ Failure Assessment (SOFA) score of at least 2 to confirm the presence of sepsis [17]. Delirium during the ICU stay was diagnosed with a The Richmond Agitation-Sedation Scale (RASS) score of ≧-3 and a positive Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) score [18]. In addition, individuals exhibiting dementia symptoms, undergoing alcohol withdrawal, experiencing drug-induced delirium, or diagnosed with delirium prior to the diagnosis of sepsis were excluded from the study.

Study population

Patients included in the database were selected based on specific criteria. The inclusion criteria were as follows: (1) age > 18 years; (2) ICU stay exceeding 24 h; (3) Patients with sepsis; and (4) RASS score of ≧-3 and positive CAM-ICU score. Exclusion criteria included: (1) no CAM-ICU score available; (2) presence of dementia, alcohol withdrawal, or delirium induced by drugs; (3) Delirium was diagnosed before sepsis was diagnosed; and (4) absence of RDW and albumin data within the first 24 h of ICU admission. (Fig. 1)

Data extraction

Data was extracted using the Structured Query Language in Navicat Premium (17.0) to extract or calculate the following variables: We collected data on demographics (age, gender, race, height, and weight) and vital signs (heart rate, systolic blood pressure, diastolic blood pressure, and temperature) 24 h prior to ICU admission. Data on comorbidities (myocardial infarction, severe

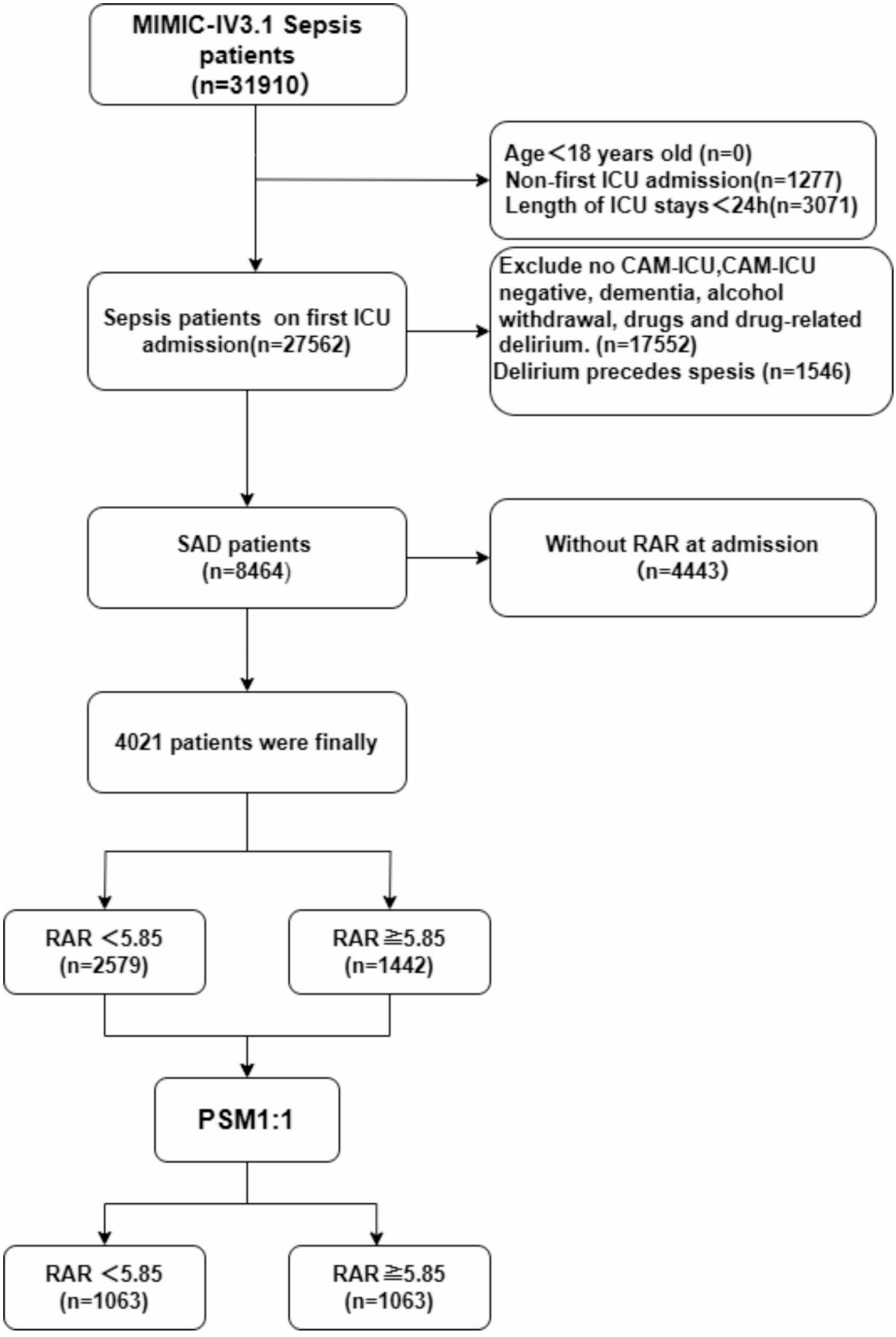

Fig. 1 A flowchart for the patient selection process

liver disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic lung disease, diabetes mellitus, renal disease, and malignancy) were extracted based on the diagnostic segments of the ICD-9 or ICD-10 codes in the MIMIC-IV3.1 database. We recorded the time to antibiotic initiation and the use of propofol and midazolam. The Charlson Comorbidity Index was also collected. Specific scores were recorded on the first day using the Simplified Acute Physiology Score II (SAPSII), Oxford Acute Severity of Illness Score (OASIS), Logical Organ Dysfunction System (LODS), and Sequential Organ Failure Assessment (SOFA). Moreover, the results of the tests performed 24 h after admission to the ICU (RDW, serum albumin, anion gap, INR, potassium, sodium, calcium, hemoglobin, glucose, white blood cells, platelets, blood glucose, and lactate) were extracted. When there were multiple values and detection results within 24 h, the value of the first measurement was selected. The treatments received (mechanical ventilation, vasopressors, and renal replacement therapy [RRT]) were recorded.

Missing data

When missing data values surpassed 15% for variables such as height (28.2%), weight (21.7%), and lactate levels (17.3%), the data were excluded. For variables with less than 5% missing data, such as anion gap (0.07%), calcium (0.63%), glucose (0.07%), INR (3.99%), sodium (0.02%), temperature (1.87%), and WBC (0.02%), the missing values were imputed with the mean.

RAR and study endpoint

The following formula was used to calculate the RAR: [RDW (%)/serum albumin (g/dL)]. This study assessed the 30-day all-cause mortality following ICU admission. Secondary endpoints included in-hospital mortality and mortality 90 days after ICU admission.

Statistical analysis

Histogram distribution and Kolmogorov–Smirnov tests were used to assess variable normality. Normally distributed continuous variables are reported as mean ± standard deviation, and skewed variables are reported as medians with interquartile ranges (IQR). Categorical variables were expressed as frequencies and percentages. Group comparisons were performed using independent samples of Student's t-test or Mann–Whitney U-test based on normality and the chi-square test for categorical data. To evaluate the predictive validity of RAR, a receiver operating characteristic (ROC) curve was constructed to determine the optimal cut-off point for RAR. Subsequently, the study population was stratified into two groups based on the optimal cut-off point, and the impact of RAR on ICU 30-day mortality was assessed using Cox proportional hazards models, presenting hazard ratios (HRs) and 95% confidence intervals (CIs) while controlling for major covariates. Participants lost to follow-up were treated as censored observations at the time of their last contact. The outcome of ICU 30-day mortality was evaluated using Kaplan–Meier survival curves stratified by the categorical variable RAR and compared using the log-rank test, which was based on clinical relevance and included all significant covariates identified in the univariate analysis. We developed three adjustment models: Model 1 was controlled for age, gender, and ethnicity; Model 2 made additional adjustments for comorbidities and test results, the time to antibiotic initiation and the use of propofol and midazolam; Model 3 was further adjusted for factor-specific scores and treatments. Smoothed curve fitting was used to explore the linear correlation between RAW and clinical outcomes. A subgroup analysis was performed.

We performed propensity score matching (PSM) to mitigate selection bias, using logistic regression to generate propensity scores based on demographics, comorbidities, vital signs, laboratory values, medications, specialized scores (SAPSII, SOFA, LODS, OASIS), RRT, and mechanical ventilation. Patients were matched 1:1 via nearest-neighbor algorithm with a caliper width of 0.2. Balance between groups was assessed pre- and post-matching using absolute standardized differences (ASDs); All ASDs fell below 0.10, confirming adequate covariate equilibrium [19].

All statistical analyses were conducted using R Statistical Software (Version 4.2.2, http://www.R-project.org, The R Foundation) and the Free Statistics Analysis Platform (Version 2.0, Beijing, China, http://www.clinicalscientists.cn/freestatistics). Free Statistics is a software package that offers user-friendly interfaces for common analyses and data visualization. It leverages R as the underlying statistical engine with a graphical user interface (GUI) developed in Python. Most analyses can be performed using only a few clicks to facilitate reproducibility and interactive computing.

In this study, a two-sided P value < 0.05 was considered statistically significant.

Results

General information

Overall, 4021 patients diagnosed with SAD, aged 65.0 ± 16.2 years, were included in the analysis, with males comprising 58% of the sample. In this cohort, the overall prevalence of ICU 30-day mortality was 29.7% (Table 1).

ROC curve analysis for predicting 30-day mortality in patients with SAD yielded an optimal RAR cutoff threshold of 5.85, with an AUC of 0.635 (95% CI, 0.617–0.653; $P < 0.001$) (Supplementary Fig. 1). Patients with SAD

Table 1 Baseline characteristics before propensity score matching

Characteristics	Total ($n=4021$)	RAR (< 5.85) ($n=2579$)	RAR(≧5.85) ($n=1442$)	*P* value
Gender, *n* (%)				0.007
Male	2333 (58.0)	1537 (59.6)	796 (55.2)	
Female	1688 (42.0)	1042 (40.4)	646 (44.8)	
Age(years)	65.0 ± 16.2	65.3 ± 16.5	64.4 ± 15.5	0.073
Ethnicity, n (%)				0.298
White	2262 (56.3)	1428 (55.4)	834 (57.8)	
Black	102 (2.5)	65 (2.5)	37 (2.6)	
Others	1657 (41.2)	1086 (42.1)	571 (39.6)	
Myocardial infarct, n (%)	734 (18.3)	493 (19.1)	241 (16.7)	0.029
Charlson comorbidity index	5.6 ± 3.1	5.4 ± 3.0	6.0 ± 3.1	< 0.001
Severe liver disease, n (%)	669 (16.6)	302 (11.7)	367 (25.5)	< 0.001
Congestive heart failure, n (%)	1296 (32.2)	851 (33)	445 (30.9)	0.164
Peripheral vascular disease, n (%)	436 (10.8)	248 (9.6)	188 (13)	< 0.001
Cerebrovascular disease, n (%)	745 (18.5)	546 (21.2)	199 (13.8)	< 0.001
Diabetes, n (%)	1352 (33.6)	876 (34)	476 (33)	0.538
Renal disease, n (%)	991 (24.6)	631 (24.5)	360 (25)	0.725
Malignant cancer, n (%)	585 (14.5)	283 (11)	302 (20.9)	< 0.001
HR (bpm)	89.1 ± 17.5	87.1 ± 17.2	92.5 ± 17.7	< 0.001
SBP (mmHg)	114.6 ± 15.3	117.0 ± 16.0	110.3 ± 12.9	< 0.001
DBP (mmHg)	62.6 ± 10.4	64.0 ± 10.6	60.0 ± 9.4	< 0.001
Temperature (℃)	37.0 ± 0.6	37.0 ± 0.6	36.9 ± 0.6	< 0.001
Inr	1.5 ± 0.7	1.4 ± 0.7	1.6 ± 0.7	< 0.001
Albumin (g/dL)	2.9 ± 0.7	3.3 ± 0.5	2.3 ± 0.5	< 0.001
Anion gap (mmol/L)	13.8 ± 4.3	13.7 ± 4.2	13.8 ± 4.6	0.635
Potassium (mmol/L)	3.9 ± 0.6	3.9 ± 0.6	3.9 ± 0.7	0.07
Sodium (mmol/L)	136.5 ± 6.4	136.8 ± 6.2	136.1 ± 6.7	0.002
Calcium (mg/dL)	7.9 ± 0.9	8.1 ± 0.9	7.6 ± 0.9	< 0.001
Rdw (%)	15.6 ± 2.6	14.6 ± 1.8	17.3 ± 3.0	< 0.001
Hemoglobin (g/dl)	9.7 ± 2.4	10.3 ± 2.3	8.5 ± 2.0	< 0.001
WBC ($\times 10^9$)	10.4 (7.0, 14.7)	10.3 (7.2, 13.9)	10.7 (6.4, 15.9)	0.096
Platelet ($\times 10^9$)	185.7 ± 110.5	191.7 ± 102.6	174.8 ± 122.8	< 0.001
Glucose (mg/d)	154.4 ± 63.3	156.9 ± 64.5	149.9 ± 60.8	< 0.001
LODS	7.0 ± 3.0	6.6 ± 3.0	7.8 ± 3.0	< 0.001
OASIS	37.6 ± 8.2	36.8 ± 7.9	39.0 ± 8.4	< 0.001
SOFA	7.5 ± 3.7	6.8 ± 3.5	8.6 ± 3.7	< 0.001
SASP II	45.7 ± 14.9	43.4 ± 14.3	49.8 ± 15.0	< 0.001
Antibiotic, time (H)	62.6 ± 10.4	64.0 ± 10.6	60.0 ± 9.4	< 0.001
Propofol use, n (%)	2857 (71.1)	1835 (71.2)	1022 (70.9)	0.852
Midazolam use, n (%)	1318 (32.8)	842 (32.6)	476 (33)	0.815
Vasoactive use, n (%)	2315 (57.6)	1360 (52.7)	955 (66.2)	< 0.001
Ventilator use, n (%)	3710 (92.3)	2382 (92.4)	1328 (92.1)	0.761
RRT, n (%)	657 (16.2)	326 (12.6)	331 (23)	< 0.001
RAR (%/g/dL)	5.6 ± 2.0	4.5 ± 0.8	7.6 ± 1.9	< 0.001
In-hospital mortality, n (%)	14.9 (8.4, 24.6)	13.9 (8.0, 22.9)	16.2 (9.0, 27.5)	< 0.001
ICU 30-day mortality, n (%)	1195 (29.7)	594 (23)	601 (41.7)	< 0.001
ICU 90-day mortality, n (%)	1499 (37.3)	762 (29.5)	737 (51.1)	< 0.001

Data are weighted estimates, and values are presented as means ± standard deviation or means (percentage). HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; Inr, International Normalized Ratio; Rdw, red blood cell distribution width; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; LODS, Logistic Organ Dysfunction System; OASIS, Oxford Acute Severity of Illness Score; WBC, white blood cell; RAR, red blood cell distribution width to albumin ratio; RRT, renal replacement therapy. Antibiotic, time: time from ICU admission to antibiotic initiation

were divided into low RAR group (RAR < 5.85) and high RAR group (RAR ≧ 5.85) (Table 1).

Compared to the low RAR group, the high RAR group exhibited a higher proportion of females and elevated proportions of severe liver disease, peripheral vascular disease, myocardial infarction, cerebrovascular disease, and malignant cancer. Moreover, in this group, increased proportions were observed for heart rate and various special scores, while blood pressure and body temperature were lower (both $P < 0.05$). The high-RAR group displayed significantly elevated levels of INR, RDW, and WBC indicators compared to the low-RAR group ($P < 0.05$), whereas albumin, sodium, calcium, hemoglobin, platelet, and glucose levels were significantly lower ($P < 0.05$) in the high-RAR group. Compared with the low-RAR group, the high-RAR group showed a decreased proportion of mechanical ventilation usage and an increased proportion of RRT, as well as elevated in-hospital mortality, ICU 30-day mortality, and ICU 90-day mortality (both $P < 0.05$) (Table 1).

The correlation between mortality rate and patients diagnosed with RAR and SAD

The association between RAR and 30-day all-cause mortality risk after ICU admission was significantly positive in both patients with RAR and SAD (nonlinear $P > 0.05$, Supplementary Fig. 2). Treating RAR as a continuous variable and adjusting for confounding factors, each unit increase in RAR was found to be associated with a 14% higher risk of 30-day all-cause mortality among patients with SAD (95% CI: 1.11–1.17, $P < 0.001$). Furthermore, even after controlling potential confounders, individuals in the high RAR group had a significantly higher risk of 30-day all-cause mortality following ICU admission compared to patients with SAD (HR = 1.53, 95% CI: 1.35–1.75, $P < 0.001$) (Table 2, Model3). The Kaplan–Meier curve demonstrated a significantly higher incidence of mortality within 30 days following ICU admission for patients with SAD in the high-RAR group than in the low-RAR group ($P < 0.001$) (Fig. 2).

Association between RAR and SAD patient mortality rates after propensity score matching

We conducted a 1:1 propensity score-matching analysis for both the low- and high-RAR patient groups, resulting in 1063 matched pairs. The effectiveness of the matching process was evaluated by determining the absolute standardized difference before and after PSM (Fig. 3). Demographics, comorbidities, specific scores, most laboratory indicators, and treatment outcomes were balanced between the two cohorts after PSM. However, a significant disparity in 30-day post-ICU admission mortality was observed between the two groups. (28.4% vs. 37.3%, $P < 0.001$), In-hospital mortality (23.1% vs. 32.4%, $P < 0$ 0.001), and within 90 days after ICU admission (35.4% vs. 47.4%, $P < 0$ 0.001) for all-cause mortality (Supplementary Table 1).

After matching propensity scores, the results of multivariate Cox regression analysis showed that RAR, as a continuous variable, was positively associated with an increased 30-day mortality rate in patients with SAD after ICU admission (HR = 1.09, 95% CI: 1.05–1.13, $P < 0.001$). Furthermore, RAR ≥ 5.85 maintained its independent predictive value for the 30-day mortality rate after ICU admission (HR = 1.39, 95% CI: 1.19–1.61, $P < 0.001$) (Table 3). Additionally, comparing the KM survival curves between the two groups emphasized that even after PSM, patients with RAR ≥ 5.85 consistently demonstrated a significantly lower survival rate at 30 days after ICU admission ($P < 0$ 0.001) (Fig. 4).

Subgroup analysis

Subgroup analysis was conducted, and no significant effects ($P > 0.05$) were observed in relation to gender, age, use of vasodilators, mechanical ventilation, or RRT. The effect of RAR on the 30-day ICU mortality rate among

Table 2 Unadjusted and multivariate Cox regression analyses for ICU 30-day mortality before propensity score matching

Outcomes	Non-adjusted Model		Model I		Model II		Model III	
Variable	HR (95%CI)	*P* value	adj.HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
RAR	1.18 (1.16 ~ 1.21)	< 0.001	1.19 (1.17 ~ 1.22)	< 0.001	1.14 (1.11 ~ 1.18)	< 0.001	1.14 (1.11 ~ 1.17)	< 0.001
RAR < 5.85	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
RAR ≧ 5.85	2.06 (1.84 ~ 2.31)	< 0.001	2.17 (1.94 ~ 2.44)	< 0.001	1.58 (1.39 ~ 1.8)	< 0.001	1.53 (1.35 ~ 1.75)	< 0.001

Non-adjusted Model: Adjusted for no other covariates

Model I: Adjust for age, gender, and Ethnicity

Model II: Adjust for Model I + Charlson comorbidity index, Myocardial infarct, Severe liver disease, Congestive heart failure, Peripheral vascular disease, Cerebrovascular disease, Chronic pulmonary disease, Diabetes, Renal disease, Malignant cancer, HR, SBP, DBP, Temperature, Inr, Anion gap, Potassium, Sodium, Calcium, Hemoglobin, WBC, Platelet. Antibiotic initiation and Propofol and Midazolam

Model III: Adjust for Model II + LODS, OASIS, SOFA, SASP II, Vasoactive use, Ventilator use, RRT

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; Inr, International Normalized Ratio; Rdw, red blood cell distribution width; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; LODS, Logistic Organ Dysfunction System; OASIS, Oxford Acute Severity of Illness Score; WBC, white blood cell; RAR, red blood cell distribution width to albumin ratio; RRT, renal replacement therapy. Antibiotic, time: time from ICU admission to antibiotic initiation

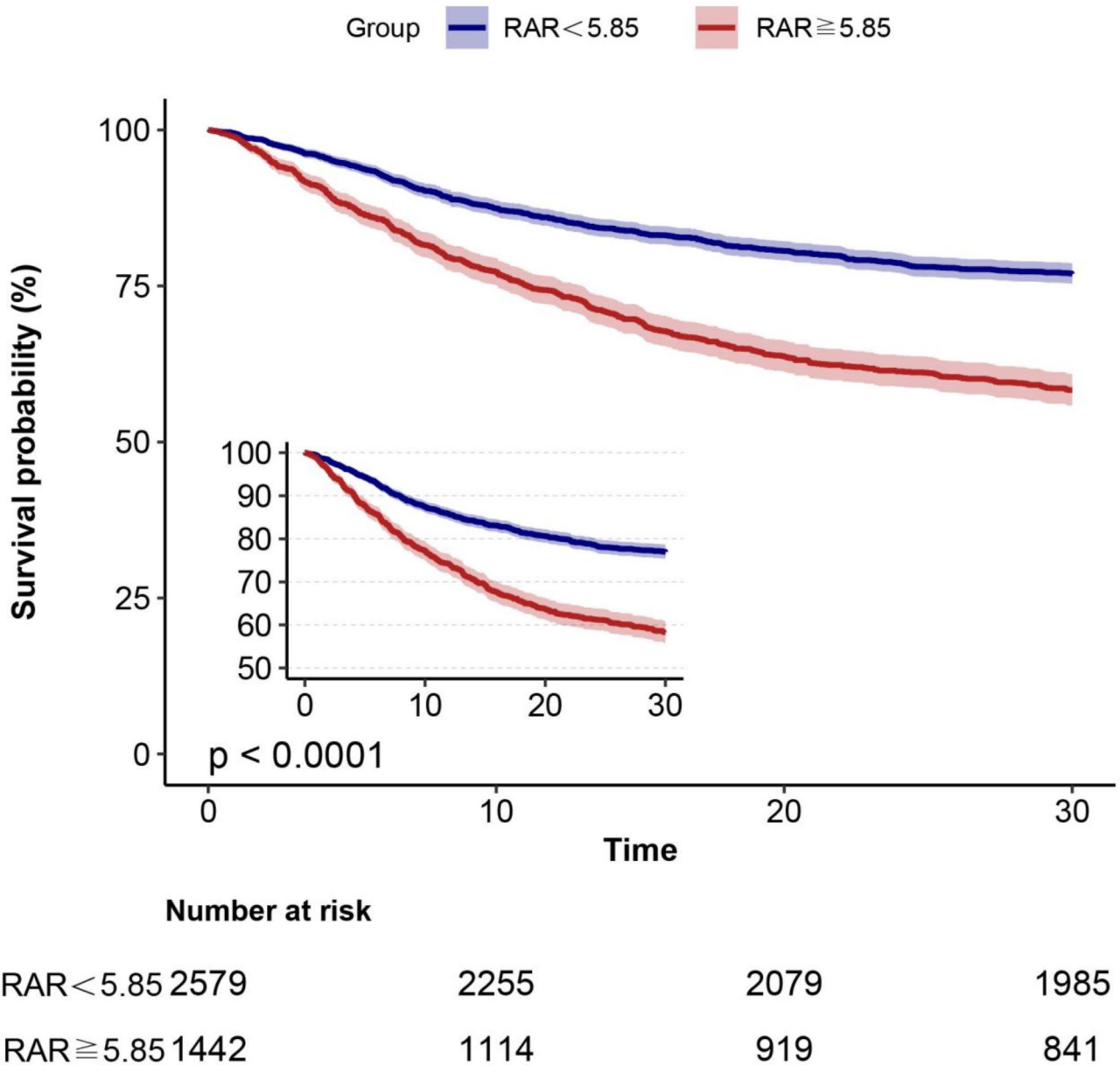

Fig. 2 Survival curve before propensity score matching

patients with SAD remained consistent across these subgroups (Fig. 5).

Discussion

This retrospective study provided preliminary evidence that RAR is independently associated with increased 30-day mortality after ICU admission in patients with SAD. Importantly, no significant interaction was observed between these associations, indicating consistent findings across different subgroups.

RAR markers are derived from routine laboratory tests and have the potential to convey a plethora of clinical information that surpasses the limitations of individual markers. Recently, RAR has been used extensively for the prognostic evaluation of patients with various diseases, encompassing stroke [20], acute respiratory distress syndrome [21], cancer [22], severe pulmonary embolism [23], severe acute pancreatitis [24], and acute cardiac infarction [25]. RAR combines RDW (marker of systemic inflammation/oxidative stress) and albumin (negative acute-phase protein reflecting endothelial integrity). Elevated RDW correlates with increased IL-6/TNF-α levels, promoting neuroinflammation [26–28]. Hypoalbuminemia impairs glutathione synthesis in hippocampal neurons (critical regions for delirium), exacerbating oxidative stress. Low albumin reduces free cortisol

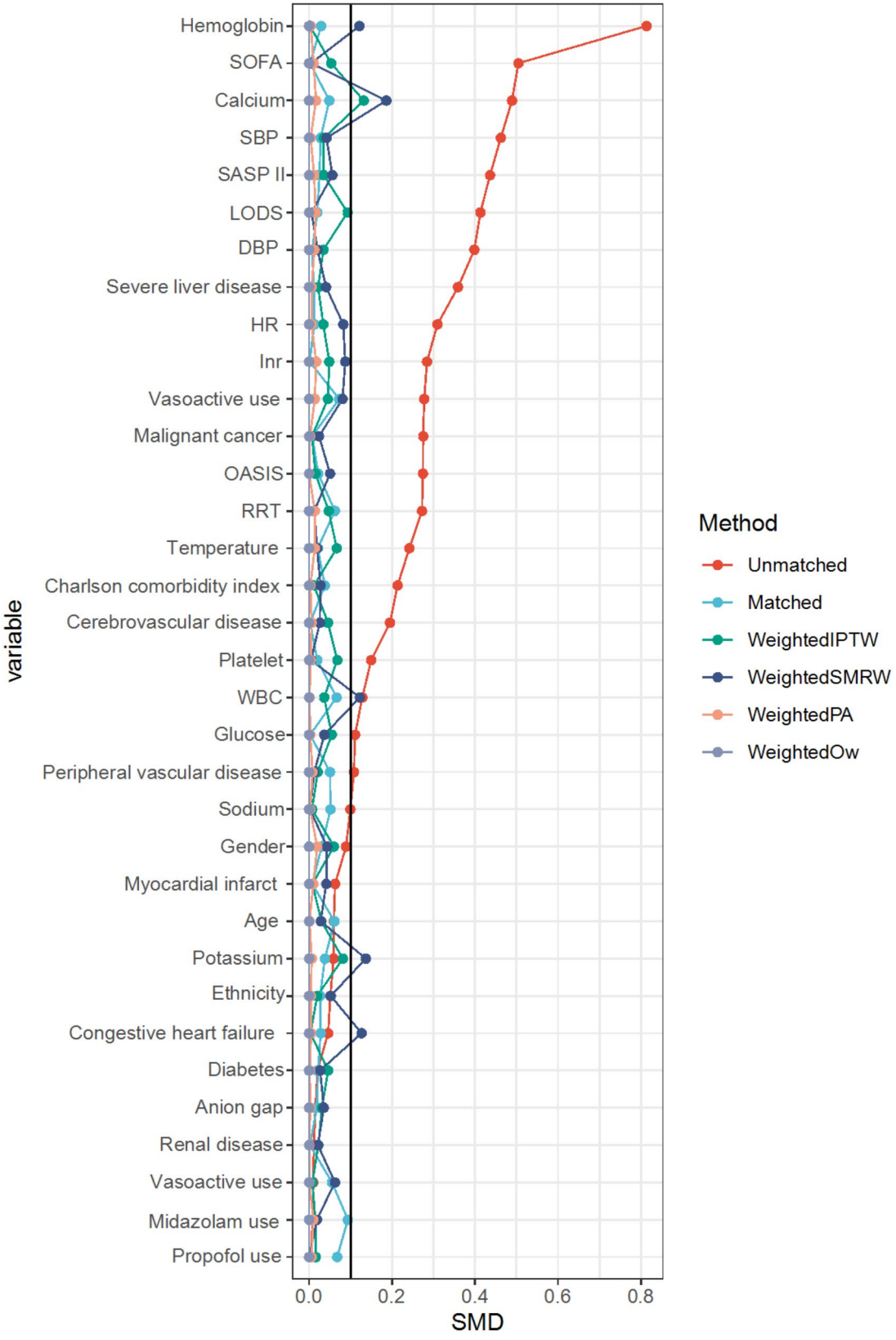

Fig. 3 The absolute standardized differences for variables used to match the two groups

Table 3 Unadjusted and multivariate Cox regression analyses for ICU 30-day mortality after propensity score matching

Outcomes	Non-adjusted Model		Model I		Model II		Model III	
Variable	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
RAR	1.11 (1.06 ~ 1.14)	< 0.001	1.11 (1.07 ~ 1.15)	< 0.001	1.09 (1.05 ~ 1.13)	< 0.001	1.09 (1.05 ~ 1.13)	< 0.001
RAR < 5.85	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
RAR ≧ 5.85	1.37 (1.18 ~ 1.59)	< 0.001	1.43 (1.23 ~ 1.66)	< 0.001	1.40 (1.21 ~ 1.62)	< 0.001	1.39 (1.19 ~ 1.61)	< 0.001

Non-adjusted Model: Adjusted for no other covariates

Model I: Adjust for age, gender, and Ethnicity

Model II: Adjust for Model I + Charlson comorbidity index, Myocardial infarct, Severe liver disease, Congestive heart failure, Peripheral vascular disease, Cerebrovascular disease, Chronic pulmonary disease, Diabetes, Renal disease, Malignant cancer, HR, SBP, DBP, Temperature, Inr, Anion gap, Potassium, Sodium, Calcium, Hemoglobin, WBC, Platelet. Antibiotic initiation and Propofol and Midazolam

Model III: Adjust for Model II + LODS, OASIS, SOFA, SASP II, Vasoactive use, Ventilator use, RRT

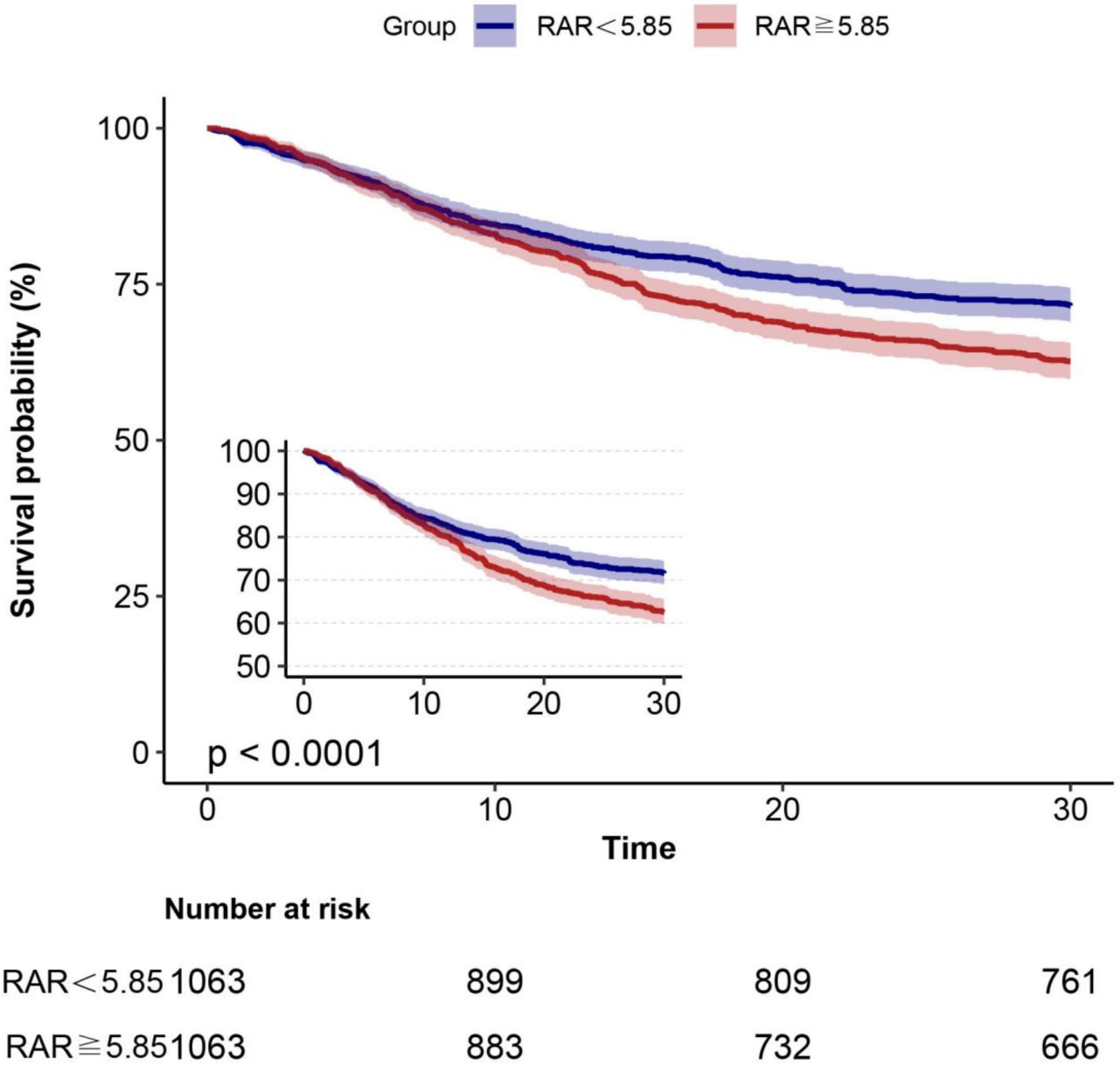

Fig. 4 Survival curve after propensity score matching

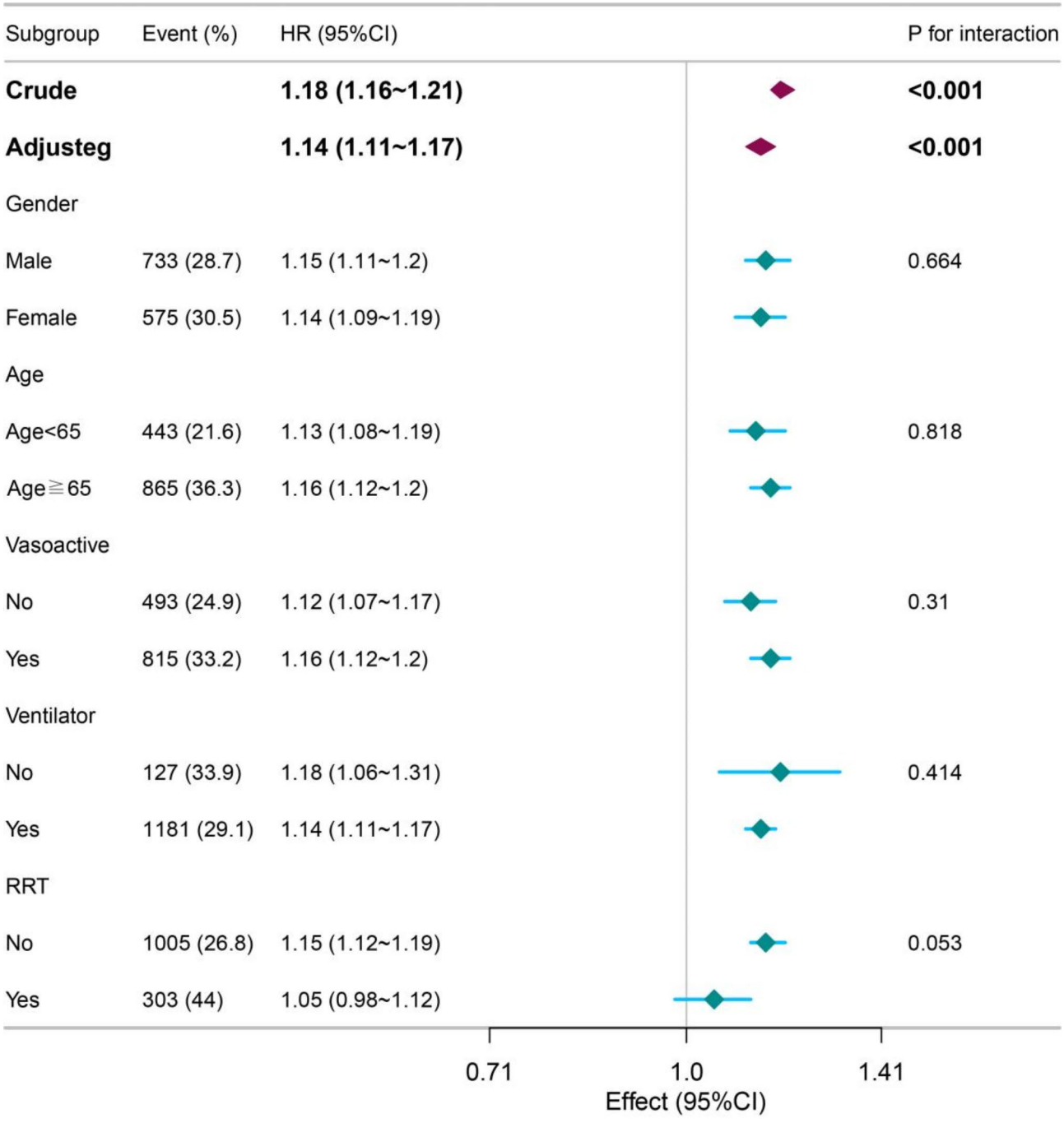

Fig. 5 Forest plot for subgroup analysis

bioavailability, impairing stress responses and delirium severity [29, 30]. All these factors are closely associated with the onset and progression of critical illness, making the integration of both indicators invaluable in predicting mortality. In a retrospective study of 3969 patients, RAR demonstrated a comparable predictive ability for 30-day mortality in critically ill patients with sepsis as the lactate-to-albumin ratio ($P = 0.133$) while outperforming the neutrophil percentage to albumin ratio ($P < 0.001$) [31]. Li et al. established a strong association between RAR and prognosis in patients with autoimmune encephalitis [32]. However, no study has utilized the RAR as a prognostic indicator in patients with SAD. These findings suggest that RAR can serve as a hematological marker for identifying high-risk patients with SAD with poor prognosis and as a target for intervention to improve the prognosis of patients with SAD admitted to the ICU. In this study, the short-term prognosis of patients with SAD in the low

RAR group was significantly better than that in the high RAR group. At present, our subgroup analysis showed that no significant effects were observed in these subgroups (gender, age, use of vasodilator, use of mechanical ventilation, and use of RRT) ($P > 0.05$).

The present study observed a higher prevalence of comorbidities in the high RAR group than in the low RAR group. This finding is consistent with previous research, which demonstrated a significant correlation between elevated RAR values and cardiac and renal diseases, as well as their prognosis [33, 34]. In this study, patients in the high RAR group were found to exhibit elevated SOFA scores, SAPS II scores, and a higher prevalence of ascending medications and RRT utilization, indicating an increased likelihood of progressing to infectious shock. Previous studies have also demonstrated a significant association between RAR and the risk of acute kidney injury in patients with sepsis undergoing ventilation treatment [35]. Finally, our study revealed that even after adjusting for all confounding factors, the risk of mortality within 30 days of ICU admission in patients belonging to the high-RAR group was 1.53 times greater than that in the low-RAR group.

RAR can be integrated into established scoring systems, such as SOFA scores, to identify high-risk patients with SAD, which could prompt clinicians to enhance monitoring on ICU admission, optimize nutritional support, or initiate early intervention. Future studies will validate this cutoff across diverse clinical settings and explore its utility in personalized treatment strategies.

The diagnostic criteria for sepsis were based on the sepsis 3.0 definition, which is defined by suspected infection and SOFA score was at least 2 points, which was consistent with other relevant studies [36, 37]. Contemporary guidelines highlight the critical role of lactate in sepsis triage. To reduce analytic bias, we excluded patients with missing lactate measurements (> 15% of the initial cohort). We did not trace suspected infections. Future studies should consider incorporating a composite lactate-based score, such as SOFA-lactate, with stratification by suspected infection status to improve diagnostic accuracy.

This study represents the first endeavor to explore the correlation between RAR and short-term mortality in patients with SAD using data from MIMIC-IV3.1. However, this study has certain limitations. First, although our study utilized rigorous methodologies, including propensity score matching and multivariate Cox regression, it still lacks external validation, which limits its generalizability. A multicenter cohort is needed to validate these findings. Our models adjusted for multiple covariates; however, residual confounding from unmeasured factors such as inflammation and fluid management may influence the association between RAR and mortality. Future studies should employ advanced techniques and incorporate additional biomarkers to mitigate such limitations. Our study acknowledges limitations in fully controlling for potential confounding factors, including hematologic and gastrointestinal disorders. Future research should employ sensitivity analyses to account for these variables and further validate the independent predictive value of RAR.

Conclusions

This study demonstrates that elevated RAR levels upon ICU admission in SAD patients are associated with increased short-term mortality. These findings indicate that RAR may serve as a direct and reliable marker for anesthesiologists and intensivists to identify high-risk SAD patients in clinical practice.

Abbreviations

SAD	Sepsis-associated delirium
RAR	Red cell distribution width-to-albumin ratio
ICU	Intensive care unit
ROC	Receiver operating characteristic
PSM	Propensity score matching
KM	Kaplan–Meier
AUC	Area under the curve
RDW	Red cell distribution width
BIDMC	Beth Israel Deaconess Medical Center
RRT	Renal replacement therapy
SAPSII	Simplified Acute Physiology Score II
OASIS	Oxford Acute Severity of Illness Score
LODS	Logical Organ Dysfunction System
SOFA	Sequential Organ Failure Assessment

Supplementary Information

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Supplementary Material 1

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Author contributions

ShengJie Yao: original draft, Investigation, Formal analysis, Data curation. GuoFen Zhang: Methodology, Formal analysis, Data curation. LiFeng Ni: original draft, Methodology, Formal analysis, Data curation.

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Data availability

The availability of data and materials can be obtained by reaching out to the corresponding author via email at 18969979720@163.com.

Declarations

Human Ethics and Consent to Participate

Not applicable.

Consent to participate

The MIMIC-IV database, which de-identifies patient records, has been approved by the institutional ethics review boards of both MIT and the Beth Israel Deaconess Medical Center and is exempt from the requirement for

informed consent. The information of all patients was anonymized prior to extraction and data analysis, thereby waiving the requirement for individual patient consent. This study adhered to the principles outlined in the Declaration of Helsinki. Lifeng Ni was authorized to access the database after successfully completing online training and assessments, as evidenced by certification number 65512516.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

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