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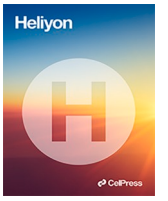

Research article

# The value of D-dimer-albumin ratio as a prognostic biomarker in critically ill patients with sepsis: A retrospective single-center study

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ABSTRACT

*Background:* This study aimed to examine the potential prognostic significance of the D-dimer-albumin ratio (DAR) in critically ill patients with sepsis.
*Methods:* A retrospective cohort study was carried out at the Affiliated Hospital of Jiangsu University, involving 1123 patients diagnosed with sepsis from January 2015 to November 2023. The patients were categorized into four groups (Q1-Q4) based on their DAR levels. The primary outcomes measured were in-hospital mortality and ICU mortality. Survival analysis was conducted using Kaplan-Meier survival curves and the log-rank test. Additionally, Cox proportional hazards regression models were utilized to investigate the relationship between the DAR and all-cause mortality.
*Results:* The study population had a median age of 75 years (interquartile range: 65–84), and the median DAR was 0.15 (interquartile range: 0.08–0.32). The rates of hospital mortality and ICU mortality were 33.7 % and 31.9 % respectively. There was an observed increase in the cumulative incidence of 30-/60-day mortality with higher DAR levels (log-rank test, $P < 0.001$). After accounting for other variables, the results from multivariable Cox proportional hazards analyses demonstrated that DAR independently predicted hospital death [HR (95%CI): 1.419 (1.205–1.670); $P < 0.001$] and ICU death [HR (95%CI): 1.437 (1.219–1.693); $P < 0.001$].
*Conclusions:* The DAR was found to be an independent predictor of all-cause mortality in critically ill patients with sepsis.

## 1. Introduction

Sepsis was a syndrome characterized by multiple organ dysfunction and high heterogeneity, resulting from infection-induced inflammatory response and immune dysfunction [1]. A retrospective study of sepsis patients worldwide in 2017 revealed that there were approximately 48.9 million cases with around 11 million deaths, resulting in a mortality rate of 19.7 % [2]. In hospitals, sepsis affected 9.3 % of all patients, and it accounted for 56.5 % of the patients in the intensive care unit (ICU). Remarkably, sepsis patients

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with organ dysfunction in the ICU faced a mortality rate as high as 52.3 % [3]. Although there had been advancements in the diagnosis and treatment of sepsis, the occurrence and death rates associated with the condition continued to be significant. Moreover, the readmission rate within one year after discharge for sepsis patients was as high as 65.0 %, posing a major challenge in global healthcare [4]. Therefore, early screening and intervention of prognostic factors in sepsis patients held crucial clinical significance.

Currently, commonly used biochemical indicators both domestically and internationally, such as interleukin-6 (IL-6), procalcitonin (PCT), C-reactive protein (CRP), were produced by the host in response to inflammation. However, these indicators could also elevate in patients without infection, such as trauma or surgery, limiting their ability to predict the prognosis of sepsis patients [5–7]. Therefore, the trend in current research was to assess the severity and prognosis of sepsis through the combined detection of multiple indicators [8–10]. In the presence and development of sepsis, inflammatory cells in the patient's body could become excessively activated, leading to a dysregulated inflammatory response and subsequent systemic coagulation abnormalities [11]. Studies had found that 50 %~70 % of sepsis patients experienced coagulation dysfunction, which rapidly led to multiple organ dysfunction and was closely associated with mortality [12]. D-dimer was a specific fibrinolysis marker, and its elevated serum levels indicate abnormal coagulation function and secondary fibrinolysis hyperactivation in patients [13]. Research had confirmed that in patients with sepsis, especially those with multiple organ dysfunction, the elevation of serum D-dimer levels was particularly significant. Furthermore, the increase in D-dimer levels was closely associated with higher mortality rates in sepsis patients [14,15]. Sepsis patients experienced increased metabolism and were in a state of high breakdown, leading to an increase in resting energy expenditure, widespread protein and fat breakdown, and negative nitrogen balance. Therefore, malnutrition was very common among sepsis patients [16,17]. Serum albumin had long been widely used as a nutritional indicator in clinical practice [18]. Studies had reported an association between low levels of albumin and adverse clinical outcomes in sepsis patients [19,20].

The D-dimer-albumin ratio (DAR) was a novel composite inflammatory marker that combined coagulation and malnutrition by comparing the levels of D-dimer and albumin. Previous studies had shown that DAR was associated with various disease risk factors, such as coronavirus disease 2019 (COVID-19), aneurysmal subarachnoid hemorrhage (aSAH), and preoperative deep vein thrombosis (DVT) [21–23]. However, the correlation between DAR and the clinical outcome of patients with sepsis had not been investigated thus far. The objective of this study was to investigate whether DAR had prognostic value in predicting all-cause mortality risk in critically ill patients with sepsis.

## 2. Methods

### 2.1. Study population

This retrospective analysis involved a review of the clinical records of 1242 individuals with sepsis who were hospitalized in the ICU at the Affiliated Hospital of Jiangsu University from January 2015 to November 2023. The inclusion criteria required patients to meet the diagnostic criteria of Sepsis 3.0 [24]. Certain conditions were excluded to avoid bias, including patients under 18 years old, those who died within 24 h of ICU admission, and those with a history of chronic kidney disease (CKD) or hepatic cirrhosis. The final

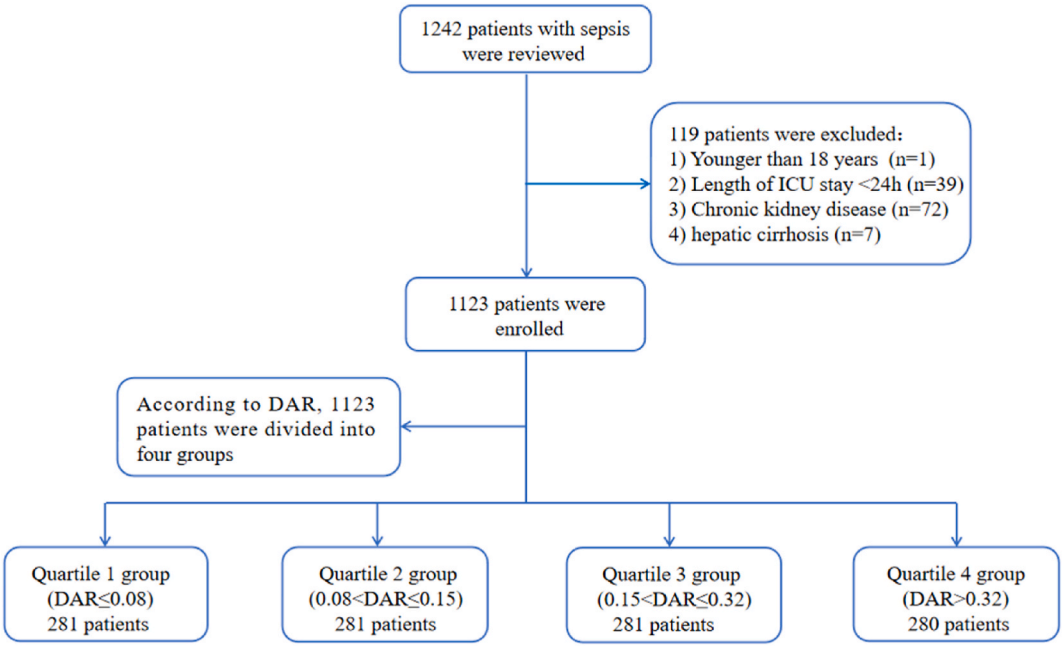


**Fig. 1.** Flow of included patients through the trial. Abbreviations: DAR, D-dimer-albumin ratio; ICU, Intensive Care Unit.

**Table 1**
Baseline characteristics grouped according to DAR.

| Variables | Overall | Q1 group (DAR ≤ 0.08) | Q2 group (0.08 < DAR ≤ 0.15) | Q3 group (0.15 < DAR ≤ 0.32) | Q4 group (DAR>0.32) | P-value |
|---|---|---|---|---|---|---|
| N | 1123 | 281 | 281 | 281 | 280 | |
| Age, years | 75 (65–84) | 75 (62–84) | 75 (65–85) | 74 (65–85) | 77 (67–84) | 0.383 |
| Male, n (%) | 707 (63.0) | 183 (65.1) | 186 (66.2) | 179 (63.7) | 159 (56.8) | 0.091 |
| BMI, kg/m$^2$ | 22.49 (20.08–25.21) | 22.86 (19.95–25.75) | 22.69 (20.20–25.21) | 22.49 (20.30–25.25) | 22.04 (19.99–24.59) | 0.144 |
| Smoking, n (%) | 229 (20.4) | 65 (23.1) | 63 (22.4) | 60 (21.4) | 41 (14.7) | 0.052 |
| **Comorbidities, n (%)** | | | | | | |
| Hypertension | 579 (51.3) | 165 (58.7) | 149 (53.0) | 133 (47.3) | 132 (47.1) | 0.017 |
| Diabetes | 309 (27.5) | 87 (31.0) | 76 (27.0) | 77 (27.4) | 69 (24.6) | 0.413 |
| Coronary artery disease | 116 (10.3) | 33 (11.8) | 28 (10.0) | 25 (8.9) | 30 (10.7) | 0.718 |
| COPD | 87 (7.7) | 30 (10.7) | 26 (9.3) | 16 (5.7) | 15 (5.4) | 0.043 |
| Cerebral infarction | 161 (14.3) | 58 (20.6) | 36 (12.8) | 33 (11.7) | 34 (12.1) | 0.007 |
| **Infection pathogens, n (%)** | | | | | | |
| Gram-positive bacteria | 136 (12.1) | 33 (11.7) | 33 (11.7) | 39 (13.9) | 31 (11.1) | 0.758 |
| Gram-negative bacteria | 335 (29.8) | 57 (20.3) | 81 (28.8) | 90 (32.0) | 107 (38.2) | <0.001 |
| Fungus | 77 (6.9) | 17 (6.0) | 16 (5.7) | 23 (8.2) | 21 (7.5) | 0.606 |
| Virus | 60 (5.3) | 31 (11.0) | 6 (2.1) | 11 (3.9) | 12 (4.3) | <0.001 |
| **Laboratory tests** | | | | | | |
| WBC *10$^9$/L | 11.4 (7.4–17.1) | 11.2 (7.9–16.55) | 10.9 (7.2–16.3) | 11.4 (7.6–16.7) | 12.4 (6.8–19.3) | 0.302 |
| Neu *10$^9$/L | 10.1 (6.3–15.5) | 9.8 (6.4–14.7) | 9.5 (6.2–14.6) | 9.9 (6.6–15.5) | 11.4 (6.0–17.7) | 0.104 |
| Lym *10$^9$/L | 0.6 (0.3–0.9) | 0.6 (0.4–1.1) | 0.6 (0.3–1.0) | 0.5 (0.3–0.8) | 0.5 (0.3–0.8) | <0.001 |
| Mon *10$^9$/L | 0.4 (0.2–0.7) | 0.5 (0.3–0.7) | 0.4 (0.2–0.7) | 0.4 (0.2–0.7) | 0.3 (0.2–0.6) | <0.001 |
| Hb, g/dL | 115 (97–130) | 119 (103–134) | 116 (98–132) | 112 (94–129) | 111 (96–126) | 0.001 |
| PLT *10$^9$/L | 149 (95–214) | 189 (125–247) | 152 (100–215) | 147 (97–218) | 109 (70–175) | <0.001 |
| CRP, mg/L | 104.2 (42.0–163.2) | 73.9 (17.5–125.1) | 103.5 (46.5–175.7) | 112.5 (49.8–169.3) | 122.7 (60.8–188.0) | <0.001 |
| Tbil, μmol/L | 17.4 (10.9–28.2) | 13.7 (8.3–21.8) | 17.4 (11.1–27.7) | 18.7 (11.9–29.6) | 20.4 (12.7–35.3) | <0.001 |
| ALT, U/L | 32.0 (21.0–56.0) | 28.0 (20.0–43.2) | 31.0 (20.0–53.1) | 32.0 (21.0–60.5) | 39.9 (25.0–79.4) | <0.001 |
| AST, U/L | 38.1 (23.9–73.0) | 30.0 (20.0–52.4) | 36.0 (23.7–65.0) | 40.0 (24.0–79.0) | 56.5 (30.0–146.5) | <0.001 |
| Alb, g/L | 28.2 (24.2–33.2) | 32.9 (28.4–37.2) | 28.5 (24.5–33.2) | 27.2 (23.5–31.3) | 25.5 (21.8–29.8) | <0.001 |
| Glucose, mmol/L | 8.2 (6.6–11.8) | 8.0 (6.4–11.2) | 8.1 (6.7–11.8) | 8.4 (6.6–11.9) | 8.6 (6.4–12.4) | 0.626 |
| Creatinine, μmol/L | 92.6 (63.7–153.1) | 76.0 (54.8–118.8) | 84.8 (62.4–132.6) | 96.7 (62.2–153.3) | 133.3 (81.2–216.7) | <0.001 |
| BUN, mmol/L | 8.89 (6.04–13.95) | 7.45 (5.45–10.48) | 8.39 (5.58–12.63) | 9.77 (6.27–14.31) | 11.59 (7.20–18.60) | <0.001 |
| Uric acid, μmol/L | 286.9 (192.3–411.7) | 276.8 (195.1–401.7) | 272.2 (181.4–391.0) | 277.5 (183.4–411.2) | 323.4 (226.1–472.2) | <0.001 |
| D-dimer, mg/L | 4.2 (2.1–8.4) | 1.3 (0.9–1.8) | 3.1 (2.5–3.8) | 6.1 (5.0–7.4) | 13.7 (9.6–22.9) | <0.001 |
| Potassium, mmol/L | 3.7 (3.3–4.2) | 3.7 (3.3–4.1) | 3.7 (3.4–4.1) | 3.7 (3.3–4.2) | 3.7 (3.3–4.3) | 0.949 |
| Lactate, mmol/L | 2.1 (1.4–3.6) | 1.8 (1.3–2.4) | 2.0 (1.3–2.9) | 2.3 (1.4–3.8) | 3.0 (1.9–5.3) | <0.001 |
| DAR | 0.15 (0.08–0.32) | 0.04 (0.03–0.06) | 0.11 (0.09–0.13) | 0.23 (0.19–0.27) | 0.53 (0.40–0.88) | <0.001 |
| **Severity scoring** | | | | | | |
| APACHE II score | 25 (19–30) | 25 (19–30) | 24 (18–28) | 25 (20–30) | 27 (21–32) | <0.001 |
| SOFA score | 12 (10–14) | 12 (9–14) | 11 (9–14) | 12 (10–15) | 13 (11–15) | <0.001 |
| **Treatments** | | | | | | |
| CRRT, n (%) | 78 (6.9) | 5 (1.8) | 14 (5.0) | 23 (8.2) | 36 (12.9) | <0.001 |
| Vasoactive drug, n (%) | 748 (66.6) | 136 (48.4) | 177 (63.0) | 204 (72.6) | 231 (82.5) | <0.001 |
| Invasive ventilation, n (%) | 752 (67.0) | 185 (65.8) | 176 (65.6) | 194 (69.0) | 197 (70.4) | 0.208 |
| **Endpoints** | | | | | | |
| 30-day mortality, n (%) | 316 (28.1) | 59 (21.0) | 53 (18.9) | 85 (30.2) | 119 (42.5) | <0.001 |
| 60-day mortality, n (%) | 375 (33.4) | 69 (24.6) | 69 (24.6) | 108 (38.4) | 129 (46.1) | <0.001 |
| AKI, n (%) | 512 (45.6) | 84 (29.9) | 109 (38.8) | 131 (46.6) | 188 (67.1) | <0.001 |
| Length of ICU stay, days | 6 (3–12) | 6 (3–12) | 6 (3–11) | 6 (3–11) | 6 (3–12) | 0.864 |
| Length of hospital stay, days | 16 (11–25) | 15 (10–24) | 18 (12–27) | 17 (11–28) | 17 (10–25) | 0.049 |
| ICU mortality, n (%) | 358 (31.9) | 66 (23.5) | 69 (24.6) | 98 (34.9) | 125 (44.6) | <0.001 |
| Hospital mortality, n (%) | 379 (33.7) | 69 (24.6) | 71 (25.3) | 108 (38.4) | 131 (46.8) | <0.001 |

Abbreviations: DAR, D-dimer-albumin ratio; BMI, body mass index; COPD, chronic obstructive pulmonary disease; WBC, white blood cell count; Neu, neutrophil; Lym, lymphocyte; Mon, monocyte; Hb, hemoglobin; PLT, platelet; CRP, C-reactive protein; Tbil, total bilirubin; ALT, alanine transaminase; AST, aspartate aminotransferase; Alb, albumin; BUN, blood urea nitrogen; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; CRRT, continuous renal replacement therapy; AKI, Acute kidney injury; ICU, Intensive Care Unit.

analysis included a total of 1123 participants. Fig. 1 illustrates the detailed inclusion and exclusion process. All patients provided written informed consent to participate in this study. The research protocol received approval from the ethics committee of the Affiliated Hospital of Jiangsu University (No. KY2023K1007).

### 2.2. Variable extraction

The clinical data were gathered from the electronic medical recording system and encompassed a range of parameters. These parameters encompassed age, gender, body mass index (BMI), smoking status, comorbidities, infection pathogens, laboratory variables, severity of illness scores, treatments, and so on. Laboratory parameters include white blood cell (WBC), neutrophil (Neu), lymphocyte (Lym), monocyte (Mon), hemoglobin (Hb), platelet (PLT), C-reactive protein (CRP), total bilirubin (Tbil), alanine transaminase (ALT), aspartate aminotransferase (AST), albumin (Alb), glucose, creatinine, blood urea nitrogen (BUN), uric acid, and D-dimer, among others. All laboratory variables were collected from data recorded within the first time after ICU admission. Moreover, severity of illness scores, such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and SOFA score, were computed using the information acquired within the first 24 h of ICU admission. Each patient's follow-up duration commenced on the date of admission and concluded on the date of discharge or demise. Serum D-dimer level was measured using the immunoturbidimetric method, while serum Alb level was determined using the bromocresol green method. The D-dimer to albumin ratio (DAR) was determined using the following formula: [D-dimer (mg/L)]/{Albumin (g/L)}.

### 2.3. Endpoint definition

The primary observational endpoint in this study was the composite of all-cause mortality. This included deaths resulting from any cause, whether they occurred in the ICU or during hospitalization. Secondary endpoints included the incidence of acute kidney injury (AKI), length of stay in the ICU, and length of stay in the hospital. AKI was defined based on the guidelines provided by Kidney Disease: Improving Global Outcomes (KDIGO) [25].

### 2.4. Statistical analysis

For the statistical analysis in this study, multiple software programs were utilized, including SPSS version 26.0, R software version 4.1.3, and GraphPad Prism 10.0. A significance level of $P < 0.05$ was used to determine statistical significance. Categorical variables were shown as numbers (percentage), while continuous variables were represented as mean ± SD or median (interquartile range). The comparison of categorical variables was conducted using the chi-square test. For normally distributed continuous variables, ANOVA was utilized, whereas skewed continuous variables were tested using the Kruskal-Wallis H test. Spearman's analysis was used to assess the correlations between the DAR and the severity of illness scores. The Kaplan-Meier survival curve analysis and log-rank test were used to group the survival outcomes according to different levels of DAR. Receiver operating characteristic (ROC) curves were utilized to evaluate the predictive value of the DLR on mortality. Univariate Cox regression analysis was employed to determine prognostic factors for sepsis patients. Multivariate Cox proportional hazards regression was then used to determine if the DAR could be considered an independent risk factor. Variables with a p-value <0.05 in the univariate analysis were selected as confounding factors. In addition, clinically relevant and prognostically significant variables were included in the multivariable model. Three models were created: model 1 (unadjusted), model 2 (adjusted for age, gender, BMI, smoking, hypertension, diabetes, WBC, Neu, Lym, PLT, and CRP), and model 3 (further adjusted for APACHE II score, SOFA score, and invasive ventilation). The DAR was included in the models as a continuous variable. The reference group for the categorical variable was the first quartile of the DAR. The p-value for the trend were calculated based on the quartile level. Furthermore, the study utilized restricted cubic spline (RCS) regression models with three knots in order to illustrate the associations between the DAR and all-cause mortality. Stratified analyses were conducted based on age, gender, smoking status, hypertension, diabetes, lactate level, and AKI to evaluate the consistency of the DAR's prognostic value for all-cause death. Additionally, we examined the interaction between the DAR and the stratified variables.

## 3. Results

The final analysis encompassed a cohort of 1123 individuals diagnosed with sepsis, with 707 (63.0 %) being male. The median age of the participants was 75 years, with an interquartile range of 65–84 years. Table 1 presented a summary of the baseline characteristics of the individuals involved in the study. The median value of the DAR among the enrolled patients was 0.15, with an interquartile range of 0.08–0.32. Among the participants, 579 (51.3 %) had comorbid hypertension, 309 (27.5 %) had diabetes, 116 (10.3 %) had coronary artery disease, 87 (7.7 %) had COPD, and 161 (14.3 %) had cerebral infarction. The hospital mortality rate for the sepsis patients was 31.9 %, while the mortality rate in the ICU was slightly higher at 33.7 %.

### 3.1. Baseline characteristics

Table 1 provided an overview of the baseline characteristics of the participants, categorized into quartiles based on their DAR (Q1, lowest quartile: DAR ≤ 0.08; Q2, second quartile: 0.08 < DAR ≤ 0.15; Q3, upper quartile: 0.15 < DAR ≤ 0.32; Q4, highest quartile: DAR>0.32). The median DAR values for each quartile were 0.04 (IQR: 0.03–0.06), 0.11 (IQR: 0.09–0.13), 0.23 (IQR: 0.19–0.27), and 0.53 (IQR: 0.40–0.88) respectively. The high DAR group of participants showed a higher prevalence of gram-negative bacteria,

elevated levels of CRP, Tbil, ALT, AST, creatinine, BUN, uric acid, D-dimer, and lactate, as well as lower levels of Lym, Mon, Hb, PLT, and Alb. Additionally, they exhibited a higher severity of APACHE II score and SOFA score, and a higher proportion of individuals requiring CRRT and vasoactive drugs compared to those in the low DAR group. Spearman's correlation analysis indicated positive correlations between DAR and APACHE II score (0.120, $P < 0.001$), as well as between DAR and SOFA score (0.154, $P < 0.001$) (Supplementary Fig. 1). As DAR increased, there was a gradual rise in the 30-day mortality rate (21.0 % vs. 18.9 % vs. 30.2 % vs. 42.5 %, $P < 0.001$), 60-day mortality rate (24.6 % vs. 24.6 % vs. 38.4 % vs. 46.1 %, $P < 0.001$), occurrence of AKI (29.9 % vs. 38.8 % vs. 46.6 % vs. 67.1 %, $P < 0.001$), length of hospital stay (15 days vs. 18 days vs. 17 days vs. 17 days, $P = 0.049$), ICU mortality rate (23.5 % vs. 24.6 % vs. 34.9 % vs. 44.6 %, $P < 0.001$), and hospital mortality rate (24.6 % vs. 25.3 % vs. 38.4 % vs. 46.8 %, $P < 0.001$). Given

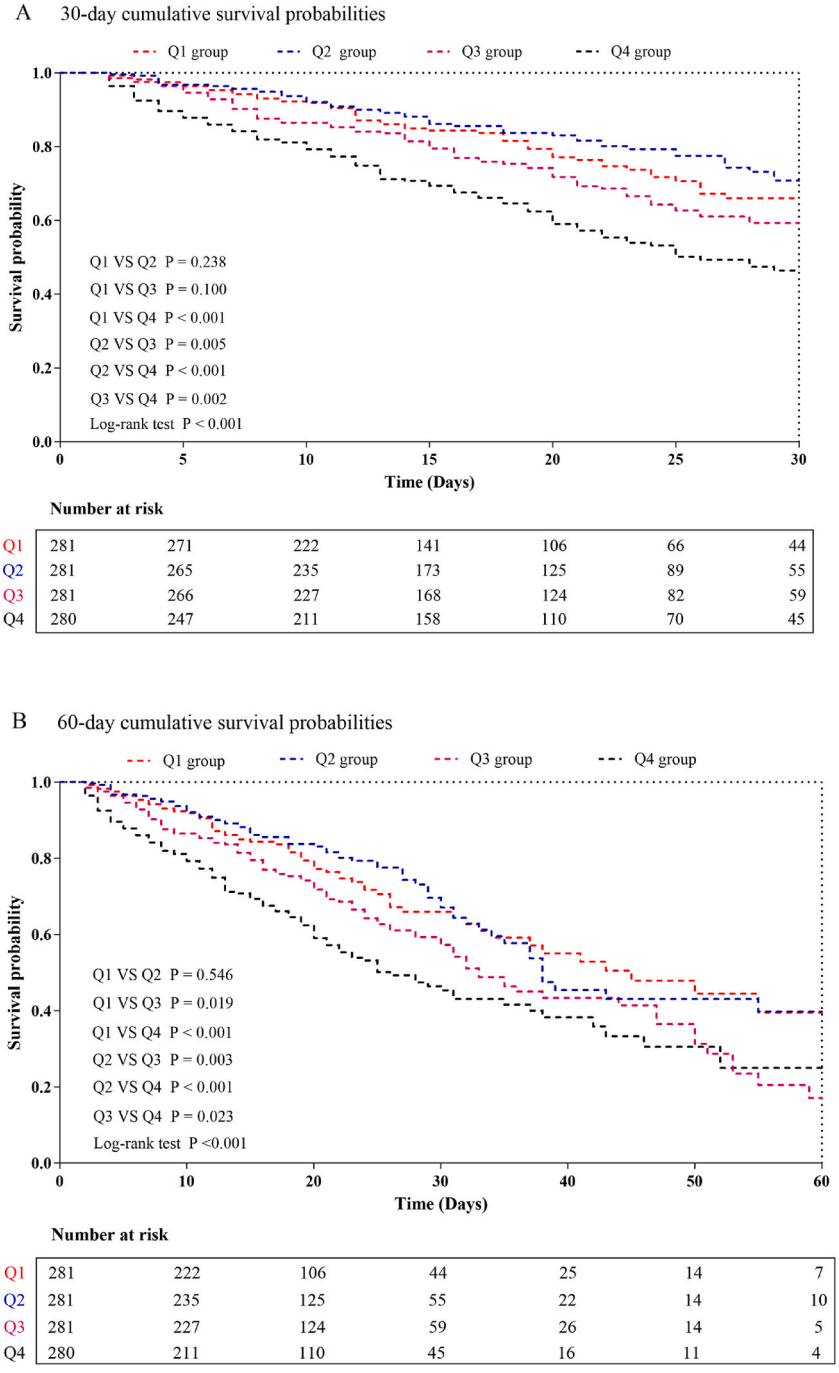


**Fig. 2.** Kaplan–Meier curves showing cumulative probability of all-cause mortality according to groups at 30 days (A), and 60 days (B). DAR quartiles: Q1 group (DAR≤0.08); Q2 group (0.08 < DAR≤0.15); Q3 group (0.15 < DAR≤0.32); Q4 group (DAR>0.32).

that the Q4 group exhibited a stronger association with all-cause mortality, we conducted further comparisons between the Q4 group and the combined Q1-3 groups. Our analysis demonstrated that different grouping approaches yielded similar results, highlighting the consistent findings. (Supplementary Table 1).

### 3.2. Association between the all-cause mortality and DAR

Supplementary Fig. 2 demonstrated the distribution of DAR categorized by the mortality status of all-cause in-hospital death and ICU death. The Kaplan-Meier survival analysis curves, displayed in Fig. 2A and B, assessed the incidence of all-cause mortality across quartile groups based on the DAR. A significant difference was observed in the 30-day mortality rate among the groups (Q1: 21.0 % vs. Q2: 18.9 % vs. Q3: 30.2 % vs. Q4: 42.5 %, log-rank $P < 0.001$, Fig. 4A) as well as the 60-day mortality rate (Q1: 24.6 % vs. Q2: 24.6 % vs. Q3: 38.4 % vs. Q4: 46.1 %, log-rank $P < 0.001$, Fig. 4B). These results indicated a rising trend in the 30-/60-day mortality rates with higher DAR values (Supplementary Fig. 3).

To further assess the prognostic value of DAR in sepsis, we conducted ROC curve analysis (Fig. 3A and. B and Supplementary Table 2). The AUC for hospital mortality prediction was 0.629 for DAR, 0.569 for Alb, and 0.643 for the SOFA score, respectively. DAR exhibited a sensitivity of 57.3 % and a specificity of 63.0 %, while Alb demonstrated sensitivity and specificity values of 58.3 % and 55.2 %, respectively. These findings indicated DAR's superior predictive capability compared to Alb. Combining DAR with the SOFA score resulted in an AUC of 0.672, signifying significantly improved predictive accuracy in contrast to using the SOFA score alone. Similar observations were made in the ROC curve analysis for predicting ICU mortality based on DAR. Supplementary Table 3 displayed the outcomes of COX regression analysis investigating the risk of all-cause death in critically ill patients with sepsis. Independent variables considered for the analysis included factors that exhibited significance in the univariate analysis ($P < 0.05$), as well as those recommended by clinicians and based on clinical experience. The analysis identified several influential factors, including age, gender, BMI, smoking, hypertension, diabetes, WBC, Neu, Lym, PLT, CRP, APACHE II score, SOFA score, and invasive ventilation. Cox proportional hazards analysis demonstrated a significant correlation between DAR and hospital death, both in the unadjusted model [HR (95%CI): 1.642 (1.434–1.881); $P < 0.001$] and fully adjusted model [HR (95%CI): 1.419 (1.205–1.670); $P < 0.001$]. Similarly, DAR also exhibited an association with ICU death, both in the unadjusted model [HR (95%CI): 1.661 (1.449–1.903); $P < 0.001$] and fully adjusted model [HR (95%CI): 1.437 (1.219–1.693); $P < 0.001$]. The risk of hospital death increased with higher quartiles of DAR (Q1 vs. Q2, HR (95%CI): 0.958 (0.680–1.351); Q3, HR (95%CI): 1.232 (0.899–1.690); Q4, HR (95%CI): 1.437 (1.046–1.976); P for trend = 0.006). In relation to ICU death, a comparable pattern was noted (Q1 vs. Q2, HR (95%CI): 0.974 (0.687–1.382); Q3, HR (95% CI): 1.162 (0.839–1.609); Q4, HR (95%CI): 1.418 (1.023–1.964); P for trend = 0.014) (Table 2, Fig. 4). In addition, the RCS regression model showed that elevated levels of DAR (>0.15) were linked to a higher risk of hospital death and ICU death (Supplementary Fig. 4).

### 3.3. Subgroup analysis

Subgroup analysis was carried out, taking into account various factors such as age, gender, smoking, hypertension, diabetes, lactate level, and AKI. The results of the combined association between DAR and hospital death among subgroups are presented in Table 3. There was no significant interaction observed between DAR and gender, smoking, hypertension, diabetes, lactate level, or AKI (all P values for interaction >0.05). However, it is noteworthy that the predictive value of DAR seemed to be more pronounced in patients aged >65 years [HR (95 % CI) aged >65 years 1.536 (1.321–1.787) vs. aged ≤65 years 2.662 (1.862–3.806), P for interaction = 0.004]. Similar findings were observed in the stratified analyses of DAR and ICU death, as shown in Table 4.

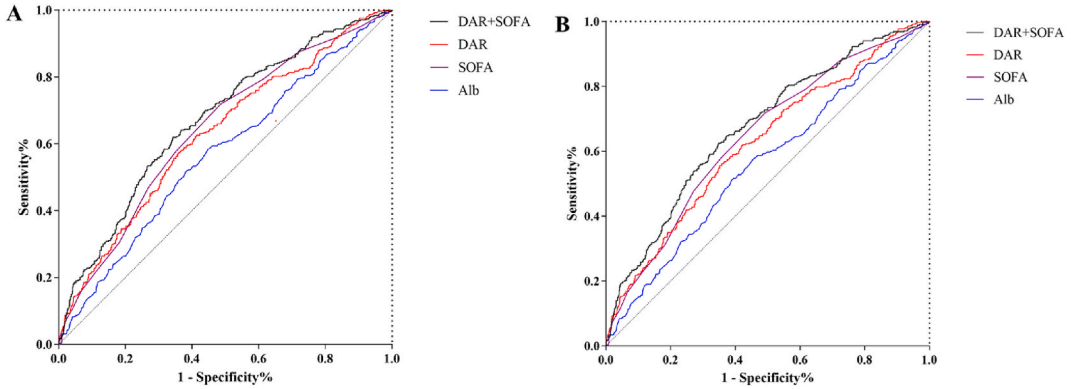


**Fig. 3.** A. The predictive value of DAR + SOFA, DAR, SOFA, and Alb for hospital mortality by ROC analysis. B. The predictive value of DAR + SOFA, DAR, SOFA, and Alb for ICU mortality by ROC analysis. Abbreviations: DAR, D-dimer-albumin ratio; SOFA, Sequential Organ Failure Assessment; Alb, albumin; ICU, Intensive Care Unit; ROC, receiver operating characteristic curve.

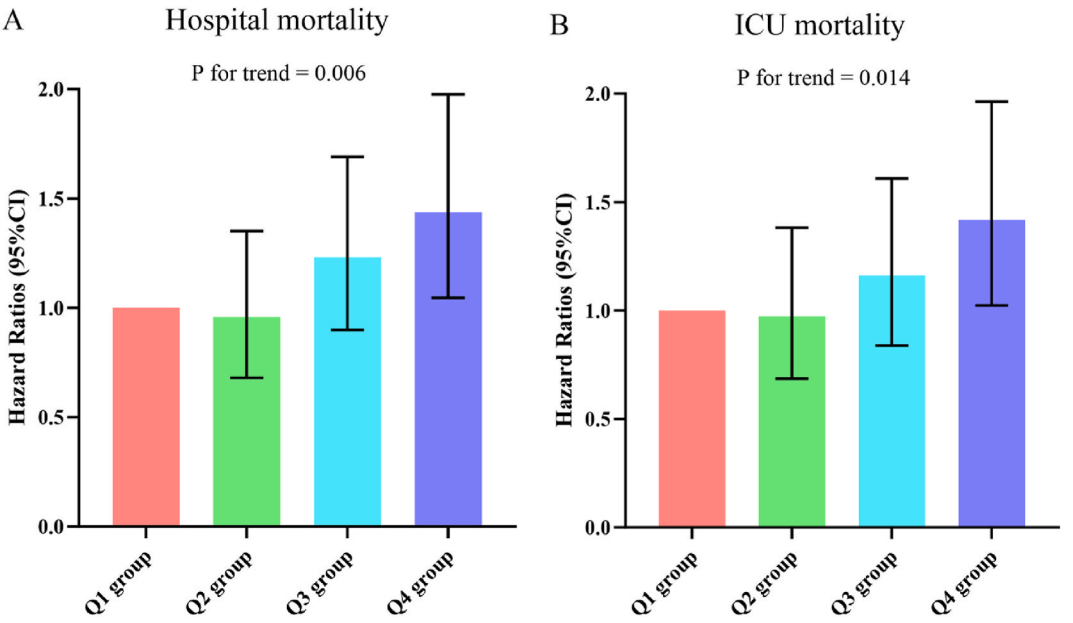


**Fig. 4.** A, B: Hazard ratios (95 % CIs) for hospital/ICU mortality according to DAR quartiles after adjusting for age, gender, BMI, Smoking, hypertension, diabetes, WBC, Neu, Lym, PLT, CRP, APACHE II score, SOFA score and Invasive ventilation. Error bars indicate 95 % CIs. The first quartile is the reference. DAR quartiles: Q1 group (DAR ≤ 0.08); Q2 group (0.08 < DAR ≤ 0.15); Q3 group (0.15 < DAR ≤ 0.32); Q4 group (DAR>0.32). Abbreviations: DAR, D-dimer-albumin ratio; BMI, body mass index; WBC, white blood cell; Neu, neutrophil; Lym, lymphocyte; PLT, platelet; CRP, C-reactive protein; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; ICU, Intensive Care Unit.

**Table 2**
Multivariable Cox regression analysis to assess the association between DAR and all-cause mortality.

| Variables | Model 1 | | | Model 2 | | | Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR (95 % CI) | P-value | P for trend | HR (95 % CI) | P-value | P for trend | HR (95 % CI) | P-value | P for trend |
| Hospital mortality | | | | | | | | | |
| Continuous variable per unit | 1.642 (1.434–1.881) | <0.001 | | 1.488 (1.284–1.724) | <0.001 | | 1.419 (1.205–1.670) | <0.001 | |
| Quartile[a] | | | <0.001 | | | <0.001 | | | 0.006 |
| Q1 group | Ref | | | Ref | | | Ref | | |
| Q2 group | 0.931 (0.668–1.296) | 0.671 | | 0.873 (0.622–1.225) | 0.433 | | 0.958 (0.680–1.351) | 0.807 | |
| Q3 group | 1.451 (1.072–1.964) | 0.016 | | 1.280 (0.938–1.746) | 0.119 | | 1.232 (0.899–1.690) | 0.195 | |
| Q4 group | 1.988 (1.485–2.663) | <0.001 | | 1.615 (1.181–2.208) | 0.003 | | 1.437 (1.046–1.976) | 0.025 | |
| **ICU mortality** | | | | | | | | | |
| Continuous variable per unit | 1.661 (1.449–1.903) | <0.001 | | 1.505 (1.298–1.745) | <0.001 | | 1.437 (1.219–1.693) | <0.001 | |
| Quartile[a] | | | <0.001 | | | <0.001 | | | 0.014 |
| Q1 group | Ref | | | Ref | | | Ref | | |
| Q2 group | 0.950 (0.677–1.331) | 0.764 | | 0.888 (0.629–1.253) | 0.498 | | 0.974 (0.687–1.382) | 0.884 | |
| Q3 group | 1.370 (1.002–1.873) | 0.048 | | 1.206 (0.875–1.662) | 0.252 | | 1.162 (0.839–1.609) | 0.367 | |
| Q4 group | 1.977 (1.466–2.665) | <0.001 | | 1.600 (1.161–2.204) | 0.004 | | 1.418 (1.023–1.964) | 0.036 | |

Model 1: unadjusted.
Model 2: adjusted for age, gender, BMI, Smoking, hypertension, diabetes, WBC, Neu, Lym, PLT, and CRP.
Model 3: Model 2 plus APACHE II score, SOFA score and invasive ventilation.
Abbreviations: DAR, D-dimer-albumin ratio; BMI, body mass index; WBC, white blood cell; Neu, neutrophil; Lym, lymphocyte; PLT, platelet; CRP, C-reactive protein; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; ICU, Intensive Care Unit.
[a] DAR: Q1 group (DAR≤0.08); Q2 group (0.08 < DAR≤0.15); Q3 group (0.15 < DAR≤0.32); Q4 group (DAR>0.32).

**Table 3**
Subgroup analysis assessing the association between DAR and hospital mortality.

| Subgroups | No. hospital mortality/No. patients | HR (95 % CI) | P-value | P for interaction |
|---|---|---|---|---|
| Age | | | | 0.004 |
| >65 | 315/840 | 1.536 (1.321–1.787) | <0.001 | |
| ≤65 | 64/283 | 2.662 (1.862–3.806) | <0.001 | |
| Gender | | | | 0.856 |
| Male | 251/707 | 1.679 (1.399–2.015) | <0.001 | |
| Female | 128/416 | 1.593 (1.294–1.960) | <0.001 | |
| Smoking | | | | 0.632 |
| Yes | 88/230 | 1.797 (1.386–2.330) | <0.001 | |
| No | 291/893 | 1.601 (1.366–2.876) | <0.001 | |
| Hypertension | | | | 0.515 |
| Yes | 211/579 | 1.578 (1.292–1.927) | <0.001 | |
| No | 168/544 | 1.724 (1.430–2.078) | <0.001 | |
| Diabetes | | | | 0.715 |
| Yes | 111/309 | 1.607 (1.285–2.009) | <0.001 | |
| No | 268/814 | 1.676 (1.412–1.990) | <0.001 | |
| Lactate | | | | 0.867 |
| >2.0 | 277/616 | 1.467 (1.264–1.702) | <0.001 | |
| ≤2.0 | 102/507 | 1.651 (0.991–2.751) | 0.054 | |
| AKI | | | | 0.279 |
| Yes | 223/512 | 1.437 (1.216–2.698) | <0.001 | |
| No | 156/611 | 1.751 (1.310–2.340) | <0.001 | |

Abbreviations:DAR, D-dimer-albumin ratio; AKI, Acute kidney injury.

**Table 4**
Subgroup analysis assessing the association between DAR and ICU mortality.

| Subgroups | No. ICU mortality/No. patients | HR (95 % CI) | P-value | P for interaction |
|---|---|---|---|---|
| Age | | | | 0.004 |
| >65 | 297/840 | 1.552 (1.333–1.807) | <0.001 | |
| ≤65 | 61/283 | 2.694 (1.883–3.854) | <0.001 | |
| Gender | | | | 0.854 |
| Male | 238/707 | 1.695 (1.410–2.036) | <0.001 | |
| Female | 120/416 | 1.617 (1.314–1.990) | <0.001 | |
| Smoking | | | | 0.637 |
| Yes | 85/230 | 1.796 (1.384–2.330) | <0.001 | |
| No | 273/893 | 1.620 (1.382–1.900) | <0.001 | |
| Hypertension | | | | 0.480 |
| Yes | 199/579 | 1.593 (1.304–1.945) | <0.001 | |
| No | 159/544 | 1.746 (1.446–2.108) | <0.001 | |
| Diabetes | | | | 0.667 |
| Yes | 104/309 | 1.613 (1.289–2.019) | <0.001 | |
| No | 254/814 | 1.702 (1.432–2.023) | <0.001 | |
| Lactate | | | | 0.943 |
| >2.0 | 266/616 | 1.480 (1.276–1.718) | <0.001 | |
| ≤2.0 | 92/507 | 1.626 (0.948–2.791) | 0.078 | |
| AKI | | | | 0.345 |
| Yes | 212/512 | 1.466 (1.242–1.731) | <0.001 | |
| No | 146/611 | 1.742 (1.293–2.349) | <0.001 | |

Abbreviations:DAR, D-dimer-albumin ratio; AKI, Acute kidney injury; ICU, Intensive Care Unit.

### *3.4. Relationship between DAR and secondary outcomes*

The univariate analysis findings revealed a notable correlation between a higher DAR and an elevated risk of AKI occurrence ($P < 0.001$), as well as the length of hospital stay ($P = 0.049$). Subsequent multivariate logistic and linear regression analyses, which accounted for confounding factors such as age, gender, BMI, smoking, hypertension, diabetes, WBC, Neu, Lym, PLT, CRP, APACHE II score, SOFA score, and invasive ventilation, consistently demonstrated a positive association between the DAR and AKI occurrence. Even after adjusting for various confounding factors, the association between DAR and AKI occurrence remained significant in the fully adjusted model ($\beta = 0.883$, $P < 0.001$) as indicated by Supplementary Table 4. However, no predictive relationship was found between the DAR and the length of hospital/ICU stay.

## 4. Discussion

In this study, we observed a clear connection between the DAR and the prognosis of critically ill patients with sepsis. The results

indicated that a higher DAR was associated with elevated rates of hospital and ICU mortality for sepsis patients. Importantly, this link remained statistically significant even when accounting for a range of clinical and laboratory factors. As such, the DAR could prove to be a convenient tool for clinicians and may be viewed as an independent risk factor for critically ill sepsis patients.

During sepsis, the damage to endothelial cells and the release of a high volume of inflammatory mediators resulted in widespread activation of coagulation factors, triggering a cascade reaction of coagulation. This led to the formation of numerous microthrombi in the microcirculation, resulting in extensive consumption of coagulation factors. Simultaneously, it caused secondary activation of the fibrinolytic system, generating large amounts of fibrinolytic enzymes, leading to hyperfibrinolysis and increased degradation products of fibrinogen. The imbalance between coagulation and anticoagulation reactions increased the risk of death in sepsis patients [26,27]. D-dimer, which was produced when fibrin was cross-linked and degraded, reflected the activity of fibrinolytic enzymes and thrombin, and indicated enhanced thrombogenesis and fibrinolysis activity. It held important significance in assessing the condition of sepsis [28,29]. Research conducted by Schwameis et al. demonstrated that elevated levels of D-dimer were commonly observed in sepsis patients, and monitoring D-dimer can be applied to predict in-hospital mortality [30]. Additionally, Innocenti et al. found that in early sequential evaluations, D-dimer levels were notably higher in the sepsis death group compared to the survival group, indicating that early monitoring of D-dimer played a critical role in assessing the prognosis of sepsis patients [31]. Research by Naderpour et al. revealed a close correlation between the severity of septicemia and the levels of serum D-dimer [32]. Shorr et al. suggested that heightened D-dimer levels raised the risk of sepsis-induced acute respiratory distress syndrome, contributing to increased mortality in sepsis patients [33].

During the acute phase of sepsis, a severe infection led to the release of a significant quantity of inflammatory mediators, which in turn promoted the secretion of catabolic hormones such as catecholamines, cortisol, and glucagon. This led to increased glucose production, glycogenolysis, lipolysis, and protein breakdown, resulting in a state of hypermetabolism [34,35]. The negative energy balance in sepsis patients correlated with a higher likelihood of infection, organ failure, prolonged use of mechanical ventilation, and an extended duration of hospitalization [36]. Serum albumin was a commonly used clinical indicator of nutritional status and an essential component for tissue repair and regeneration. It played a protective role in organ function under various disease conditions and can serve as an indicator of the severity of acute illness [37]. Several studies had demonstrated that low serum albumin levels independently contributed to a negative prognosis in sepsis [10,38,39]. Kendall et al. identified low serum albumin as a significant and unique predictor of mortality in ICU patients with sepsis [40]. Frenkel et al. discovered that the decrease in serum albumin levels one week after admission served as a more potent predictor of mortality in younger patients with sepsis [41]. Arnau-Barrés et al. suggested that factors strongly associated with mortality in elderly patients with sepsis, such as albumin levels, should be considered when determining prognosis and potential interventions in the future [42].

In summary, sepsis led to coagulation disorders, causing an increase in D-dimer levels and an imbalance in nutritional status, characterized by a decrease in albumin levels. Therefore, investigating the combination of D-dimer, indicating coagulation, with albumin levels, reflecting malnutrition, held significant research value. Our study introduced a novel marker called the DAR, which integrated D-dimer and albumin. Several clinical studies had explored the association between DAR and adverse outcomes in different patient populations. For instance, Wu et al. conducted a study that revealed a correlation between a high DAR and the severity of disease as well as unfavorable short-term outcomes in patients with aSAH [43]. Yao et al. discovered that elevated DAR levels ($>0.24$) were statistically linked to a higher vulnerability to preoperative DVT in elderly hip fracture patients [22]. Another study involving 717 COVID-19 patients suggested that the DAR could serve as a valuable predictor of in-hospital mortality [44]. Senol et al. also indicated that DAR may be a parameter for predicting in-hospital mortality and ICU admission in patients with COVID-19 [23]. However, the predictive value of DAR for in-hospital mortality among sepsis patients had not been definitively established. Our examination revealed that DAR could serve as a reliable predictor in a clinical practice and was identified as an independent risk factor for both ICU mortality and overall hospital mortality. Additionally, we conducted a risk stratification analysis among various subgroups. The subgroup analysis revealed consistent predictive value of DAR for all-cause mortality in both male and female patients. However, no correlation was observed between DAR and in-hospital all-cause mortality in patients with hypertension, diabetes, smoking, and AKI. Additionally, our study found that patients with elevated DAR levels were generally older, and the link between DAR and all-cause mortality was notably significant within this specific age demographic, even though the numerical differences in DAR were relatively small. Therefore, clinicians should allocate heightened attention to older patients, who were more prone to having multiple comorbidities.

Gram-negative bacteria were known to trigger robust inflammatory responses that can lead to coagulopathy, which may subsequently influence D-dimer levels [45]. Elevated D-dimer was often associated with thrombin generation and fibrinolysis activation, which were key components in the pathological mechanisms underlying sepsis [28]. In patients with sepsis resulting from gram-negative bacteria, we might observe higher D-dimer levels due to enhanced systemic inflammation and endothelial dysfunction, potentially altering the DAR. On the other hand, viral infections in the context of sepsis might have a different impact. Certain viruses can cause direct injury to endothelial cells, triggering alterations in coagulation pathways [46,47]. Although the interplay between viral infections and the DAR required further exploration, it was plausible that the effects of viral sepsis on coagulation and inflammation could similarly contribute to variations in this ratio. Therefore, understanding how different pathogens, such as gram-negative bacteria and viruses, specifically influence this ratio could provide deeper insights into their diagnostic and prognostic implications in sepsis patients.

The SOFA score was frequently utilized to evaluate the severity of the illness in sepsis patients. A study by Thakur et al. identified the SOFA score as an independent risk factor for poor prognosis in sepsis patients [48], which aligned with the findings of our study. Moreover, Spearman's test demonstrated a positive correlation between DAR and the SOFA score. This indicated that sepsis patients with higher DAR values tend to have higher SOFA score, indicating a more severe illness condition, and thus an increased likelihood of

experiencing adverse all-cause mortality. ROC curve analysis demonstrated that DAR exhibited strong predictive capability for both hospital and ICU mortality in sepsis patients. It was observed that the AUC of DAR outperformed that of Alb. Furthermore, the AUC of DAR in combination with SOFA differed significantly from that of SOFA alone. The integration of DAR and SOFA further enhanced the predictive capacity of SOFA for sepsis-related mortality. These findings suggested that DAR may serve as a more valuable indicator to assist clinicians in forecasting outcomes for sepsis patients. Dynamic monitoring of the SOFA score presented challenges and substantial costs due to the multitude of involved markers, which can impose significant burdens on both patients and physicians. In contrast, the DAR involved fewer markers, significantly reducing the time, costs, and resources required for monitoring. In terms of secondary outcomes, our investigation indicated that an increased DAR upon ICU admission can function as a valuable inflammatory indicator for predicting the development of AKI in sepsis patients. These results underscored the significance of evaluating the initial DAR value at the time of ICU admission to enable early detection of potential adverse consequences. Therefore, providing timely interventions for patients with high DAR values was crucial in preventing further deterioration.

Although there was a correlation, the precise mechanisms that underlie the association between DAR and sepsis remained unclear. It was possible that the involvement of serum D-dimer and serum Alb played a partial role in explaining this relationship. First, D-dimer was a fibrinolytic marker; studies had shown that elevated levels of D-dimer often indicated impaired coagulation function and secondary hyperfibrinolysis in patients [49]. In individuals with sepsis, the inflammatory response can damage vascular endothelial cells, leading to the release of tissue factor and resulting in disturbances in coagulation and fibrinolysis, which consequently raised D-dimer levels [26,27]. Second, serum Alb acted as a circulating antioxidant protein, and its reduced synthesis, coupled with increased catabolism, reflected an inflammatory state [50,51]. Third, the pathophysiology of sepsis was multifactorial, with apoptosis, endothelial dysfunction, oxidative stress, and immune/inflammatory responses playing significant roles in its development [52]. Therefore, the DAR was closely linked to the pathogenesis of sepsis, which could contribute to clarifying this association.

As far as we known, this research was the first to explore the link between DAR and all-cause mortality in ICU patients with sepsis. However, it was important to recognize several limitations of our study. Firstly, being a retrospective study carried out in a single center, it cannot conclusively establish causation. Despite efforts to control for confounding variables through multivariate adjustment and subgroup analyses, there may still be residual confounding elements impacting the prognosis. Secondly, our analysis only focused on commonly used biomarkers in clinical practice, overlooking other potentially more intricate combinations that might have superior predictive capabilities compared to DAR. Thirdly, the study specifically targeted sepsis patients aged 18 and above from China, which may restrict the applicability of the findings to the wider population or other disease categories. Finally, our analysis exclusively examined the prognostic value of baseline DAR, and it remained uncertain whether changed in DAR during follow-up can also anticipate mortality. To address these limitations, more extensive data from multicenter studies with larger sample sizes and longer follow-up periods will be essential to validate our results and enhance our understanding of the correlation between DAR and prognosis in sepsis patients.

## 5. Conclusion

To summarize, our study indicated that the DAR held prognostic significance for critically ill sepsis patients. The straightforward calculation of the DAR and its availability in clinical settings suggested its potential as an indicator for risk assessment of in-hospital and ICU mortality in these patients. Consequently, measuring the DAR could prove beneficial in evaluating risk and forecasting prognosis in this patient population. Further exploration should examine whether interventions aimed at the DAR can contribute to enhanced clinical outcomes for these patients.

## CRediT authorship contribution statement

**Jinhui Zhang:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization. **Chao Song:** Writing – review & editing, Conceptualization. **Zhenkui Hu:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

## Human rights

This manuscript was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines.

## Ethics statement

The studies involving human participants were reviewed and approved by the Affiliated Hospital of Jiangsu University ethics committee (No. KY2023K1007). The patients/participants provided written informed consent to participate in this study.

## Data availability

The data supporting the findings of this study will be provided by the corresponding author upon reasonable request.

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## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e39057.

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