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ORIGINAL RESEARCH

Red blood cell distribution width to albumin ratio is linked to all-cause mortality in critically ill patients with acute kidney injury: a retrospective cohort study

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Abstract

The red blood cell distribution width (RDW) to albumin ratio (RAR), a novel indicator of inflammation, is known to be associated with a poor prognosis in various diseases. The purpose of this study was to investigate whether RAR is also associated with mortality in critically ill patients with acute kidney injury (AKI). A retrospective observational study was conducted using the Medical Information Mart for Intensive Care III (MIMIC-III) database, which contains comprehensive clinical data relating to patients with AKI between 2001 and 2012. Patients were grouped into quartiles (Q1–Q4) according to the RAR. All-cause mortality was then compared across the four groups using Kaplan-Meier analysis. Cox proportional hazard models and subgroup analyses were use to investigate RAR and the prognosis of patients with AKI. A total of 3826 critically ill patients with AKI were included in this study. Based on Kaplan-Meier curve analysis, the patient group with a high-RAR exhibited elevated rates of mortality at 28 days (log-rank $p <$ 0.001). Multivariable Cox proportional hazard models identified RAR as a significant predictor of mortality at 28 days (Hazard ratio, HR (95% Confidence Interval, CI) 1.07 (1.03–1.11), $p < 0.001$), in the hospital (HR (95% CI) 1.08 (1.05–1.12), $p < 0.001$), and in the intensive care unit (ICU) (HR (95% CI) 1.06 (1.02–1.11), $p = 0.004$). Furthermore, the subgroup analysis showed that the effect of the RAR was significantly greater in patients with diabetes than in those without diabetes (p for interaction = 0.005). As the RAR increased, the mortality rate within 28 days of hospitalization and in the ICU also increased. Thus, the RAR has the potential to become an important and practical indicator for identifying a poor prognosis in critically ill patients with AKI.

Keywords

Acute kidney injury; Red blood cell distribution width; Albumin; RAR; Mortality; Prognosis

1. Introduction

Acute kidney injury (AKI) is a serious clinical condition that can cause functional disability and mortality in affected patients, especially patients who are critically ill patients [1]. AKI is a frequent cause of ICU admission and remains the leading cause of hospital mortality, thus placing a heavy burden on both families and society [2, 3]. Therefore, it is critical to be able to identify or predict potential risks in order to direct medical intervention in a timely manner. Over recent years, disease severity scores have shown significant efficacy in predicting prognoses, such as mortality and the length of hospital stay for AKI patients [4, 5]. However, these scores are not perfect predictors of disease severity and prognosis. In addition, these scores require a wide range of clinical data and cannot be used if this clinical information is not available [6]. Therefore, it is imperative to develop efficient and reliable predictive tools that can effectively enhance the management of patients with AKI. Hematological parameters are more advantageous than the more classical disease severity scores with regard to the prognostic assessment of AKI [7]. As an alternative, the red blood cell distribution width (RDW) to albumin ratio (RAR) is an easily available, inexpensive and reliable indicator, making this ratio highly appropriate for use in clinical practice.

The RDW is a common hematological parameter that reflects heterogeneity in the volume of red blood cells (RBCs) in the peripheral circulation. RDW is typically combined with other hematological indicators to facilitate the diagnosis of anemia. The RDW has been proven to be highly effective in predicting the prognosis of various diseases [8, 9], including cardiovascular disease, diabetes and other critical illnesses. More importantly, studies have indicated that RDW is also strongly associated with the mortality of patients with AKI [10, 11]. Inflammation is omnipresent in the development of

AKI [12]. Serum albumin is a routine indicator of nutritional status or inflammatory response and levels of serum albumin can be used as a simple prognostic factor for AKI [13].

Currently, the RAR is considered a simple and effective novel biomarker of inflammation. Previous research has also demonstrated the significance of the RAR for determining the prognosis of numerous conditions, such as acute myocardial infarction [14], heart failure [15], cancer [16] and sepsis [17]. Nevertheless, the association between the RAR and the prognosis of AKI has yet to be fully elucidated. The objective of this study was to investigate the correlation between the RAR and mortality from any cause and determine the influence of the RAR on patients with AKI who are critically ill and admitted to the ICU.

2. Methods

2.1 Data source

This retrospective observational study is based on a large, freely available database: the Medical Information Mart for Intensive Care III (MIMIC-III). The MIMIC-III database incorporates comprehensive clinical data from ICU patients who were admitted to Beth Israel Deaconess Medical Center in Boston, Massachusetts, from 2001 to 2012. Access to the database was granted after the responsible author passed the required examination and received an authorized certificate. One author (Lin Liao) was granted access to the dataset (record ID: 30165505) and was responsible for the extraction of data. The dataset was then screened for demographic features, laboratory indicators, and the medical histories of patients with AKI.

2.2 Inclusion and exclusion criteria

Patients diagnosed with AKI were enrolled based on specified criteria provided by the Acute Kidney Injury Network (AKIN), including a rise in serum creatinine (SCr) levels of at least 26.5 µmol/L or 1.5-fold the baseline values within 48 hours, or a urinary output of $<$0.5 mL/(kg·h) for a duration exceeding 6 hours [18]. Due to the majority of data in the MIMIC-III database being documented before the publication of the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [19], we used the AKIN criteria rather than the KDIGO criteria in the present study. It must also be noted that some previous studies have utilized the AKIN criteria for identical rationale [10, 20]. In addition, renal function was evaluated to diagnose AKI within 48 hours of admission, taking into account potential confounding factors, such as the use of antibiotics and hospital-acquired infections during the 7-day follow-up. Baseline values of SCr levels were measured for the first time following admission to the ICU. AKI staging was determined by considering both SCr levels and urinary output within the initial 48 hours of ICU admission. We included patients admitted to the ICU with a diagnosis of AKI within 48 hours of admission and recorded in the MIMIC-III database. Only patients who were above 18-years-of-age at the point of their initial admission were selected. Patients were excluded if they satisfied any of the subsequent conditions: (1) multiple hospital or ICU admissions; (2) discharged or died within 48 hours after ICU admission; (3) missing RDW and albumin records on the first day of admission, and (4) pregnant women and oncology patients. On the first day of ICU admission, the 3826 patients included in the study were categorized into four groups according to RAR quartiles. Fig. 1 shows a flowchart depicting the patient screening process.

2.3 Data extraction

Within 24 hours of ICU admission, we acquired a range of baseline characteristic data from the MIMIC-III database, including sex, age, ethnicity, vital signs (such as temperature, heart rate, respiratory rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP)), AKI stage, sequential organ failure assessment (SOFA) scores, and simplified acute physiological score II (SAPS II) scores. In addition, common laboratory indicators and comorbidities were extracted. We identified several comorbidities, including congestive heart failure (CHF), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), sepsis, hypertension, diabetes, liver disease and renal failure, all based on the documented International Classification of Diseases-9 (ICD-9) codes. The laboratory parameters consisted of RDW, albumin, white blood cell (WBC), hemoglobin, platelet, glucose, blood urea nitrogen (BUN), bilirubin, SCr and lactate concentrations. The study variable (RAR) represented RDW divided by albumin. In this study, we used RDW and albumin test results from patients admitted to the ICU for 24 hours; the maximum RDW value and the minimum albumin value were used for calculations if more than one test result was available. If data relating to continuous variables data were missing, then we interpolated with the average of the available values.

2.4 Study endpoints

The primary outcome of this study was the 28-day mortality rate of AKI patients admitted to the ICU. Secondary outcomes included in-hospital and in-ICU mortality rates.

2.5 Statistical analysis

Based on the quartiles of RAR levels on the initial day of ICU admission, the study population was categorized into four groups. First, the Kolmogorov-Smirnov method was used to perform normality tests on continuous variables initially. Data that were normally distributed characteristics are expressed as mean ± standard deviation (SD), and between-group comparisons were conducted by one-way analysis of variance (ANOVA). Data that was not normally distributed is represented by the median and interquartile range (IQR) and comparisons were performed with the non-parametric Kruskal-Wallis test. Categorical variables are given by numbers and percentages and were compared by either Pearson's Chi-squared or Fisher's exact tests. We performed a Kaplan-Meier survival analysis to evaluate the correlation between primary and secondary outcomes and RAR levels. Our analysis aimed to determine the variations in mortality rates between different groups based on various RAR indicators; differences between groups were evaluated by log-rank tests. To investigate the relationship between the RAR and mortality rates within 28 days, during hospitalization,

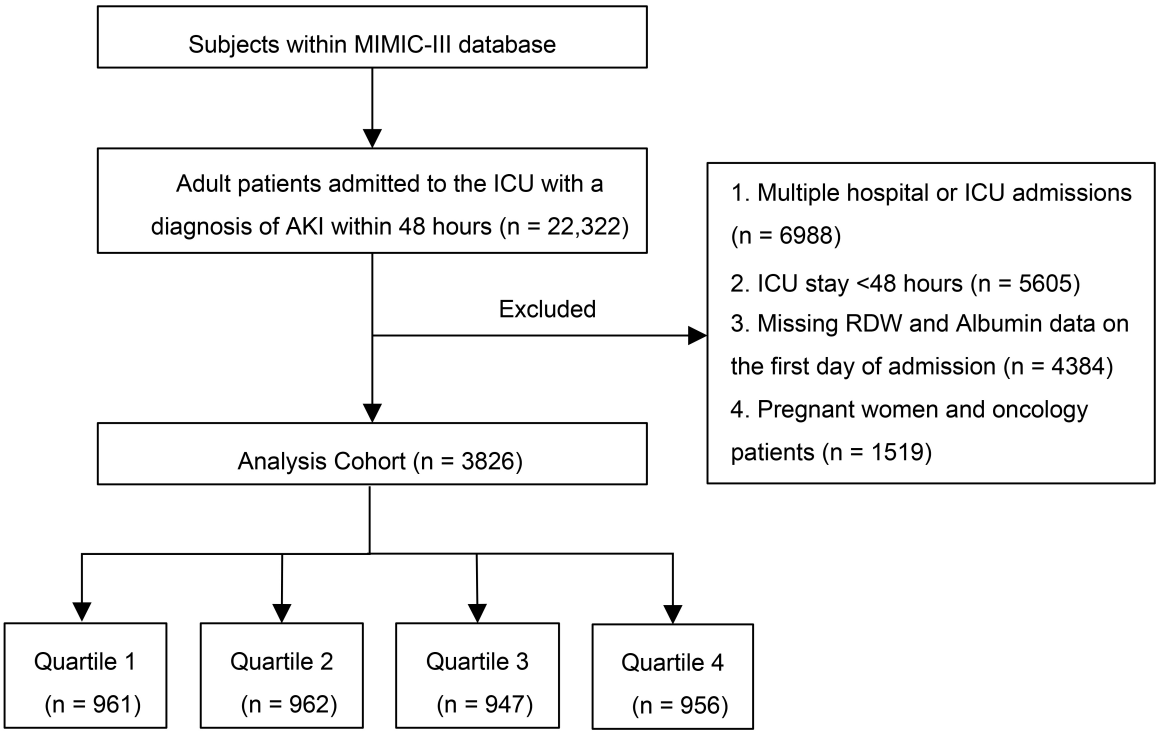

FIGURE 1. Flowchart of patient selection for analysis. MIMIC-III: Multiparameter Intelligent Monitoring in Intensive Care Database III; AKI: acute kidney injury; ICU: intensive care unit.

and in the ICU, we developed multivariate Cox proportional hazard models. These models were used to calculate the hazard ratio (HR) and the corresponding 95% confidence interval (CI). To account for possible confounding factors, three distinct models were established. No adjustments were made to covariates in model I. Model II adjusted for sex, age and ethnicity, and Model III incorporated various covariates, including sex, age, ethnicity, temperature, SBP, DBP, SOFA score, SAPS II score, WBC, hemoglobin, platelet, glucose, BUN, bilirubin, SCr, lactate, as well as the presence of CHF, CHD, COPD, hypertension, diabetes, renal failure, liver disease and sepsis. Furthermore, we conducted a subgroup investigation to evaluate the correlation between the RAR and the 28-day mortality rates of individuals with AKI, including sex, age, congestive heart failure, coronary heart disease, high blood pressure, diabetes and kidney dysfunction. SPSS statistical software (IBM SPSS Statistics, Version 25.0; Armonk, NY, USA) was used for all data analyses. For all analyses, p-value < 0.05 indicated statistical significance.

3. Results

3.1 Baseline characteristics

After screening the MIMIC-III database, a total of 3826 critically ill patients with AKI were selected for inclusion. Table 1 shows the baseline characteristics categorized according to RAR quartiles. The median RAR was 5.0 (4.1–5.3). The enrolled patients had a median age of 65.3 years, ranging from 51.6 to 78.0 years; 1655 (43.3%) were male. White patients accounted for the majority (68.2%) of the cases; sepsis (74.8%) and hypertension (52.8%) were the primary comorbid conditions. Analysis showed that the mortality rates within 28 days, during hospitalization, and in the ICU were 21.3%, 20.2% and 16.1%, respectively. The patients were categorized into four groups based on RAR quartiles of the RAR levels: RAR $\leq$4.11 (n = 961), 4.11 $<$ RAR $\leq$ 5.00 (n = 962), 5.00 $<$ RAR $\leq$ 6.33 (n = 947), and RAR $>$6.33 (n = 956). Patients exhibiting elevated RAR levels upon admission exhibited higher scores for SOFA and SAPS II scores, an increased prevalence of sepsis and liver disease, elevated levels of WBCs, BUN, SCr, bilirubin and lactate, as well as reduced levels of hemoglobin and platelets. The number of days patients spent in the hospital and the ICU gradually increased as the RAR levels increased; furthermore, the same trend was observed for 28-day, in-hospital, and in-ICU mortality rates.

3.2 The incidence rate for allcause mortality between different groups

Fig. 2 shows the Kaplan-Meier survival analysis curves; these demonstrate the occurrence of all-cause mortality in critically ill patients with AKI, categorized into quartile groups based on the RAR. The survival graphs indicated that individuals in the high RAR category experienced higher rate of mortality within 28 days when compared to those in the remaining categories ($p < 0.001$). This suggests that patients in the high-RAR quartile generally exhibited lower rates of short-term survival. There was a notable variance in mortality rate between the four groups (Q1: 11.4% *vs.* Q2: 17.3% *vs.* Q3: 20.9% *vs.* Q4: 30.5%, log-rank $p < 0.001$, Fig. 2A). Similar survival curves were obtained for in-hospital and ICU mortality rates during follow-up.

TABLE 1. Baseline characteristics of ICU patients grouped according to RAR quartiles.

Categories	Overall	Q1	Q2	Q3	Q4	*p*-value
	(N = 3826)	(N = 961)	(N = 962)	(N = 947)	(N = 956)	
Demographic						
Age, years	65.3 (51.6–78.0)	62.7 (49.9–75.9)	68.4 (52.7–79.9)	66.3 (52.2–79.0)	63.9 (51.6–77.1)	<0.001
Sex, n (%)						
Male	1655 (43.3)	341 (35.5)	439 (45.6)	424 (44.8)	451 (47.2)	<0.001
Female	2171 (56.7)	620 (64.5)	523 (54.4)	523 (55.2)	505 (52.8)	
Ethnicity, n (%)						
White	2609 (68.2)	656 (68.3)	675 (70.2)	652 (68.8)	626 (65.5)	0.473
Black	372 (9.7)	96 (10.0)	87 (9.0)	92 (9.7)	97 (10.1)	
Other	845 (22.1)	209 (21.7)	200 (20.8)	203 (21.4)	233 (24.4)	
Vital signs						
Temperature, °C	37.6 (37.1–38.2)	37.7 (37.1–38.2)	37.6 (37.1–38.2)	37.6 (37.1–38.3)	37.6 (37.0–38.1)	0.104
Heart rate, beats/min	108.0 (92.0–124.0)	105.0 (90.0–118.5)	106.5 (91.0–122.0)	109.3 (94.0–125.0)	112.0 (96.0–129.0)	<0.001
Respiratory rate, beats/min	28.0 (24.0–32.0)	26.0 (23.0–30.0)	28.0 (24.0–32.0)	28.0 (24.0–33.0)	28.0 (24.0–33.0)	<0.001
SBP, mmHg	149.0 (133.0–166.0)	147.0 (132.0–165.0)	149.0 (134.0–167.0)	149.0 (132.0–166.0)	149.0 (133.0–166.0)	0.468
DBP, mmHg	82.0 (72.0–94.0)	82.0 (72.0–95.0)	83.0 (73.0–95.0)	81.0 (72.0–94.0)	82.0 (71.0–93.8)	0.110
ICU admission						
SOFA score	6.0 (4.0–9.0)	4.0 (2.0–6.0)	6.0 (4.0–8.0)	7.0 (5.0–9.0)	8.0 (6.0–11.0)	<0.001
SAPS II score	42.0 (33.0–53.0)	35.0 (28.0–45.0)	41.0 (33.0–50.3)	44.0 (35.0–54.0)	49.0 (39.0–58.0)	<0.001
Comorbidities						
CHF, n (%)	620 (16.2)	153 (15.9)	200 (20.8)	150 (15.8)	117 (12.2)	<0.001
CHD, n (%)	926 (24.2)	304 (31.6)	275 (28.6)	200 (21.1)	147 (15.4)	<0.001
COPD, n (%)	85 (2.2)	16 (1.7)	31 (3.2)	24 (2.5)	14 (1.5)	0.033
Sepsis, n (%)	2861 (74.8)	596 (62.0)	710 (73.8)	757 (79.9)	798 (83.5)	<0.001
Hypertension, n (%)	2020 (52.8)	545 (56.7)	562 (58.4)	484 (51.1)	429 (44.9)	<0.001
Diabetes, n (%)	1107 (28.9)	261 (27.2)	322 (33.5)	272 (28.7)	252 (26.4)	0.003
Liver disease, n (%)	504 (13.2)	41 (4.3)	77 (8.0)	149 (15.7)	237 (24.8)	<0.001
Renal failure, n (%)	798 (20.9)	140 (14.6)	219 (22.8)	223 (23.5)	216 (22.6)	<0.001

TABLE 1. Continued.

Categories	Overall	Q1	Q2	Q3	Q4	*p*-value
	(N = 3826)	(N = 961)	(N = 962)	(N = 947)	(N = 956)	
AKI stage, n (%)						
Stage 1	1187 (31.0)	378 (39.3)	308 (32.0)	276 (29.1)	225 (23.5)	
Stage 2	1514 (39.6)	444 (46.2)	389 (40.4)	366 (38.6)	315 (32.9)	<0.001
Stage 3	1125 (29.4)	139 (14.5)	265 (27.5)	305 (32.2)	416 (43.5)	
Laboratory tests						
WBC, 10^9/L	14.4 (10.3–19.7)	13.7 (10.0–17.9)	14.0 (10.6–19.2)	14.9 (10.4–20.1)	15.3 (10.0–21.8)	<0.001
Hemoglobin, g/dL	9.8 (8.5–11.4)	11.4 (9.8–12.7)	10.4 (9.1–11.6)	9.5 (8.3–10.6)	8.6 (7.5–9.8)	<0.001
Platelet, 10^9/L	169.0 (109.0–234.0)	189.0 (146.0–233.0)	181.0 (128.0–246.3)	155.0 (103.0–243.0)	124.0 (70.0–214.0)	<0.001
RDW, %	15.0 (13.9–16.6)	13.8 (13.3–14.4)	14.6 (13.8–15.6)	15.5 (14.5–16.9)	17.1 (15.4–18.9)	<0.001
Albumin, g/dL	3.1 (2.6–3.5)	3.8 (3.6–4.1)	3.2 (3.0–3.4)	2.8 (2.6–3.0)	2.2 (1.9–2.5)	<0.001
Glucose, mg/dL	177.0 (138.0–241.0)	180.0 (142.0–243.5)	181.5 (144.0–250.3)	173.0 (132.0–240.0)	173.0 (134.0–231.8)	<0.001
BUN, mg/dL	32.0 (20.0–54.0)	24.0 (16.0–37.5)	33.5 (22.0–52.0)	38.0 (23.0–62.0)	38.0 (23.0–60.0)	<0.001
SCr, mg/dL	1.6 (1.1–2.8)	1.3 (1.0–1.9)	1.6 (1.2–2.7)	1.9 (1.2–3.1)	1.9 (1.2–3.2)	<0.001
Bilirubin, mg/dL	0.9 (0.5–2.4)	0.7 (0.4–1.4)	0.7 (0.4–1.7)	1.0 (0.5–2.4)	1.4 (0.6–3.5)	<0.001
Lactate, mmol/L	3.7 (2.0–4.4)	3.7 (2.2–4.0)	3.3 (1.9–4.0)	3.6 (1.9–4.5)	4.0 (2.2–6.0)	<0.001
RAR	5.0 (4.1–6.3)	3.7 (3.4–3.9)	4.5 (4.3–4.8)	5.6 (5.3–5.9)	7.6 (6.9–8.7)	<0.001
Events						
Hospital LOS, day	10.8 (6.4–18.9)	8.6 (5.6–13.9)	9.6 (6.0–16.0)	11.8 (7.0–19.6)	14.9 (8.3–25.8)	<0.001
ICU LOS, day	4.9 (3.0–9.9)	4.0 (2.8–7.6)	4.4 (3.0–8.2)	5.2 (3.1–10.8)	6.5 (3.4–13.2)	<0.001
Mortality						
28-day, n (%)	814 (21.3)	125 (13.0)	188 (19.5)	214 (22.6)	287 (30.0)	<0.001
In-hospital, n (%)	771 (20.2)	110 (11.4)	171 (17.8)	198 (20.9)	292 (30.5)	<0.001
In-ICU, n (%)	615 (16.1)	92 (9.6)	138 (14.3)	153 (16.2)	232 (24.3)	<0.001

Q1 (RAR <4.11), Q2 (4.11 < RAR ≤ 5.00), Q3 (5.00 < RAR ≤ 6.33), Q4 (RAR >6.33). Abbreviations: ICU: intensive care unit; RAR: the ratio of red blood cell distribution width to albumin; SBP: systolic blood pressure; DBP: diastolic blood pressure; SOFA: sequential organ failure assessment; SAPS II: simplified acute physiological score II; CHF: congestive heart failure; CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; WBC: white blood cell; RDW: red cell distribution width; BUN: blood urea nitrogen; SCr: serum creatinine; LOS: length of stay; AKI: acute kidney injury.

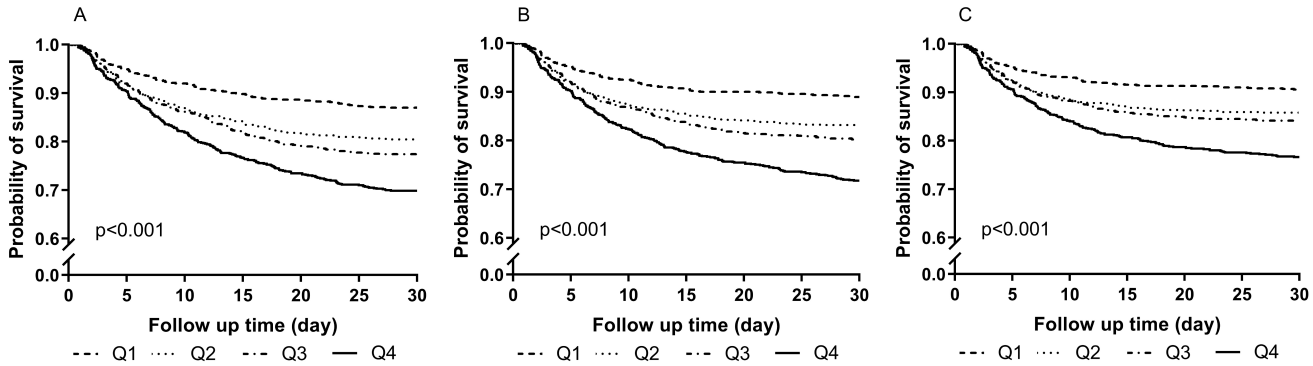

FIGURE 2. Kaplan-Meier survival analysis curves for mortality. (A) represents 28-day mortality; (B) represents in-hospital mortality; (C) represents in-ICU mortality. Q1 (RAR ≤4.11), Q2 (4.11 < RAR ≤ 5.00), Q3 (5.00 < RAR ≤ 6.33), Q4 (RAR >6.33).

3.3 Association between all-cause mortality and the RAR

Table 2 shows the Cox proportional hazard models for all-cause mortality. The Cox proportional hazard models indicated a significant correlation between the RAR and 28-day mortality both in the unadjusted model (HR (95% CI) 1.14 (1.11–1.17), $p < 0.001$) and the fully adjusted model (HR (95% CI) 1.07 (1.03–1.11), $p < 0.001$). For 28-day mortality, the HR (95% CI) was 1.57 (1.25–1.97), 1.83 (1.47–2.28), and 2.54 (2.06–3.13) for quartiles 2, 3 and 4, respectively, when compared with quartile 1 of the reference group in model 1 without adjustment for variables (all $p < 0.001$). Even after accounting for various factors, this correlation remained statistically significant. The Cox proportional hazard models of the RAR and mortality rates yielded comparable findings for both the hospital (model 3: HR (95% CI) 1.08 (1.05–1.12), $p < 0.001$) and in the ICU (model 3: HR (95% CI) 1.06 (1.02–1.11), $p = 0.004$). Furthermore, subgroup analysis (Table 3) revealed that the impact of RAR was significantly greater in individuals with CHD when compared to those without CHD (p for interaction = 0.035). Comparable findings were noted among individuals with diabetes (p for interaction = 0.005).

4. Discussion

In this study, we discovered an association between elevated RAR levels and higher mortality rates within 28 days, during hospitalization, and in the ICU for patients with AKI. Our data also suggested that elevated RAR levels could potentially be used as a predictive factor for increased mortality rates in critically ill patients with AKI. However, it is important to consider confounding factors including multiple clinical and laboratory variables, as these factors may weaken the observed correlation between RAR levels and mortality rates.

AKI originates from a complex interaction between renal insufficiency and subsequent inflammation and coagulation [21]. Studies have indicated that RDW is closely linked to unfavorable prognosis in critically ill patients with AKI and represents an indicator of chronic inflammation that is considered a valid predictor for the prognosis of AKI [10, 11, 22]. Although we identified the predictive value of RDW for all-cause mortality risk has been revealed, the mechanisms underlying the relationship between these factors remain unclear. Both inflammation and oxidative stress may play a key role. Inflammatory cytokines inhibit iron metabolism and bone marrow function, thereby suppressing the production of erythropoietin; this subsequently affects the maturation of erythrocytes, thus leading to impaired erythrocyte synthesis and increased RDW values [23]. AKI patients in the ICU often exhibit symptoms associated with the activation of oxidative stress, including metabolic disorders, sepsis, and hemodynamic dysregulation [24]. The rate of erythrocyte destruction and the release of immature erythrocytes into the circulation are also increased by oxidative stress, consequently leading to an increase in RDW values. Serum albumin, a vital protein with anti-inflammatory, nutritional, and hematological characteristics, effectively suppresses platelet activation and aggregation [25]. Serum albumin is traditionally evaluated to assess the nutritional status of patients who are critically ill. Hypoproteinemia is regarded as a dependable indicator of prognosis in numerous critically ill patients with chronic conditions [26]. Research has shown that low levels of albumin levels may be associated with hemodilution due to blood volume overload, chronic inflammation, malnutrition, and cachexia; these factors may lead to reduced albumin synthesis [15]. Malnutrition is common in critically ill patients, and both nutritional status and chronic inflammation are known to reduce the levels of albumin in patients with AKI. Junhua Lv *et al.* [27] recently reported a strong correlation between mortality rates and serum albumin levels in critically ill patients with AKI. Furthermore, these authors suggested that there is an inverse relationship between albumin levels and mortality rates at both day 28 and day 90 in critically ill patients with AKI. Our study expands on previous discoveries by additionally identifying the amalgamation of these indicators as favorable indicators for the prognosis of critically ill individuals suffering from AKI.

The RAR has been reported as a simple and novel indicator of inflammation that can be widely used to determine the prognosis of various inflammatory diseases. The RAR combines RDW and albumin indicators to reflect the levels of these two factors and the pathological states of both hematopoietic dysfunction and hypoproteinemia. The RAR has been demon-

TABLE 2. Cox proportional hazard ratios (HRs) for all-cause mortality.

Categories	Model 1		Model 2		Model 3	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
28-day mortality						
RAR	1.14 (1.11–1.17)	<0.001	1.12 (1.09–1.16)	<0.001	1.07 (1.03–1.11)	<0.001
RAR quartiles						
Q1 (N = 961)	Ref.		Ref.		Ref.	
Q2 (N = 962)	1.57 (1.25–1.97)	<0.001	1.51 (1.21–1.90)	<0.001	1.35 (1.07–1.71)	0.011
Q3 (N = 947)	1.83 (1.47–2.28)	<0.001	1.78 (1.43–2.23)	<0.001	1.35 (1.07–1.71)	0.013
Q4 (N = 956)	2.54 (2.06–3.13)	<0.001	2.52 (2.04–3.11)	<0.001	1.54 (1.20–1.97)	0.001
Hospital death						
RAR	1.17 (1.14–1.20)	<0.001	1.14 (1.11–1.17)	<0.001	1.08 (1.05–1.12)	<0.001
RAR quartiles						
Q1 (N = 961)	Ref.		Ref.		Ref.	
Q2 (N = 962)	1.62 (1.28–2.06)	<0.001	1.58 (1.24–2.01)	<0.001	1.41 (1.10–1.80)	0.006
Q3 (N = 947)	1.93 (1.53–2.44)	<0.001	1.90 (1.50–2.40)	<0.001	1.39 (1.08–1.79)	0.010
Q4 (N = 956)	2.95 (2.37–3.68)	<0.001	2.93 (2.35–3.65)	<0.001	1.69 (1.30–2.18)	<0.001
ICU death						
RAR	1.16 (1.12–1.19)	<0.001	1.12 (1.08–1.16)	<0.001	1.06 (1.02–1.11)	0.004
RAR quartiles						
Q1 (N = 961)	Ref.		Ref.		Ref.	
Q2 (N = 962)	1.56 (1.20–2.03)	0.001	1.54 (1.18–2.00)	0.001	1.36 (1.04–1.78)	0.026
Q3 (N = 947)	1.77 (1.36–2.29)	<0.001	1.76 (1.35–2.27)	<0.001	1.26 (0.96–1.67)	0.101

Model 1: unadjusted; Model 2: adjusted for age, sex, ethnicity; Model 3: adjusted for age, sex, ethnicity, temperature, SBP, DBP, SOFA score, SAPS II score, white blood cell, hemoglobin, platelet, glucose, BUN, bilirubin, serum creatinine, lactate, congestive heart failure, coronary heart disease, COPD, hypertension, diabetes, renal failure, liver disease and sepsis. Abbreviations: HR: hazard ratio; CI: confidence interval; ICU: intensive care unit; RAR: the ratio of red blood cell distribution width to albumin.

TABLE 3. Subgroup analysis of the relationship between 28-day mortality and the RAR.

Subgroup	NO. of patients (%)	HR (95% CI)	*p*-value	*p* for interaction
Sex				
Male	484/2171 (22.3)	1.14 (1.10–1.19)	<0.001	0.920
Female	330/1655 (19.9)	1.15 (1.10–1.19)	<0.001	
Age				
<65 years	300/1897 (15.8)	1.15 (1.11–1.20)	<0.001	0.379
≥65 years	514/1929 (26.6)	1.17 (1.12–1.22)	<0.001	
CHD				
No	638/2900 (22.0)	1.13 (1.10–1.16)	<0.001	0.035
Yes	176/926 (19.0)	1.23 (1.14–1.32)	<0.001	
CHF				
No	678/3206 (21.1)	1.15 (1.12–1.18)	<0.001	0.311
Yes	136/620 (21.9)	1.10 (1.00–1.20)	0.058	
Hypertension				
No	407/1806 (22.5)	1.13 (1.10–1.17)	<0.001	0.501
Yes	407/2020 (20.1)	1.16 (1.11–1.21)	<0.001	
Diabetes				
No	582/2719 (21.4)	1.13 (1.09–1.16)	<0.001	0.005
Yes	232/1107 (21.0)	1.26 (1.17–1.35)	<0.001	
Renal failure				
No	624/3028 (20.6)	1.15 (1.12–1.84)	<0.001	0.286
Yes	190/798 (23.8)	1.11 (1.03–1.19)	0.005	

Abbreviations: HR: hazard ratio; CI: confidence interval; CHD: Coronary artery disease; CHF: Congestive heartfailure.

strated to be a better predictor of adverse disease outcomes than RDW and albumin levels alone [17, 28]. Qingwei Ni *et al.* [15] reported that the RAR is a promising predictor of mortality rates in patients with heart failure. Elevated RAR levels have also been reported to be significantly associated with increased all-cause mortality in patients with sepsis [17] and chronic obstructive pulmonary disease (COPD) [29]. AKI is a common cause of death in the ICU along with the above-mentioned diseases. Our present results show that the RAR is closely related to mortality rates in critically ill patients with AKI, although the influence of confounding factors, such as comorbidities, cannot be completely excluded. As the RAR increases, the clinical prognosis of critically ill patients with AKI is likely to be exacerbated. It is interesting to note that several severity scoring systems, including the SOFA and SAPS II, have been widely used to predict the prognosis of critically ill patients. However, Shigehiko Uchino *et al.* [30] concluded that these evaluation methods do not exhibit a significant level of differentiation or accuracy in terms of forecasting death rates among individuals suffering from acute kidney failure. In addition, the scoring systems of SOFA and SAPS II scoring systems are complex and may be time-consuming. In contrast, RDW and albumin results are readily available in the laboratory and are simpler and more efficient. However, RAR can be affected by the patient's course of treatment resulting in less stable results; consequently, we do not have sufficient evidence to conclude that RAR is superior to existing severity scoring systems. Notably, in this study, we discovered a positive correlation between RAR levels and both SOFA and SAPS II scores in critically ill patients with AKI; these findings concur with those reported previously [31]. Further studies are now needed to evaluate the prognostic efficacy of combining the RAR indicator and severity scoring systems to predict the outcomes of patients with AKI. This combined approach has the potential to provide more accurate predictive results for critically ill patients with AKI.

In addition, we used subgroup analysis to investigate the correlation between RAR levels and 28-day mortality rates among critically ill patients with AKI and found that individuals with AKI and diabetes had elevated 28-day mortality rates when compared to those without diabetes. Previous studies have shown that individuals with diabetes have a higher likelihood of developing AKI compared to those without diabetes [32]. Recently, Guozhi Jiang *et al.* [33] showed that patients with diabetes and AKI had a higher risk of all-cause mortality than patients without AKI; we obtained similar results in the present study. In addition, we identified a relatively higher mortality rate in AKI patients with CHD than patients without CHD. Therefore, the RAR could serve as a significant indicator for forecasting the outlook of individuals with AKI who have diabetes or heart failure. We are concerned about the findings of our subgroup analysis due to the potential impact of variations among diverse populations. Thus, additional research is required to validate our discoveries.

The present study also has some limitations that need to be considered. First, the study was conducted as a retrospective cohort investigation, and although we made significant attempts to account for potential confounding factors, it proved challenging to completely mitigate selection and confounding biases which represent a limitation for all retrospective studies. Second, only patients diagnosed with AKI within 48 hours of ICU admission and who had RDW and albumin levels tested on the first day were included; this may be an important source of selection bias and potential confounding; therefore, our conclusions require a well-designed multicenter prospective study for further validation. Third, the generalizability of our findings is inherently limited by the fact that the investigated study period was from 2001 to 2012; during this period, the diagnostic criteria and treatment choices of the investigated patient population have changed. Consequently, the results of this study are only used as a reference to support subsequent studies. Fourth, the MIMIC-III database only included patients with AKI admitted to the ICU; thus, it remains unclear whether our conclusions apply to other AKI populations.

5. Conclusions

In critically ill AKI patients, we identified a positive correlation between the RAR and the rates of all-cause mortality within 28 days, during hospitalization, and in the ICU. The monitoring of RAR levels is cost-effective, efficient, simple, and has the potential to be an important and practical indicator for identifying a poor prognosis in critically ill patients with AKI. However, further research is required to determine its value in clinical practice.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

FL and LL—were responsible for the study concept and study design; critical revision of the manuscript for important intellectual content. LL—performed data extraction; XTL and MC—were responsible for data analysis; XTL—drafting of the manuscript. All authors have read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Approval for the project was granted by the Institutional Review Boards (IRB) at both the Massachusetts Institute of Technology (MIT, Cambridge, MA, USA) and Beth Israel Deaconess Medical Center (BIDMC). Private patient information was removed from the database to protect patient privacy; thus, informed consent was waived.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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