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CORRELATION BETWEEN RED BLOOD CELL DISTRIBUTION WIDTH–TO–PLATELET RATIO AND MORTALITY IN PATIENTS WITH ACUTE RESPIRATORY DISTRESS SYNDROME: A RETROSPECTIVE COHORT STUDY

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ABSTRACT—**Background:** This study aims to assess the prognostic value of red blood cell distribution width–to–platelet ratio (RPR) in acute respiratory distress syndrome (ARDS) patients. **Methods:** The data collected from 540 ARDS patients from 2001 to 2012 were obtained from the Medical Information Mart for Intensive Care III Database. The 28-day all-cause mortality risk was considered as the primary outcome parameter, and the secondary outcomes were 60- and 90-day all-cause mortality. The association between RPR (≥0.19 vs. <0.19) and mortality was assessed by Cox proportional hazards models, and potential nonlinear associations were assessed by restricted cubic spline regression analysis. **Results:** The 28-day all-cause mortality was 22.4%. Among the 121 deaths, 92 (20.0%) presented with an RPR <0.19, and 29 patients had RPR ≥0.19 ($P < 0.001$). The 60- and 90-day all-cause mortality was 27% and 28.7%, respectively. After adjusting for the relevant factors in the multivariate model, RPR ≥0.19 was independently correlated with the 28-day all-cause mortality (hazard ratio, 2.74; 95% confidence interval, 1.46–5.15; $P = 0.002$). There was no nonlinear relationship between RPR and the risk of 28-day all-cause mortality (P for overall association <0.001, P for nonlinear = 0.635). Similar results were observed for both the pneumonia and nonpneumonia subgroups and sensitivity analyses. **Conclusions:** The data promote the use of RPR as a valuable prognostic indicator for ARDS patients.

KEYWORDS—ARDS, platelet, mortality, red blood cell distribution width

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a common syndrome of acute onset with high mortality in the medical intensive care unit (ICU). The estimated incidence of ARDS in 2014 was 193.4 cases per 100,000 people (1). Although the treatment methods including lung protective ventilation strategy and prone position have been optimized in recent years, the mortality rate for ARDS patients has not reduced significantly. The results of 459 ICUs from 50 countries implied that the mortality of ARDS increased as the disease worsened with the hospital mortalities of mild, moderate, and severe ARDS found to be 34.9%, 40.3%, and 46.1%, respectively (2).

Hypoxemia and respiratory failure are the main clinical features of ARDS. Its pathogenesis is complex and often accompanied by the impairment of other organ functions. It was generally found that nonpulmonary organ dysfunction had already occurred before patients met the criteria for ARDS (3). Nonpulmonary organ failure often precedes development of the disease (4). Multiorgan failure rather than refractory hypoxemia was found to be responsible for most ARDS-related deaths (5,6). However, early detection and intervention can reduce the progress of the disease to a certain extent. The red blood cell distribution width (RDW) and platelet (PLT) counts are routine test items for hospitalized patients. Several studies were conducted to investigate the potential predictive functions of the RDW-to-PLT ratio (RPR) (7–10). However, the correlation between RPR and the prognosis of ARDS patients had not been analyzed in detail. The purpose of this study was to determine the predictive value of the RPR and short-term prognosis of ARDS patients.

METHODS

Data source

The database used for analysis was from the open resources of Medical Information Mart for Intensive Care (MIMIC-III, version 1.4, the Laboratory for Computational Physiology, MIT Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, 02139, Massachusetts, USA) (11). The MIMIC-III database contains 53,423 hospital admissions of adult patients (aged ≥16 years) admitted to critical care units at Beth Israel Deaconess Medical Center in Boston from 2001 to 2012. The database was deprivatized and approved by the institutional review board of Beth Israel Deaconess Medical Center (Boston, MA) and the Massachusetts Institute of Technology (Cambridge, MA). A course in "protecting human research participants that includes Health Insurance Portability and Accountability Act requirements" on the Web site of the National Institutes of health was completed by all the authors in this study. Access to the database was subsequently approved (no. 30165505).

Study population

The included diseases in the present study were classified by using the *International Classification of Diseases, Ninth Revision*. The inclusion criteria were as follows: (*a*) ≥18 years and (*b*) all patients with ARDS were diagnosed according to the Berlin definition (12): (1) within 1 week of a known clinical insult or new or worsening respiratory symptoms; (2) bilateral opacities on chest imaging not fully explained by effusions, lobar or lung collapse, or nodules; (3) respiratory failure not fully

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explained by cardiac failure or fluid overload; (4) ARDS was divided into mild, moderate, and severe according to the arterial oxygen (PaO_2) to fraction of inspired oxygen (FIO_2): mild (200 < PaO_2/FIO_2 ≤ 300 mmHg with positive end-expiratory pressure (PEEP) or continuous positive airway pressure ≥5 cmH_2O), moderate (100 < PaO_2/FIO_2 ≤ 200 mmHg and PEEP ≥5 cmH_2O), and severe (PaO_2/FIO_2 <100 mmHg and PEEP ≥5 cm H_2O); and (*c*) RDW and PLT data were complete.

Certain patients were excluded by the following criteria: admitted to the ICU for less than 3 days; suffering from cancer, AIDS, hematologic diseases, or rheumatoid arthritis; or a history of chronic alcohol or drug abuse.

Data extraction

The data were extracted from the database using transact-SQL language and codes from the MIMIC code repository. Clinical data of all eligible patients were collected: the RDW used was the maximum value obtained during the first and third days after ICU admission, and the PLT was the minimum value; the RPR is RDW-to-PLT ratio; demographic information included gender, ethnicity, and smoking; clinical pathology data included the temperature, heart rate, respiratory rate, and mean blood pressure; comorbidities included pneumonia, atrial fibrillation, chronic obstructive pulmonary disease, respiratory failure, acute kidney injury, weight loss, congestive heart failure, hypertension, chronic pulmonary, hypothyroidism, renal failure, coagulopathy, diabetes, and obesity; the worst biochemical data collected during the first day of ICU admission records were as follows: white blood cells, hemoglobin, potential of hydrogen, base excess, arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FIO_2), hematocrit, creatinine, prothrombin time, partial thromboplastin time, glucose, and arterial partial pressure of carbon dioxide ($PaCO_2$) were used; whether there was a need for therapeutic interventions such as mechanical ventilation, vent hours, PEEP, and renal replacement therapy or vasopressors during the stay in

TABLE 1. **Baseline demographic and clinical characteristics of the 540 participants in this study based on the first-day RPR groups***

Characteristics	Overall (n = 540)	1st-day RPR		*P*
		<0.19 (n = 461)	≥0.19 (n = 79)	
Age, y	57.80 ± 18.40	58.96 ± 18.16	51.03 ± 18.49	<0.001
Gender, n (%)				0.659
Female	231 (42.8)	199 (43.2)	32 (40.5)	
Male	309 (57.2)	262 (56.8)	47 (59.5)	
Ethnicity, n (%)				0.417
White	362 (67.0)	314 (68.1)	48 (60.8)	
Black	32 (5.9)	27 (5.9)	5 (6.3)	
Other	146 (27.0)	120 (26.0)	26 (32.9)	
Smoking, n (%)				0.048
No	132 (24.4)	116 (25.2)	16 (20.3)	
Yes	270 (50.0)	236 (51.2)	34 (43.0)	
Unknown	138 (25.6)	109 (23.6)	29 (36.7)	
Temperature, °C	37.94 ± 0.91	37.95 ± 0.91	37.91 ± 0.87	0.696
Heart rate, beats/min	114.87 ± 21.88	113.53 ± 21.81	122.70 ± 20.71	0.001
Respiratory rate, beats/min	31.33 ± 7.90	31.28 ± 7.67	31.57 ± 9.15	0.767
MBP, mmHg	55.37 ± 13.64	55.71 ± 13.28	53.39 ± 15.56	0.162
SOFA score	7.04 ± 3.19	6.48 ± 2.86	10.32 ± 3.09	<0.001
qSOFA score, n (%)				0.487
0	9 (1.7)	7 (1.5)	2 (2.5)	
1	90 (16.7)	79 (17.1)	11 (13.9)	
2	364 (67.4)	306 (66.4)	58 (73.4)	
3	77 (14.3)	69 (15.0)	8 (10.1)	
SAPS II	42.20 ± 13.98	41.75 ± 13.86	44.85 ± 14.42	0.068
Atrial fibrillation, n (%)	136 (25.2)	123 (26.7)	13 (16.5)	0.053
COPD, n (%)	15 (2.8)	13 (2.8)	2 (2.5)	>0.999
Respiratory failure, n (%)	432 (80.0)	369 (80.0)	63 (79.7)	0.951
Pneumonia, n (%)	312 (57.8)	275 (59.7)	37 (46.8)	0.033
Diabetes, n (%)	143 (26.5)	134 (29.1)	9 (11.4)	0.001
Congestive heart failure, n (%)	211 (39.1)	192 (41.6)	19 (24.1)	0.003
Hypertension, n (%)	213 (39.4)	200 (43.4)	13 (16.5)	<0.001
Chronic pulmonary, n (%)	115 (21.3)	106 (23.0)	9 (11.4)	0.02
Hypothyroidism, n (%)	41 (7.6)	35 (7.6)	6 (7.6)	0.999
Renal failure, n (%)	61 (11.3)	55 (11.9)	6 (7.6)	0.261
Coagulopathy, n (%)	99 (18.3)	63 (13.7)	36 (45.6)	<0.001
Obesity, n (%)	38 (7.0)	34 (7.4)	4 (5.1)	0.458
Weight loss, n (%)	31 (5.7)	25 (5.4)	6 (7.6)	0.614
Alcohol abuse, n (%)	62 (11.5)	49 (10.6)	13 (16.5)	0.133
AKI, n (%)				0.002
Stage 1	125 (23.1)	111 (24.1)	14 (17.7)	
Stage 2	237 (43.9)	212 (46.0)	25 (31.6)	
Stage 3	125 (23.1)	94 (20.4)	31 (39.2)	
Sepsis, n (%)	451 (83.5)	384 (83.3)	67 (84.8)	0.738
Septic shock, n (%)	72 (13.3)	61 (13.2)	11 (13.9)	0.867
ARDS, n (%)				<0.001
Mild	64 (11.9)	58 (12.6)	6 (7.6)	
Moderate	252 (46.7)	228 (49.5)	24 (30.4)	
Severe	224 (41.5)	175 (38.0)	49 (62.0)	

*Data are n presented as mean ± SD or median (IQR) of the percentages, unless specified otherwise. Because of rounding of values, the total percentage may not be exactly 100%.

AKI, acute kidney injury; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MBP, mean blood pressure; qSOFA, quick Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

TABLE 2. **Baseline laboratory characteristics the 540 participants in this study based on the first-day RPR groups***

Characteristics	Overall (n = 540)	1st-day RPR		P
		<0.19 (n = 461)	≥0.19 (n = 79)	
WBC, $\times 10^9$/L	16.52 ± 7.60	16.94 ± 7.58	14.06 ± 7.33	0.002
Hemoglobin, g/dL	10.20 ± 2.13	10.48 ± 2.02	8.54 ± 2.01	<0.001
Hematocrit, %	30.02 ± 6.25	30.93 ± 5.89	24.67 ± 5.62	<0.001
Creatinine, mg/dL	1.20 (0.90, 1.90)	1.20 (0.90, 1.80)	1.20 (0.85, 2.20)	0.278
PT, s	14.90 (13.60, 17.60)	14.60 (13.40, 16.70)	18.70 (16.15, 23.25)	<0.001
PTT, s	34.65 (28.60, 52.92)	33.20 (27.80, 46.20)	49.40 (36.50, 78.65)	<0.001
Glucose, mg/dL	203.52 ± 94.64	204.08 ± 96.54	200.24 ± 83.16	0.739
PH	7.26 ± 0.12	7.27 ± 0.11	7.23 ± 0.12	0.002
BE, mmol/L	–5.00 (–9.00, –1.00)	–4.00 (–8.00, 0.00)	–9.00 (–12.00, –5.00)	<0.001
$PaCO_2$, mmHg	52.51 ± 16.12	53.10 ± 16.59	49.03 ± 12.59	0.038
PaO_2/FIO_2, mmHg	114.00 (76.92, 166.00)	120.00 (80.00, 170.00)	87.00 (57.75, 130.00)	<0.001
Vent times, h	159.87 (73.45, 309.25)	147.00 (68.33, 309.58)	181.25 (91.22, 297.88)	0.159
RRT, n (%)	78 (14.4%)	51 (11.1%)	27 (34.2%)	<0.001
Vasopressor, n (%)	353 (65.4%)	295 (64.0%)	58 (73.4%)	0.104
PEEP, cm H_2O	8.60 ± 4.04	8.36 ± 3.89	10.00 ± 4.60	0.001
1st-day RDW, %	14.99 ± 2.08	14.67 ± 1.74	16.83 ± 2.80	<0.001
3rd-day RDW, %	15.11 ± 1.97	14.84 ± 1.73	16.71 ± 2.48	<0.001
1st-day PLT, $\times 10^9$/L	179.00 (118.75, 246.25)	194.00 (145.00, 257.00)	58.00 (45.00, 71.50)	<0.001
3rd-day PLT, $\times 10^9$/L	167.50 (104.00, 232.00)	186.00 (134.00, 243.00)	67.00 (45.50, 79.50)	<0.001
1st-day RPR	0.08 (0.06, 0.13)	0.07 (0.06, 0.10)	0.28 (0.23, 0.36)	<0.001
3rd-day RPR	0.09 (0.06, 0.15)	0.08 (0.06, 0.11)	0.26 (0.20, 0.39)	<0.001
28-d Mortality, n (%)	121 (22.4%)	92 (20.0%)	29 (36.7%)	0.001
60-d Mortality, n (%)	146 (27.0%)	113 (24.5%)	33 (41.8%)	0.001
90-d Mortality, n (%)	155 (28.7%)	122 (26.5%)	33 (41.8%)	0.005

*Data are presented as mean ± SD or median (IQR) of the percentages, unless specified otherwise. Because of rounding of values, the total percentage may not be exactly 100%.

1st-day RDW, the 1st day of red blood cell distribution width after ICU admission; 3rd-day RDW, the third day of red blood cell distribution width after ICU admission; 1st-day PLT, the first day of platelet after ICU admission; 3rd-day PLT, the third day of platelet after ICU admission; 1st-day RPR, the first day of red blood cell distribution width–to–platelet ratio after ICU admission; 3rd-day RPR, the third day of red blood cell distribution width–to–platelet ratio after ICU admission; BE, base excess; ICU, intensive care unit; IQR, interquartile range; PaO_2/FIO_2, arterial partial pressure of oxygen to fraction of inspired oxygen; PEEP, positive end-expiratory pressure; PH, potential of hydrogen; PT, prothrombin time; PTT, partial thromboplastin time; RRT, renal replacement therapy; WBC, white blood cells.

ICU; the worst scores obtained during the first day of ICU admission for Simplified Acute Physiology Score (SAPS II), Sequential Organ Failure Assessment (SOFA) and quick Sequential Organ Failure Assessment (qSOFA) were used.

Statistical analysis

The overall variables were divided into three groups: numeric, binary (with two levels), and factor variables (≥2 levels). For each type of variables, different imputation methods were applied. Predictive mean matching was used to impute numeric variables, and logistic regression and Bayesian polytomous regression were used for binary and factor variables, respectively. In order to obtain the missing values, we performed a missing data analysis on the 540 patients used in this study (Supplementary Table 1, http://links.lww.com/SHK/B538). Data were presented as means and SDs for normally distributed continuous variables, and as medians and interquartile ranges for non–normally distributed continuous variables. The Shapiro-Wilk test was used to determine normality. Frequency with percentages was used to describe categorical variables. The optimal cutoff value (0.19) of the first-day RPR was calculated by maximally selected rank statistics based on primary outcome using the surv_cutpoint function in R package survminer version 0.4.9 (Supplementary Fig. 1, http://links.lww.com/SHK/B539). Baseline characteristics were summarized according to the first-day RPR and compared between the participants' first-day RPR <0.19 and the first-day RPR ≥0.19 using the χ^2 test, ANOVA, or Mann-Whitney *U* test, as appropriate. Survival curves were designed using the Kaplan-Meier method, and comparisons were made using the log-rank test. Correlation analyses of the first- and third-day RPR values were conducted by using the Pearson test, and comparisons were made using Wilcoxon signed rank test. To examine the association between the first-day RPR (≥0.19 vs. <0.19) and 28-, 60-, and 90-day all-cause mortality, the Cox proportional hazards models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). To evaluate the performance of the models, a receiver operating characteristic (ROC) curve analysis was conducted, and Delong test comparisons among the area under the ROC curves (AUCs) were performed.

Sensitivity analyses were conducted as follows: repeating all analyses using the complete data set (480 patients) without multiple imputations. Two-sided $P < 0.05$ was considered as statistically significant. All analyses were performed using R statistical software version 4.1.0 (R Foundation, Indianapolis, IN).

RESULTS

Baseline characteristics

The patients' baseline characteristics are presented in Tables 1 and 2. A total of 540 patients were included into the final cohort, including 309 men (57.2%) and 231 women (42.8%) with a mean age of 57.80 ± 18.40 years. The first- and the third-day RPR distributions are shown in Figure 1, A and B. The first- and third-day RPR correlation analysis showed a high correlation ($r = 0.84$, $P < 0.001$, Fig. 1, C and D)).

The baseline clinical characteristics of each group stratified by the RPR cutoff value of 0.19 were calculated by maximally selected rank statistics Supplementary Figure 1, http://links.lww.com/SHK/B539. Among the 540 patients, 461 and 79 patients were in the RPR <0.19 and ≥0.19 groups, respectively. The proportion of severe ARDS patients in the RPR ≥0.19 group was significantly higher than that in RPR <0.19 group ($P \leq 0.001$).

Association between RPR and mortality on the ARDS

Overall, the 28-day all-cause mortality was 22.4%. This was significantly higher in patients with RPR ≥0.19 when compared with RPR <0.19 ($P < 0.001$). The 60- and 90-day all-cause mortality was 27% and 28.7%, respectively. A Kaplan-Meier survival

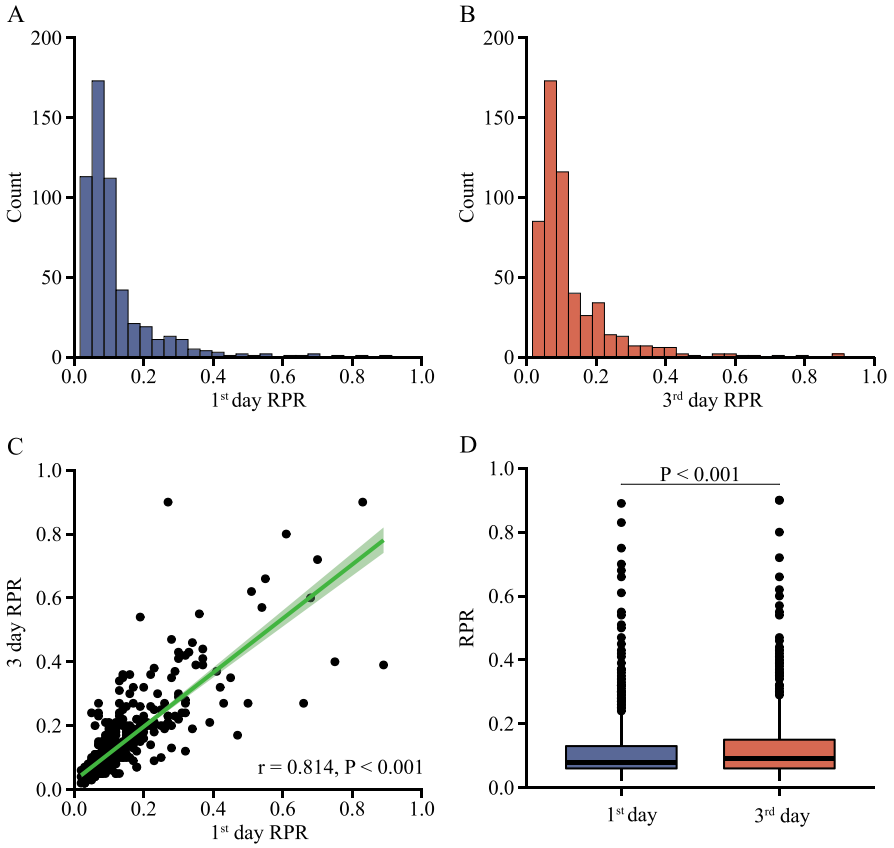

FIG. 1. **The distribution of the first- and third-day RPR values.** A, A histogram of the first-day RPR. B, A histogram of the third-day RPR. C, Correlation analysis of first- and third-day RPR using the Pearson test. D, Comparison of first- and third-day RPR using the Wilcoxon signed rank test. First-day RPR, the first day of red blood cell distribution width–to–platelet ratio after ICU admission; ICU, intensive care unit; third-day RPR, the third day of red blood cell distribution width–to–platelet ratio after ICU admission.

curve implicated that the RPR ≥0.19 group had the highest mortality rate during the 28-, 60-, and 90-day all-cause mortality during follow-up when compared with the RPR <0.19 (log-rank $P < 0.001$, Fig. 2).

Table 3 shows the associations between RPR and 28-, 60-, and 90-day all-cause mortality using the Cox regression model. After adjusting for all potential confounders (in model 5), RPR ≥0.19 was independently associated with a higher risk of 28-day all-cause mortality (HR, 2.74; 95% CI, 1.46–5.15; $P = 0.002$). A similar result was obtained for the 60-day (HR, 2.23; 95% CI, 1.27–3.92; $P = 0.005$) and 90-day all-cause mortality (HR, 2.05; 95% CI, 1.18–3.57; $P = 0.011$). Similar results were also found when a complete data analysis was conducted (Supplementary Table 2, http://links.lww.com/SHK/B538).

The potential nonlinear associations were explored by using a 3-knotted restricted cubic spline regression analysis (Fig. 3). After controlling for confounders, there was no nonlinear relationship between the first-day RPR and the risk of 28-day all-cause mortality (P for overall association <0.001, P for nonlinear = 0.635). Likewise, there was no nonlinear relationship between the first-day RPR and the risk of 60-day (P for overall association <0.001, P for nonlinear = 0.597) and 90-day all-cause mortality (P for overall association <0.001, P for nonlinear = 0.795).

Subgroup analyses

Among the 540 patients with ARDS, 228 patients (43.2%) had no pneumonia, and 312 (57.8%) had pneumonia. The Kaplan-Meier curves are shown in Figure 4. Patients who had a higher

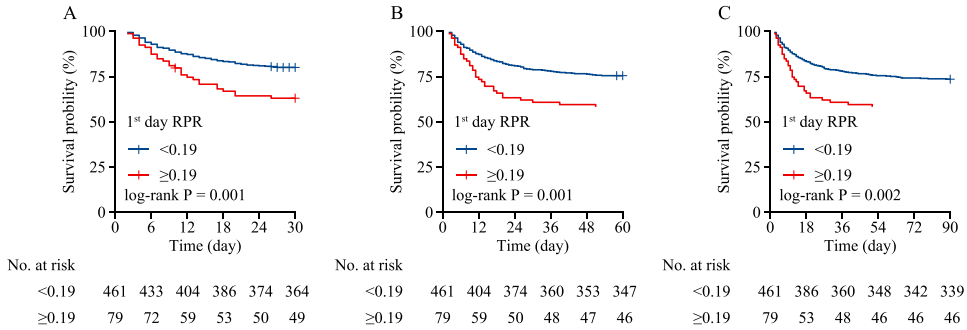

FIG. 2. **Kaplan-Meier plots examining the risk for 28- (A), 60- (B), and 90-day (C) all-cause mortality in patients with first-day RPR <0.19 and first-day RPR ≥0.19.** First-day RPR, the first day of red blood cell distribution width–to–platelet ratio after ICU admission; ICU, intensive care unit.

TABLE 3. **Association of the first-day RPR with 28-, 60-, and 90-day all-cause mortality**

	28-d All-cause mortality			60-d All-cause mortality			90-d All-cause mortality		
Model	No. of deaths	HR (95% CI)	*P*	No. of deaths	HR (95% CI)	*P*	No. of deaths	HR (95% CI)	*P*
Model 1*									
RPR <0.19	92	1.00		113	1.00		122	1.00	
RPR ≥0.19	29	2.12 (1.38–3.27)	0.001	33	2.01 (1.34–3.00)	0.001	33	1.86 (1.25–2.77)	0.002
Model 2†									
RPR <0.19	92	1.00		113	1.00		122	1.00	
RPR ≥0.19	29	2.34 (1.41–3.89)	0.001	33	2.08 (1.30–3.31)	0.002	33	1.88 (1.19–2.99)	0.007
Model 3‡									
RPR <0.19	92	1.00		113	1.00		122	1.00	
RPR ≥0.19	29	2.30 (1.33–3.99)	0.003	33	1.99 (1.20–3.31)	0.008	33	1.83 (1.11–3.01)	0.018
Model 4§									
RPR <0.19	92	1.00		113	1.00		122	1.00	
RPR ≥0.19	29	2.63 (1.42–4.85)	0.002	33	2.16 (1.24–3.78)	0.007	33	2.03 (1.17–3.52)	0.011
Model 5‖									
RPR <0.19	92	1.00		113	1.00		122	1.00	
RPR ≥0.19	29	2.74 (1.46–5.15)	0.002	33	2.23 (1.27–3.92)	0.005	33	2.05 (1.18–3.57)	0.011

*Model 1 adjusted for age, gender, ethnicity and smoking.

†Model 2 adjusted for age, gender, ethnicity, smoking, temperature, heart rate, respiratory rate, mean blood pressure, SOFA score, qSOFA score, and SAPS II.

‡Model 3 adjusted for age, gender, ethnicity, temperature, heart rate, respiratory rate, mean blood pressure, SOFA score, qSOFA score, SAPS II, atrial fibrillation, COPD, respiratory failure, pneumonia, diabetes, congestive heart failure, hypertension, chronic pulmonary, hypothyroidism, renal failure, coagulopathy, obesity, weight loss, alcohol abuse, AKI, sepsis, septic shock, and ARDS severity.

§Model 4 adjusted for age, gender, ethnicity, temperature, heart rate, respiratory rate, mean blood pressure, SOFA score, qSOFA score, SAPS II, atrial fibrillation, COPD, respiratory failure, pneumonia, diabetes, congestive heart failure, hypertension, chronic pulmonary, hypothyroidism, renal failure, coagulopathy, obesity, weight loss, alcohol abuse, AKI, sepsis, septic shock, ARDS severity, WBC, hemoglobin, hematocrit, creatinine, PT, PTT, glucose, PH, BE, PCO_2, and PaO_2/FIO_2.

‖Model 5 adjusted for age, gender, ethnicity, temperature, heart rate, respiratory rate, mean blood pressure, SOFA score, qSOFA score, SAPS II, atrial fibrillation, COPD, respiratory failure, pneumonia, diabetes, congestive heart failure, hypertension, chronic pulmonary, hypothyroidism, renal failure, coagulopathy, obesity, weight loss, alcohol abuse, AKI, sepsis, septic shock, ARDS severity, WBC, hemoglobin, hematocrit, creatinine, PT, PTT, glucose, PH, BE, PCO_2, PaO_2/FIO_2, vent time, RRT, vasopressor, and PEEP.

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; BE, base excess; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; first-day RPR, the first day of red blood cell distribution width–to–platelet ratio after ICU admission; HR, hazard ratio; ICU, intensive care unit; PaO_2/FIO_2, arterial partial pressure of oxygen to fraction of inspired oxygen; PEEP, positive end-expiratory pressure; PH, potential of hydrogen; PT, prothrombin time; PTT, partial thromboplastin time; qSOFA, quick Sequential Organ Failure Assessment; RPR, red blood cell distribution width–to–platelet ratio; RRT, renal replacement therapy; SAPS II, Simplified Acute Physiology Score; SOFA, Simplified Acute Physiology Score; WBC, white blood cell.

RPR were more strongly associated with 28-day all-cause mortality. Similar results were obtained for the association between the first-day RPR and 60- and 90-day mortality.

After adjustment for potential confounders, the first-day RPR showed a stronger and linear positive association with 28-day all-cause mortality in both the nonpneumonia (*P* for overall association = 0.028, *P* for nonlinear = 0.348) and pneumonia (*P* for overall association = 0.004, *P* for nonlinear = 0.179) groups (Fig. 5, A and B). The all-cause mortality tended to increase as the first-day RPR increased. The association between RPR and

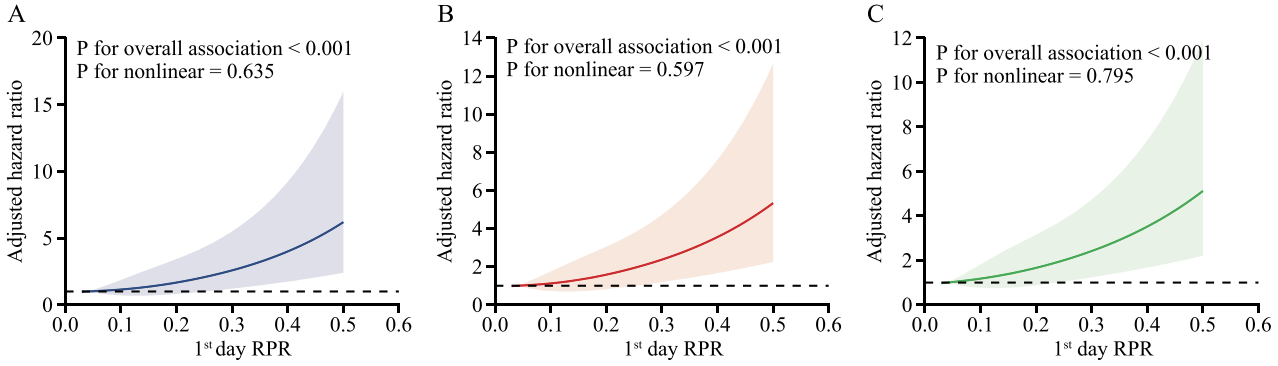

FIG. 3. **Adjusted HRs of 28- (A), 60- (B), and 90-day (C) all-cause mortality risk according to first-day RPR.** Graphs show HRs for 28- (A), 60- (B), and 90-day (C) all-cause mortality adjusted for age, gender, ethnicity, smoking, temperature, heart rate, respiratory rate, MBP, SOFA score, qSOFA score, SAPS II, atrial fibrillation, COPD, respiratory failure, pneumonia, diabetes, CHF, hypertension, chronic pulmonary, hypothyroidism, renal failure, coagulopathy, obesity, weight loss, alcohol abuse, AKI, sepsis, septic shock, ARDS severity, WBC, hemoglobin, minimum hematocrit, maximum creatinine, PT, PTT, glucose, PH, BE, PCO_2, PaO_2/FIO_2, vent time, RRT, vasopressor and PEEP. The data were fitted by a restricted cubic spline Cox proportional hazards regression model. The first-day RPR ranged from 0.02 to 0.89. The solid lines indicate the HRs, and the shading indicates 95% CIs. AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; BE, base excess; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; first-day RPR, the first day of red blood cell distribution width–to–platelet ratio after ICU admission; HRs, hazard ratios; ICU, intensive care unit; MBP, mean blood pressure; PaO_2/FIO_2, arterial partial pressure of oxygen to fraction of inspired oxygen; PEEP, positive end-expiratory pressure; PH, potential of hydrogen; PT, prothrombin time; PTT, partial thromboplastin time; qSOFA, quick Sequential Organ Failure Assessment; RRT, renal replacement therapy; SAPS II, Simplified Acute Physiology Score; SOFA, Simplified Acute Physiology Score; WBC, white blood cell.

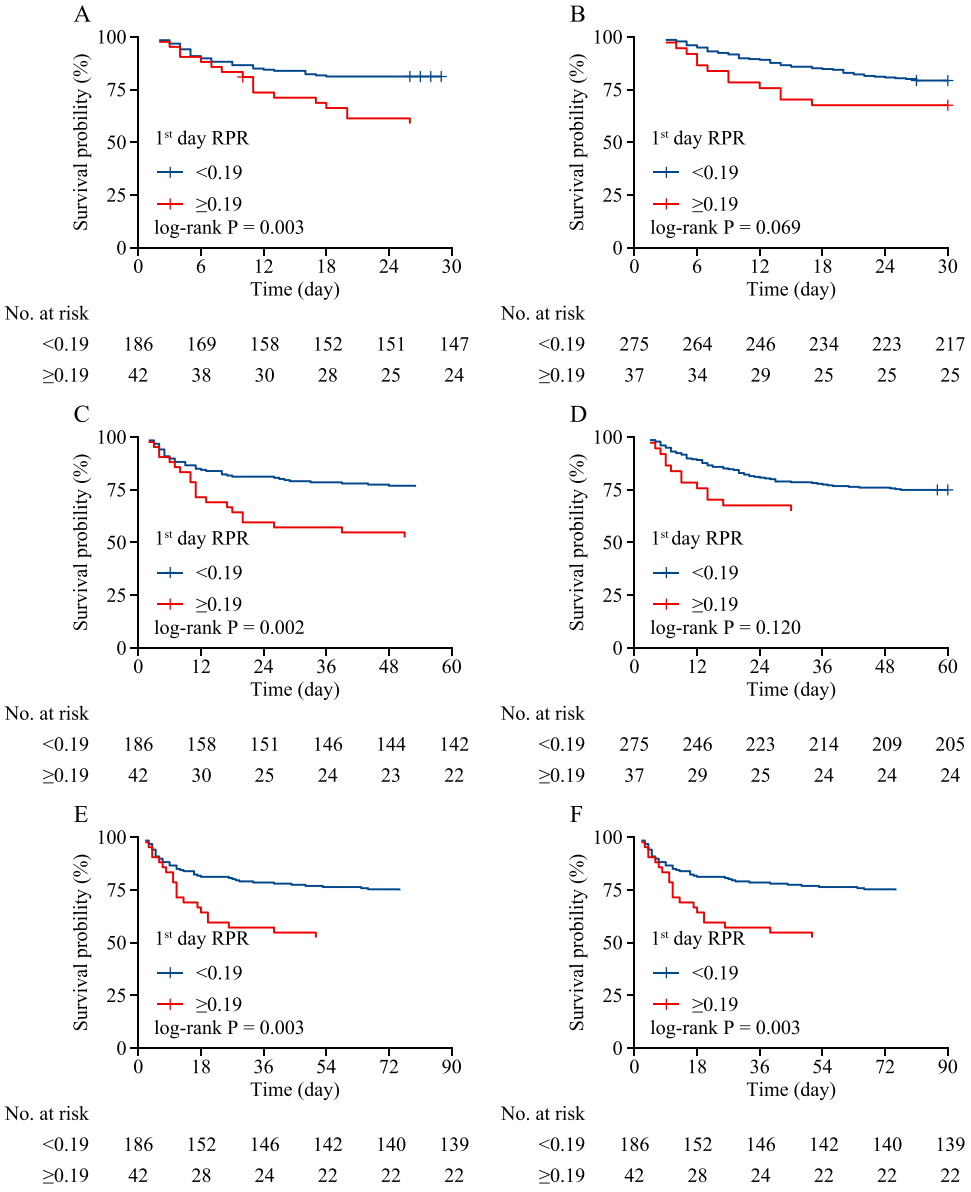

FIG. 4. **Kaplan-Meier plots examining the risk for 28- (A, B), 60- (C, D), and 90-day (E, F) all-cause mortality in nonpulmonary and pulmonary patients with first-day RPR <0.19 and first-day RPR ≥0.19.** First-day RPR, the first day of red blood cell distribution width–to–platelet ratio after ICU admission; ICU, intensive care unit.

60- and 90-day all-cause mortality was similarly linear among the pneumonia and nonpneumonia groups (Fig. 5, C–F).

ROC curves of RPR and other scores for predicting the 28-day all-cause mortality of ARDS patients

The 28-day all-cause mortality in ARDS patients was predicted through the ROC curves of SOFA, qSOFA, and SAPS II and the first-day RPR (Fig. 6). The AUCs of the first-day RPR and SOFA, qSOFA, and SAPS II were 0.59 (0.53–0.65), 0.60 (0.54–0.66), 0.58 (0.53–0.63), and 0.66 (0.60–0.71), respectively. There were no statistically significant differences between the AUCs of RPR and those of SOFA and qSOFA. The difference was statistically significant between the SAPS II and the first-day RPR at $P < 0.05$ (Table 4).

DISCUSSION

In this retrospective cohort study, we investigated the predictive value of the dynamic change of RPR for the short-term prognosis of ARDS patients. RPR ≥0.19 was correlated with increased risk of ARDS mortality in this study. Such a correlation remained unchanged over time and was still significant after multiple adjustments for relevant covariates. In addition, the RPR was correlated with the severity of ARDS patients. During the first to third day of ICU admission, the dynamic change of RPR was related to ARDS prognosis. Consequently, RPR could be used as a predictor for the short-term prognosis for ARDS patients. To the best of our knowledge, this is the first study to reveal the above correlation for ARDS patients.

Red blood cell distribution width and PLTs are routinely conducted tests during hospitalization. The RPR is derived from only two simple and easily conducted laboratory tests, whereas the SOFA, qSOFA, and SAPS II consist of 6, 3, and 17 variables, respectively. However, in this study, the SOFA and qSOFA scores had similar predictive value to the RPR. This conforms to the predictability of RPR for the prognosis of ARDS patients. In addition, our finding that there is a statistically significant difference between the SAPS II and the first-day RPR would be expected.

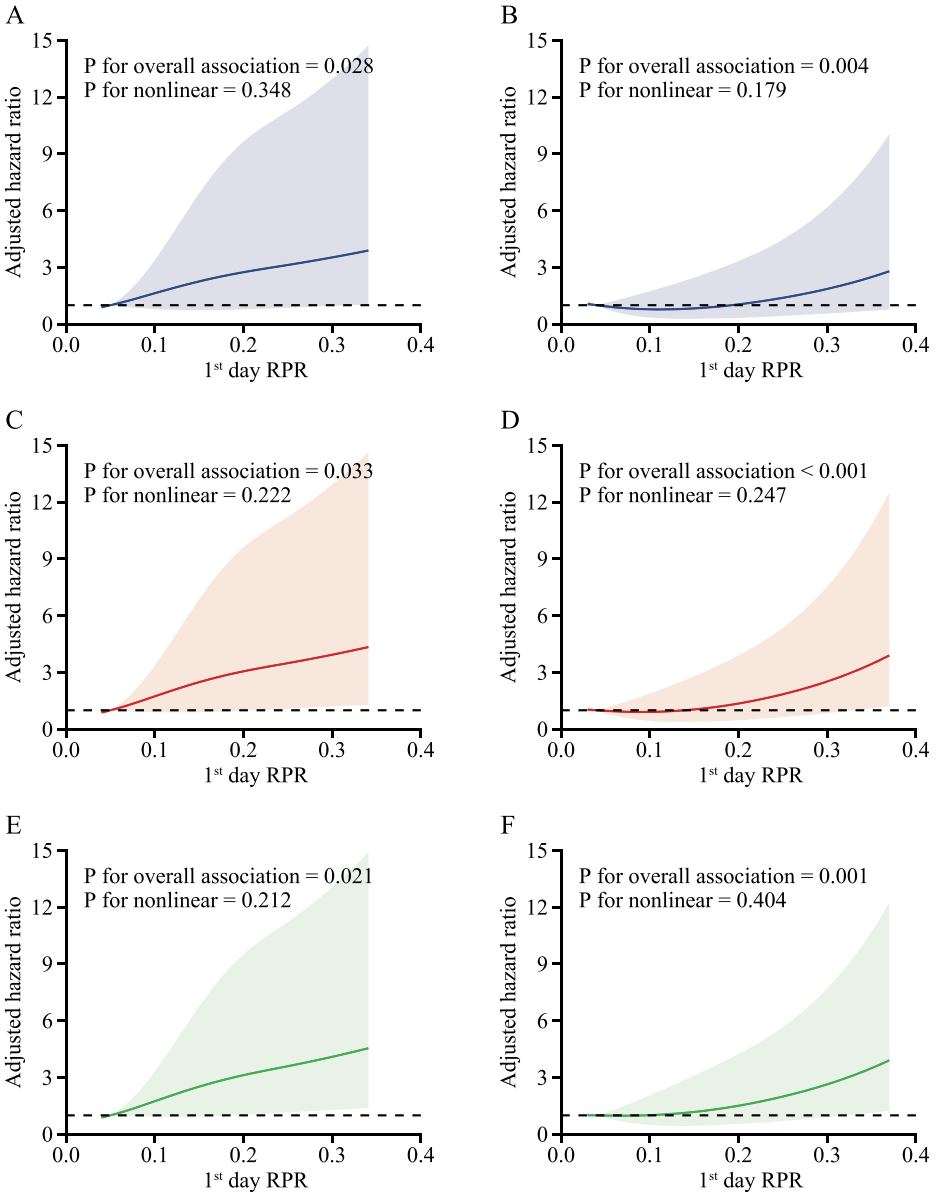

FIG. 5. **Adjusted HR of 28- (A, B), 60- (C, D), and 90-day (E, F) all-cause mortality risk in nonpulmonary and pulmonary patients based on the first-day RPR.** The graphs show the HRs for 28- (A, B), 60- (C, D), and 90-day (E, F) all-cause mortality adjusted for age, gender, ethnicity, smoking, temperature, heart rate, respiratory rate, MBP, SOFA score, qSOFA score, SAPS II, atrial fibrillation, COPD, respiratory failure, pneumonia, diabetes, CHF, hypertension, chronic pulmonary, hypothyroidism, renal failure, coagulopathy, obesity, weight loss, alcohol abuse, AKI, sepsis, septic shock, ARDS severity, WBC, hemoglobin, minimum hematocrit, maximum creatinine, PT, PTT, glucose, PH, BE, Pco_2, Pao_2/Fio_2, vent time, RRT, vasopressor and PEEP. AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; BE, base excess; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; first-day RPR, the first day of red blood cell distribution width–to–platelet ratio after ICU admission; HRs, hazard ratios; ICU, intensive care unit; MBP, mean blood pressure; Pao_2/Fio_2, arterial partial pressure of oxygen to fraction of inspired oxygen; PEEP, positive end-expiratory pressure; PH, potential of hydrogen; PT, prothrombin time; PTT, partial thromboplastin time; qSOFA, quick Sequential Organ Failure Assessment; RRT, renal replacement therapy; SAPS II, Simplified Acute Physiology Score; SOFA, Simplified Acute Physiology Score; WBC, white blood cell.

Red blood cell distribution width is not only an indicator of the change of erythrocytes size, but it also reflects the degree of heterogeneity of their volume. Red blood cell distribution width has been shown to be of great significance in the diagnosis of anemia. At present, there are many studies that found RDW is related to the prognosis of cardiovascular disease, sepsis, ARDS, and other diseases (13–16). A positive correlation between RDW and the mortality of ARDS patients was revealed in the study by Wang et al. (15). Although the AUC of the RDW was lower than either SOFA or SAPS II, it still had certain predictive performance. The result of another study implied that an increase of 1% in RDW corresponded to a 29% increase in the risk of developing ARDS after a severe burn (16). The study by Braun et al. (17) suggested that elevated RDW was associated with a significant increase in complicated hospitalization and 90-day mortality rates, but this was irrespective of their hemoglobin levels. Red blood cell distribution width is an earlier marker of prognosis as it is seen earlier than low levels of hemoglobin.

This study also yielded the similar results, although the hemoglobin value in the high RPR group was lower than that in the low RPR group, but this was not statistically significant for predicting the prognosis of ARDS. The exact mechanism of the correlation between RDW and ARDS remains unclear. Previous studies have

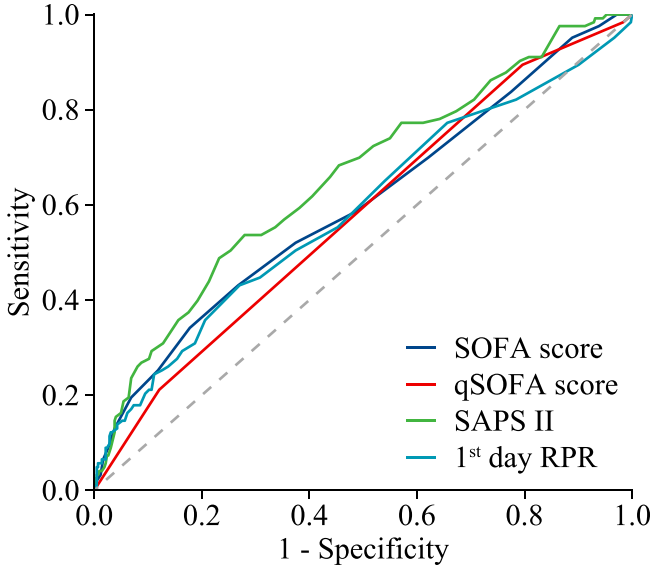

FIG. 6. **ROC curve of SOFA score, qSOFA score, SAPS II, and first-day RPR predicting the 28-day all-cause mortality in ARDS patients.** ARDS, acute respiratory distress syndrome; first-day RPR, the first day of red blood cell distribution width–to–platelet ratio after ICU admission; ICU, intensive care unit; qSOFA, quick Sequential Organ Failure Assessment; ROC, receiver operating characteristic; SAPS II, Simplified Acute Physiology Score; SOFA, Simplified Acute Physiology Score.

suggested that ARDS is an acute and inflammatory clinical syndrome characterized by diffuse lung injury, alveolar inflammation, and destruction of alveolar capillary barrier (18). Inflammatory cytokines can promote the structural and functional changes of erythrocytes and impair their deformability. In addition, inflammation may contribute to polycythemia by impounding iron metabolism and disrupting the erythropoietin response, which can impinge on erythrocytes maturation and cause immature ones to enter the bloodstream (19–21). In addition, oxidative stress injury is one of the major reasons that lead to the occurrence and development of ARDS. This leads to the destruction of red blood cells and the release of a large number of immature cells into peripheral blood, which results in an increase in RDW (22,23).

As the main effector cells of both hemostasis and the inflammatory response, PLTs also participate in the occurrence and development of ARDS (24). The most basic function of PLTs is hemostasis, and it has a major role in coordinating the inflammatory and immunological responses (25). Platelets are thought to make an important contribution to the pulmonary origin of ARDS among critically ill patients by acting in conjunction with fibrinogen to mediate endothelial damage through multiple signal transduction pathways (26).

The RDW-to-PLT ratio is the ratio of the two independent parameters, RDW and PLTs. The increase in RPR was caused by an increase in RDW or a decrease in PLTs. Recently, Lee et al. (7) demonstrated the accuracy of RPR for liver fibrosis in patients with chronic hepatitis B where the RPR may be used to evaluate the need for liver biopsies in patients with chronic hepatitis B, especially when transient elastography is not available. Clinicopathological characteristics and prognosis of 299 breast carcinoma patients revealed that RPR could independently predict poor prognosis in these patients (8). Ge et al. (9) studied 2,220 patients with clinically acute traumatic brain injury, and *in vivo* experiments showed that although the RDW and PLT values in the survivors were higher and lower than those in nonsurvivors, respectively, further statistical analysis implied that they had no effect on predicting the prognosis of patients. The RDW-to-PLT ratio is a reliable predictor for the outcome of acute traumatic brain injury. Zhu et al. (10) found that the sensitivity and specificity of the RPR for predicting cardiovascular events in hemodialysis patients were 0.87 and 0.82, respectively. Consequently, the RPR was an independent risk factor for the prognosis with respect to cardiovascular events in hemodialysis patients. Although the mechanisms underlying the association of RPR and poor prognosis remain unclear, they may be partially ascribed to the inflammatory response. The combination of RDW and PLTs at different stages of the inflammatory process may better reflect the correlation between the state of inflammation and prognosis.

Pneumonia is one of the most common causes for ARDS. The subgroup analysis performed in this study with pneumonia and nonpneumonia ARDS patients showed that the latter was 1.3 times higher in the high RPR when compared with the low RPR group. Luo et al. (27) showed that patients with indirect (nonpulmonary sepsis or pancreatitis) ARDS had higher SAPS II and Acute Physiology and Chronic Health Evaluation II scores and more nonpulmonary organ failures when compared with patients with direct (pneumonia or aspiration of gastric contents) ARDS. Therefore, it is speculated that RPR is likely to be linked to systemic inflammation and the functional state of systemic organs. Further analysis showed that in both the subgroups, the risk of death increased significantly as high RPR, which further suggested the robustness of the results.

The study had several limitations. First, this was a retrospective study with a relatively small sample size, and the data were extracted from a database obtained 10 years ago. These results may therefore be biased. In addition, baseline RDW and PLTs were not recorded before the onset of the disease, and only the lowest or highest values within the first and third days after admission to the ICU were used as monitoring points. Moreover, it was also found that from the first to the third day the change in the RPR value was relatively very small (0.01), and therefore, it may take more time to monitor the dynamic changes of RPR. In addition, we did not exclude further treatment measures for anemia and thrombocytopenia, such as blood transfusion and PLT promotion, which may have led to a bias in the results obtained.

CONCLUSIONS

In conclusion, RPR, a simple and readily available test, was found to be independently associated with short-term adverse outcomes in ARDS patients. This study suggests that RPR can be a valuable prognostic indicator for ARDS patients.

TABLE 4. **Performance metrics for the ROC curve**

Variable	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
SOFA score	0.60 (0.54–0.66)	0.34 (0.26–0.43)	0.82 (0.79–0.86)
qSOFA score	0.58 (0.53–0.63)	0.89 (0.84–0.95)	0.20 (0.17–0.24)
SAPS II	0.66 (0.60–0.71)	0.54 (0.45–0.62)	0.72 (0.68–0.76)
1st-day RPR	0.59 (0.53–0.65)*	0.43 (0.34–0.52)	0.73 (0.69–0.77)

*$P < 0.05$, compared with SAPS II.

AUC, area under the curve; CI, confidence interval; qSOFA, quick Sequential Organ Failure Assessment; ROC, receiver operating characteristic; RPR, red blood cell distribution width–to–platelet ratio; SAPS II, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

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