

The Association of Red Blood Cell Distribution Width to Platelet Count Ratio and 28-Day Mortality of Patients with Sepsis: A Retrospective Cohort Study

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Shanhui Ge

Shan Lin 

Lishan Zhang 

Mian Zeng 

Department of Medical Intensive Care Unit, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong 510080, China; Institute of Pulmonary Diseases, Sun Yat-sen University, Guangzhou, Guangdong, People's Republic of China

Background: Sepsis is a life-threatening and inflammatory disease with high morbidity and mortality. Red blood cell distribution width to platelet count ratio (RPR) was known as an inflammatory biomarker and was related to poor outcomes of various diseases.

Aim: This study was intended to explore the association between RPR and mortality of sepsis patients.

Methods: A retrospective cohort study was undertaken in patients with sepsis, and the data were collected from a public database called Medical Information Mart for Intensive Care III (MIMIC-III). The primary outcome was 28-day mortality while the secondary outcomes were 90-day mortality and ICU mortality. Multivariable regression analyses, as well as interaction and stratified analyses, were conducted to investigate the relation between RPR and sepsis mortality.

Results: In total, we enrolled 7531 patients with 1316 deaths. RPR was independently correlated with 28-day mortality (per 0.1 increase: HR=1.04; 95% CI 1.02–1.06), 90-day mortality (per 0.1 increase: HR=1.04; 95% CI 1.03–1.06) and ICU mortality (per 0.1 increase: OR=1.06; 95% CI 1.02–1.10). Twenty-eight-day survival was worse in the high RPR (≥ 0.134) group according to the Kaplan–Meier curve analyses (Log rank test, $p < 0.001$). In stratified analyses, Sequential Organ Failure Assessment (SOFA) score and length of ICU stay had interactive effects with the high RPR (≥ 0.134) group on 28-day mortality.

Conclusion: RPR is a novel biomarker that indicates poor prognosis of sepsis patients. Clinicians are required to pay more attention to those patients with high RPR.

Keywords: ICU, sepsis, prognosis, inflammatory marker, MIMIC-III

Introduction

Sepsis, a life-threatening condition that contributes to high mortality in intensive care units, is a substantial burden to public health worldwide.¹ It is reported that global sepsis-related deaths were estimated up to 11.0 million in 2017, although the incidence and mortality of sepsis show a decreasing trend over the years.² Caused by infections, sepsis manifests as systemic inflammation with organ dysfunction and immune disorder. Several common inflammation biomarkers including c-reactive protein, procalcitonin, and white blood cell count have shown prognostic values on sepsis.^{3,4} Early identification of those who are in danger of adverse outcomes might be conducive to prompt and adequate treatments of sepsis.⁵

Correspondence: Mian Zeng
Department of Medical Intensive Care Unit, The First Affiliated Hospital of Sun Yat-sen University, No. 58 Zhongshan Road 2, Guangzhou, Guangdong 510080, People's Republic of China
Email zengmian@mail.sysu.edu.cn

Complete blood count (CBC) is one of the most common and inexpensive laboratory tests in the hospital. Derived from CBC, red blood cell distribution width (RDW) is a parameter that reflects the heterogeneity of red blood cell (RBC) volume, and classifies anemia. Elevated RDW is considered to be an inflammatory marker and predicts poor outcomes of several diseases including heart failure,⁶ acute kidney injury,⁷ sepsis,⁸ and cancers.⁹ Platelets play a major role in regulating inflammation and innate immunity. Platelets adhere to endothelium and mediate neutrophil chemotaxis, infiltration, and secretion of proinflammatory chemokines in the progress of acute inflammation.¹⁰ Platelet count decreases in severe diseases and is a predictor for mortality.^{11,12} Red blood cell distribution width to platelet count ratio (RPR) is a novel and simple indicator of inflammation. Studies have reported the value of RPR in detecting hepatic fibrosis¹³ and predicting poor prognosis of severe burn injury.¹⁴ However, few studies have investigated the correlation between RPR and sepsis. Herein, our study aimed to explore the relationship between RPR and sepsis mortality.

Methods

Database

Patient information was collected from the freely available Medical Information Mart for Intensive Care III (MIMIC-III) Database (v1.4) which contains clinical data of more than 40,000 patients admitted to the intensive care units of Beth Israel Deaconess Medical Center between 2001 and 2012.¹⁵ Access to the MIMIC-III database was approved by the institutional review boards of both the Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology Affiliates after finishing the required training course, i.e., the CITI (Collaborative Institutional Training Initiative) “Data or Specimens Only Research” course (Record ID: 29459220). No informed consent was required as the private information of patients was de-identified in the database.

Study Design and Participants

We conducted the retrospective cohort study on adult patients (age \geq 18 years) with the diagnosis of sepsis. Patients who were included had a length of stay in ICU of more than one day and less than that of the hospitalization. Sepsis was defined using the criteria of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) which defines sepsis as infections with

two or more points of Sequential Organ Failure Assessment (SOFA) scores.¹⁶ Patients were excluded when: (1) Repeated hospital admissions were recorded; (2) RPR could not be calculated. Also, we only calculated the RPR of the first ICU admission if the patient had several ICU admissions in one hospitalization.

Data Collection

Our data were extracted from the database using Transact-SQL language and codes from the MIMIC Code Repository (<https://github.com/MIT-LCP/mimic-code>).¹⁷ Patients’ information consists of age, gender, mechanical ventilation on the first day, renal replacement therapy on the first day, ICU length of stay, Sequential Organ Failure Assessment (SOFA) scores, Elixhauser Comorbidity Index (SID30), comorbidities, and laboratory parameters which contained white blood cell, red blood cell distribution width, hemoglobin, and platelet count from the blood sample. The severity scores and laboratory parameters were both collected within 24 hours after ICU admission. The exposure factor RPR was equal to red blood cell distribution width divided by platelet count. The primary outcome was 28-day mortality while the secondary outcomes were 90-day mortality and ICU mortality.

Statistical Analysis

All analyses were conducted using EmpowerStats (www.empowerstats.com; X&Y Solutions Inc.) and statistical packages R (The R Foundation; <http://www.r-project.org>; version 3.4.3 2018–02–18). Qualitative variables were described with median and interquartile range while categorical variables were expressed as counts and percentages. Continuous and categorical variables were analyzed using Kruskal–Wallis and Chi-square (or Fisher’s exact) tests, respectively. We constructed univariate and multivariable Cox proportional hazards models for the association of RPR with 28-day and 90-day mortality and performed logistic regression models to analyze the correlation between RPR and ICU mortality, using two adjusted models to adjust potential confounding factors (details in Table 2). Smooth curve fitting based on a generalized additive model was utilized to identify the relation between RPR and 28-day mortality. We further performed a two-piecewise linear regression model to assess the threshold effect of RPR on 28-day mortality based on the smoothing plot. The threshold was determined according to the log-likelihood ratio test comparing the non-segmented model to the segmented regression model. Kaplan–

Meier curve method was used to compare the survival probability between low RPR group and high RPR group if the threshold effect existed. To assess the robustness of

our results, we conducted interaction and stratified analyses on subgroups which were classified according to gender, age, SOFA, length of ICU stay, mechanical

Table I Characteristics of the Patients with Sepsis

	Survivor(n=6215)	Non-Survivor(n=1316)	P-value
Age (years)	67.56 (54.34–78.98)	75.50 (61.68–83.51)	<0.001
Male	3325 (53.50%)	700 (53.19%)	0.839
Mechanical ventilation on first day	3547 (57.07%)	677 (51.44%)	<0.001
Renal replacement therapy on first day	297 (4.78%)	95 (7.22%)	<0.001
SOFA	5.00 (4.00–7.00)	7.00 (4.00–9.00)	<0.001
Length of ICU stay (days)	4.22 (2.22–9.52)	4.38 (2.27–8.67)	0.427
Elixhauser Comorbidity Index (SID30)	17.00 (9.00–26.00)	24.00 (15.00–33.00)	<0.001
Platelet	178.00 (115.00–249.00)	166.00 (89.00–253.25)	<0.001
RDW	14.90 (13.90–16.40)	16.20 (14.70–18.00)	<0.001
RPR	0.09 (0.06–0.13)	0.10 (0.06–0.19)	<0.001
White blood cell	13.30 (9.60–18.80)	13.90 (9.17–19.70)	0.187
Hemoglobin	9.80 (8.50–11.20)	9.40 (8.40–10.80)	<0.001
Comorbidities			
Congestive heart failure	2152 (34.63%)	531 (40.35%)	<0.001
Cardiac arrhythmias	1998 (32.15%)	520 (39.51%)	<0.001
Valvular disease	834 (13.42%)	173 (13.15%)	0.791
Pulmonary circulation disorder	505 (8.13%)	119 (9.04%)	0.273
Peripheral vascular disorder	734 (11.81%)	151 (11.47%)	0.731
Hypertension	3305 (53.18%)	650 (49.39%)	0.012
Paralysis	277 (4.46%)	44 (3.34%)	0.069
Other neurological disease	890 (14.32%)	183 (13.91%)	0.696
Chronic pulmonary disease	1303 (20.97%)	303 (23.02%)	0.098
Uncomplicated diabetes	1353 (21.77%)	240 (18.24%)	0.004
Complicated diabetes	481 (7.74%)	80 (6.08%)	0.037
Hypothyroidism	647 (10.41%)	141 (10.71%)	0.743
Renal failure	1193 (19.20%)	285 (21.66%)	0.041
Liver disease	636 (10.23%)	231 (17.55%)	<0.001
Peptic ulcer	13 (0.21%)	2 (0.15%)	1.000
AIDS	97 (1.56%)	15 (1.14%)	0.252
Lymphoma	157 (2.53%)	58 (4.41%)	<0.001
Metastatic cancer	270 (4.34%)	206 (15.65%)	<0.001
Solid tumor	298 (4.79%)	75 (5.70%)	0.170
Rheumatoid arthritis	212 (3.41%)	35 (2.66%)	0.164
Coagulopathy	1369 (22.03%)	396 (30.09%)	<0.001
Obesity	407 (6.55%)	53 (4.03%)	<0.001
Weight loss	477 (7.67%)	118 (8.97%)	0.115
Fluid and electrolyte disorders	2847 (45.81%)	724 (55.02%)	<0.001
Blood loss anemia	184 (2.96%)	35 (2.66%)	0.555
Deficiency anemia	1601 (25.76%)	280 (21.28%)	<0.001
Alcohol abuse	565 (9.09%)	101 (7.67%)	0.100
Drug abuse	266 (4.28%)	23 (1.75%)	<0.001
Psychoses	304 (4.89%)	31 (2.36%)	<0.001
Depression	577 (9.28%)	86 (6.53%)	0.001

Notes: Patients were divided into two groups according to the 28-day survival status. Data were expressed as median (interquartile range) or n (%). Kruskal–Wallis and Chi-square (or Fisher's exact) tests were used to analyze continuous and categorical variables, respectively. Statistically significant p-values ($p < 0.05$) are shown in bold. Comorbidities were defined using International Classification of Diseases, 9th edition (ICD-9) criterion (Table S1).

Abbreviations: SOFA, Sequential Organ Failure Assessment; AIDS, acquired immune deficiency syndrome; RDW, red blood cell distribution width; RPR, red blood cell distribution width to platelet count ratio.

Table 2 Association of RPR with Clinical Outcomes

	Non-Adjusted		Model I		Model II	
	HR/OR (95% CI)	P	HR/OR (95% CI)	P	HR/OR (95% CI)	P
28-day mortality	1.07 (1.06, 1.09)	<0.001	1.03 (1.01, 1.05)	0.001	1.04 (1.02, 1.06)	<0.001
90-day mortality	1.07 (1.06, 1.08)	<0.001	1.03 (1.01, 1.04)	<0.001	1.04 (1.02, 1.06)	<0.001
ICU mortality	1.13 (1.10, 1.16)	<0.001	1.06 (1.02, 1.09)	0.001	1.05 (1.02, 1.09)	0.003

Notes: HR/OR represent the increased risk of mortality per 0.1 increase of RPR. Adjusted Model I was adjusted for age, gender, SOFA, mechanical ventilation on the first day, renal replacement therapy on the first day, Elixhauser Comorbidity Index (SID30) and hemoglobin. Adjusted Model II was adjusted for age, gender, SOFA, mechanical ventilation on the first day, renal replacement therapy on the first day, hemoglobin, and comorbidities (congestive heart failure, pulmonary circulation disorder, hypertension, chronic pulmonary disease, uncomplicated diabetes, complicated diabetes, renal failure, liver disease, AIDS, lymphoma, metastatic cancer, solid tumor, rheumatoid arthritis, coagulopathy, obesity, fluid and electrolyte disorders). Statistically significant p-values ($p < 0.05$) are shown in bold.

Abbreviations: SOFA, Sequential Organ Failure Assessment; RPR, red blood cell distribution width to platelet count ratio; OR, odds ratio; HR, hazard ratio; CI, confidence interval.

ventilation or renal replacement therapy on the first day, and hematological disorder.

Result

Patient Demographics

Finally, we enrolled 7531 patients who fulfilled the criteria of sepsis 3, of which 1316 patients (17.47%) died. The median age was 68.77 years (range 55.49–80.05) and the median length of ICU stay was 4.24 days (range 2.23–9.27). 56.09% of patients received mechanical ventilation within 24 hours after ICU admission while 5.21% of patients underwent renal replacement therapy. The most common comorbidities of sepsis patients were hypertension (52.52%), followed by fluid and electrolyte disorders (47.42%), congestive heart failure (35.63%), and cardiac

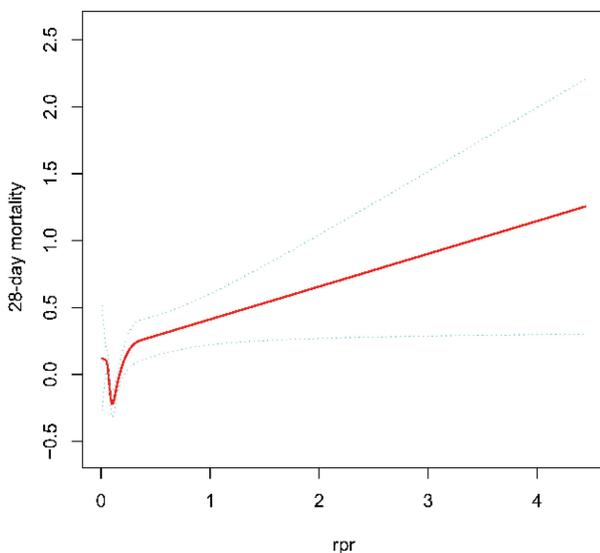


Figure 1 Smooth curve fitting for the association between RPR and 28-day mortality. A non-linear relationship was detected after adjusting for Model II in Table 2.

Table 3 Threshold Effect Analysis of RPR on 28-Day Mortality with Piecewise Linear Regression

Non-Segmented Regression Model		
	HR (95% CI)	P
	1.04 (1.02, 1.06)	<0.001
Segmented regression model		
	HR (95% CI)	P
RPR<0.134	0.86 (0.71, 1.04)	0.110
RPR≥0.134	1.04 (1.02, 1.06)	<0.001
Log-likelihood ratio test: P=0.047		

Note: HR represents the increased risk of 28-day mortality per 0.1 increase of RPR and was adjusted for Model II in Table 2. Statistically significant p-values ($p < 0.05$) are shown in bold.

Abbreviations: HR, hazard ratio; CI, confidence interval, RPR, red blood cell distribution width to platelet count ratio.

arrhythmias (33.44%). As shown in Table 1, the following variables indicated statistically significant differences between survivors and non-survivors: age, mechanical ventilation on the first day, renal replacement therapy on the first day, SOFA scores, Elixhauser Comorbidity Index (SID30), platelet count, RDW, and RPR. As expected, non-survivors had higher RDW and RPR values compared with survivors.

Association of RPR with Clinical Outcomes

To analyze the association between sepsis mortality and RPR, we performed univariate and multivariable regression analysis. As shown in Table 2, after adjustment for potential confounding factors (model II), mortality increased by 4% in 28-day mortality per 0.1 increase of RPR (HR=1.04; 95% CI 1.02–1.06), 4% in 90-day mortality (HR=1.04; 95% CI 1.02–1.06), and 5% in ICU mortality (OR=1.05; 95% CI 1.02–1.09).

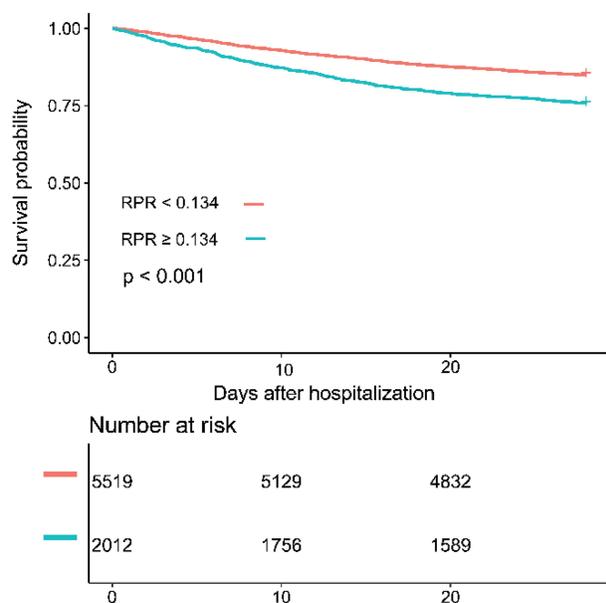


Figure 2 Kaplan–Meier curve of 28-day survival in sepsis patients. Patients were divided into two groups according to RPR (RPR<0.134 and RPR ≥0.134).

Threshold Effect Analysis

As shown in Figure 1, we observed a non-linear relationship between RPR and 28-day mortality after adjustment for model II (shown in Table 2). We further found a significant threshold of RPR (0.134) using the two-piecewise linear regression model (Table 3). As a significant p-value (0.047) was detected by Log-likelihood ratio test, the segmented regression model was more suitable to describe the correlation between RPR and 28-day mortality. In our segmented regression model, when $RPR \geq 0.134$, 28-day mortality increased by 4% per 0.1 increase of RPR (adjusted HR=1.04, 95% CI 1.02~1.06, $p < 0.001$), but RPR was not associated with 28-day mortality when it was less than 0.134 (per 0.1 adjusted HR=0.86, 95% CI 0.71~1.04, $p = 0.110$).

Subgroup Analyses

We divided patients into high and low RPR groups according to the threshold of 0.134. Kaplan–Meier analysis (Figure 2) showed that 28-day survival was better for the low RPR group (Log rank test, $p < 0.001$), and 28-day mortality increased by 16% in the high RPR group (adjusted HR=1.16, 95% CI 1.01~1.34). For the purpose of identifying the potential factors that influence the impact of RPR on 28-day mortality, we conducted subgroup analyses (Table 4, Figure 3). SOFA score had a significant interaction with RPR on 28-day mortality. Patients whose SOFA scores were not less than 6 points had a higher risk of 28-day mortality (HR=1.38, 95% CI 1.18~1.63). The association between RPR and 28-day

mortality was similar for other subgroups with no statistically significant interactions (p for interaction > 0.05 in the adjusted model).

Discussion

In the present study, we confirmed that elevated RPR was correlated to increased risk of sepsis mortality after adjustment for potentially confounding factors. We further observed a non-linear association between RPR and 28-day mortality of sepsis patients and discovered a significant threshold of 0.134. What's more, in light of our result, SOFA score was interactive with RPR on 28-day mortality.

Hematopoietic dysfunction is common in sepsis. Systemic infection and inflammation contributed to increased rupture of peripheral erythrocytes and decreased iron bioavailability, which correlated with the incidence of sepsis-associated anemia.^{18,19} In the meantime, inflammatory cytokines inhibited RBC maturation and nucleated red blood cell counts increased.^{20,21} These hematopoietic changes might lead to increased erythrocytes heterogeneity and then elevated RDW. Platelets are known to be the intersection of immune response and coagulation reaction in infectious diseases.²² Sepsis caused the transcriptional and translational changes in platelets and thrombocytopenia was detected in sepsis patients.²³ Increased RDW⁸ and decreased platelets²⁴ were independently related to the mortality of sepsis, respectively. A previous study reported that a simple scoring system including RDW, platelet count, and delta neutrophil index was a significant predictor for 28-day mortality of patients with severe sepsis and septic shock.²⁵ Red blood cell distribution width to platelet count ratio (RPR) might be an index which reflects the status of red blood cells and platelets, simultaneously.

RPR, as an inflammation marker, was widely studied in predicting hepatic fibrosis and cirrhosis with cutoff points varying from 0.06 to 0.14 and good diagnostic accuracy.^{13,26–29} Recent researches have explored the potential diagnostic value of RPR for other diseases. Bilgin et al.³⁰ revealed that RPR was useful for predicting the overall survival of patients with right-sided advanced colorectal cancer. Celik et al.³¹ reported that admission RPR dependently correlated with the no-reflow phenomenon in patients who were diagnosed with myocardial infarction and had undergone a primary percutaneous coronary intervention. Besides, RPR showed good predictive ability for mortality of acute pancreatitis and severe burn injury,^{14,32} which are common causes of sepsis. Therefore, we hypothesized RPR also related to sepsis. Two studies have reported the correlation between

Table 4 Stratified Analyses of the Association Between RPR and 28-Day Mortality

	RPR		p	p for Interaction
	<0.134	≥0.134		
Total	1.00	1.16 (1.01, 1.34)	0.047	
Gender				0.420
Male	1.00	1.23 (1.01, 1.49)	0.035	
Female	1.00	1.09 (0.88, 1.35)	0.418	
Age				0.116
<65 years	1.00	1.32 (1.01, 1.73)	0.041	
≥65 years	1.00	1.06 (0.89, 1.27)	0.491	
SOFA score				0.013
<6	1.00	1.01 (0.76, 1.34)	0.947	
≥6	1.00	1.38 (1.17, 1.63)	<0.001	
Length of ICU stay				0.008
<4 days	1.00	1.00 (0.79, 1.26)	1.000	
≥4 days	1.00	1.19(0.98, 1.45)	0.075	
MV or RRT				0.819
No	1.00	1.17 (0.95, 1.44)	0.146	
Yes	1.00	1.11 (0.91, 1.35)	0.288	
Hematological disorder				0.688
No	1.00	1.25 (1.02, 1.53)	0.035	
Yes	1.00	1.18 (0.98, 1.42)	0.075	

Notes: Cox proportional hazards model was adjusted for Model II in Table 2. Variable was excluded from the adjusted model when considered as a stratification variable. Statistically significant p-value ($p < 0.05$) was shown in bold.

Abbreviations: MV, mechanical ventilation on the first day; RPR, red blood cell distribution width to platelet count ratio; RRT, renal replacement therapy on the first day; SOFA, Sequential Organ Failure Assessment.

RPR and sepsis in children. Wang et al.³³ revealed that RPR had high diagnostic utility for the prognosis of pediatric sepsis with an AUROC of 0.937. Similarly, the work of Karabulut and Arcagok showed that RPR was an available biomarker for the prediction of early-onset neonatal sepsis with an AUROC of 0.816.³⁴ However, no study has investigated the relationship between RPR and adult sepsis. So, our study was the first to explore the underlying connection between RPR and adult sepsis. Our results indicated that RPR was an independent risk factor for 28-day mortality, 90-day mortality, and ICU mortality of adult sepsis patients. In our further stratified analyses, gender, age, mechanical ventilation or renal replacement therapy on the first day, length of ICU stay, and hematological disorder showed no interaction effect. Interestingly, SOFA (≥ 6) exhibited significant interaction with RPR (cutoff point 0.134) on 28-day mortality, which indicated that RPR might be a more useful biomarker in severe patients.

Some limitations of the present study need to be discussed. First of all, as a retrospective observational study, it is inevitable to have potential selection bias and confounding bias. We could only analyze the hazard ratio or odds ratio instead of relative risk. Further, the present study only collected the value of RPR within 24 hours of ICU admission, with a lack of analysis of baseline level and continuous fluctuations in RPR value. Finally, our data were collected from a single central electronic database and not representative enough for the general population. Our results need to be further verified in multi-center studies.

Conclusion

In short, we confirmed that RPR was a simple and effective biomarker independently related to mortality of adult sepsis patients in the present study. Patients with RPR value not less than 0.134 ought to be paid more attention as they are more

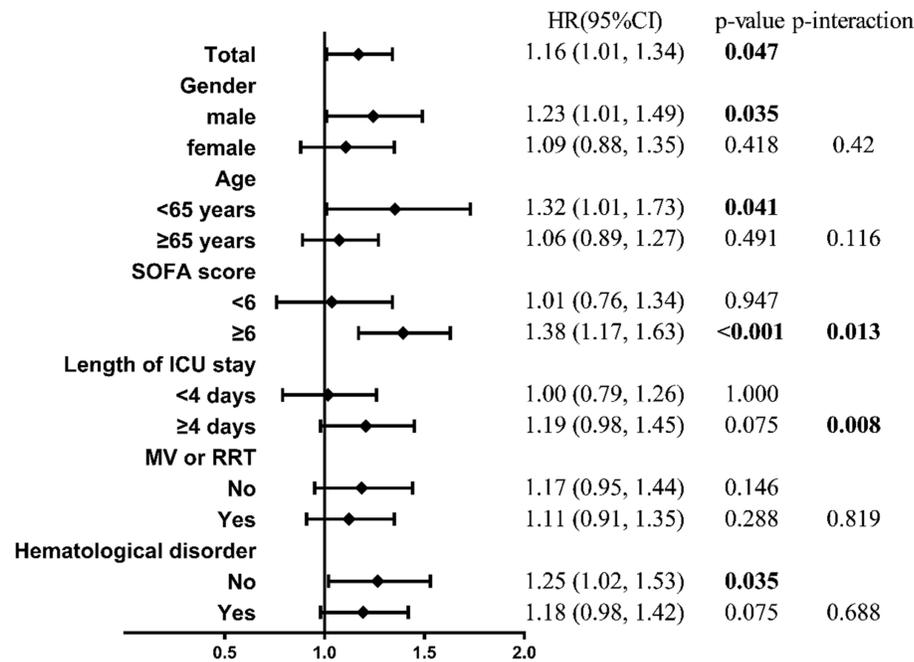


Figure 3 Forest plot for stratified analyses.

Notes: Cox proportional hazards model was adjusted for Model II in Table 2. Variable was excluded from the adjusted model when considered as a stratification variable. Statistically significant p-value ($p < 0.05$) was shown in bold.

Abbreviations: MV, mechanical ventilation on the first day; RRT, renal replacement therapy on the first day; SOFA, Sequential Organ Failure Assessment.

likely to have an adverse prognosis. Further studies with multi-center design should be conducted to validate our results.

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Disclosure

The authors declare that they have no conflicts of interest for this work.

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