


BMJ Open Enhanced red blood cell distribution width to platelet ratio is a predictor of mortality in patients with sepsis: a propensity score matching analysis based on the MIMIC-IV database

Yuanjun Zhou , Liping Zhong, Weiming Chen, Fei Liang, Yilin Liao, Yuting Zhong

To cite: Zhou Y, Zhong L, Chen W, *et al.* Enhanced red blood cell distribution width to platelet ratio is a predictor of mortality in patients with sepsis: a propensity score matching analysis based on the MIMIC-IV database. *BMJ Open* 2022;**12**:e062245. doi:10.1136/bmjopen-2022-062245

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-062245>).

Received 22 February 2022
Accepted 14 September 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

Department of Anesthesiology, Meizhou People's Hospital, Meizhou, Guangdong, China

Correspondence to

Dr Yuting Zhong;
mzhospitalyztzhong@163.com

ABSTRACT

Objective To explore the association between dynamic changes in red blood cell distribution width to platelet count ratio (RPR) during hospitalisation and short-term mortality in patients with sepsis.

Design A retrospective cohort study using propensity score matching.

Setting Intensive care units (ICUs) of Beth Israel Deaconess Medical Center.

Participants A total of 8731 adult patients with sepsis were included in the study. The patients were identified from the ICU of the Medical Information Mart for Intensive Care database. The observed group included patients who experienced an increase in RPR of more than 30% during the first week of ICU admission, whereas the control group included the rest.

Main outcome and measure Using propensity score matching, a matched control group was created. The primary outcome was 28-day mortality, and the length of hospital stay and in-hospital mortality were the secondary outcomes.

Results The difference was evident in 28-day mortality between the two groups (85.8% vs 74.5%, $p < 0.001$, Kaplan-Meier analysis, and $HR = 1.896$, 95% $CI = 1.659$ to 2.168 , $p < 0.001$, Cox regression). In the secondary outcomes, there was a significant difference in in-hospital mortality ($p < 0.001$). In addition, the study discovered that the observed groups had a significantly longer hospital stay ($p < 0.001$). Meanwhile, the results of subgroup analyses were consistent with those of the primary analyses.

Conclusions In patients with sepsis, a significantly increased RPR is positively associated with the short-term death rate. Continuous RPR monitoring could be a valuable measure for predicting short-term mortality in patients with sepsis.

INTRODUCTION

Sepsis has been a paramount global public health concern in the past and continues to be so now, draining health resources. Sepsis is a severe systemic inflammatory condition with organ dysfunction caused by the body's

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The analysed data originated from the high-volume and high-quality public Medical Information Mart for Intensive Care-IV database.
- ⇒ The propensity score matching was used to generate a matched group from the control group for the observed group, and the confounding variables were effectively controlled.
- ⇒ Exclusion of patients with missing data caused a limitation of selection bias in the study design.
- ⇒ The study was unable to determine the differences in long-term outcomes between groups as the long-term follow-up data were not available in the database.

uncontrolled responses to infection.¹ This severe condition is the leading cause of death in intensive care units (ICUs) and emergency departments. Despite a long-term downward trend in sepsis-related mortality worldwide, it remains persistently high.²⁻⁴

For decades, novel biomarkers of poor prognosis for patients with sepsis have been a hot topic.⁵⁻⁷ The inflammatory factors, including complete blood count, C reactive protein and procalcitonin, have been found to play a vital role in the pathogenesis and prognosis of sepsis.⁸⁻¹⁰ Apart from those above, both red blood cell distribution¹¹ and platelet count¹² are acute and chronic systemic inflammation biomarkers. An increase in red blood cell distribution width (RDW) and thrombocytopenia are relatively common in patients with severe infectious diseases.^{13 14} RDW is a crucial index, reflecting the heterogeneity of circulating erythrocyte size.¹⁵ An elevated RDW during sepsis increases sepsis-related mortality.¹⁶ Thrombocytopenia is induced by the response of the human body to bacterial infection and is associated with high mortality.¹⁷

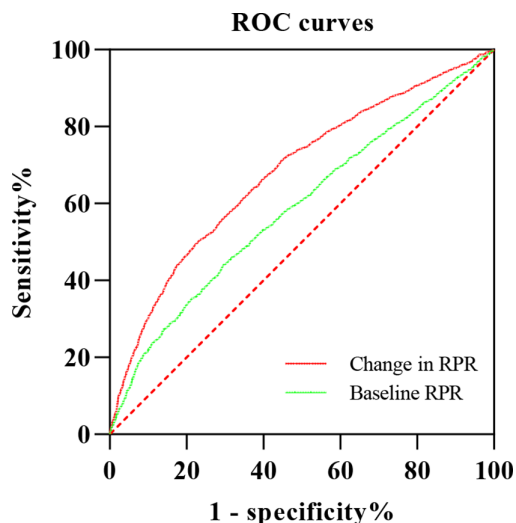


Figure 1 ROC for the change in RPR. Change in RPR: AUC=0.680, $p < 0.001$, 95% CI 0.663 to 0.696, sensitivity value 49% and specificity value 78%; baseline RPR: AUC=0.588, $p < 0.001$, 95% CI 0.570 to 0.606, sensitivity value 44% and specificity value 70%. AUC, area under the curve; ROC, receiver operating characteristics; RPR, red cell distribution width to platelet ratio.

A new compound indicator, red blood cell distribution width to platelet count ratio (RPR), has drawn the attention of researchers. The RPR is calculated by dividing the RDW-CV (the variation coefficient of red blood cell volumes) by the number of platelet counts. The severity of the inflammatory response is considered to be reflected by a single RPR at baseline, which can be used to predict the sepsis-related adverse outcomes.¹⁸ According to the two previous studies, RPR has a significant diagnostic and prognostic potential in paediatric and neonatal sepsis.^{19,20} Furthermore, baseline RPR has been recommended as a potentially valuable prognostic index for breast cancer,²¹

liver fibrosis,²² severe burn injuries²³ and deep-seated intracerebral bleeding.²⁴

However, previous results were based only on the baseline RPR data and did not take the dynamic characteristics of RPR into account. Whether an increase in RPR during hospitalisation could predict outcomes of patients with sepsis remains unclear. The hypothesis that the significantly increased RPR has a relationship with clinical outcomes was tested in the current study. The study also aimed to preliminarily explore the feasibility of using changes of RPR to monitor inflammation during the treatment of sepsis.

MATERIALS AND METHODS

The results were reported according to the Strengthening the Reporting of Observational studies in Epidemiology guidelines.²⁵

Data sources

All patient data were collected from the free, publicly available Medical Information Mart for Intensive Care-IV (MIMIC-IV) database (version 0.4).²⁶ The MIMIC-IV was established by the researchers at the Massachusetts Institute of Technology Laboratory for Computational Physiology and collaborating research groups. This relational critical care database contains unidentifiable high-quality and clinical-related data for tens of thousands of patients admitted to the ICUs of Beth Israel Deaconess Medical Center from 2008 to 2019. Dr Yuanjun Zhou, the principal investigator, received the permission to use this database to conduct the related research project after the completion of the required course Collaborative Institutional Training Initiative and course Data or Specimens Only Research (Certification no. 39149215).

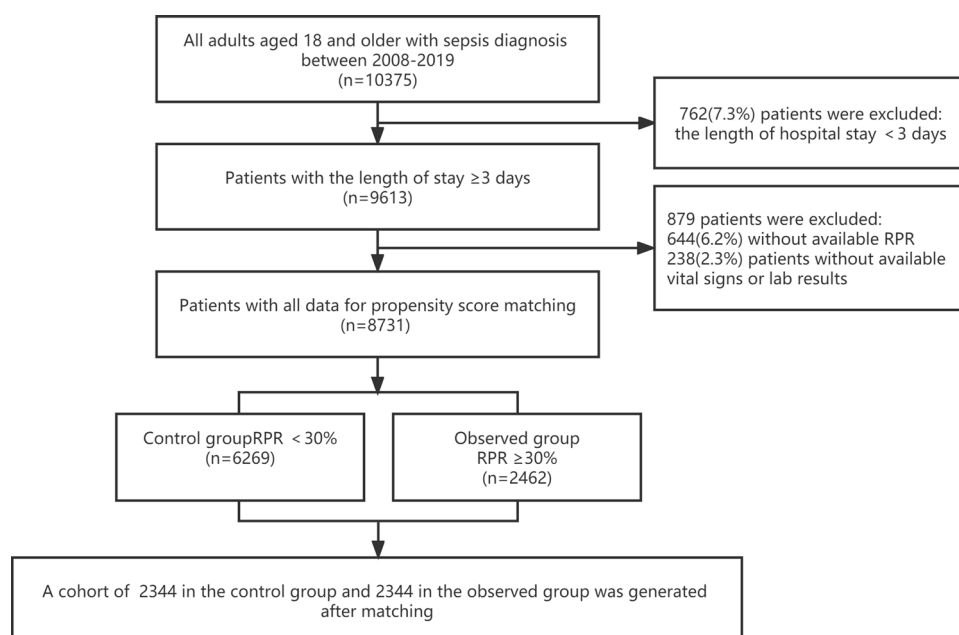


Figure 2 Flow chart for the process of inclusion steps and exclusion steps. RPR, red cell distribution width to platelet ratio.

Table 1 Patients' baseline characteristics

	Cohort before PSM			Cohort after PSM		
	Control group N=6269	Observed group N=2462	P value	Control group N=2344	Observed group N=2344	P value
			SMD			SMD
Sex, female	47.6%	49.4%	0.122	48.4%	49.2%	0.579
Age	68.8 (57.0–80.3)	66.7 (56.8–77.9)	0.002	67.7 (56.8–79.3)	67.8 (57.2–78.0)	0.571
SOFA within 1st day	6 (4–8)	8(5–12)	<0.001	8 (5–11)	8 (5–11)	0.644
Ethnicity			0.030			0.972
White	67.3%	66.9%		65.8%	66.8%	
Black	10.8%	9.7%		11.0%	9.8%	<0.01
Asian	2.9%	2.2%		2.8%	2.3%	<0.01
Others	19.1%	21.2%		20.4%	21.1%	0.017
Emergency admission	20.2%	25.5%	<0.001	24.7%	25.0%	0.787
RRT	5.2%	9.9%	<0.001	8.3%	9.1%	0.351
Vasopressors	46.0%	70.1%	<0.001	68.9%	68.8%	0.900
Comorbidities						
MI	14.6%	17.0%	0.005	17.3%	16.8%	0.614
CHF	29.0%	32.5%	0.001	33.4%	32.4%	0.494
CVD	15.7%	13.8%	0.024	14.0%	14.0%	1.000
CPD	24.7%	26.1%	0.158	27.0%	26.1%	0.487
Diabetes	31.8%	30.1%	0.235	31.1%	31.0%	0.975
Renal disease	23.8%	24.6%	0.475	25.1%	24.7%	0.736
Liver disease	13.9%	24.2%	<0.001	21.9%	22.1%	0.833
Malignancy	11.1%	17.0%	<0.001	15.2%	16.2%	0.356
Metastatic solid tumour	5.1%	7.0%	<0.001	6.6%	6.7%	0.815
AIDS	1.0%	0.7%	0.185	0.8%	0.8%	0.869
Heart rate	72 (62–83)	75 (63–87)	<0.001	75 (64–86)	75 (63–87)	0.532
White cell count	13.5 (9.4–18.5)	14.9 (10.0–21.5)	<0.001	14.6 (10.1–20.3)	14.7 (9.9–21.0)	0.647
Haemoglobin	96 (82–111)	93 (80–110)	<0.001	94 (80–110)	94 (80–110)	0.887
Bicarbonate	21 (18–24)	20 (16–23)	<0.001	20 (17–23)	20 (17–24)	0.148
BUN	25.0 (16.0–41.0)	32.0 (19.0–52.3)	<0.001	30.0 (19.0–51.0)	31.0 (19.0–51.0)	0.756

All variables were extracted within 24 hours of admission to intensive care unit. Malignancy included solid tumours, lymphoma and leukaemia; heart rate is expressed in beats per minute; the reference range of white cell count is $4 \times 10^9/L$; the reference range of haemoglobin is 115–127 g/L; the reference range of bicarbonate is 22–32 mmol/L; the reference range of BUN is 6–20 mg/dL.

BUN, blood urea nitrogen; CHF, congestive heart failure; CPD, chronic pulmonary disease; CVD, cerebrovascular disease; MI, myocardial infarction; PSM, propensity score matching; RRT, renal replacement treatment; SMD, standardised mean difference; SOFA, Sequential Organ Failure Assessment.

Table 2 Outcomes comparison for the patients with sepsis from the two groups

	Control group N=2344	Observed group N=2344	P value
Mortality in hospital	15.4%	27.0%	<0.001
Length of hospital stay	13.2 (7.7–23.0)	15.9 (9.7–26.4)	<0.001

The relative risk of mortality in hospital for patients with sepsis in the observed group was 1.756 (95% CI 1.563 to 1.972).

Study population

We enrolled all adult patients with sepsis older than 18 years who had available RPR within 24 hours of admission in one hospitalisation and the RPR value between third and seventh days after ICU admission. The sepsis-3 criteria were used to define sepsis. Sepsis is defined by the Third International Consensus Definitions for Sepsis and Septic Shock as infections with 2 or more points of Sequential Organ Failure Assessment (SOFA) scores.²⁷

Exclusion criteria: individuals without the available RPR and those with less than 3 days of hospital stay were excluded. Patients with incomplete information and data were also excluded.

Variable extraction

PostgreSQL (version 13.0) was used to collect baseline characteristics directly, including age, sex, ethnicity, admission type, SOFA scores, laboratory findings, treating measures and comorbidities. Laboratory findings included white cell count, RDW, platelet count, bicarbonate and blood urea nitrogen. Treating measures consisted of vasopressors and renal replacement therapies. Vasopressors included dopamine, dobutamine, norepinephrine, epinephrine and milrinone. Comorbid conditions had cardiovascular diseases (myocardial infarction and congestive heart failure), cerebrovascular diseases, chronic pulmonary diseases, diabetes mellitus, kidney diseases and hepatic diseases, and malignancy, metastatic solid tumours and AIDS were also included. The heart rate was one of the vital indications. All baseline variables

were collected within 24 hours of admission to the ICU. The RDW and platelet count were collected from day 3 to 7 of ICU admission.

SOFA score was calculated following the grading standards.

The computational formulae are listed below:

$$\text{RPR} = \frac{\text{red blood cell distribution width}}{\text{platelet count}} \quad (1)$$

$$\text{Magnitude of RPR change} = \frac{\text{RPR}_{3-7 \text{ days after ICU admission}} - \text{RPR}_{\text{baseline}}}{\text{RPR}_{\text{baseline}}} \quad (2)$$

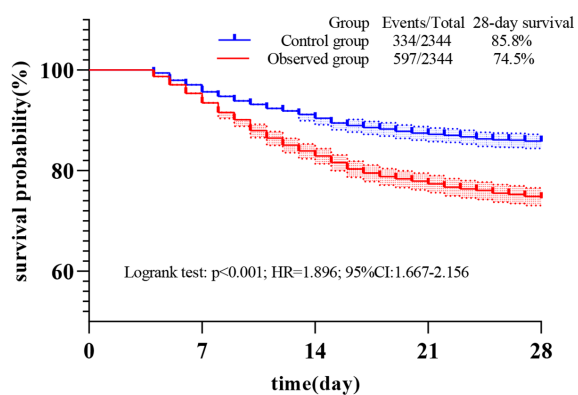
Outcomes

The primary outcome was mortality at 28 days and the secondary outcomes were the length of hospital stay and the mortality in hospital. The 28-day mortality rate was determined using the ICU admission and death dates. In-hospital mortality was found in the corresponding table. The duration of hospital stay was calculated with the admission and discharge times.

Statistical analysis

The optimal cut-off value of change in RPR was determined using the receiver operating characteristics (ROC) curve and the highest Youden index. Patients with RPR greater than the selected cut-off value were classified as the observed group, while those who did not were designated as controls. Proportions (%) were used to describe categorical variables. The χ^2 test examined the unordered categorical variables. Simultaneously, the Kruskal-Wallis H test was performed to analyse intergroup differences for the ordered categorical data. The Kolmogorov-Smirnov test was used to determine if the data distribution was normal. Non-normally distributed continuity variables were expressed as median with IQR and the Mann-Whitney test was performed to check the differences between groups. The R language 'psmatching' extension package (V.3.04) in SPSS V.26.0 was used to develop a matched control group for the observed group with a ratio of 1:1. All the matching parameters were predefined and previously described. The propensity matching score was calculated using logistic regression. The matching was done through the nearest neighbour method with calliper value limited to 0.1. The quality of the match was determined using standardised mean differences (SMDs). Further, collinear analysis was performed to confirm that redundant variables were not included in the matching procedure to avoid over-matching. Kaplan-Meier curves were used to represent 28-day survival differences between groups, analysed with the log-rank test. Mortality in hospitals was compared with the χ^2 test. Subgroup analysis was used to assess the

Kaplan-Meier curve for 28-day survival



Control group	2344	2243	2119	2044	2010
Observed group	2344	2191	1944	1814	1747

Figure 3 Kaplan-Meier curves for 28-day survival. The 28-day mortality of the patients with an elevated levels of RPR $\geq 30\%$ compared with the others. RPR, red blood cell distribution width to platelet count ratio.

Hazard ratio for 28-day mortality

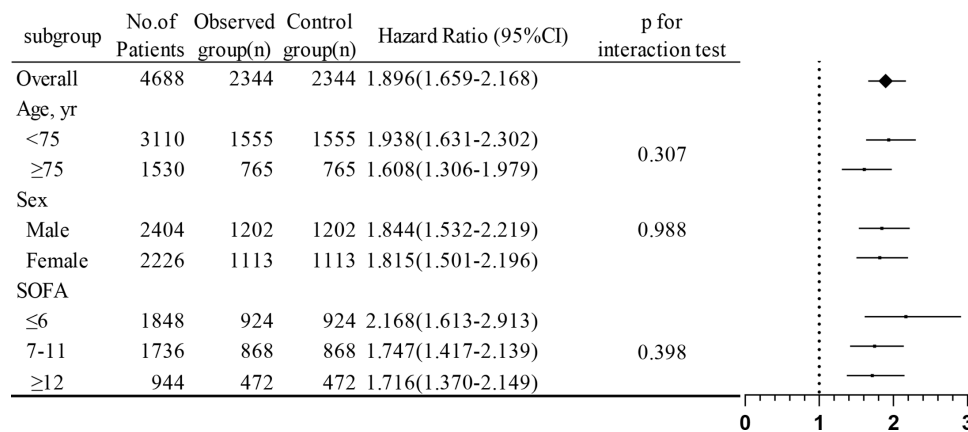


Figure 4 Subgroup analysis comparing the hazard of 28-day mortality in subgroups of patients with sepsis with an increased RPR greater than 30% and other patients with an increased RPR lower than 30%. Independent propensity score matching was performed for each subgroup. The flow chart of the subgroup analysis was provided in the online supplemental material 2. RPR, red blood cell distribution width to platelet count ratio; SOFA, Sequential Organ Failure Assessment.

relationship between the dynamic change in RPR and 28-day mortality, including age, gender and three SOFA groups. Each subgroup was subjected to independent propensity score matching (PSM). P value of <0.05 was regarded as significantly different. All statistical analyses were carried out using SPSS V.26.0.

Patient and public involvement

No patients or members of the public were involved in the design and the execution of the study.

RESULT

ROC analysis

The best cut-off value for 28-day mortality is 0.33. The area under the curve (AUC) value was moderate at 0.697 ($p<0.001$, sensitivity value 49%, and specificity value 78%) (figure 1). For clinical practicality, 0.30 was selected as grouping criteria.

Populations

Figure 2 depicts details of the inclusion steps and exclusion steps. Initially, this study included a total of 10 375 patients with sepsis. Of which, 8731 (84.2%) patients were included and 1644 individuals were excluded as they did not meet the inclusion criteria of the study.

PSM procedure

Table 1 lists all the matching variables. Collinear analysis (online supplemental material 1) revealed that all variables included in the PSM procedure had no collinearity, and the risk of overmatching was low. After propensity matching, 2344 (95.2% of patients in the observed group) pairs were matched. SMDs after PSM (table 1) showed that baseline demographic characteristics were well balanced after PSM.

Baseline characteristics

Table 1 summarises the demographic characteristics of patients. Between the two groups, significant differences were noted in age distribution, admission type and ethnic composition. The SOFA score was also significantly different between the two groups according to the Whitney test. In addition, clinically significant differences were noted regarding the laboratory results and heart rate (table 1).

Outcomes

The Kaplan-Meier analysis indicated significant differences in 28-day survival curves between the two groups ($p<0.001$) (figure 3). Patients with an increased RPR of more than 30% had 1.896 times increased risk of mortality higher than patients in the control group (HR 1.896, 95% CI 1.659 to 2.168, $p<0.001$). Meanwhile, a significant difference was observed among in-hospital mortality (table 2). Based on another secondary outcome, the duration of stay in the hospital was longer in the patients from the observed group than the others from controls with RPR change $<30\%$ (table 2).

Subgroup analysis

An exploratory subgroup analysis of 28-day mortality was performed concerning age, gender and SOFA score (online supplemental material 2). The results of subgroup analyses of HR remained consistent with those from the analyses of the overall cohort ($\geq 30\%$ in RPR during hospitalisation is an independent risk factor for short-term sepsis-related mortality). No significant differences were noted in all subgroups by interaction test (figure 4).

DISCUSSION

This study investigated the association between the increased RPR during hospitalisation and clinical outcomes in patients with sepsis. The patients with sepsis

with increased RPR were found to have an increased risk of sepsis-related death and had longer hospital stays. The findings are significant as they offer the feasibility of using continuous variability in RPR as an independent predictor of adverse outcomes in patients with sepsis. To our knowledge, there are few studies on the prognosis associated with changes in RPR during hospitalisation due to sepsis.

Ge *et al* revealed that the basal RPR is associated with an increased risk of death in individuals with sepsis,¹⁸ consistent with our findings. The study measured RPR only once; however, in our study, an increased amplitude in RPR was used as exposure of interest. Continuous RPR monitoring is more discriminating compared with static RPR. Moreover, the intergroup difference in the length of hospital stay was compared, which has not been previously described. The subgroup analyses were also conducted for 28-day mortality in terms of critical clinical characteristics. The subgroup analysis was designed to identify potential subgroup effects (figure 4). No significant statistical difference or interactive effects between subgroups were revealed, which increased the robustness of the main results. However, the findings of subgroup analysis should still be taken into consideration.

The systemic inflammation process is the core mechanism of sepsis. Many inflammatory biomarkers were used to assess the diagnosis, treatment and prognosis of patients with sepsis.^{28–30} The pathophysiological processes of RPR from the RDW and platelet variations in patients with sepsis can be identified; however, the mechanisms of the association between an elevated RPR during hospitalisation and adverse outcomes are still elusive. Patients with sepsis exhibit significant hemorheological alteration.³¹ Patients with severe sepsis experience haemolytic reaction due to the deterioration in erythrocytes membrane stabilisation.^{32–35} Baskurt³⁶ has shown that the decrease in sialic membrane content makes red blood cells more prone to be spherical in patients with sepsis.³⁶ Following severe infections, the deformability and surface area of spherical erythrocytes decrease, whereas the erythrocytes become fragile. The deformability of red blood cells is critical for oxygen utilisation in patients with sepsis.³⁷ Spherocytes are more easily destroyed when they pass through the splenic capillaries, resulting in haemolytic anaemia.³⁸ The release of reticulocytes into the circulation produced by haemolytic anaemia increases the wide distribution of red blood cells significantly. In a community-based prospective cohort study, Perlstein *et al*³⁹ found that increased RDW has a strong positive relationship with several inflammatory factors, including erythrocyte sedimentation rate in a community-based prospective cohort study.³⁹ Meanwhile, sepsis-related thrombocytopenia has an important role in the excessive inflammatory reaction and activation of coagulation.^{40 41} Thrombocytopenia has been associated with platelet consumption⁴² and enhanced platelet desialylation.⁴³

Furthermore, previous research suggests that platelet TLR4 causes platelet activation and microvascular thrombosis in dogs with sepsis, leading to organ failure.^{44 45} Platelet count is an important target to improve the clinical outcomes of patients with sepsis with thrombocytopenia.⁴⁶ Although the combination of RDW and platelet count has been thought to represent the severity of the inflammatory process,^{21 47} additional studies are needed to determine the exact mechanisms between RPR and the mortality of patients with sepsis.

Furthermore, ROC analysis indicated AUC of change in RPR was greater than the AUC of baseline RPR, indicating that dynamic change of RPR has a higher diagnostic value than a single RPR (figure 1). This result is consistent with the published study by Gong *et al*.⁴⁸ Gong *et al* reported that only the elevation of RDW but not the baseline RDW has a relationship with the short-term mortality in patients with sepsis.⁴⁸

Our research team believes that the RPR is a valuable and low-cost biomarker for assessing inflammation responses and can be used to better predict the prognosis of infected patients. RPR might be beneficial for physicians to evaluate the efficacy of therapies, such as antibiotic treatment, and surveillance of inflammation, but these require further investigation.

An advantage of this study is its large sample size. The PSM was used to improve the group comparability. Most of the patients from the observed group were successfully matched with those from the control group. However, the study has certain limitations. This study has a selection bias due to the retrospective cohort study design. Furthermore, the results could have been affected by the unadjusted potential confounders. In this study, the long-term outcomes were not assessed. RPR changes during hospitalisation for sepsis could not be directly applied to be a predictive factor of long-term prognosis.

CONCLUSION

The dramatic elevated RPR during hospitalisation predicted adverse outcomes in patients with sepsis. Serial monitoring of RPR can aid in the prognostic evaluation of patients with sepsis. Future research should focus on investigating the association between the RPR and long-term outcomes. More research is needed to explore the possibility of using the dynamic RPR determination to monitor inflammatory responses during the treatment of sepsis.

Contributors YZhou—study design, data collection and examination, data analysis and manuscript drafting. LZ—data examination, data analysis and manuscript drafting. YZhong—study design, data examination, supervision of the study process and responsible for the overall content as guarantor. WC—data examination and data analysis. FL—data examination and data analysis. YL—supervision of the study process.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval The study obtained the approval from the Institutional Review Boards of MIT and BIDMC. Informed consent was exempted due to the anonymous data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data used in this study can be obtained by the corresponding author upon request.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Yuanjun Zhou <http://orcid.org/0000-0002-6709-8546>

REFERENCES

- Shankar-Hari M, Phillips GS, Levy ML, *et al*. Developing a new definition and assessing new clinical criteria for septic shock: for the third International consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:775–87.
- Rhee C, Gohil S, Klompas M. Regulatory mandates for sepsis care—reasons for caution. *N Engl J Med* 2014;370:1673–6.
- Stearns-Kurosawa DJ, Osuchowski MF, Valentine C, *et al*. The pathogenesis of sepsis. *Annu Rev Pathol* 2011;6:19–48.
- Delano MJ, Ward PA. Sepsis-induced immune dysfunction: can immune therapies reduce mortality? *J Clin Invest* 2016;126:23–31.
- Pierrakos C, Vincent J-L. Sepsis biomarkers: a review. *Crit Care* 2010;14:R15.
- Giannakopoulos K, Hoffmann U, Ansari U, *et al*. The use of biomarkers in sepsis: a systematic review. *Curr Pharm Biotechnol* 2017;18:499–507.
- Larsen FF, Petersen JA. Novel biomarkers for sepsis: a narrative review. *Eur J Intern Med* 2017;45:46–50.
- Sampson D, Yager TD, Fox B, *et al*. Blood transcriptomic discrimination of bacterial and viral infections in the emergency department: a multi-cohort observational validation study. *BMC Med* 2020;18:185.
- Shapiro NI, Trzeciak S, Hollander JE, *et al*. A prospective, multicenter derivation of a biomarker panel to assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis. *Crit Care Med* 2009;37:96–104.
- Suarez-de-la-Rica A, Maseda E, Anillo V, *et al*. Biomarkers (procalcitonin, C reactive protein, and lactate) as predictors of mortality in surgical patients with complicated intra-abdominal infection. *Surg Infect* 2015;16:346–51.
- Kim CH, Park JT, Kim EJ, *et al*. An increase in red blood cell distribution width from baseline predicts mortality in patients with severe sepsis or septic shock. *Crit Care* 2013;17:R282.
- Venkata C, Kashyap R, Farmer JC, *et al*. Thrombocytopenia in adult patients with sepsis: incidence, risk factors, and its association with clinical outcome. *J Intensive Care* 2013;1:9.
- Jo YH, Kim K, Lee JH, *et al*. Red cell distribution width is a prognostic factor in severe sepsis and septic shock. *Am J Emerg Med* 2013;31:545–8.
- Claushuis TAM, van Vught LA, Scicluna BP, *et al*. Thrombocytopenia is associated with a dysregulated host response in critically ill sepsis patients. *Blood* 2016;127:3062–72.
- Sultana GS, Haque SA, Sultana T, *et al*. Value of red cell distribution width (RDW) and RBC indices in the detection of iron deficiency anemia. *Mymensingh Med J* 2013;22:370–6.
- Zhang L, Yu C-H, Guo K-P, *et al*. Prognostic role of red blood cell distribution width in patients with sepsis: a systematic review and meta-analysis. *BMC Immunol* 2020;21:40.
- Andonegui G, Kerfoot SM, McNagny K, *et al*. Platelets express functional Toll-like receptor-4. *Blood* 2005;106:2417–23.
- Ge S, Lin S, Zhang L, *et al*. The association of red blood cell distribution width to platelet count ratio and 28-day mortality of patients with sepsis: a retrospective cohort study. *Ther Clin Risk Manag* 2020;16:999–1006.
- Karabulut B, Arcagok BC. New diagnostic possibilities for early onset neonatal sepsis: red cell distribution width to platelet ratio. *Fetal Pediatr Pathol* 2020;39:297–306.
- Wang L, Cai Q. [Value of red blood cell distribution width-to-platelet count ratio in predicting the prognosis of children with sepsis]. *Zhongguo Dang Dai Er Ke Za Zhi* 2019;21:1079–83.
- Takeuchi H, Abe M, Takumi Y, *et al*. Elevated red cell distribution width to platelet count ratio predicts poor prognosis in patients with breast cancer. *Sci Rep* 2019;9:3033.
- Lee HW, Kang W, Kim BK, *et al*. Red cell volume distribution width-to-platelet ratio in assessment of liver fibrosis in patients with chronic hepatitis B. *Liver Int* 2016;36:24–30.
- Qiu L, Chen C, Li S-J, *et al*. Prognostic values of red blood cell distribution width, platelet count, and red cell distribution width-to-platelet ratio for severe burn injury. *Sci Rep* 2017;7:13720.
- Lehmann F, Schenk LM, Bernstock JD, *et al*. Elevated red cell distribution width to platelet ratio is associated with poor prognosis in patients with spontaneous, deep-seated intracerebral hemorrhage. *Front Neurol* 2021;12:751510.
- von Elm E, Altman DG, Egger M, *et al*. The strengthening of reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;370:1453–7.
- Johnson ABL, Pollard T, Horng S, *et al*. MIMIC-IV (version 0.4), 2020.
- Singer M, Deutschman CS, Seymour CW, *et al*. The third International consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;315:801–10.
- Vincent J-L, Marshall JC, Namendys-Silva SA, *et al*. Assessment of the worldwide burden of critical illness: the intensive care over nations (icon) audit. *Lancet Respir Med* 2014;2:380–6.
- Machado FR, Cavalcanti AB, Bozza FA, *et al*. The epidemiology of sepsis in Brazilian intensive care units (the sepsis prevalence assessment database, spread): an observational study. *Lancet Infect Dis* 2017;17:1180–9.
- Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013;369:2063:840–51.
- Reggiori G, Occhipinti G, De Gasperi A, *et al*. Early alterations of red blood cell rheology in critically ill patients. *Crit Care Med* 2009;37:3041–6.
- Machiedo GW, Powell RJ, Rush BF, *et al*. The incidence of decreased red blood cell deformability in sepsis and the association with oxygen free radical damage and multiple-system organ failure. *Arch Surg* 1989;124:1386–9.
- Baskurt OK, Gelmont D, Meiselman HJ. Red blood cell deformability in sepsis. *Am J Respir Crit Care Med* 1998;157:421–7.
- Piagnerelli M, Boudjeltia KZ, Vanhaeverbeek M, *et al*. Red blood cell rheology in sepsis. *Intensive Care Med* 2003;29:1052–61.
- Kempe DS, Akel A, Lang PA, *et al*. Suicidal erythrocyte death in sepsis. *J Mol Med* 2007;85:273–81.
- Baskurt O. Pathophysiological significance of blood rheology. *Turk J Med Sci* 2003;33:347–55 <https://journals.tubitak.gov.tr/medical/vol33/iss6/2>
- Fernandes CJ. Red blood cell deformability is critical for oxygen utilization in sepsis. *Crit Care Med* 2009;37:3172–3.
- Wiley JS. Red cell survival studies in hereditary spherocytosis. *J Clin Invest* 1970;49:666–72.
- Perlstein TS, Weuve J, Pfeffer MA, *et al*. Red blood cell distribution width and mortality risk in a community-based prospective cohort. *Arch Intern Med* 2009;169:588–94.
- Manne BK, Xiang SC, Rondina MT. Platelet secretion in inflammatory and infectious diseases. *Platelets* 2017;28:155–64.
- Mavrommatis AC, Theodoridis T, Orfanidou A, *et al*. Coagulation system and platelets are fully activated in uncomplicated sepsis. *Crit Care Med* 2000;28:451–7.
- Koyama K, Katayama S, Muronoi T, *et al*. Time course of immature platelet count and its relation to thrombocytopenia and mortality in patients with sepsis. *PLoS One* 2018;13:e0192064.
- Li M-F, Li X-L, Fan K-L, *et al*. Platelet desialylation is a novel mechanism and a therapeutic target in thrombocytopenia during



- sepsis: an open-label, multicenter, randomized controlled trial. *J Hematol Oncol* 2017;10:104.
- 44 Li RHL, Nguyen N, Tablin F. Canine platelets express functional toll-like receptor-4: lipopolysaccharide-triggered platelet activation is dependent on adenosine diphosphate and thromboxane A2 in dogs. *BMC Vet Res* 2019;15:245.
- 45 Larkin CM, Hante NK, Breen EP, *et al.* Role of matrix metalloproteinases 2 and 9, toll-like receptor 4 and platelet-leukocyte aggregate formation in sepsis-associated thrombocytopenia. *PLoS One* 2018;13:e0196478.
- 46 Zhou Z, Feng T, Xie Y, *et al.* The effect of recombinant human thrombopoietin (rhTPO) on sepsis patients with acute severe thrombocytopenia: a study protocol for a multicentre randomised controlled trial (rescue trial). *BMC Infect Dis* 2019;19:780.
- 47 Taefi A, Huang C-C, Kolli K, *et al.* Red cell distribution width to platelet ratio, a useful indicator of liver fibrosis in chronic hepatitis patients. *Hepatol Int* 2015;9:454–60.
- 48 Gong Y, Long X, Jin J, *et al.* [Elevation of red cell distribution width during hospitalization predicts mortality in patients with sepsis]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2017;29:481–5.