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

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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 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
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. According to the two previous studies, RPR has a significant diagnostic and prognostic potential in paediatric and neonatal sepsis. Furthermore, baseline RPR has been recommended as a potentially valuable prognostic index for breast cancer, liver fibrosis, severe burn injuries and deep-seated intracerebral bleeding.

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.

**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). 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).

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**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.

**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 | Control group | N=6269 | Cohort after PSM | Observed group | N=2462 |
|-------------------|---------------|--------|-------------------|----------------|--------|
| **Sex**           | male          | 47.6%  | female            | 52.4%          |        |
| **Age**           | 50.9 years    | 49.3%  | 51.4 years        | 49.3%          |        |
| **SOFa within 1st day** | 6 (4–8)      | 6 (4–8) | 6 (5–11)         | 6 (5–11)       |        |
| **Ethnicity**     | White         | 67.3%  | Black             | 10.8%          |        |
| **Emergency admission** | 20.2%      | 21.2%  | 21.2%             | 21.2%          |        |
| **RRT**           | 5.1%          | 5.1%   | 9.9%              | 9.9%           |        |
| **Vasopressors**  | 46.0%         | 46.0%  | 46.0%             | 46.0%          |        |
| **Comorbidities** | MI            | 17.0%  | CHF               | 29.0%          |        |
| **Heart rate**    | 72 (62–83)    | 72 (62–83) | 75 (63–87)       | 75 (63–87)    |        |
| **White cell count** | 13.9 (8.4–18.9) | 13.9 (8.4–18.9) | 14.9 (10.0–21.5) | 14.9 (10.0–21.5) |        |
| **Haemoglobin**   | 96 (82–111)   | 96 (82–111) | 93 (80–110)      | 93 (80–110)   |        |
| **Bicarbonate**   | 21 (18-24)    | 21 (18-24) | 20 (16-24)       | 20 (16-24)    |        |
| **BUN**           | 25.0 (16.0–41.0) | 25.0 (16.0–41.0) | 32.0 (19.0–52.3) | 32.0 (19.0–52.3) |        |

| **Sex, female**   | 0.037          | 0.002  | 0.001             | 0.001          |        |
| **Age**           | <0.01          | <0.01  | <0.01             | <0.01          |        |
| **SOFa within 1st day** | <0.01      | <0.01  | <0.01             | <0.01          |        |
| **Ethnicity**     | <0.01          | <0.01  | <0.01             | <0.01          |        |
| **Emergency admission** | <0.01      | <0.01  | <0.01             | <0.01          |        |
| **RRT**           | <0.01          | <0.01  | <0.01             | <0.01          |        |
| **Vasopressors**  | <0.01          | <0.01  | <0.01             | <0.01          |        |
| **Comorbidities** | <0.01          | <0.01  | <0.01             | <0.01          |        |
| **Heart rate**    | <0.01          | <0.01  | <0.01             | <0.01          |        |
| **White cell count** | <0.01      | <0.01  | <0.01             | <0.01          |        |
| **Haemoglobin**   | <0.01          | <0.01  | <0.01             | <0.01          |        |
| **Bicarbonate**   | <0.01          | <0.01  | <0.01             | <0.01          |        |
| **BUN**           | <0.01          | <0.01  | <0.01             | <0.01          |        |

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 4×10⁹/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.
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:

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RPR = \frac{\text{red blood cell distribution width}}{\text{platelet count}}
\]

\[
\text{Magnitude of RPR change} = \frac{RPR_{3-7 \text{ days after ICU admission}} - RPR_{\text{baseline}}}{RPR_{\text{baseline}}}
\]

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.

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).

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

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).

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, 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. 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. Patients with severe sepsis experience haemolytic reaction due to the deterioration in erythrocytes membrane stabilisation. Baskurt has shown that the decrease in sialic membrane content makes red blood cells more prone to be spherical in patients with sepsis. 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. Spherocytes are more easily destroyed when they pass through the splenic capillaries, resulting in haemolytic anaemia. 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 found that increased RDW has a strong positive relationship with several inflammatory factors, including erythrocyte sedimentation rate in a community-based prospective cohort study. Meanwhile, sepsis-related thrombocytopenia has an important role in the excessive inflammatory reaction and activation of coagulation. Thomboctopenia has been associated with platelet consumption and enhanced platelet desialylation. Furthermore, previous research suggests that platelet TLR4 causes platelet activation and microvascular thrombosis in dogs with sepsis, leading to organ failure. Platelet count is an important target to improve the clinical outcomes of patients with sepsis with thrombocytopenia. Although the combination of RDW and platelet count has been thought to represent the severity of the inflammatory process, 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. 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.

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.

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