Red Cell Distribution Width to Platelet Count Ratio as a Promising Indicator of Mortality for Acute Traumatic Brain Injury: a Study on Large ICU Cohorts

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Abstract

**Background:** Outcome prediction is crucial for the effective treatment of patients with acute traumatic brain injury (TBI). However, there is still a lack of reliable and routinely available blood predictors with sufficient clinical evidence till now. This research is designed to investigate the association between red cell distribution width to platelet count ratio (RPR) and mortality risk of TBI patients, thereby providing a promising indicator for prognosis evaluation of TBI.

**Methods:** Clinical data of 2,220 patients with TBI that extracted from two large ICU cohorts (MIMIC-III database and eICU Collaborative Research Database), were integratively analyzed using our developed method named MeDICS. The association between RPR and hospital mortality was determined using the logistic regression model and Lowess Smoothing technique. Multivariable logistic regression analyses were used to control for confounders. The receiver-operating characteristic (ROC) curve was depicted to show the prognostic performance. The stepwise backward elimination method was performed to develop a nomogram, where tenfold cross-validation was used to protect it against overfitting.

**Results:** Higher RPR can be observed among non-survivors than survivors with TBI (p < 0.001). Besides, high RPR was associated with increased mortality, with the odds ratio (OR) increasing from RPR of 0.074-0.098 (OR: 2.13, 95% CI 1.39 to 3.28, p = 0.001) to > 0.098 (OR: 3.82, 95% CI 2.55 to 5.72, p < 0.001), using RPR of < 0.057 as the reference. RPR had a moderately good prognostic performance with an area under ROC Curve (AUC) of 0.7367, which was greater than that of Glasgow Coma Scale (GCS, AUC = 0.6022). The nomogram consisting of RPR, GCS and other risk factors can further improve the prognostic value of RPR (Harrell’s C-index = 0.8582, p value of Hosmer-Lemeshow test = 0.3159). In addition, in-vivo experiments indicated that the continuous change in RPR after TBI was attributed to the development of inflammatory response.

**Conclusions:** As an easily accessible index, RPR is a promising predictor of mortality for acute TBI. The nomogram generated from RPR can be used in resource-limited settings, thus be proposed as a prognosis evaluation aid for patients with TBI in all levels of medical system.

Introduction

Traumatic brain injury (TBI) is one of the leading causes of disease that induced death and long-term disability, especially in children and young adults [1]. More than 50 million people worldwide are affected by a new TBI case annually, with an overall economic cost of about $US 406 billion [2]. As a growing public health problem, the incidence of TBI increases rapidly each year with the acceleration of urbanization, the increase of traffic accidents, and the frequent occurrence of local wars. Although great progress in clinical management has been made in the past few decades, there are still many clinical problems that need to be resolved.

Predicting outcome is crucial for the effective management of patients with acute TBI in neurosurgical ICU, neurological ICU, and emergency ICU. Firstly, early recognition of the disease severity contributes to
early treatment interventions, thus reducing hospital mortality. Secondly, the information provided to relatives should be based on solid clinical and scientific evidence, which will help them prepare for the future and understand the unpredictable risks and potentially painful interventions that the patients need to undergo. Glasgow Coma Scale (GCS) is a classic indicator to evaluate the severity of TBI. However, the GCS score alone cannot predict the outcome well in the early stage post-injury, as it can be influenced by multiple factors, such as alcohol drinking, intermediate awake of epidural hematoma, and past history of neurological diseases [3]. In addition, various researches have focused on exploring diagnostic and prognostic biomarkers for TBI in recent years. Although some potential biomarkers, including S100B, NSE, GFAP, UCH-L1, Neurofilament light and Tau have been reported with diagnostic or prognostic values in clinical trials, most of them have not been used in clinical work due to the lack of clinically compatible analysis platforms that ensure standardization and reproductive testing, except for S100B and Neurofilament light which was only used in diagnosis of mild TBI and chronic TBI [4–7].

Routine complete blood count (CBC) analysis is one of the most extensively applied noninvasive laboratory tests in clinical practice. Although the parameters of CBC analysis have been widely studied to determine the severity and mortality risk of TBI, there is still a lack of reliable and routinely available blood indicators with sufficient clinical evidence for predicting the prognosis till now [8]. Red blood cell distribution width (RDW) and platelets (Plt) count represents the heterogeneity of peripheral circulating red blood cells and the pathophysiology of hemostasis individually. As previously reported, RDW was increased at 1–7 days after TBI. Although some scientists suggested that RDW could be a prognostic indicator for acute TBI, the research with larger study population indicated that it was a poor predictor (Area Under Receiver-Operating Characteristic Curve, AUC = 0.66) for the mortality risk [9, 10]. Besides, Plt count was observed to be decreased after TBI, and its lowest value appeared at 1–5 days after TBI, followed by a rebound to the admission level by day 5–9 [11]. However, Plt count as well as other parameters of routine coagulation tests, including prothrombin time and activated partial thromboplastin time, demonstrated poor sensitivity to the clinical outcome of patients with TBI [12]. Conjunctively, the RDW to Plt count ratio (RPR) is a simple and easily calculated index, and a potential more powerful predictive indicator for the severity and mortality risk of acute TBI in theory, because it amplifies the imbalances between RDW and Plt count. In addition, in view of the fact that the CBC parameters, including RDW and Plt count at the first day after TBI may be interfered by shock, acute stress reaction and emergency treatments, we selected days 3–5 post-admission as the main time point to study the prognostic value of RPR. The time point is also the peak period of brain edema with central nervous system (CNS) and peripheral inflammation following injury [13].

To the best of our knowledge, rare studies regarding the prognostic capability of RPR in patients with TBI have been conducted. In the present study, we developed a new method that integratively used two large cohorts from online Intensive Care Unit (ICU) databases to clarify the association between RPR and the mortality risk of TBI, thus providing a simple and useful parameter for outcome prediction.

Methods
Database Introduction

All data in the current study were extracted from the online international databases – the Multiparameter Intelligent Monitoring in Intensive Care III (MIMIC-III, version 1.4) database and the eICU Collaborative Research Database (eICU-CRD, version 2.0) – that are maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology (Cambridge, MA, USA). The MIMIC-III database was approved by the institutional review boards of Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center (Boston, MA, USA). It contains 61,532 ICU admissions of 46,476 patients at this medical center from 2001 to 2012. The eICU-CRD was released under the Health Insurance Portability and Accountability Act safe harbor provision, and the re-identification risk was certified as meeting safe harbor standards by Privacert (Cambridge, MA; Certification no. 1031219-2). It covers 200,859 ICU admissions of 139,367 patients in 2014 and 2015 at 335 ICUs from 208 hospitals across the USA. Specifically, the source hospital of MIMIC-III does not participate in the eICU-CRD program.

The data from the MIMIC-III database and the eICU-CRD are openly available. All personal information has been removed to protect the privacy of the patients. To access the databases, author Ge completed the National Institutes of Health's web-based course Protecting Human Research Participants (certification number: 36320014). Data extraction was performed using Navicat Premium Version 12.1.11 (Preimumsoft™ CyberTech Ltd., Hongkong SAR, China).

Study Population

Patients with a diagnosis of TBI, defined as intracranial wound in the MIMIC-III database, and intracranial injury in the eICU-CRD, were potentially eligible for inclusion. Only those of the first ICU admission were chosen if they had more than one ICU stay record. Patients were excluded if they met the criteria: had no records of GCS within 24 h after admission, younger than 18 years old, had no binary sex, and/or had no records of whole blood RDW and Plt count at 72–120 h after admission.

Data extraction using the MeDICS method

Structure Query Language was used to extract data from the two databases. The following information was extracted: age, sex, GCS within the first 24 h after admission, neurosurgical operations, comorbidities, hospital mortality, RDW and Plt count (72–120 h after admission). The neurosurgical operations include therapeutic craniotomy, intracranial pressure monitoring, intracranial hemorrhage evacuation, burr-hole drainage of subdural hematoma, external ventricular drainage, etc. The comorbidities include arteriosclerotic heart disease (ASHD), chronic obstructive pulmonary disease (COPD), high blood pressure (HBP), stroke, hematopathy/coagulopathy, CNS infection, and pneumonia. Hospital mortality was used as the endpoint.

For patients with GCS that recorded more than once within the first 24 h after admission, the lowest one was employed as the first-day GCS. In addition, the average RDW and Plt count for each patient after admission were calculated respectively, and the RPR value of 72–120 h (approximately 4 days) after admission (4-DAA RPR) was then figured out using the two values.
To integrate the data from the MIMIC-III database and the eICU-CRD, ICU-stay-ID or patient-unit-stay-ID was regarded as the unique ID for each patient. Incompatible data such as patient-health system-stay-ID was excluded. The two databases have different definitions of the same diseases, thus they were unified by manual review, and the disease codes were extracted accordingly. Besides, the same variables with inconsistent data types in the two databases, such as numbers and strings were also unified. Through the above method, the data quality could be greatly improved. This procedure of data integration and procession was developed and named as MeDICS (MIMIC-III and eICU Database Integration Cases Study) by our team.

**Subgroup analysis and stratification**

Subgroup analysis was conducted to explore the possible interaction between RPR, TBI severity, neurosurgical operations, and other important factors affecting hospital mortality in clinical practice. Stratification was performed according to the first-day GCS (9–15, mild-moderate TBI; 3–8, severe TBI), whether underwent neurosurgical operations and the comorbidities.

**Management of missing data and outliers**

Variables with missing data are common in the MIMIC-III database and the eICU-CRD. As described in Study Population, patients with missing records of first-day GCS, RDW, and Plt count were excluded from the analysis. Variables with more than 20% missing values such as patients' height and weight were also excluded. Besides, the RPR outliers that more than 0.36, the 85% quantile of (upper quartile + 1.5 × interquartile range) were excluded as an erroneous entry.

**In-vivo experiments**

Adult male C57BL/6 mice were randomly divided into 4 groups: Sham, TBI, TBI + SC75741, and TBI + MCC950. A controlled cortical impact (CCI) was induced to build the TBI model [14, 15], and the treatments of SC75741 (NF-κB selective inhibitor) or MCC950 (specific inhibitor of pyroptosis initiating receptor NLRP3) were applied to the mice after injury [16]. After that, RDW and Plt count determination were obtained using automated Hematology Analyzer at 1 and 3 DPI, and the expression levels of inflammatory mediators from the injured cerebral cortex were determined by ELISA assay at 3DPI. In addition, the neurological outcome of TBI mice was evaluated by the Modified Neurological Severity Score (mNSS) [17], Morris Water Maze (MWM) [18, 19], and Novel Object Recognition (NOR) test [20, 21]. Detailed description for in-vivo experiments methods were provided in Supplemental Methods.

**Statistical analysis**

For the data collected from the MIMIC-III database and the eICU-CRD, continuous variables were expressed as mean ± SD, and compared using the Student's t-test, Wilcoxon rank sum test or Kruskal-Wallis rank sum test, as appropriate. Categorical data were expressed as number (percentage) and compared using the chi-square test.
The association between RPR and mortality was determined using the logistic regression model and presented as OR with 95% CI. The RPR values were divided into quartiles, with the first quartile (< 0.057) selected as the reference group. Multivariable logistic regression analyses were used to control confounders. Model 1 was adjusted for the confounders age and sex. Model 2 was adjusted for the confounders age, sex, first-day GCS, and neurosurgical operations. Model 3 was adjusted for the confounders age, sex, first-day GCS, neurosurgical operations, and comorbidities including ASHD, COPD, HBP, stroke, hematopathy/coagulopathy, CNS infection, and pneumonia. These confounders were selected based on their potential influences on RPR or hospital mortality. Potential multicollinearity was tested using the variance inflation factor, with a value of ≥ 5 indicating the presence of multicollinearity.

The Lowess Smoothing technique was used to explore the crude relationship between RPR and hospital mortality. A Receiver-Operating Characteristic (ROC) curve was depicted to show the prognostic performance and confirm the best cut-off value. The stepwise backward elimination method with a significance level of 0.05 was used to develop a nomogram. The Harrell's C-index was determined to evaluate its discriminative ability, and the Hosmer-Lemeshow test was performed to test the goodness of fit. Tenfold cross-validation was used to confirm the prognostic value of the model, and protects against overfitting.

All data from the in-vivo study were based on at least 3 independent experiments. The data were expressed as mean ± SD, except for that of the spatial acquisition trials of the MWM test, which are expressed as mean ± SEM. Data of the mNSS test and the spatial acquisition trials of the MWM test were analyzed using a two-way ANOVA followed by the LSD post-hoc test. For other data, statistical comparisons were analyzed using Student's t-test or one-way ANOVA followed by LSD post-hoc test, as appropriate. Pearson's correlation test was utilized to calculate the correlation coefficients between RPR and the neurological outcome of TBI mice.

All statistical analyses were performed using Stata/MP Version 14.0 (Stata Corp., College Station, TX, USA) and RStudio Version 1.3.1056 (Rstudio Corp., Boston, MA, USA). A two-tailed p value of less than 0.05 was considered to be statistically significant.

Results

Study population and baseline characteristics

In all, 2,220 patients who met the selection criteria were enrolled, including 1,966 survivors and 254 non-survivors, establishing a hospital mortality rate of 11.4%. The detailed procedure for population selection was shown in Fig. 1. Demographic characteristics of the survivors and non-survivors were presented in Table 1 (the study population with the data of first-day RDW and Plt count were shown in Table S1). The survivors tended to be younger than non-survivors, with a higher first-day GCS and a lower neurosurgical operation rate. It suggested that the survivors had milder primary injury than the non-survivors. In addition, there were fewer survivors with the history of hematopathy/coagulopathy and pneumonia.
complication than non-survivors. For the indicators of the laboratory tests, RPR and RDW were lower for survivors than non-survivors, and Plt count was higher for survivors.
Table 1
Baseline characteristics of the patients with TBI (72–120 h after admission)

| Variables                        | Total (n = 2,220) | Survivors (n = 1,966) | Non-survivors (n = 254) | p value |
|----------------------------------|-------------------|-----------------------|-------------------------|---------|
| Age, Years                       | 63.2 ± 21.1       | 62.5 ± 21.2           | 68.2 ± 19.6             | < 0.001*** |
| Male, n (%)                      | 1363 (61.4)       | 1,201 (61.1)          | 162 (63.8)              | 0.407   |
| First-day GCS, n (%)             |                   |                       |                         | < 0.001*** |
| 3–8                              | 604 (27.2)        | 485 (24.7)            | 119 (46.9)              |         |
| 9–15                             | 1616 (72.8)       | 1,481 (75.3)          | 135 (53.1)              |         |
| Neurosurgical Operations, n (%) |                   |                       |                         | 0.031*  |
| Yes                              | 438 (19.7)        | 375 (19.1)            | 63 (24.8)               |         |
| No                               | 1782 (80.3)       | 1591 (80.9)           | 191 (75.2)              |         |
| Comorbidities, n (%)             |                   |                       |                         |         |
| ASHD                             | 0.641             |                       |                         |         |
| Yes                              | 192 (13.5)        | 172 (12.5)            | 20 (21.3)               |         |
| No                               | 2028 (86.5)       | 1794 (87.5)           | 234 (78.7)              |         |
| COPD                             | 0.547             |                       |                         |         |
| Yes                              | 34 (1.5)          | 29 (1.5)              | 5 (2.0)                 |         |
| No                               | 2186 (98.5)       | 1937 (98.5)           | 249 (98.0)              |         |
| HBP                              | 0.692             |                       |                         |         |
| Yes                              | 212 (9.5)         | 186 (9.5)             | 26 (10.2)               |         |
| No                               | 2008 (90.5)       | 1780 (90.5)           | 228 (89.8)              |         |
| Stroke                           | 0.302             |                       |                         |         |
| Yes                              | 95 (4.3)          | 81 (4.1)              | 14 (5.5)                |         |
| No                               | 2125 (95.7)       | 1885 (95.9)           | 240 (94.5)              |         |
| Hematopathy/Coagulopathy         |                   |                       |                         | < 0.001*** |
| Yes                              | 108 (4.9)         | 82 (4.2)              | 26 (10.2)               |         |

***p < 0.001, **p < 0.01, *p < 0.05

Abbreviations: ASHD arteriosclerotic heart disease; CNS central nervous system; COPD chronic obstructive pulmonary disease; GCS Glasgow Coma Scale; HBP high blood pressure; Plt platelet; RDW red cell distribution width; RPR RDW to Plt count ratio
| Variables         | Total (n = 2,220) | Survivors (n = 1,966) | Non-survivors (n = 254) | p value |
|-------------------|------------------|----------------------|------------------------|---------|
| No                | 2112 (95.1)      | 1884 (95.8)          | 228 (89.8)             | 0.569   |
| CNS infection     |                  |                      |                        |         |
| Yes               | 12 (0.5)         | 10 (0.5)             | 2 (0.8)                |         |
| No                | 2208 (99.5)      | 1956 (99.5)          | 252 (99.2)             |         |
| Pneumonia         |                  |                      |                        | < 0.001*** |
| Yes               | 294 (13.2)       | 238 (12.1)           | 56 (22.0)              |         |
| No                | 1926 (86.8)      | 1728 (87.9)          | 198 (78.0)             |         |
| Laboratory tests  |                  |                      |                        |         |
| RDW, %            | 14.55 ± 1.89     | 14.45 ± 1.87         | 15.33 ± 1.93           | < 0.001*** |
| Plt count, 10^9/L | 203.08 ± 83.44   | 206.63 ± 82.90       | 175.54 ± 82.63         | < 0.001*** |
| RPR (L/10^9)      | 0.085 ± 0.045    | 0.083 ± 0.043        | 0.107 ± 0.055          | < 0.001*** |

***p < 0.001, **p < 0.01, *p < 0.05

Abbreviations: ASHD arteriosclerotic heart disease; CNS central nervous system; COPD chronic obstructive pulmonary disease; GCS Glasgow Coma Scale; HBP high blood pressure; Plt platelet; RDW red cell distribution width; RPR RDW to Plt count ratio

High RPR associates with increased hospital mortality of TBI

The relationship between 4-DAA RPR and hospital mortality for patients was shown in Fig. 2a using the Lowess Smoothing technique (the Lowess Smoothing for the first-day RPR and hospital mortality was shown in Figure S1a). It yielded an approximate linear relationship, with the largest slope in the RPR interval of 0.05–0.2.

There were 254 hospital deaths in the study population. As shown in Table 2, the group with the first RPR quartile (< 0.057) was selected as the reference in all comparisons and multivariable logistic regression models. In the crude model, the odds ratio (OR) with 95% confidence interval (CI) for the second (0.057–0.074), third (0.074–0.098), and fourth (> 0.098) quartile was 1.07 (0.67–1.73), 2.13 (1.39–3.28), and 3.82 (2.55–5.72), respectively. Therefore, high RPR was associated with increased hospital mortality, and the association between them was more significant in the relatively higher RPR quartiles (> 0.074), while the second quartile showed no increased mortality risk (also shown in Fig. 2b). A similar trend was also observed in Model 1, Model 2, and Model 3, in which the confounders including age, sex, first-day GCS,
neurosurgical operations, and morbidities were successively adjusted. For example, the fourth quartile had a higher OR (95% CI) and a lower p value than the third quartile in all models.
Table 2
The ORs for all-cause mortality across groups of the 4-DAA RPR

| RPR Quartiles | ORs | 95% CI       | p value |
|---------------|-----|--------------|---------|
| Crude         |     |              |         |
| < 0.057       | 1   |              |         |
| 0.057–0.074   | 1.07| 0.67–1.73    | 0.772   |
| 0.074–0.098   | 2.13| 1.39–3.28    | 0.001** |
| > 0.098       | 3.82| 2.55–5.72    | < 0.001*** |
| Model 1       |     |              |         |
| < 0.057       | 1   |              |         |
| 0.057–0.074   | 1.04| 0.64–1.67    | 0.880   |
| 0.074–0.098   | 2.02| 1.31–3.12    | 0.001** |
| > 0.098       | 3.59| 2.39–5.40    | < 0.001*** |
| Model 2       |     |              |         |
| < 0.057       | 1   |              |         |
| 0.057–0.074   | 0.99| 0.61–1.62    | 0.982   |
| 0.074–0.098   | 1.86| 1.19–2.89    | 0.006** |
| > 0.098       | 3.35| 2.20–5.08    | < 0.001*** |
| Model 3       |     |              |         |
| < 0.057       | 1   |              |         |
| 0.057–0.074   | 0.99| 0.61–1.61    | 0.960   |
| 0.074–0.098   | 1.84| 1.18–2.88    | 0.007** |
| > 0.098       | 3.13| 2.05–4.77    | < 0.001*** |

Multivariable logistic regression models were used to calculate ORs with 95% CI. Model 1 was adjusted for the confounders age and sex. Model 2 was adjusted for the confounders age, sex, first-day GCS, and neurosurgical operations. Model 3 was adjusted for the confounders age, sex, first-day GCS, neurosurgical operations, and comorbidites including ASHD, COPD, HBP, stroke, hematopathy/coagulopathy, CNS infection, and pneumonia. The mean variance inflation factor was 3.34 and 2.27 for Model 2 and Model 3, respectively.

***p < 0.001, **p < 0.01, *p < 0.05

Abbreviations: ASHD arteriosclerotic heart disease; CI Confidence Interval; CNS central nervous system; COPD chronic obstructive pulmonary disease; DAA days after admission; GCS Glasgow Coma Scale; HBP high blood pressure; OR Odds Ratio; Plt platelet; RDW red cell distribution width; RPR RDW to Plt count ratio
The outcome prediction value of 4-DAA RPR was examined using the ROC curve. As shown in Fig. 2c, its prognostic performance was moderately good for hospital mortality (AUC = 0.7362) with a cut-off value of 0.0734. Besides, compared with RDW (AUC = 0.6624), Plt count (AUC = 0.6339) and first-day GCS (AUC = 0.6022), which could not be regarded as an effective indicator for the poor outcome of TBI, 4-DAA RPR had an obvious advantage on prognosis prediction.

For the first-day RPR analysis, its association with mortality was shown in Figure S1b. The results indicated that only the fourth RPR quartile (> 0.089) referred to increased risk for mortality, while the second (0.055–0.069) and third (0.069–0.089) quartile showed no significance in all models (Table S2). In addition, the AUC value for first-day RPR was 0.6065 (Figure S1c), and the cut-off value was 0.0915 (higher than that of 4-DAA RPR). These results suggested poor discrimination of first-day RPR. Therefore, the mortality prediction value of 4-DAA RPR was much higher than that of first-day RPR.

**Subgroup analysis confirms the association between RPR and hospital mortality of TBI**

Subgroup analysis revealed the associations between 4-DAA RPR and mortality risk of TBI patients with different injury severity, neurosurgical operations, and comorbidities (Table 3). After adjusting for covariates, the interactive effects were detected in the first-day GCS, neurosurgical operations, hematopathy/coagulopathy, and pneumonia subgroups. The forest plot for subgroup analysis with RPR of 0074-0.098 and > 0.098 were shown in Fig. 3. For subgroup analysis of the associations between first-day RPR and hospital mortality (Table S3), the interactive effects were only detected in the first-day GCS and hematopathy/coagulopathy.
Table 3
Subgroup analysis of the associations between 4-DAA RPR and mortality

| Subgroups                  | ORs (95% CI)                | p for interaction |
|----------------------------|-----------------------------|-------------------|
|                            | RPR < 0.057 | RPR 0.057–0.074 | RPR 0.074–0.098 | RPR > 0.098 |
| First-day GCS              |              |                  |                  |              |
| 3–8                        | 1            | 1.95 (0.78–4.87) | 3.50 (1.47–8.30) | 5.88 (2.50–13.80) | < 0.001*** |
| 9–15                       | 1            | 0.77 (0.42–1.42) | 1.33 (0.76–2.33) | 2.42 (1.45–4.04) |
| Neurosurgical Operations   |              |                  |                  |              |
| Yes                        | 1            | 0.65 (0.24–1.81) | 1.83 (0.80–4.19) | 4.33 (2.03–9.24) | 0.023*     |
| No                         | 1            | 1.13 (0.63–2.03) | 1.85 (1.07–3.17) | 2.92 (1.73–4.91) |
| ASHD                       |              |                  |                  |              |
| Yes                        | 1            | 3.77 (0.68–20.91)| 2.18 (0.31–15.23)| 2.74 (0.50–14.84)| 0.189      |
| No                         | 1            | 0.85 (0.51–1.43) | 1.84 (1.16–2.92) | 3.19 (2.05–4.94) |
| COPD                       |              |                  |                  |              |
| Yes                        | 1            | U.C.              | U.C.              | U.C.         |
| No                         | 1            | 1.00 (0.61–1.64) | 1.91 (1.22–3.00) | 3.15 (2.06–4.84)| 0.911      |
| HBP                        |              |                  |                  |              |
| Yes                        | 1            | 2.88 (0.51–16.38)| 2.16 (0.37–12.65)| 4.43 (0.81–24.35)| 0.558      |
| No                         | 1            | 0.91 (0.54–1.52) | 1.87 (1.18–2.98) | 3.10 (1.99–4.81) |
| Stroke                     |              |                  |                  |              |
| Yes                        | 1            | 0.21 (0.01–3.16) | 0.59 (0.06–6.04) | 3.44 (0.45–26.26)| 0.912      |
| No                         | 1            | 1.07 (0.65–1.77) | 1.99 (1.26–3.15) | 3.24 (2.09–5.03) |

Confounders adjustment were performed as in Model 3. Multivariable logistic regression models were used to calculate ORs with 95% CI.

***p < 0.001, **p < 0.01, *p < 0.05

Abbreviations: ASHD arteriosclerotic heart disease; CI Confidence Interval; CNS central nervous system; COPD chronic obstructive pulmonary disease; DAA days after admission; GCS Glasgow Coma Scale; HBP high blood pressure; OR Odds Ratio; RPR red cell distribution width to platelet count ratio; U.C. unable to calculate
| Subgroups                        | ORs (95% CI) | p for interaction |
|---------------------------------|--------------|-------------------|
|                                 | RPR < 0.057  | RPR 0.057–0.074   | RPR 0.074–0.098 | RPR > 0.098 |
| Hematopathy/Coagulopathy        |              |                   |                 |             |
| Yes                             | 1            | 0.77 (0.09–6.86)  | 1.01 (0.27–4.32)| 2.32 (0.37–14.66)| 0.011*         |
| No                              | 1            | 0.99 (0.60–1.63)  | 2.06 (1.31–3.25)| 3.05 (1.97–4.73)|                   |
| CNS infection                   |              |                   |                 |             |
| Yes                             | 1            | U.C.              | U.C.            | U.C.         | 0.534           |
| No                              | 1            | 1.00 (0.61–1.64)  | 1.90 (1.21–2.97)| 3.21 (2.09–4.92)|                   |
| Pneumonia                       |              |                   |                 |             |
| Yes                             | 1            | 1.54 (0.51–4.67)  | 2.06 (0.71–5.94)| 2.48 (0.91–6.71)| 0.004**         |
| No                              | 1            | 0.94 (0.54–1.63)  | 1.78 (1.08–2.93)| 3.50 (2.17–5.62)|                   |

Confounders adjustment were performed as in Model 3. Multivariable logistic regression models were used to calculate ORs with 95% CI.

***p < 0.001, **p < 0.01, *p < 0.05

Abbreviations: ASHD arteriosclerotic heart disease; CI Confidence Interval; CNS central nervous system; COPD chronic obstructive pulmonary disease; DAA days after admission; GCS Glasgow Coma Scale; HBP high blood pressure; OR Odds Ratio; RPR red cell distribution width to platelet count ratio; U.C. unable to calculate

Although the discriminative ability of RPR is moderately good, a monogram was constructed to further improve the prognostic value for TBI mortality. Six factors that found correlated with hospital mortality of TBI, including RPR, age, GCS, neurosurgery, pneumonia, and hematopathy/coagulopathy were included in the stepwise backward eliminating logistic model (Fig. 4). Nomogram weightings for each factor were derived from the β coefficients. The factors contributed points, so increased total points were associated with greater probability of mortality. A C-index of 0.8582 was obtained. It suggested that the nomogram had a good discriminative ability with respect to the C indices of the univariable models incorporating each of the individual variables used to construct the nomogram. In addition, the Hosmer-Lemeshow test showed a p value of 0.3159, which indicated no reason to reject the null hypothesis of no difference between predicted and observed mortality probabilities. Tenfold cross-validation suggested that the mean C-index was 0.8523 and the mean Brier Score was 0.0766, thus confirmed the model does not have overfitting, and has a high prognostic value.

**Anti-inflammatory treatments decrease RPR after TBI on mice model**
To validate the clinical findings on in-vivo model, the whole blood RDW and Plt count of TBI mice were determined. We observed that RPR was decreased at 1 and 3 days post-injury (DPI), which was more significant at 3 DPI than 1 DPI (Figure S2a). Meanwhile, changes with marginal statistical differences in the RDW and Plt count were observed at 3 DPI, but not 1 DPI (Figure S2b). In addition, the anti-inflammatory agents SC75741 and MCC950 that inhibited the expression levels of inflammatory mediators (TNF-α, IL-1β, and IL-10) in brain and serum (Figure S2c-h), could reverse the level changes on RPR at 1 and 3 DPI (Figure S2a, S2b). These results suggested that increased RPR after TBI were a manifestation of CNS and systemic inflammatory response.

**RPR is negatively correlated with the neurological outcome of TBI mice**

The neurological outcome of TBI mice was evaluated by the mNSS, MWM and NOR test. In the mNSS test, lower neurological scores demonstrate better neurological function. As shown in Figure S3a, no difference on the neurological score at 1 DPI was observed in the experimental groups. The recovery of neurological function began at 3 DPI, and lasted to 14 DPI, when the injured mice still had residual neurological deficiencies. Compared to the TBI group, the neurological score was decreased in the TBI + SC75741 and TBI + MCC950 group at 14 DPI, suggesting that the anti-inflammatory treatments improved the neurological score of TBI mice.

In the MWM test, the spatial acquisition trials were performed to test spatial learning ability. Escape latency, which represents the capability to navigate from a starting location to a submerged platform, was gradually decreased in the testing procedure, indicating that a spatial memory was established \[F (3, 128) = 327.7, p < 0.001\] (Figure S3b). The probe trials were conducted to test the retrograde reference memory, in which more time spent in goal quadrant indicates better memory. Compared to the TBI group, TBI + SC75741 and TBI + MCC950 group showed shortened escape latency in the spatial acquisition trials, and prolonged time spent in goal quadrant in the probe trials (Figure S3c). It indicated that the anti-inflammatory treatments improved the spatial learning and memory ability of TBI mice.

In the NOR test, the amount of time taken to explore the new object provides an indicator for cognitive memory. We found that the index of exploring time on the novel object over the total exploring time was increased in the TBI + SC75741 and TBI + MCC950 group, compared to the TBI group (Figure S3d). Hence, the anti-inflammatory treatments contributed to the recovery of cognitive function after TBI.

As the anti-inflammatory treatments could decrease RPR in TBI mice, the Pearson's correlation coefficients for RPR and the neurological outcome were further calculated. The results suggested strong associations between 1) RPR and latency-time in the MWM test; 2) RPR and time spent in goal quadrant in the MWM test; 3) RPR and NOR index (Figure S3e). To sum up, RPR was negatively correlated with the neurological outcome of TBI mice. These results further confirmed the results of our clinical findings.

**Discussion**
Hemodynamic changes and systemic inflammation are always observed in patients with acute TBI. The release of inflammatory mediators following injury could induce tissue damage, red blood cell destruction and structural changes, as well as platelet aggregation and accelerated consumption, which finally result in the dysfunction of neurovascular unit and increased risk of poor prognosis [22]. Routinely conducted during hospitalization, the CBC analyses contain several parameters that reflect the above pathological changes. Of these parameters, RDW and Plt count which have potential to indicate the mortality risk of TBI was selected to be investigated in this research. Using the MeDICS method, we found that their ratio – RPR, a novel easily accessible index, is a reliable predictor for the outcome of acute TBI.

RDW represents the heterogeneity in size of erythrocytes, of which the higher values indicate greater variation. Recently, it has gained substantial attention as an indicator of inflammation [23], and a prognostic marker for various diseases independent of hemoglobin values [24]. A research on the association between aging of hematopoietic stem cells and oxidative stress molecules, such as reactive oxygen species, super-oxide dismutase and glutathione peroxides, revealed that abnormally increased RDW can well indicated the above pathological changes [25]. It has also been suggested that elevated RDW was related to suboptimal health status that involves chronic inflammatory response and impairment of red cell generation. Specifically, pro-inflammatory cytokines can affect the survival of erythrocytes in circulation, suppress maturation, and accelerate the entry of newer, larger reticulocytes into the peripheral circulation, thereby leading to the increase of RDW [26]. In the present study, RDW was observed to be increased in patients with TBI at 3–5 days post-admission. However, although the RDW value were lower in survivors than in non-survivors, further statistical analysis found that it had no effect on predicting the prognosis of acute TBI.

Platelets, along their well-known roles in hemostasis, are an active participant in regulating inflammation. Specifically, while adhering to coagulation factors, platelets also carry a large number of inflammatory factors such as TNF-α, interleukins and serotonin, which are involved in tissue damage and repair. Decreased Plt count is a common pathological phenomenon in patients with acute and critical illness. Its underlying mechanism may involve: 1) Reduced platelet production due to infectious and inflammatory damage to megakaryocytes, and bacterial endotoxins that inhibit the function of bone marrow megakaryocytes. 2) Increased platelet destruction and consumption caused by severe infection-induced diffuse intravascular coagulation. 3) Destruction of platelet production led by complement activation through immune pathways [27]. Studies on sepsis observed a reduction of Plt count in patients, which was correlated with the severity of the disease, and a risk factor for poor prognosis [28]. Besides, platelets played a pivotal role in the inflammatory response in hepatic injury and burn injury [29, 30]. In the present study, a substantial decline in Plt count was observed at 3–5 days post-admission, and the decrease of Plt count in non-survivors were lower than that of survivors. Even so, similar to RDW, Plt count could not independently infer prognostic information of acute TBI.

Recently, RPR has been considered as a novel index that reflects inflammation severity by combining the prognostic advantages of RDW and Plt count. As a routinely available marker, RPR was recognized as a strong predictor for hepatic fibrosis and hepatitis [31, 32], inflammation in acute pancreatitis [33],
ascending thoracic aortic aneurysm [34], and myocardial infarction [35]. In addition, high RPR on days 3 and 7 could be observed in patients with severe burn injury, which indicated poor prognosis of the disease [36]. Parallel to these studies, the increased RPR was also reported to be correlated with the severity (disease scores) of inflammatory factors in systemic lupus erythematosus [37]. From this, RPR would be a powerful indicator of inflammation.

Although the exact mechanism underlying the poor prognosis of TBI patients with elevated RPR remains unclear, it may be partially attributed to the development inflammation following injury. In-vivo experiments were thus designed to explore related mechanisms. As an upstream switch of inflammatory response, NF-κB signaling exerts important effects on regulating the development of neuroinflammation in acute TBI [38] and chronic traumatic encephalopathy [39]. In addition, our previous researches found that pyroptosis in injured brain after TBI can trigger the inflammatory cascade, and lead to the dysfunction of neurovascular unit [16, 40]. In the present study, we used specific inhibitors that block NF-κB and pyroptosis-activated receptor NLRP3 to observe the level changes on RDW, Plt count, and RPR under the condition of inflammatory suppression. RDW decline and Plt count increase with marginal statistical differences were observed after anti-inflammatory treatments at 3DPI. Meanwhile, RPR was also decreased notably after the treatments, suggesting that it is a powerful indicator of inflammation in acute TBI. In addition, the results of neuro-functional tests indicated that RPR value was closely related to the neurological outcome of TBI mice receiving anti-inflammatory treatments. These findings confirmed the association between RPR, post-traumatic inflammation and neuro-outcome after TBI, and further emphasized the importance of controlling inflammatory response in clinical treatment.

Our research simultaneously explored the association between RPR and the mortality risk of acute TBI at two important time points post-injury. We found that 4-DAA RPR turned out to be strongly associated with the endpoint of TBI, but first-day RPR had no prognostic value. Besides, similar results were also observed in in-vivo experiments. We believe that these findings could be explained by the development of inflammation. Specifically, the inflammation peak after TBI mostly occurs at 3–5 days post-injury. This time point is also the peak period of brain edema with massive activation of microglia and astrocytes, release of inflammatory mediators into the CNS and peripheral circulation, and homing of activated neutrophils and immune cells (e.g., T cells and NK cells) to the injured brain tissue [13]. However, in the hyper-acute phase of TBI (< 24 h post-injury), the CBC parameters may be interfered by shock and acute stress reaction. In addition, the glial cells in the brain are not widely activated at this time, and the peripheral inflammatory and immune cells have not completed their homing, leading to the limitation of focal brain inflammation to the injury site [41]. Consequently, the prognostic value of 4-DAA RPR for TBI was much higher than that of first-day RPR. Moreover, with the use of our nomogram that consisted of RPR, GCS and other risk factors, the predicting value of RPR can be further improved. The strength of this nomogram is that it was built from physical examination and easily diagnosed medical history or comorbidities. Therefore, it can be used in resource-limited settings, where clinicians are still likely to have all the data required to use it effectively. The nomogram is able to be applied to all levels of medical system, thus we propose it as a prognosis evaluation aid for all patients with TBI.
Several limitations of this study should be taken into account when interpreting the results. First, the retrospective nature of the design limited the research. Patients’ information of Abbreviated Injury Scale - Injury Severity Score at admission and Glasgow Outcome Scale – Extended on discharge were not designed to be collected in the databases. Second, this research failed to include other risk factors, such as chronic liver disease, chronic renal disease, diabetes mellitus, sepsis, and malignancy, as well as other endpoints including ICU mortality and hospital/ICU length of stay. Third, the continuous fluctuations in RDW, Plt count, and RPR in acute TBI were not determined. These fluctuations may be necessary for the formulation of a comprehensive conclusion on their prognostic value. To address the questions, a multicenter prospective study is being planned to further confirm the findings of this research and promote its clinical application in the future.

Conclusions

Due to the low cost, highly reproducible and ease of calculation, RPR can be a useful clinical predictor of mortality for patients with acute TBI. The level change of RPR after TBI is attributed to the development of inflammation, which further emphasizes the importance of controlling inflammatory response in clinical treatment. In addition, the nomogram generated from RPR, GCS and other risk factors can further improve the prognostic value of RPR, thus be proposed as a prognosis evaluation aid for TBI in all levels of medical system.

Abbreviations

ASHD: arteriosclerotic heart disease; AUC: Area Under ROC Curve; CBC: complete blood count; CCI: controlled cortical impact; CI: Confidence Interval; CNS: central nervous system; COPD: chronic obstructive pulmonary disease; DAA: days after admission; eICU-CRD: eICU Collaborative Research Database; GCS: Glasgow Coma Scale; HBP: high blood pressure; ICU: Intensive Care Unit; MeDICS: MIMIC-III and eICU Database Integration Cases Study; MIMIC-III: Multiparameter Intelligent Monitoring in Intensive Care III; mNSS: Modified Neurological Severity Score; MWM: Morris Water Maze; NOR: Novel Object Recognition; OR: Odds Ratio; Plt: platelet; RDW: red cell distribution width; ROC: Receiver-Operating Characteristic; RPR: RDW to Plt count ratio; TBI: traumatic brain injury

Declarations

Ethics approval and consent to participate

The establishment of the datasets was approved by the Institutional Review Boards of the Massachusetts Institute of Technology (Boston, MA, USA). The in-vivo experimental procedures were performed in adherence to the Directive 2010/63/EU for animal experiments, and the Policy of Animal Care and Use Committee of Tianjin Medical University.
Consent for publication

Requirement for individual patient consent was waived because the project did not impact clinical care, and all protected health information was de-identified.

Availability of data and materials

Data from the MIMIC database and eICU-CRD can be accessed at the website (https://mimic.mit.edu/, https://eicu-crd.mit.edu/). The datasets used in the present study are available from the first author and corresponding authors upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

XTG., PL, and JNZ were responsible for the study concept. XTG. designed the study, performed data extraction and analysis. LYZ and WZL conducted laboratory examination, in-vivo experiments and data validation. XTG prepared the figures and wrote the manuscript. JS provided comments and critical revision. RCJ reviewed the manuscript. All authors read and approved the final manuscript.

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Figures
Figure 1

Flow chart of the study population. In all, 2,220 patients who met the selection criteria were enrolled. GCS: Glasgow Coma Scale; Plt: platelet; RDW: red cell distribution width; RPR: RDW to Plt count ratio; TBI: traumatic brain injury
Association between 4-DAA RPR and hospital mortality of patients with TBI. (a) The Lowess Smoothing revealed an approximate linear relationship between RPR and hospital mortality. The linear relationship was most significant (with the largest slope), when RPR was at the interval of 0.05-0.2. (b) The RPR values were divided into quartiles, and the third (0.074-0.098) and fourth quartile (>0.098) was associated with high hospital mortality, compared to the first (<0.057) and second quartile (0.057-0.074). (c) The
ROC curve for 4-DAA RPR, RDW, Plt count, and first-day GCS. AUC: area under curve; DAA: days after admission; GCS: Glasgow Coma Scale; ROC: receiver-operating characteristic; RPR: red cell distribution width to platelet count ratio; TBI: traumatic brain injury

Figure 3

Forest plot for subgroup analysis of the association between hospital mortality and RPR. The interactive effects were detected in the first-day GCS, neurosurgical operations, hematopathy/coagulopathy, and...
pneumonia subgroups. GCS: Glasgow Coma Scale; RPR: red cell distribution width to platelet count ratio

**C-index = 0.8582**

Figure 4

Nomogram to predict hospital mortality of patients with TBI. To estimate the mortality risk for a given patient, locate the RPR value and draw a line straight up to the Points axis to determine the associated score. Repeat the process for GCS, age, neurosurgery, pneumonia, and hematopathy/coagulopathy. Then, sum the scores and locate them on the Total Points axis. Finally, draw a vertical line to the Mortality Risk axis and read off the probability. GCS: Glasgow Coma Scale; RPR: red cell distribution width to platelet count ratio; TBI: traumatic brain injury

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