Red Blood Cell Distribution Width Predicts Postoperative Death of Infective Endocarditis

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Summary
Infectious endocarditis (IE) is a rare disease with high mortality rate. Recently, red cell distribution width (RDW) has drawn special attention for predicting cardiovascular disease. This study aims to explore the relationship between RDW value and postoperative death of IE patients.

Clinical records of patients with definite IE from Chinese People’s Liberation Army General Hospital department of cardiovascular surgery were collected and analyzed. Clinical, echocardiographic, and biochemical variables were evaluated along with RDW.

Results: A total of 158 consecutive IE patients (mean age 47.0 ± 16.3 years, male 61.4%) were enrolled in this study. According to receiver operating characteristic (ROC) curve analysis, the optimal RDW cutoff value for predicting mortality was 15.45% (area under the curve 0.913, \( P < 0.001 \)). A total of 28 patients (17.8%) died postoperatively; of these, 89.3% had RDW value >15.45%. Binary regression analysis showed that aging, multiple valvular involved, valvular vegetation formation, pulmonary hypertension, and high RDW are strong predictors of postoperative death. Multiple regression analysis revealed that high RDW value was independent predictors of postoperative mortality in patients with IE (\( \beta \): 3.704, 95% confidence interval (95%CI): 2.729-60.692, \( P < 0.05 \)).

IE has a high inhospital mortality rate, and increased RDW is an independent predictor of postoperative death in these patients.

Key words: Inhospital mortality

Infective endocarditis (IE) is a rare disease, but its impact is significant. It affects 3-10 per 100,000 per year in the population at large, and epidemiological studies suggest that the incidence is rising.\(^1\) Although there have been significant improvements in the treatment of most cardiovascular diseases in recent decades, prognosis still remains poor in IE. The current inhospital mortality rate is as high as around 20%.\(^2\)

It is still a challenging job for clinicians to identify patients who are at high risk of adverse outcomes immediately due to the broad spectrum of the cardiac pathology and infecting organisms. Recently, red cell distribution width (RDW) has drawn attention for predicting cardiovascular disease. RDW is determined by red blood cell size heterogeneity. The increased value has been always linked with inflammatory and oxidative states.\(^3\) It is proved to be a special risk factor for increased cardiovascular mortality.\(^4\) Additionally, RDW is also a ubiquitous biomarker, which is obtained as a part of complete blood count routinely and periodically in the outpatient or inpatient setting. Thus, RDW is cheap, safe, and easy to obtain, unlike other cardiovascular disease biomarkers such as high-sensitivity C-reactive protein (hs-CRP). The purpose of this study is to explore the relationship between RDW value and postoperative death of IE patients.

Methods
Study patients: Between January 2016 and December 2018, patients diagnosed as definite IE (according to the modified Duke criteria) at Chinese People’s Liberation Army General Hospital department of cardiovascular surgery were enrolled in this study. Patients with hepatic insufficiency and those with a history of hematological disease (such as anemia, leukemia, or bone marrow infiltration) were excluded. The prospective data of 158 consecutive IE patients were analyzed retrospectively. In addition to RDW levels on admission, clinical, echocardiographic,
and other laboratory findings were recorded for each subject. Predisposing heart diseases, including prosthetic valve, preexisting valvular disease, congenital heart disease, nosocomial infection, previous history of IE, and arrhythmia (atrial fibrillation), were assessed.

Complications during hospitalization, such as renal failure, embolic events (excluding cerebral), cerebrovascular events, heart failure, and surgical treatment procedure for IE, were all recorded. Postoperative death is defined as in-hospital death occurring after surgery. This study was performed in accordance with the Declaration of Helsinki for human research and was approved by our hospital’s ethics committee.

Data collection: All blood samples were collected on an empty stomach the morning after admission. Baseline RDW, hemoglobin, hematocrit, platelet count, and white blood cell count values were measured using an automated hematology analyzer. C-reactive protein and creatinine concentrations were measured accordingly. All patients underwent echocardiography examination by the same experienced ultrasound doctor within 48 hours of admission. All patients underwent repeated blood culture (≥ twice) to determine the type of pathogenic bacteria. Vegetation, abscess formation, and valvular destruction, such as perforation of leaflet and chordal rupture, were evaluated. Vegetation size was measured using different echocardiographic windows. The maximal length was obtained. Severe valvular regurgitation or stenosis was identified according to guideline recommendations. Pulmonary artery systolic pressure was estimated by continuous wave Doppler imaging of the tricuspid regurgitation using the Bernoulli equation. The operation procedure, extracorporeal circulation time, aortic occlusion time, and blood product application were recorded.

Statistical analysis: Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as number and percentage. A chi-squared test or Fisher’s exact test was performed to compare categorical variables. Student’s t-test was used for normally distributed continuous variables. The discrimination of RDW for postoperative death was evaluated using the area under the receiver operating characteristic (ROC) curve. The optimal cutoff point for ROC curves was determined for maximizing the sensitivity and specificity of the RDW values. The sensitivity and specificity of the cutoff value are calculated. Univariate Cox proportional-hazards analyses were used to evaluate the relationship between variables and overall mortality. Variables that had a P value < 0.05 in the univariate analysis were used in a multivariable Cox proportional-hazards model to determine the independent prognostic factors of mortality. The results of the regression analysis are presented as hazard ratios and 95% confidence intervals (95%CI). All statistical analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, IL, USA). A P value of 0.05 was considered statistically significant.

Results

The number of patients, who met the inclusion criteria, with men comprising 61.8% (n = 34) of the cohort, enrolled in this study was 158. The mean age was 47.0 ± 16.3 years. The mean duration of ICU stay was 6.7 ± 6.7 days. Staphylococcus (27.3%, n = 43) and streptococcus (21.0%, n = 33) were the most common pathogens. There were 20 cases (12.7%) of prosthetic valve IE and 138 cases of native valve IE. A total of 148 people underwent simultaneous multiple valve surgery. The cardiopulmonary bypass (CPB) time and aortic clamping (AC) time are 166.5 ± 49.3 and 133.9 ± 44.4, respectively. The inotropic blood loss and plasma infusion volume were 470.4 ± 161.0 and 6.4 ± 3.1, respectively. There was no statistical difference between the surgical data of survivors and non-survivors (P < 0.05, Table I).

A total of 28 patients (17.7%) died postoperatively, of which 26 patients (89.3%) died of septic shock and 3 died of cerebral infarction. A total of 13 patients (8.2%) received reoperations, of which 8 cases (61.5%) received reoperations due to prosthetic mitral valve dysfunction and the other 5 cases (38.5%) for vegetation formation. Table I shows the differences between survivors and non-survivors regarding demographic, clinical, and echocardiographic properties.

RDW was significantly increased in fatal cases (P < 0.001). Figure 1 shows median RDW values in survivors and non-survivors. According to ROC curve analysis, the optimal cutoff value of RDW results on admission for predicting postoperative death was 15.45%, with 89.3% sensitivity and 55.6% specificity (area under the curve: 0.913, 95%CI: 0.867-0.959, P < 0.001, Figure 2). To evaluate associations between RDW and clinical outcome, patients were divided into two groups (low RDW group and high RDW group) according to RDW cutoff value (≤ 15.45% versus > 15.45%). Table II shows that there is no difference in surgical data (e.g., multiple valve procedure, CPB time, AC time, and application of blood products) between patients in the high RDW group and in the low RDW group (P < 0.05). The properties of these subgroups were compared, as shown in Table II. Inhospital complications such as heart failure, pleural effusion, cerebrovascular events, and prosthetic valve dysfunction were more common in patients with high RDW group. Systolic pulmonary artery pressures were elevated significantly in this group compared with in the lower RDW group. Also, C-reactive protein and white blood cell count were higher and Staphylococcus aureus infection was more common in patients with increased RDW.

Discussion

The most remarkable finding of our study was the association between RDW and postoperative outcome. There was no significant difference between the survivors and the non-survivors in terms of operation procedure and extracorporeal circulation time. But the in-hospital mortality rate was significantly higher in the high RDW group (55.6% versus 2.7%). In the Cox proportional-hazards analysis, elevated RDW on admission was an indicator of postoperative death before and after adjusting for other potential confounders. Our results suggest that RDW may become a valuable biomarker for estimating poor postoperative outcome in patients with IE. To the best of our knowledge, this is the first study that evaluated the asso-
tion between RDW and in-hospital mortality of patients with IE.

RDW, determined by red blood cell size heterogeneity, is a ubiquitous biomarker obtained as a part of complete blood count, which is performed routinely and periodically in the inpatient setting. Increased value has been considered linked with inflammatory and oxidative states. But there are no clear putative pathophysiologic mechanisms to explain this relationship. Chronic subclinical inflammation may play a significant role.\(^\text{7}\) Investigators have proposed that inflammation causes myelosuppression, decreases renal erythropoietin synthesis, reduces iron storage and bioavailability, and promotes apoptosis of erythroid precursors in bone marrow,\(^\text{8}\) all of which can result in a higher degree of anisocytosis and thereby a higher RDW value. Hence, it can be inferred that high RDW is associated with a pro-inflammatory state.\(^\text{9}\) Our data supports this hypothesis, by demonstrating significantly higher mean CRP levels in high RDW group. Veeranna, et al.\(^\text{10}\) found that RDW was a stronger predictor of cardiovascular disease mortality compared to CRP in subjects with no preexisting heart valve disease. Another theory is that elevated RDW can increase oxidative and hemodynamic stress, which accelerates the development

| Table 1. Baseline Characteristics and Outcomes of the Study Patients |
|---------------------------------------------------------------|
| **Demographics and predisposing conditions**                   |
| Male sex                                                      | 97                              | 16                               | 81                              | 0.627                      |
| Age (years) *                                                 | 47.0 ± 16.3                      | 58.3 ± 15.6                       | 45.0 ± 16.6                      | 0.031                      |
| Prosthetic valve                                              | 20                              | 8                                | 12                              | 0.679                      |
| Congenital cardiac disease*                                   | 21                              | 4                                | 17                              | 0.031                      |
| Renal insufficiency                                           | 17                              | 6                                | 11                              | 0.242                      |
| Previous IE                                                   | 7                               | 2                                | 5                               | 0.662                      |
| History of cerebral infarction                                | 35                              | 9                                | 26                              | 0.975                      |
| Hypertension                                                 | 32                              | 4                                | 28                              | 0.556                      |
| Diabetes                                                     | 26                              | 8                                | 18                              | 0.735                      |
| Atrial fibrillation                                           | 22                              | 4                                | 18                              | 0.876                      |
| Affected valve                                                |                                  |                                  |                                 |                           |
| Aortic                                                       | 23                              | 4                                | 19                              | 0.876                      |
| Mitral                                                       | 43                              | 5                                | 38                              | 0.242                      |
| Tricuspid                                                    | 25                              | 3                                | 22                              | 0.755                      |
| Multiple                                                     | 76                              | 21                               | 55                              | 0.046                      |
| **Echocardiography**                                          |                                  |                                  |                                 |                           |
| Severe valvular regurgitation                                 | 67                              | 16                               | 49                              | 0.249                      |
| Severe valve stenosis                                         | 5                               | 2                                | 3                               | 0.197                      |
| Vegetation maximum diameter                                   | 15.2 ± 6.2                       | 11.0 ± 5.0                       | 15.7 ± 6.2                       | 0.159                      |
| Valvular destruction                                          | 21                              | 4                                | 17                              | 0.876                      |
| Pulmonary hypertension*                                       | 36                              | 15                               | 21                              | 0.007                      |
| LVEF (%)                                                      | 64.8 ± 6.3                       | 64.1 ± 8.3                       | 65.0 ± 6.0                       | 0.771                      |
| **Laboratory variables on admission**                         |                                  |                                  |                                 |                           |
| WBC count (× 10^3/L) *                                        | 9.7 ± 4.3                        | 12.4 ± 6.7                       | 9.1 ± 3.5                       | 0.037                      |
| CRP (mg/dL)                                                   | 3.5 ± 2.9                        | 4.3 ± 4.1                        | 3.3 ± 2.5                       | 0.412                      |
| Creatinine (mg/dL)                                            | 108.7 ± 103.1                    | 116.7 ± 93.0                    | 87.5 ± 57.3                     | 0.264                      |
| RDW (%)                                                      | 15.0 ± 2.3                       | 17.2 ± 2.1                       | 14.3 ± 1.5                       | < 0.001                    |
| **Microorganism**                                             |                                  |                                  |                                 |                           |
| Staphylococcus                                                | 46                              | 6                                | 40                              | 0.716                      |
| Streptococcus species                                        | 33                              | 4                                | 29                              | 0.105                      |
| Brucella species                                              | 10                              | 2                                | 8                               | 0.432                      |
| Enterococcus species                                         | 26                              | 7                                | 19                              | 0.611                      |
| Gram-negative bacilli                                         | 11                              | 3                                | 8                               | 0.635                      |
| Fungi                                                        | 23                              | 3                                | 20                              | 0.484                      |
| Culture negative                                             | 9                               | 2                                | 7                               | 0.635                      |
| **Perioperative outcome**                                     |                                  |                                  |                                 |                           |
| Multiple valve procedure                                      | 148                             | 25                               | 123                             | 0.209                      |
| Cardiopulmonary bypass time (minutes)                        | 166.5 ± 49.3                     | 151.0 ± 53.5                     | 169.0 ± 48.8                    | 0.375                      |
| Aortic clamping time (minutes)                               | 133.9 ± 44.4                     | 112.1 ± 41.9                     | 137.3 ± 44.2                    | 0.165                      |
| Intraoperative blood loss (mL)                               | 470.4 ± 161.0                    | 480.4 ± 166.8                    | 412.5 ± 112.6                   | 0.275                      |
| Plasma transfusion (u)                                       | 6.4 ± 3.1                        | 6.5 ± 3.1                        | 5.6 ± 3.2                       | 0.473                      |
| Red blood cell transfusion (u)                                | 2.8 ± 2.3                        | 2.9 ± 2.3                        | 2.5 ± 2.6                       | 0.599                      |
| Platelet transfusion (u)                                     | 0.7 ± 0.5                        | 0.7 ± 0.5                        | 0.8 ± 0.5                       | 0.596                      |
| 24-hour drainage volume                                      | 396.7 ± 150.8                    | 375.5 ± 160.6                    | 455.1 ± 188.1                   | 0.386                      |
| Reoperation for bleeding or prosthetic valve dysfunction      | 31                              | 5                                | 26                              | 0.635                      |

\(*P < 0.05.\)
of coronary artery disease. Gerdine, et al. found that elevated RDW at hospital discharge is significantly associated with 90-day mortality following adjustment for potential confounders. Further, discharge RDW is associated with placement in a care facility and 90-day unplanned hospital readmission.

Previous studies on the relationship between elevated RDW and IE are rare. Jo, et al. found that the increase of RDW (> 15.8%) has important value in the prediction of early death from septic shock. Guray, et al. found that increased RDW is an independent predictor of overall mortality in IE patients. In the Cox proportional-hazards analysis, RDW value > 15.3% on admission was an indicator of 1-year survival before and after adjusting for other potential confounders. The use of RDW as a prognostic marker may provide valuable information for early risk stratification in IE. In our study, complications of IE and inhospital events were more common in subjects with elevated RDW.

IE has a broad-ranging disease course, and biomarkers may facilitate risk stratification at early stages in this complex disease. Previous studies have found that C-reactive protein was not found to be useful in identifying worse outcome, although it was elevated in fatal cases. We believe that RDW has greater value in predicting postoperative death of IE patients. However, these studies did not specifically target IE. In addition, although some biomarkers have important value in predicting the postoperative death of IE patients, their high price increases the economic burden of patients. In our study, aging, multiple valvular involved, valvular vegetation formation, pulmonary hypertension, and high RDW are strong predictors of postoperative death. Univariate and multivariate logistics regression analysis confirmed that high RDW was an effective predictor of postoperative death in IE patients. The threshold found in this study can alert clinicians to take more aggressive measures to prevent poor outcome (Tables III, IV).

An unresolved question remains: Is abnormal RDW the cause of postoperative death, or do both hematological abnormalities and postoperative death occur as a consequence of underlying metabolic derangements common in patients with multiple comorbidities? Because erythropoiesis is influenced by inflammatory cytokines, oxidative stress, and nutritional status, it is reasonable to hypothesize that abnormal RDW may simply be markers of patient frailty rather than directly causing adverse outcomes. Dai, et al. pointed out that, actually, RBCs have roles beyond oxygen delivery. RBCs affect blood viscosity, promote platelet marginalization, and interact directly and indirectly with endothelial cells and platelets. RBCs also form a procoagulant surface through exposure of phosphatidylserine, thereby actively participating in hemostasis and thrombosis. As such, it is also reasonable to suspect that the size, stiffness, and uniformity of RBC may di-
were retrospective design and small sample size. Referral limitations:

The main limitations of the present study were retrospective design and small sample size. Referral bias may have affected clinical data. Besides, being a referral center might also have resulted in more culture-negative results due to possible antibiotic use prior to hospital admission. Additionally, due to retrospective data-gathering limitations, we could not analyze the data on transfusion status or nutritional deficiencies before admission, which may have affected RDW value. However, after adjusting RDW by multivariable analysis, a significant association remained between RDW and mortality. Our study findings are not applicable to patients with chronic liver disease and those with a history of hematological disease, since they were excluded. We used self-reported history of hypertension, smoking, diabetes mellitus, hyper-

Table II. Comparison of the Characteristics and Outcomes of the Patients According to Their RDW Values

| Demographics and predisposing conditions                  | High RDW Group | Low RDW Group | P value |
|----------------------------------------------------------|----------------|---------------|---------|
| Male sex*                                                 | 28             | 69            | 0.017   |
| Age (years) *                                            | 57.4 ± 13.4    | 43.0 ± 16.8   | 0.004   |
| Prosthetic valve                                         | 11             | 9             | 0.083   |
| Congenital cardiac disease                               | 4              | 17            | 0.493   |
| Previous IE                                              | 2              | 5             | 0.975   |
| History of cerebral infarction                           | 9              | 26            | 0.730   |
| Hypertension                                             | 2              | 30            | 0.147   |
| Diabetes                                                 | 7              | 19            | 0.679   |
| Affected valve                                           |                |               |         |
| Aortic                                                   | 6              | 17            | 0.975   |
| Mitral                                                   | 8              | 35            | 0.373   |
| Tricuspid                                                | 4              | 21            | 0.272   |
| Multiple                                                 | 27             | 49            | 0.312   |
| Echocardiography                                          |                |               |         |
| Severe valvular regurgitation                            | 24             | 43            | 0.256   |
| Severe valve stenosis                                    | 1              | 4             | 0.516   |
| Vegetation ≥ 10 mm                                       | 20             | 52            | 0.874   |
| Valvular destruction                                     | 8              | 13            | 0.412   |
| Pulmonary hypertension*                                   | 25             | 11            | 0.001   |
| LVEF (%)                                                 | 65.5 ± 7.1     | 64.6 ± 6.1    | 0.624   |
| Laboratory variables on admission                        |                |               |         |
| WBC count (× 10^9/L)                                      | 11.3 ± 5.4     | 9.1 ± 3.7     | 0.120   |
| C-reactive protein (mg/dL)                               | 3.9 ± 3.3      | 3.2 ± 2.6     | 0.504   |
| Creatinine (mg/dL)                                       | 128.1 ± 103    | 101.2 ± 143.3 | 0.543   |
| RDW (%)                                                  | 17.2 ± 1.8     | 13.8 ± 0.9    | < 0.001 |
| Microorganism                                            |                |               |         |
| Staphylococcus                                           | 5              | 41            | 0.813   |
| Streptococcus species                                    | 4              | 29            | 0.106   |
| Brucella species                                         | 5              | 5             | 0.146   |
| Enterococcus species                                     | 11             | 15            | 0.276   |
| Gram-negative bacilli                                    | 3              | 8             | 0.855   |
| Fungi                                                    | 4              | 19            | 0.579   |
| Culture negative                                         | 2              | 7             | 0.855   |
| Perioperative outcome                                    |                |               |         |
| Multiple valve procedure                                 | 26             | 122           | 0.671   |
| Cardiopulmonary bypass time (minutes)                    | 171.0 ± 49.3   | 154.5 ± 48.9  | 0.290   |
| Aortic clamping time (minutes)                           | 140.2 ± 44.3   | 116.7 ± 41.1  | 0.900   |
| Intraoperative blood loss (mL)                           | 438.3 ± 367.3  | 345.0 ± 367.3 | 0.551   |
| Plasma transfusion (u)                                   | 6.3 ± 3.1      | 6.4 ± 3.3     | 0.943   |
| Red blood cell transfusion (u)                            | 2.9 ± 2.3      | 2.8 ± 2.6     | 0.849   |
| Platelet transfusion (u)                                 | 0.6 ± 0.5      | 0.8 ± 0.4     | 0.409   |
| 24-hour drainage volume                                  | 424.8 ± 146.7  | 358.3 ± 80.6  | 0.322   |
| Reoperation for bleeding or prosthetic valve dysfunction | 14             | 17            | 0.348   |
| Postoperative death*                                     | 8              | 3             | < 0.001 |

*P < 0.05.
to improve IE risk prediction. RDW can also be combined with other novel biomarkers such as diet and lifestyle modification or pharmacologic therapy in individuals with high baseline RDW values. Over time to find out the influence of preventive measures more, it would be pertinent to follow serial RDW values and randomized control trials are needed to assess the usefulness of RDW in risk stratification of IE. Further directions: Future multicenter prospective studies and randomized control trials are needed to assess the usefulness of RDW in risk stratification of IE. Furthermore, it would be pertinent to follow serial RDW values over time to find out the influence of preventive measures such as diet and lifestyle modification or pharmacologic therapy in individuals with high baseline RDW values. RDW can also be combined with other novel biomarkers to improve IE risk prediction.

Conclusion

Our results suggest that IE has a high inhospital mortality rate and that increased RDW (> 15.45%) is an independent predictor of postoperative death in these patients. The use of RDW as a prognostic marker may provide valuable information for early risk stratification in IE.

Disclosure

Conflicts of interest: The authors declare no conflicts of interest. This manuscript has been approved by all authors and has not been submitted to any other journal.

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