

A Practical Nomogram Based on RDW-CV for Predicting Clinical Outcome in Elderly Septic Patients

Chengying Hong¹, Zhenmi Liu¹, Chuanchuan Nan¹, Yinjing Xie², Jinquan Xia³, Yichun Jiang¹, Xiaojun Liu¹, Zhikun Xu¹, Kangping Hui⁴, Yihan Xiong⁴, Wei Wang⁵, Huaisheng Chen¹

¹Department of Critical Care Medicine, Shenzhen People's Hospital, The Second Clinical Medical College, Jinan University, Shenzhen, Guangdong, 518020, People's Republic of China; ²Laboratory Department, Shenzhen People's Hospital, The Second Clinical Medical College, Jinan University, Shenzhen, Guangdong, 518020, People's Republic of China; ³Department of Clinical Medical Research Center, Shenzhen People's Hospital, The Second Clinical Medical College, Jinan University, Shenzhen, Guangdong, 518020, People's Republic of China; ⁴Shenzhen People's Hospital, The Second Clinical Medical College, Jinan University, Shenzhen, Guangdong, 518020, People's Republic of China; ⁵Department of Endocrinology, Shenzhen People's Hospital, The Second Clinical Medical College, Jinan University, Shenzhen, Guangdong, 518020, People's Republic of China

Correspondence: Huaisheng Chen, Department of Critical Care Medicine, Shenzhen People's Hospital, The Second Clinical Medical College, Jinan University, Shenzhen, Guangdong, 518020, People's Republic of China, Email sunshinic@hotmail.com; Wei Wang, Department of Endocrinology, Shenzhen People's Hospital, The Second Clinical Medical College, Jinan University, Shenzhen, Guangdong, 518020, People's Republic of China, Email windy97333@aliyun.com

Objective: The retrospective study established a prognostic nomogram based on red blood cell distribution width-coefficient of variation (RDW-CV) for elderly septic patients.

Methods: We analyzed 1997 critically ill patients admitted between December 2016 and June 2019, and 986 elderly septic patients were included in the study and stratified into survival and non-survival groups. Using machine learning-based feature importance analysis and multivariate logistic regression, we evaluated predictors of mortality in the elderly septic patients, with particular focus on RDW-CV. We constructed a nomogram incorporating RDW-CV to predict clinical outcomes in elderly septic patients and evaluated its performance.

Results: The mortality of 986 elderly sepsis patients was 27.48%. Importance analysis showed that RDW-CV demonstrated superior predictive value for mortality. The RDW-CV (17.22 ± 3.98%) in the non-survival group was significantly higher than that (15.30 ± 2.81%) in the survival group, $p < 0.0001$. The RDW-CV was used to predict the mortality of patients and the AUC was 0.65 (95% CI: 0.61, 0.69). Multivariate logistic regression showed that mechanical ventilation, drug-resistant bacterial infection, hemofiltration, and RDW-CV independently influenced mortality, a predictive nomogram was developed based on a final model that included RDW-CV and other clinical indicators, the area under the curve (AUC) was found to be 0.755 (95% CI: 0.714, 0.797), decision curve analyses (DCA) revealed superior net benefit of the nomogram across threshold probabilities of 0.30–1.00 in both derivation and validation cohorts. The calibration curve demonstrates strong agreement between the model's predicted probabilities and the validation cohort's predicted probabilities.

Conclusion: Higher RDW-CV was found to have a significant association with mortality prediction, the nomogram based on RDW-CV with other clinical indicators could more accurately predict the clinical outcome of elderly septic patients, validation analysis confirmed the accuracy of the nomogram, the predictive model offered clinical applicability.

Keywords: RDW-CV, elder, sepsis, mortality, predictive model, nomogram

Introduction

Sepsis is a serious condition characterized by multiple organ dysfunction syndrome (MODS) due to a dysfunctional response of the body to infection.¹ According to a statistical analysis conducted by the Institute for Health Metrics and Evaluation (IHME) of the University of Washington, sepsis accounted for 19.7% of deaths worldwide in 2017, with an estimated 489 million cases.² The morbidity and mortality rates are extremely high, and sepsis poses a significant socio-economic burden.³ With the increasing proportion of elderly patients in the aging society, the unique characteristics of elderly patients with sepsis have been the focus of attention in recent studies.^{4,5} Age is an important factor that affects the prognosis of sepsis, and the mortality rate increases with age.^{6,7} Age may affect the morphology of patients' blood cells, increase red blood cell distribution width (RDW), and affect disease recovery, leading to an increase in mortality.⁸

RDW is a specific indicator which reflects the heterogeneity of erythrocyte volume in the blood circulation. Previous studies have shown that an increased RDW can predict the prognosis of the diseases,^{9–13} such as decompensated heart failure, liver failure, acute pancreatitis, colon and rectal tumors, etc. A meta-analysis was conducted in 2022, and a total of 24 studies were included, the results demonstrated that RDW was an available and valuable biomarker for predicting the mortality of adult patients with sepsis, high levels of RDW were associated with higher mortality.¹⁴ For septic patients, some studies have suggested that RDW has a high predictive value for prognosis of sepsis with an AUC of ROC as high as 0.80, while others have reported a lower AUC of 0.60.^{15–17} The research results regarding RDW as a predictor of prognosis for patients with sepsis are not consistent.

Clinically, RDW is usually expressed as coefficient variation (CV). RDW-CV which is rapidly and automatically calculated by all modern hematological analyzers is a calculated value that utilizes both RDW and mean corpuscular volume (MCV) measurements.⁹ Theoretically, RDW-CV and RDW have similar diagnostic significance. Moreover, RDW-CV is a comprehensive indicator and has more advantages compared to RDW. Our previous study had shown that RDW-CV was associated with the outcome of sepsis.¹⁸ Given the potential socio-economic value of using a cost-effective blood routine to effectively predict sepsis prognosis, we conducted a retrospective analysis of data from septic patients and found that RDW-CV had an area under the ROC curve (AUC) of 0.65 (95% CI 0.61, 0.69) for predicting sepsis mortality. Furthermore, there are limited researches on the prognostic value of RDW-CV in elderly septic patients. Therefore, we aim to explore the predictive value of RDW-CV in elderly patients with sepsis and construct a predictive model based on RDW-CV to improve the predictive efficiency of prognosis.

Materials and Methods

Inclusion Criteria

A total of 1997 patients admitted to the critical care department between December 1, 2016, and June 31, 2019, were retrospectively analyzed according to the diagnostic criteria of the International Sepsis Guidelines (sepsis-3.0).¹⁹ The inclusion criteria of the study were: 1) patients diagnosed with infection, 2) patients with organ dysfunction due to infection (Sequential Organ Failure Assessment (SOFA) score ≥ 2). The inclusion criteria were based on clinical manifestations and laboratory results. The infection site had been determined by reviewing the discharge diagnosis on the first page of the medical record, as well as the results of chest X-ray, abdominal ultrasound, and bacterial culture.

Exclusion Criteria

Patients under the age of 60 were excluded.

Intervention Measures

Upon admission to the intensive care unit (ICU), blood culture and anti-infective treatment were administered to patients, and mechanical ventilation and blood purification were initiated according to organ failure. Antibiotics, other medications, and organ support programs were adjusted based on the patient's condition and bacterial culture results.

Observation Indicators

Recorded cases requiring organ support, including the following: 1) MV needed: patients with respiratory failure require mechanical ventilation support; 2) Shock: mean arterial pressure less than 65 mmHg or requiring norepinephrine as a vasoactive agent to maintain blood pressure; 3) HF needed: requiring blood purification therapy. AND the SOFA score was calculated by extracting data.

Laboratory indicators included: blood routine: red blood cell counts (RBC, $\times 10^{12}/L$), RDW-CV (%), mean corpuscular hemoglobin (MCH, pg), mean corpuscular hemoglobin concentration (MCHC, g/L), mean corpuscular volume (MCV, fl), haemoglobin (HGB, g/L), haematocrit (HCT, %), white blood cell counts (WBC, $\times 10^9/L$), percentage of neutrophils (N, %), percentage of lymphocytes (L, %), percentage of monocytes (M, %), platelet counts (PLT, $\times 10^9/L$), platelet distribution with (PDW, %), mean platelet volume (MPV, fl); inflammation Index: C-reactive protein (CRP, mg/L), procalcitonin (PCT, ng/L); Blood Lipid Index: total cholesterol (CHOL, mmol/L), high-density

lipoprotein (HDL, mmol/L), low-density lipoprotein (LDL, mmol/L), triglyceride (TG, mmol/L); Coagulation function Index: antithrombin III (AT III, %), activated partial prothrombin time (APTT, s/second); Renal function: blood urea nitrogen (BUN, mmol/L), serum creatinine (SCr, $\mu\text{mol/L}$); liver function: total bilirubin (TBIL, $\mu\text{mol/L}$); others including glycosylated hemoglobin (HBA1C, %); elevated lactic acid levels ($\geq 1.5\text{mmol/L}$). Recorded variables included positive cultures for multiple drug-resistant microorganisms, ICU stay duration (in days), mechanical ventilation duration (in hours), and final clinical outcome (death or improvement). Additional laboratory indicators were documented upon ICU admission.

Statistical Analysis

The patients were categorized into two groups, the survival group, and the non-survival group, based on their clinical outcomes. The baseline characteristics of the two groups were compared. Normally distributed data were presented as mean \pm standard deviation, and the differences between the groups were analyzed using Student's *t*-test. Non-normally distributed data were expressed by quartile method, and the differences between groups were compared using Mann Whitney test.

The importance analysis, which is a machine learning method called XGboot, was used to analyze the significance of the different indicators in predicting the prognosis of mortality. The area under the curves (AUC) of Receiver Operating Characteristic (ROC) Curves was calculated to predict the clinical outcome of patients. The AUC confidence interval and significance were tested using the nonparametric repeated sampling method (Bootstrap resampling times=500). The diagnostic specificity, sensitivity, accuracy, positive, and negative likelihood ratio, positive predictive value, and negative predictive value were calculated based on the optimal threshold. The patients were divided into groups according to the optimal threshold of the ROC curve, and the Kaplan-Meier survival curve was drawn. The difference between the two curves was analyzed using the log-rank method.

The relevant predictors with $p < 0.05$ in the multivariate logistic regression analysis were selected and included in the model. A nomogram model based on RDW-CV combined with other indicators was developed to improve the predictive value for the clinical outcome of elderly patients with sepsis. The AUC of ROC curve was used to evaluate the discrimination of the Nomogram model. The calibration curve was used to evaluate the predictive ability of the prediction model. Furthermore, decision curve analyses (DCA) were utilized to validate the clinical utility of the nomograph.

The statistical significance was defined as $P < 0.05$. Odds ratio (OR) and 95% confidence interval (CI) were calculated. The data was analyzed using SPSS for Window 20.0 and eBay software (EmpowerState2.0, R language, pROC, ROCR).

Results

Patient Characteristics and Baseline Comparisons

From December 1, 2016, to June 31, 2019, 1997 patients were admitted to the critical care department. Among them, 264 patients did not meet the inclusion criteria and 747 patients met the exclusion criteria. Finally, 986 elderly patients diagnosed with sepsis were included in this study (see [Supplementary Figure 1](#)), consisting of 590 males and 396 females, with a mean age of 76.97 ± 9.43 years. There was no statistically significant difference in age between the survival group and the non-survival group ($p = 0.289$). In terms of organ dysfunction, the SOFA score of the non-survival group was significantly higher than that of the survival group, and there was a statistically significant difference, $P < 0.001$ (see [Table 1](#)). The analysis results of laboratory indicators are shown in [Table 2](#), among which RDW-CV is normally distributed, the median is 14.9% after calculation.

The Predictive Value of RDW-CV for Mortality in Elderly Septic Patients

By using importance analysis (a machine learning method called XGboot), the Factors influencing prognosis were visually ranked. Among RDW-CV, hemofiltration, shock, thrombocytopenia, mechanical ventilation, DRBI and hyperbilirubinemia, RDW-CV ranks first in its contribution to predicting patient mortality (see [Figure 1Ai](#)). In comparison to other laboratory parameters, RDW-CV demonstrated superior predictive value for mortality (see [Figure 1Aii](#)).

We conducted microscopic observation of peripheral blood cells, when RDW-CV was less than 14%, the diameter of red blood cells was uniform and the staining remains consistent (see [Figure 1Bi](#)). Conversely, when RDW-CV was more

Table 1 Comparison of Baseline Between Survival Group and Non-Survival Group in Elderly Patients with Sepsis

indicator	Survival Group	Non-Survival Group	p value
Case n, (%)	715 (72.52)	271 (27.48)	-
Gender			0.016
Male n, (%)	411 (57.48)	179 (66.05)	
Female n, (%)	304 (42.52)	92 (33.95)	
Age (y)	76.78±9.21	77.49±9.97	0.289
Infectious site			
Respiratory tract n, (%)	460 (64.34)	162 (59.78)	0.186
Abdomen n, (%)	35 (4.90)	17 (6.27)	0.387
Biliary tract n, (%)	11 (1.54)	3 (1.11)	0.609
Urinary tract n, (%)	4 (0.56)	2 (0.74)	0.748
Septicemia n, (%)	70 (9.79)	79 (29.15)	<0.001
DRBI n, (%)	59 (8.25)	74 (27.31)	
Assessment of Organ Dysfunction			
SOFA score (score)	7.81±3.20	13.43±4.43	<0.001
Shock n, (%)	617 (86.29)	252 (92.99)	0.004
Hyperlacticaemia n, (%)	189 (26.43)	104 (38.38)	<0.001
MV needed n, (%)	408 (57.06)	211 (77.86)	<0.001
Thrombocytopenia n, (%)	188 (26.29)	163 (60.15)	<0.001
HF needed n, (%)	83 (11.61)	113 (41.70)	<0.001
Hyperbilirubinemia n, (%)	88 (12.31)	94 (34.69)	<0.001
Outcome assessments [†]			
ICUstay (mean, days) [†]	8.27 (7.41, 9.12)	14.75 (11.97, 17.53)	<0.001
MV duration (mean, hours) [†]	98.40 (84.42, 112.37)	248.14 (194.15, 302.14)	<0.001

Note: [†]Mean and 95% CI.

Abbreviations: SOFA score, sequence organs failure assessment score; DRBI, drug-resistance bacterial infection; MV, mechanical ventilation; HF, hemofiltration.

Table 2 Laboratory Indicators Included in the Analysis

Indicator	Mean	SD	Indicator	Mean/Median	SD/Quartile
RBC (×10 ¹² /L)	3.50	0.87	CRP (mg/L)	71.09	27.31, 139.25
HGB (g/L)	97.83	18.18	PCT (ng/L)	1.11	0.23, 7.04
HCT (%)	30.06	5.51	CHOL (mmol/L)	3.01	1.10
RDW-CV (%) [†]	15.83	3.29	HDL (mmol/L)	0.74	0.38
MCH (pg)	29.11	3.03	LDL (mmol/L)	1.29	0.96
MCHC (g/L)	300.55	88.56	TG (mmol/L)	1.04	0.75, 1.55
MCV (fl)	89.29	7.69	ATIII (%)	65.42	17.53
PLT (×10 ⁹ /L)	197.55	108.92	APTT (s)	43.56	14.74
PDW (%)	12.70	2.88	BUN (mmol/L)	10.56	8.98
MPV (fl)	10.83	1.19	Cr (μmol/L)	97.00	68.08, 163.75
WBC (×10 ⁹ /L)	12.46	8.13	TBIL (μmol/L)	13.75	8.40, 19.88
N (%)	84.35	11.51	HbA1c (%)	6.39	1.56
L (%)	10.09	9.29			
M (%)	10.09	9.29			

Note: [†]The median of RDW-CV is 14.9% after calculation.

Abbreviations: SD, standard deviation; RBC, red blood cell counts; RDW-CV, the coefficient of variation of erythrocyte distribution width; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; HGB, haemoglobin; HCT, haematocrit; WBC, white blood cell counts; N, percentage of neutrophils; L, percentage of lymphocytes; M, percentage of monocytes; PLT, platelet counts; PDW, platelet distribution width; MPV, mean platelet volume; CRP, C-reactive protein; PCT, procalcitonin; CHOL, total cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride; AT III, antithrombin III; APTT, activated partial prothrombin time; BUN, blood urea nitrogen; SCr, serum creatinine; TBIL, total bilirubin; HBA1C, glycosylated hemoglobin.

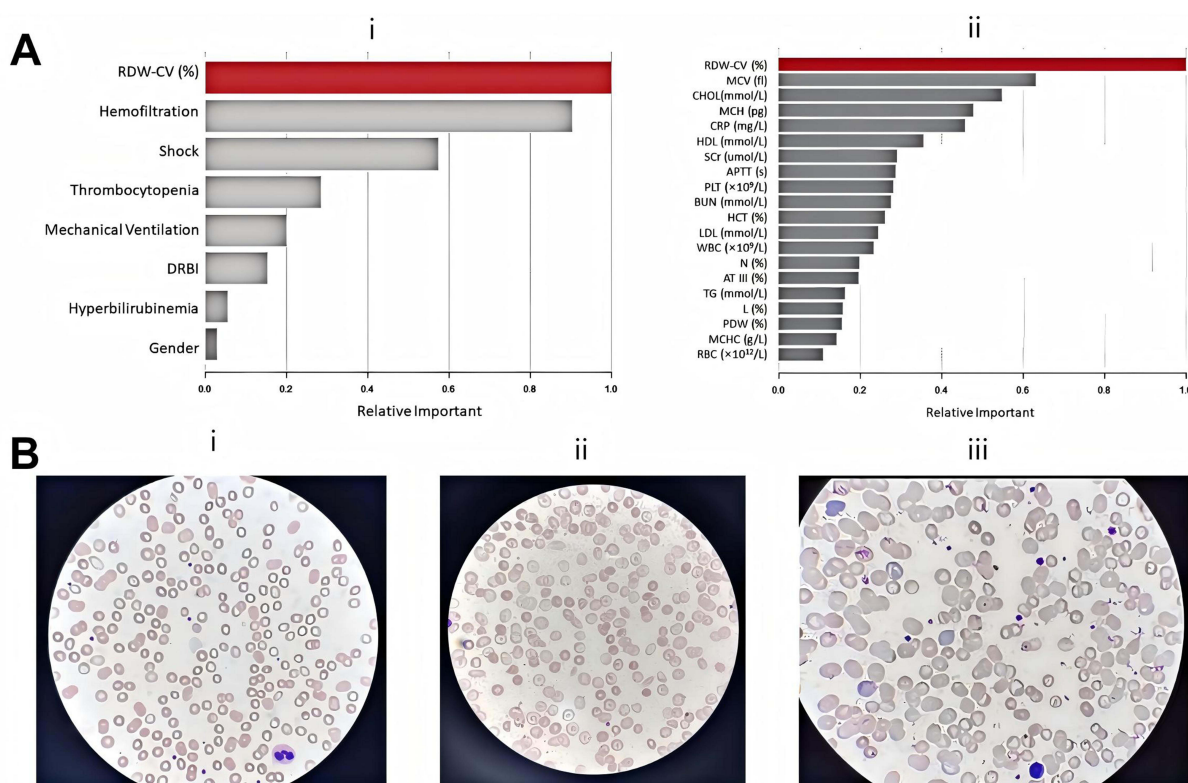


Figure 1 The predictive value of RDW-CV for mortality in elderly septic patients.

Notes: **(Ai)** Among RDW-CV, hemofiltration, shock, thrombocytopenia, mechanical ventilation, DRBI and hyperbilirubinemia, RDW-CV ranks first in its contribution to predicting patient mortality. **(Aii)** In comparison to other laboratory parameters, RDW-CV demonstrated superior predictive value for mortality. **(Bi)** Peripheral blood red cell morphology observed under microscopy when RDW-CV was less than 14%, the diameter and color of red blood cells were uniform and consistent. **(Bii)** Peripheral blood red cell morphology observed under microscopy when RDW-CV was more than 14%, the red blood cells showed variations in size and uneven staining. **(Biii)** Peripheral blood red cell morphology observed under microscopy when RDW-CV was more than 20%, the erythrocytes demonstrate marked anisocytosis and polychromasia, with evident rouleaux formation of red cells.

than 14%, the red blood cells showed variations in size and uneven staining (see [Figure 1Bii](#)). And when RDW-CV was more than 20%, the erythrocytes demonstrate marked anisocytosis and polychromasia (see [Figure 1Biii](#)).

The mortality of 986 elderly sepsis patients was 27.48%. The RDW-CV ($17.22 \pm 3.98\%$) in the non-survival group was significantly higher than that ($15.30 \pm 2.81\%$) in the survival group, $p < 0.0001$. The RDW-CV was used to predict the mortality of patients. A ROC curve was plotted, and the results showed that the AUC was 0.65 (95% CI: 0.61, 0.69) (see [Supplementary Figure 2](#)). The best threshold (BT) was found to be 15.05%, with a specificity of 0.60, sensitivity of 0.70, and accuracy of 0.63. The positive likelihood ratio (positive-LR) was 1.74 and the negative likelihood ratio (negative-LR) was 0.50. The diagnostic odds ratio (Diagnosis-OR) was 3.49, and the number needed for diagnosis (NND) was 3.34.

The Relationship Between RDW-CV and Mortality of the Patients

There was a nonlinear relationship RDW-CV and patient mortality through smooth curve fitting analysis ([Figure 2A](#)). We identified an inflection point at RDW-CV=12.20. Beyond it, mortality risk increase significantly ($P < 0.001$). A second turning point at 15.20 (15.20, 15.50) marked a weaker, non-significant trend ($P = 0.578$). Patients were then stratified based on a threshold of the median RDW-CV value of 14.9%, resulting in two groups: RDW-CV $> 14.9\%$ and $\leq 14.9\%$. Kaplan–Meier survival analysis demonstrated a significant difference between the two groups, $\text{Chisq} = 7.6034$ on 1 degree of freedom, $P = 0.0058$ ([Figure 2B](#)). The result indicates that patients with sepsis whose RDW-CV was less than 14.9% had a better clinical outcome.

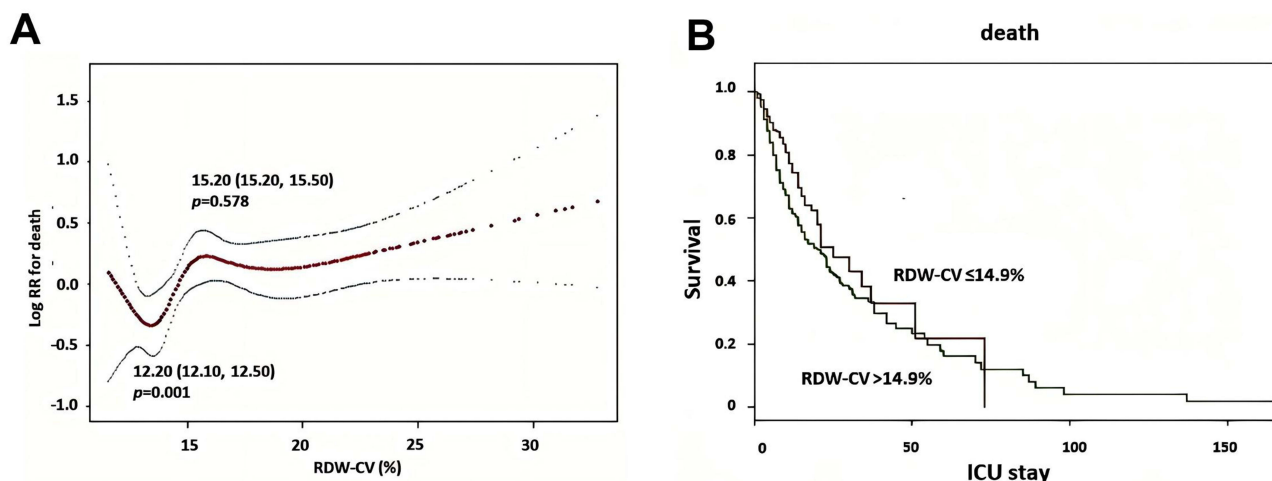


Figure 2 The relationship between the RDW-CV and the mortality of the patients. **Notes:** (A) There was a nonlinear relationship RDW-CV and patient mortality through smooth curve fitting analysis. Mortality risk rose significantly with RDW-CV above 12.20 ($P < 0.001$), but the association beyond 15.20, while positive, lacked statistical significance ($P 0.578$). (B) Kaplan–Meier survival analysis demonstrated a significant difference between the two groups, $\text{Chisq}=7.6034$ on 1 degree of freedom, $P0.0058$.

A Nomogram Based on RDW-CV and Other Indicators for Predicting Clinical Outcome in Elderly Septic Patients

Multivariate logistic regression analysis revealed that mechanical ventilation, drug-resistance bacterial infection (DRBI), hemofiltration, and RDW-CV were significantly associated with mortality in elderly sepsis patients, the P values were all less than 0.05 (see Table 3).

A prediction model was developed to improve the predictive value based on RDW-CV combined with other clinical and laboratory indicators. The algorithm included:

$$-4.42802 + 0.83454 \times (\text{MV needed} = \text{yes}) + 0.73399 \times (\text{drug-resistant bacteria infection} = \text{yes}) + 1.40391 \times (\text{HF needed} = \text{yes}) + 0.15192 \times \text{RDW-CV}.$$

A nomogram was drawn based on the algorithm to predict the clinical outcome of elderly patients with sepsis. The data was stratified into ten groups based on the predicted probabilities, with deciles used as the stratification criterion. To visually represent the observed values and predicted values for each group, a coordinate form was employed. Line graphs were utilized to depict the observed values and predicted values separately. This graphical representation effectively demonstrated the disparities between the actual observed values and the model-predicted values for each group. Additionally, it facilitated a comprehensive evaluation of the model’s calibration performance. The close alignment observed between the actual values and predicted values across the groups indicated a well-calibrated predictive model.

Table 3 Variables Associated with Mortality in Elderly Patients with Sepsis (Multivariate Analysis)

Indicator	Estimate	Std Error	OR	95% CI		p value
				Lower	Upper	
Interaction	-4.4280	0.5211	0.0119	0.0043	0.0332	0.0000
MV needed	0.8345	0.2219	2.3038	1.4911	3.5593	0.0002
DRBI	0.7340	0.2501	2.0834	1.2760	3.4016	0.0033
HF needed	1.4039	0.2114	4.0711	2.6900	6.1611	0.0000
RDW-CV	0.1519	0.0296	1.1641	1.0985	1.2336	0.0000

Note: Std error, standard error; CI, confidence interval; MV, mechanical ventilation; DRBI, drug-resistance bacterial infection; HF, hemofiltration; RDW-CV, the coefficient of variation of erythrocyte distribution width.

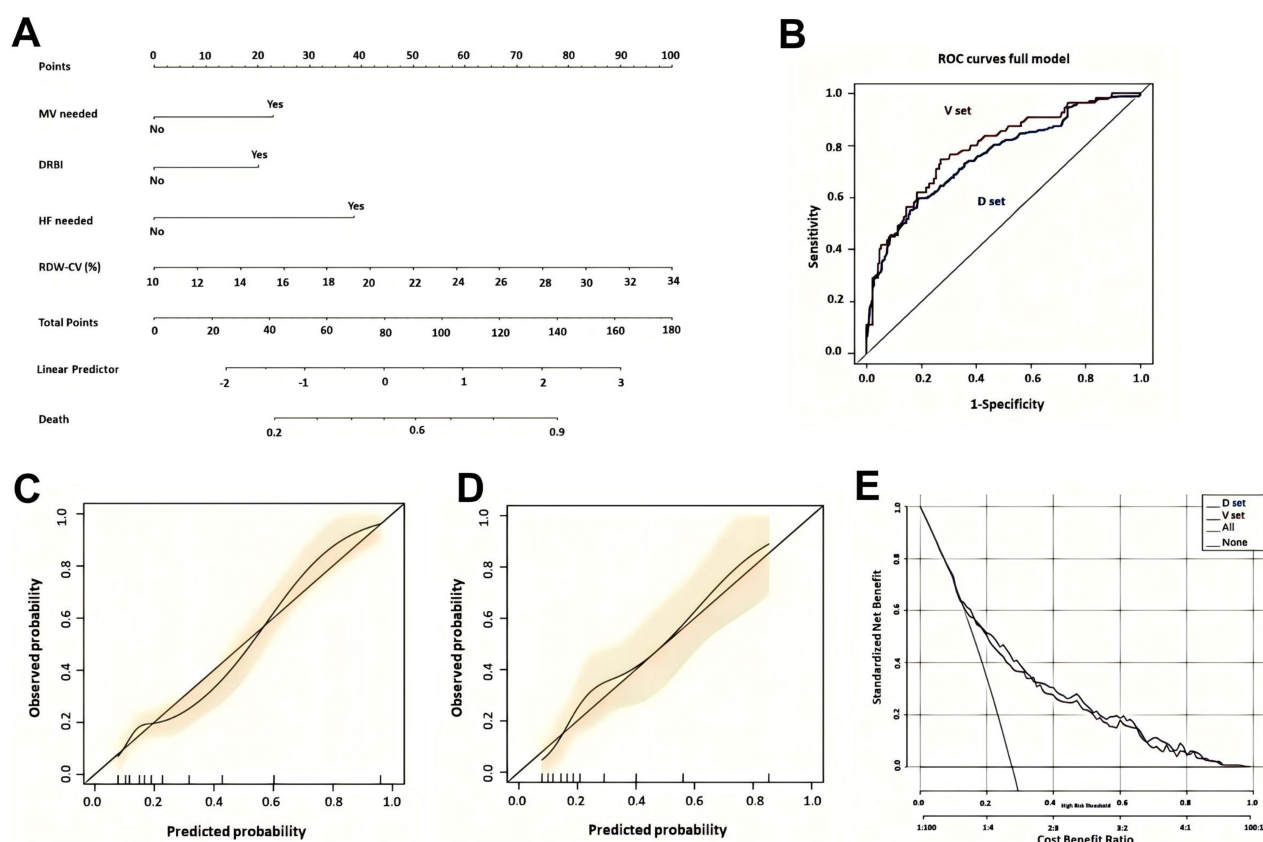


Figure 3 The nomogram for predicting mortality in elderly patients with sepsis.

Notes: (A) The RDW-CV had the greatest contribution to predicting mortality in Elderly Patients with Sepsis, as identified by the nomogram. (B) ROC curves of the nomogram, The AUC of the D set was 0.755 (95CI:0.714, 0.797), and The AUC of the V set was 0.789 (95CI:0.718, 0.859). (C) The calibration curve of D set. (D) The calibration curve of V set. Compared with D set, the actual curve of V SET is very close to the ideal curve. (E) Decision curve analysis showed a net benefit of the predictive model in predicting mortality in elderly patients with sepsis both in the D set and V set within the threshold probability ranging from 0.30 to 1.00.

According to the nomogram, RDW-CV had the highest predictive contribution for mortality in elderly patients with sepsis (Figure 3A). In this study, the sample size consisted of 986 elderly patients with sepsis. 75% of them were used for the derivation set, and 25% for the validation set. The AUC of ROC curve was used to evaluate the discrimination of the Nomogram model. In derivation set (D set), the AUC was 0.755 (95% CI: 0.714, 0.797), with specificity 0.810, sensitivity 0.597, accuracy 0.749, positive likelihood ratio 3.147, negative likelihood ratio 0.497, positive predictive value 0.560, and negative predictive value 0.833. In validation set (V set), the AUC was 0.789 (95% CI: 0.718, 0.859) (Figure 3B). The statistical result confirmed that the Nomogram model had good discriminative ability in predicting outcomes.

The calibration curve was used to evaluate the predictive ability of the prediction model. The calibration curve was very close to the reference curve, the results showed that the constructed prediction model had good predictive ability. Moreover, similar results were also observed in the V set (Figure 3C and D).

The decision curve analysis shows that in D set or V set, within the threshold probability ranging from 0.30 to 1.00 (refer to Figure 3E). The net benefit of the nomogram model was higher than that of the single-factor model, and the predictive model offered clinical applicability.

Discussion

Sepsis is a common syndrome observed in the intensive care unit (ICU),^{20,21} which can lead to life-threatening multiple organ dysfunction caused by a severe infection.^{2,22} Sepsis is marked by high mortality and exorbitant healthcare expenditures, making the assessment of its prognosis of significant socio-economic importance.^{23,24} The proportion of elderly patients among those with sepsis is relatively high (58–65%), and the mortality of the elderly is significantly

higher.^{25,26} Unfortunately, there are currently no specific preventive measures or optimal treatment methods for sepsis, approaches to identifying sepsis and estimating its prognosis have yet to be discovered. Therefore, it is crucial to develop a simple and efficient method for predicting the severity and prognosis of elderly septic patients.

RDW-CV is calculated by dividing the standard deviation of the mean erythrocyte volume by the mean erythrocyte volume and multiplying it by 100 to obtain a percentage. RDW-CV, a routine component of complete blood count (CBC), is a readily accessible and cost-effective prognostic predictor, and it can predict the prognosis of the diseases. The measurement of RDW-CV has shown promise in predicting drug resistance and inflammation in polycystic ovary syndrome.²⁷ RDW-cv elevation is an independent prognostic risk factor for severe acute pancreatitis.²⁸ Furthermore, RDW-CV is a useful predictor of clinical outcomes in critically ill patients with infection and sepsis. Previous studies have suggested that RDW-CV was an independent predictor of sepsis-related liver injury.²⁹ Higher RDW-CV was found to have a significant association with clinical severity and mortality prediction of the patients in COVID-19.³⁰ Raised RDW-CV in clinically septic neonates was associated with poor outcomes in terms of length of hospital stay, mechanical ventilation, and deaths.³¹ Our previous study had shown that RDW-CV was associated with the outcome of sepsis.¹⁸ However, there are few studies assessing the relationship between RDW-CV and the mortality of elderly patients with sepsis. Therefore, we examined the data of 986 elderly patients with sepsis to investigate whether RDW-CV could predict the prognosis of elderly patients with sepsis. The analysis revealed that RDW-CV plays a crucial role in predicting mortality in elderly sepsis patients, surpassing the significance of etiology of infection, clinical status, and other laboratory tests. The RDW-CV ($17.22 \pm 3.98\%$) in the non-survival group was significantly higher than that ($15.30 \pm 2.81\%$) in the survival group, $p < 0.0001$. There was a nonlinear relationship RDW-CV and patient mortality through smooth curve fitting analysis. When RDW-CV was greater than 12.2, mortality risk increase significantly ($P < 0.001$). The findings from this study suggested that a higher RDW was correlated with increased ICU mortality rates among elderly septic patients. However, in our own study, we found that RDW-CV alone only modestly predicted clinical outcomes, the area under the ROC curve (AUC) for RDW-CV was 0.65 (0.61–0.69).

RDW-CV is often used in combination with other indicators for diagnosis or prediction. Studies have combined RDW-CV with homocysteine to diagnose acute myocardial infarction³² and with carcinoembryonic protein (CEA) to improve the predictive value of prognosis in patients with colorectal cancer.³³ Prediction models constructed by multiple variables including alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), carbon dioxide binding force (CO2-CP), antithrombin III (AT III), fibrin/fibrinogen degradation products (FDP), and RDW-CV. It has good diagnostic value for liver injury associated with sepsis.²⁹ The results of a multi-center study in our country showed that RDW-CV, included in a validated prognostic nomogram, could be a very good prognostic predictor of adverse outcomes in both severe COVID infection and sepsis.³⁴ Similarly, in our study, through multivariate analysis, we identified several factors with significant prognostic value, such as mechanical ventilation (MV) needed, drug-resistant bacterial infection, hemofiltration (HF) needed, etc. In order to improve the predictive value, we combined RDW-CV and other indicators to predict clinical outcomes in elderly patients with sepsis. Our model had a specificity of 0.81, a negative predictive value of 0.833, and an accuracy of 0.749, suggesting good predictive value for clinical outcomes in elderly patients with sepsis. The internal validation demonstrated the stability of the predictive model. Our study indicates that combining RDW-CV with other clinical status indicators, such as mechanical ventilation, drug-resistant bacterial infection, and hemofiltration, can more accurately predict the clinical outcome of elderly patients with sepsis compared to using RDW-CV alone. And the calibration plot further confirms the good prediction effect of the model. In addition, different from previous studies, DCA was conducted to confirm the predictive effectiveness to verify the validity of our nomogram prediction model. Our study indicated that RDW-CV was one of the significant predictors of mortality, the nomogram based on RDW-CV with other clinical indicators could more accurately predict the clinical outcome of elderly sepsis patients, validation analysis confirmed the accuracy of the nomogram, the predictive model offered clinical applicability. This is also the important significance of this study.

Limitation

Our study has distinct features and limitations when compared with previous research. First, we utilize RDW-CV as the focus of our investigation. RDW-CV is influenced by both RDW and MCV, it is possible for homogenous erythrocytes with narrow distribution curves and low MCV values to have increased RDW-CV values, while heterogeneous erythrocytes with wide distribution curves and high MCV values may exhibit normal RDW-CV values. These factors

can impact the predictive value of RDW-CV. Second, the study did not undergo external validation, which may affect the reliability and generalizability of the research conclusions. Third, while we have a considerable number of cases, sepsis can result in varying body responses and organ failure states at different times. The study cannot differentiate the specific onset period of the patients and cannot remove the influence of time factors on clinical outcomes. Finally, the possible mechanisms between RDW-cv and outcomes of sepsis in elderly patients remain largely unknown. During sepsis, a large amount of pro-inflammatory mediators are released, and oxygenation stress becomes abnormal. Previous studies had indicated that the pro-inflammatory state and oxidative stress disrupted erythropoiesis, inhibited erythrocyte maturation, shorten the lifespan of red blood cells, accelerated the entrance of immature RBCs into circulation,^{35–38} leading to alterations in red cell distribution width. Furthermore, red cell distribution width is believed to be associated with various organ dysfunction. An increase in red cell distribution width in patients with sepsis indicates that the patients may have organ dysfunction and a poorer prognosis.³⁹ While we attempt to stratify the analysis, explore the mechanism further, the study's limitations prevent us from conducting more in-depth research and discussion on the mechanism. Additionally, this study is retrospective, and as such, the results can only serve as a reference and provide a basis for future research. It is difficult to draw positive or negative conclusions from them. Therefore, more scientific, rigorous, and multicenter studies about the prognostic role of RDW-CV in sepsis need to be performed, and our understanding of RDW-CV needs to be developing continually.

Conclusion

RDW-CV was one of the significant predictors of mortality. In elderly patients with sepsis, raised RDW-CV was associated with a higher prediction of mortality. The use of RDW-CV in combination with mechanical ventilation, drug-resistant bacterial infection, and hemofiltration can provide a better prediction of clinical outcomes for elderly patients with sepsis, compared to using RDW-CV alone. And the prediction model was superior in this study and could be extended for clinical application. Our study highlights the importance of considering multiple factors in predicting clinical outcomes and provides a basis for future research in this area.

Ethical Approval

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and complied with relevant Chinese regulations. And the study was authorized by the Medical Department of Shenzhen People's Hospital and approved by the hospital's Ethics Committee, with the serial number LL-KY-2019508. Patient information was obtained through the hospital's information system for retrospective review. Our study utilized anonymized retrospective data, making it impossible to identify individual participants. Therefore, obtaining signed consent was deemed unnecessary by our hospital's Ethics Committee. All data were anonymized prior to analysis, with identifiers such as names, addresses, and medical record numbers removed to ensure participant confidentiality. The research was conducted in the critical care department of the hospital, which had a capacity of 22 beds. This study was approved by the Medical Department and its affiliated institution, the Medical Research Ethics Committee of Shenzhen People's Hospital.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Natural Science Foundation of Guangdong Province (Grant No. 2021A1515012119); Shenzhen People's Hospital Physician Scientist Training "Five Three Program"(NO.SYWGSLCYJ202401); and Shenzhen Key Medical Discipline Construction Fund (No. SZXK045).

Disclosure

The authors declare no conflicts of interest in this work.

References

- Oczkowski S, Alshamsi F, Belley-Cote E, et al. Surviving sepsis campaign guidelines 2021: highlights for the practicing clinician. *Pol Arch Intern Med.* 2022;132(7–8):16290. doi:10.20452/pamw.16290
- Rudd Kristina E, Charlotte JS, Agesa Kareha M, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the global burden of disease study. *Lancet.* 2020;395:200–211. doi:10.1016/S0140-6736(19)32989-7
- Schorr CA, Seckel MA, Papatthanasoglou E, Kleinpell R. Nursing implications of the updated 2021 surviving sepsis campaign guidelines. *Am J Crit Care.* 2022;31(4):329–336. doi:10.4037/ajcc2022324
- Cruz NI, Santiago E, Cabrera V. Increasing proportion of elderly patients that make use of the surgery services of the UPR-affiliated hospitals. *P R Health Sci J.* 2022;41(4):243–246.
- Sarasoja M, Nilson B, Wide D, Å L, Torisson G, Holm K. Epidemiology, aetiology and clinical characteristics of clostridial bacteraemia: a 6-year population-based observational study of 386 patients. *Eur J Clin Microbiol Infect Dis.* 2022;41(11):1305–1314. doi:10.1007/s10096-022-04491-8
- Chen H, Matsumoto M, Horita N, Hara Y, Kobayashi N, Kaneko T. Prognostic factors for mortality in invasive pneumococcal disease in adult: a system review and meta-analysis. *Sci Rep.* 2021;11(1):11865. doi:10.1038/s41598-021-91234-y
- Grandbois van Ravenhorst C, Schluep M, Endeman H, Stolker RJ, Hoeks SE. Prognostic models for outcome prediction following in-hospital cardiac arrest using pre-arrest factors: a systematic review, meta-analysis and critical appraisal. *Crit Care.* 2023;27(1):32. doi:10.1186/s13054-023-04306-y
- Marom O, Paz I, Topaz G, Ohana N, Yaacobi E. Red cell distribution width-A mortality predictor in older adults with proximal femoral fracture. *Arch Gerontol Geriatr.* 2022;100:104623. doi:10.1016/j.archger.2022.104623
- Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: a simple parameter with multiple clinical applications. *Crit Rev Clin Lab Sci.* 2015;52(2):86–105. doi:10.3109/10408363.2014.992064
- Uemura Y, Shibata R, Takemoto K, et al. Elevation of red blood cell distribution width during hospitalization predicts mortality in patients with acute decompensated heart failure. *J Cardiol.* 2016;67(3):268–273. doi:10.1016/j.jcc.2015.05.011
- Wu J, Zhang X, Liu H, Guo N, Pan Q, Wang YRDW. NLR and RLR in predicting liver failure and prognosis in patients with hepatitis E virus infection. *Clin Biochem.* 2019;63:24–31. doi:10.1016/j.clinbiochem.2018.11.012
- Zhou H, Mei X, He X, Lan T, Guo S. Severity stratification and prognostic prediction of patients with acute pancreatitis at early phase: a retrospective study. *Medicine.* 2019;98(16):e15275. doi:10.1097/MD.00000000000015275
- Wen ZL, Zhou X, Xiao DC. Is red blood cell distribution width a prognostic factor for colorectal cancer? A meta-analysis. *Front Surg.* 2022;9:945126. doi:10.3389/fsurg.2022.945126
- Wu H, Liao B, Cao T, Ji T, Huang J, Ma K. Diagnostic value of RDW for the prediction of mortality in adult sepsis patients: a systematic review and meta-analysis. *Front Immunol.* 2022;13:997853. doi:10.3389/fimmu.2022.997853
- Chen CK, Lin SC, Wu CC, et al. STARD-compliant article: the utility of red cell distribution width to predict mortality for septic patients visiting the emergency department. *Medicine.* 2016;95. doi:10.1097/MD.0000000000003692
- Moreno-Torres V, Royuela A, Muñoz-Rubio E, et al. Red blood cell distribution width as prognostic factor in sepsis: a new use for a classical parameter. *J Crit Care.* 2022;71:154069. doi:10.1016/j.jcc.2022.154069
- Lorente L, Martín MM, Abreu-González P, et al. Red blood cell distribution width during the first week is associated with severity and mortality in septic patients. *PLoS One.* 2014;9(8):e105436. doi:10.1371/journal.pone.0105436
- Hong C, Xiong Y, Xia J, et al. LASSO-based identification of risk factors and development of a prediction model for sepsis patients. *Ther Clin Risk Manag.* 2024;20:47–58. doi:10.2147/TCRM.S434397
- Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med.* 2021;49(11):e1063–e1143. doi:10.1097/CCM.0000000000005337
- Bateson M, Marwick CA, Staines HJ, Patton A, Stewart E, Rooney KD. Performance of bedside tools for predicting infection-related mortality and administrative data for sepsis surveillance: an observational cohort study. *PLoS One.* 2023;18(3):e0280228. doi:10.1371/journal.pone.0280228
- Lei S, Li X, Zhao H, Xie Y, Li J. Prevalence of sepsis among adults in China: a systematic review and meta-analysis. *Front Public Health.* 2022;10:977094. doi:10.3389/fpubh.2022.977094
- Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA.* 2016;315(8):762–774. doi:10.1001/jama.2016.0288
- Song KH, Kim CJ, Choi NK, et al; Korea Infectious Diseases (KIND) Study Group. Clinical and economic burden of bacteremia due to multidrug-resistant organisms in Korea: a prospective case control study. *J Glob Antimicrob Resist.* 31;2022:379–385. doi:10.1016/j.jgar.2022.11.005
- Blythe R, Lister P, Seaton R, et al; Queensland State-wide Sepsis Collaborative. Patient and economic impact of implementing a paediatric sepsis pathway in emergency departments in Queensland, Australia. *Sci Rep.* 2022;12(1):10113. doi:10.1038/s41598-022-14226-6
- Starr ME, Saito H. Sepsis in old age: review of human and animal studies. *Aging Dis.* 2014;5(2):126–136. PMID: 24729938; PMCID: PMC3966671. doi:10.14336/AD.2014.0500126
- Kotfis K, Wittebole X, Jaschinski U, et al. A worldwide perspective of sepsis epidemiology and survival according to age: observational data from the ICON audit. *J Crit Care.* 2019;51:122–132. doi:10.1016/j.jcc.2019.02.015
- Peker N, Ege S, Bademkiran MH, et al. Can clomiphene citrate resistance be predicted by RDW-CV levels in infertile women with PCOS? *Niger J Clin Pract.* 2019;22(11):1463–1466. doi:10.4103/njcp.njcp_666_18
- Zhang FX, Li ZL, Zhang ZD, Ma XC. Prognostic value of red blood cell distribution width for severe acute pancreatitis. *World J Gastroenterol.* 2019;25(32):4739–4748. doi:10.3748/wjg.v25.i32.4739
- He Y, Wang C, He W, et al. Analysis of risk factors for sepsis-related liver injury and construction of a prediction model. *Front Public Health.* 2024;12. doi:10.3389/fpubh.2024.1475292

30. SakthiKannamma M, Srinivasamurthy B, Sinhasan S, et al. A study on significance and correlation of red cell distribution width with severity of clinical illness in COVID-19 patients. *Iraqi J Hematol.* 2025;11. doi:10.4103/ijh.ijh_45_21
31. Asghar R, Tariq J, Ali S, et al. Role of red cell distribution width as a prognostic marker in neonatal sepsis. *Ann Pak Inst Med Sci.* 2025;18. doi:10.48036/apims.v18i4.677
32. Hu GX, Zhang J, Tian YG, Li YH, Mou L, Qiao LJ. Diagnostic value of joint detection of homocysteine and RDW CV on acute myocardial infarction. *Eur Rev Med Pharmacol Sci.* 2017;21(20):4472.
33. Li Y, Xing C, Wei M, et al. Combining Red Blood Cell Distribution Width (RDW-CV) and CEA predict poor prognosis for survival outcomes in colorectal cancer. *J Cancer.* 2019;10(5):1162–1170. doi:10.7150/jca.29018
34. Gong J, Ou J, Qiu X, et al. A tool for early prediction of severe Coronavirus Disease 2019 (COVID-19): a multicenter study using the risk nomogram in Wuhan and Guangdong, China. *Clin Infect Dis.* 2020;71(15):833–840. doi:10.1093/cid/ciaa443
35. Bommenahalli Gowda S, Gosavi S, Ananda Rao A, et al. Prognosis of COVID-19: red cell distribution width, platelet distribution width, and C-reactive protein. *Cureus.* 2021;13. doi:10.7759/cureus.13078
36. Macdougall IC, Cooper A. The inflammatory response and epoetin sensitivity. *Nephrol Dial Transpl.* 2002;17(Suppl 1):48–52. doi:10.1093/ndt/17.suppl_1.48
37. Montagnana M, Cervellin G, Meschi T, et al. The role of red blood cell distribution width in cardiovascular and thrombotic disorders. *Clin Chem Lab Med.* 2011;50:635–641. doi:10.1515/cclm.2011.831
38. Ghaffari S. Oxidative stress in the regulation of normal and neoplastic hematopoiesis. *Antioxid Redox Sign.* 2008;10. doi:10.1089/ars.2008.2142
39. Hu ZD, Lippi G, Montagnana M. Diagnostic and prognostic value of red blood cell distribution width in sepsis: a narrative review. *Clin Biochem.* 2020;77:1–6. doi:10.1016/j.clinbiochem.2020.01.001

Infection and Drug Resistance

Publish your work in this journal

Infection and Drug Resistance is an international, peer-reviewed open-access journal that focuses on the optimal treatment of infection (bacterial, fungal and viral) and the development and institution of preventive strategies to minimize the development and spread of resistance. The journal is specifically concerned with the epidemiology of antibiotic resistance and the mechanisms of resistance development and diffusion in both hospitals and the community. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/infection-and-drug-resistance-journal>

Dovepress
Taylor & Francis Group