RESEARCH ARTICLE

Red cell distribution width (RDW) is independently associated with all-cause mortality in adult patients with osteomyelitis admitted to the intensive care unit

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Data availability statement: The data underlying the results presented in this study are available from the MIMIC-IV repository, accessible at https://physionet.org/content/mimiciv/2.0/. The MIMIC-IV repository imposes certain restrictions on data access to protect

Abstract

Objective

This study aims to investigate the correlation between red cell distribution width (RDW) and overall mortality in adults diagnosed with osteomyelitis.

Methods

In this retrospective study, we examined data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, comprising 2,700 patients with osteomyelitis and available RDW data on the initial day of admission. Employing Kaplan-Meier survival analysis, we assessed the incidence rate of primary outcome events among groups categorized by RDW levels (Q1: RDW ≤ 13.5, Q2: 13.5 < RDW ≤ 14.6, Q3: 14.6 < RDW ≤ 16.1, Q4: 16.1 < RDW), with differences evaluated using the Log-rank test. Subsequently, Cox proportional hazards analyses were conducted to investigate the correlation between RDW and the overall mortality risk. Additionally, we performed stratified analyses based on factors such as gender, congestive heart failure, diabetes, and myocardial infarction to scrutinize the consistency of RDW's prognostic significance.

Results

Over the 90-day follow-up, 10.7% of patients with osteomyelitis succumbed. Unadjusted RDW correlated significantly with in-hospital, 30-day, and 90-day mortality ($p < 0.05$). Higher RDW levels proved more effective in predicting increased risks. RDW emerged as an independent prognostic indicator, showing no significant interactions with sex, congestive heart failure, diabetes, and myocardial infarction (interaction p-values: 0.254 to 0.920).

patient privacy, and it is managed by PhysioNet under the oversight of the Massachusetts Institute of Technology (MIT) and the Beth Israel Deaconess Medical Center. To access the data associated with this manuscript, users must: • Register as a credentialed user on the PhysioNet repository website. • Complete the required Collaborative Institutional Training Initiative (CITI) training for "Data or Specimens Only Research." • Sign the MIMIC-IV Data Use Agreement for the project. Once these prerequisites have been met, access to the data contained in the MIMIC-IV repository will be granted. In this study, Yang Chen has registered as a certified user of PhysioNet, completed the required CITI Programme training (certificate no. 53753450), and signed the Project Data Use Agreement. Additionally, our raw data has been submitted in the Supplementary Files section of this manuscript for reference. For readers who would like to request access to the data, please follow the instructions outlined on the MIMIC-IV repository page linked above. Further assistance can be obtained by contacting PhysioNet support directly through their website.

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Conclusions

The noteworthy link between RDW and heightened all-cause mortality in patients with osteomyelitis who were hospitalized in the intensive care unit highlights RDW's potential as a valuable marker for identifying at-risk individuals during hospitalization.

Introduction

Osteomyelitis, a challenging infectious bone condition, poses difficulties for health-care professionals and patients alike. The incidence is 21.8 cases per 100,000 person-years in the United States [1]. Osteomyelitis frequently arises as a complication of open fractures, internal fixation procedures, diabetic foot ulcers, or hematogenous bone infections. The primary anatomical locations for the occurrence of osteomyelitis are typically the tibia and femur [2]. In recent years, there has been a noticeable rise in the incidence of vertebral osteomyelitis. The overall mortality rate has been documented as high as 20%, with a notably heightened risk observed in the first year following diagnosis [3,4]. The diagnosis of osteomyelitis mainly depends on clinical manifestation, laboratory tests and imaging studies. In the early stage of the disease, clinical manifestations are often subtle, and imaging shows no obvious signs of infection, making early diagnosis challenging [5]. Inflammatory markers, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), procalcitonin (PCT), and C-reactive protein (CRP), serve as pivotal indicators in assessing the severity of osteomyelitis. These markers underscore the significant impact of inflammation levels on both the diagnostic and prognostic aspects of osteomyelitis [6,7]. Red cell distribution width (RDW), typically expressed as a percentage (%), is a parameter routinely evaluated in standard blood analyses. It serves as an indicator of the variability in the size of erythrocytes, and has long been used in the hematology laboratory to distinguish various types of anemia [8]. In recent years, numerous studies have highlighted the predictive potential of RDW in anticipating the occurrence or prognosis of various medical conditions. These encompass pneumonia, chronic obstructive pulmonary disease, myocardial infarction, stroke, drug-induced liver injury, Hodgkin's lymphoma, sepsis, fractures, anemia, brain death, cancer and other diseases [9–17]. Remarkably, the significance of RDW is increasingly recognized as a robust and independent predictor of mortality in the general population [18,19]. Perlstein et al. discovered a noteworthy correlation, indicating that a one-standard-deviation (1-SD) increase in RDW is associated with a 23% higher risk of all-cause mortality, a 28% higher risk of mortality due to cancer, and a 32% higher risk of mortality from chronic lower respiratory diseases. Importantly, these associations remained significant even after comprehensive adjustments for factors such as age, sex, race/ethnicity, and other variables [20].

Although RDW is a known prognostic factor in many diseases, its role in patients with osteomyelitis, especially those in the intensive care unit (ICU), has not been well studied. The association between RDW and overall mortality in adult patients with osteomyelitis admitted to the ICU remains to be elucidated. In this study, our

objective was to examine the association between RDW and overall mortality, and to assess the influence of RDW on the prognostic outcomes of patients with osteomyelitis admitted to the ICU.

Methods

Study population

This study represents a retrospective observational inquiry. Data for analysis was retrieved from an online international database known as the Medical Information Mart for Intensive Care IV (MIMIC-IV). The MIMIC-IV database comprises clinical information related to 454,324 patients admitted to the ICU at Beth Israel Deaconess Medical Center (BIDMC), Boston, USA, between 2008 and 2019. Upon successfully completing an examination and obtaining certification, access to this database is authorized. Author YC obtained the required permissions to access the dataset (Record ID 36328122) and took on the responsibility of extracting the data. The project received approval from the Institutional Review Boards of both the Massachusetts Institute of Technology and BIDMC. Additionally, a waiver for informed consent was granted.

We conducted a thorough analysis of data obtained from 5,437 patients (aged 18 years and older) with osteomyelitis (ICD-9code: 730.x; ICD-10: M90.9) who were admitted to MIMIC-IV. Patients without RDW data on the initial day of admission were excluded from the study. Furthermore, our analysis was confined to the initial hospital admission for patients whose hospital stay exceeded 24 hours. Patients with records of multiple hospital admissions were also excluded. The final study cohort consisted of a total of 2,700 patients with osteomyelitis, who were stratified into four groups according to the quartiles of their RDW values on the initial day of admission. The patient screening flow chart is presented in Fig 1.

Variable extraction

The baseline characteristic data from the initial 24 hours of patients with osteomyelitis was retrieved from the MIMIC-IV database, including age, sex, race, comorbidities, laboratory results, interventions and clinical outcomes. The comorbidities included congestive heart failure (CHF), myocardial infarction (MI), peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, paraplegia, diabetes, liver disease, cancer and renal disease. Laboratory results included anion gap, sodium, potassium, calcium, creatinine, blood urea nitrogen, bicarbonate, chloride, glucose, hematocrit, red blood cell, mean red blood cell volume, mean corpuscular hemoglobin, white blood cell, platelet and hemoglobin. Interventions included mechanical ventilation, hemodialysis and vasopressor

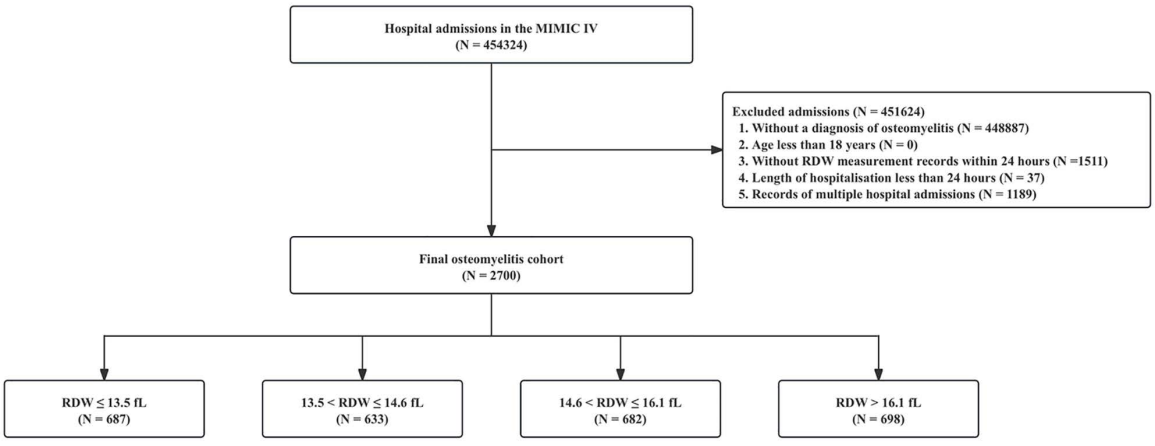

Fig 1. The patient screening flow chart.

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administration. Clinical outcomes included length of hospital stay, in-hospital mortality, 30-day post-admission mortality and 90-day post-admission mortality. If a variable was recorded more than once in the first 24 hours, we used its average value. The original data is presented in S1 Table.

Outcomes

The primary outcome of this study was in-hospital all-cause mortality. The secondary outcomes included 30-day and 90-day post-admission mortality.

Statistical analysis

All statistical analyses were performed using R software (version 4.2.1) and SPSS (version 27). A two-sided p-value < 0.05 was considered statistically significant. Group Stratification: Patients were divided into four groups according to the quartiles of RDW values measured on the first day of hospital admission. Quartile cut-off points were derived from the distribution of RDW in the study cohort. This stratification enables the comparison of outcomes across increasing RDW levels. Descriptive Statistics: Baseline characteristics were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) for continuous variables, and as counts with percentages for categorical variables. Comparisons of continuous variables between RDW quartile groups were performed using one-way ANOVA or Kruskal-Wallis test, depending on data normality. Categorical variables were compared using Chi-square test or Fisher's exact test when appropriate. These tests assess whether baseline characteristics and outcomes vary significantly across RDW levels. Survival Analysis: We used Kaplan–Meier survival curves to visualize survival probabilities across RDW quartile groups. Differences between groups were evaluated using the log-rank test. This non-parametric test determines whether the survival experiences of different groups are statistically different.

Multivariate Cox Proportional Hazards Models: To quantify the association between RDW and all-cause mortality (in-hospital, 30-day, and 90-day), we fitted Cox regression models. Results were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs).

Model 1: Categorized red cell distribution width without adjustment.

Model 2: Model 1 adjusted by age, gender, race.

Model 3: Model 2 additionally adjusted for comorbidities (CHF, MI, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, paraplegia, diabetes, liver disease, cancer, renal disease) and interventions (mechanical ventilation, hemodialysis and vasopressor administration).

Subgroup and Interaction Analysis: Stratified Cox regression was performed based on variables including gender, CHF, diabetes, and MI to assess the consistency of RDW's prognostic value. Interaction terms were included to test for effect modification.

Predictive Performance Evaluation: To assess the discriminatory power of RDW, we constructed Receiver Operating Characteristic (ROC) curves and calculated the Area Under the Curve (AUC) for each mortality outcome. AUC values of 0.7–0.8, 0.8–0.9, and >0.9 indicate acceptable, excellent, and outstanding discrimination, respectively.

Non-linear Relationship Assessment: We applied Restricted Cubic Spline (RCS) regression to model the potential non-linear association between RDW and mortality risk. This method provides a smoothed estimate of the risk relationship and helps detect thresholds or non-linear patterns that linear models may miss.

Results

Baseline characteristics and clinical outcomes

The baseline characteristics and clinical outcomes of patients with osteomyelitis are presented in Table 1. A total of 2700 patients were included: 1,748 (64.7%) were female and 952 (35.3%) were male, with a mean age of 72.52 years; 1942

Table 1. Baseline characteristics and clinical outcomes of patients with osteomyelitis.

Characteristics	All	Q1	Q2	Q3	Q4	*p*-value
N	2700	687	633	682	698	
Age (years)	63.33 ± 15.03	59.51 ± 15.39	62.59 ± 15.06	65.13 ± 14.76	66.00 ± 14.08	< 0.001; ***
Male, n (%)	1748 (64.7)	490 (71.3)	416 (65.7)	438 (64.2)	404 (57.9)	< 0.001; ***
Race, n (%)						0.920
White	1942 (71.9)	494 (71.9)	454 (71.1)	497 (72.9)	497 (71.2)	
Non-white	758 (28.1)	193 (28.1)	179 (28.3)	185 (27.1)	201 (28.8)	
Comorbidities, n (%)						
Congestive heart failure	690 (25.6)	72 (10.5)	109 (17.2)	196 (28.7)	313 (44.8)	< 0.001; ***
Myocardial infarction	326 (12.1)	42 (6.1)	68 (10.7)	96 (14.1)	120 (17.2)	< 0.001; ***
Peripheral vascular disease	665 (24.6)	146 (21.3)	153 (24.2)	164 (24.0)	202 (28.9)	0.010; **
Cerebrovascular disease	194 (7.2)	29 (4.2)	45 (7.1)	55 (8.1)	65 (9.3)	0.002; **
Chronic pulmonary disease	471 (17.4)	82 (11.9)	89 (14.1)	138 (20.2)	162 (23.2)	< 0.001; ***
Rheumatic disease	102 (3.8)	10 (1.5)	18 (2.8)	35 (5.1)	39 (5.6)	< 0.001; ***
Peptic ulcer disease	41 (1.5)	2 (0.3)	10 (1.6)	10 (1.5)	19 (2.7)	0.003; **
Paraplegia	141 (5.2)	15 (2.2)	29 (4.6)	36 (5.3)	61 (8.7)	< 0.001; ***
Diabetes	1571 (58.2)	399 (58.1)	366 (57.8)	385 (56.5)	421 (60.3)	0.536
Liver disease	268 (9.9)	45 (6.6)	57 (9.0)	75 (11.0)	91 (13.0)	< 0.001; ***
Cancer	134 (5.0)	18 (2.6)	24 (3.8)	39 (5.7)	53 (7.6)	< 0.001; ***
Renal disease	901 (33.4)	148 (21.5)	172 (27.2)	238 (34.9)	343 (49.1)	< 0.001; ***
Laboratory results						
Anion gap (%)	15.00 (13.00, 17.00)	15.00 (13.00, 17.00)	15.00 (13.00, 17.00)	15.00 (13.00, 17.00)	15.00 (13.00, 18.00)	< 0.001; ***
Sodium (mmol/L)	138.00 (135.00, 140.00)	138.00 (135.00, 140.00)	138.00 (136.00, 140.00)	138.00 (135.00, 141.00)	138.00 (135.00, 141.00)	0.008; **
Potassium (mmol/L)	4.30 (3.90, 4.70)	4.30 (4.00, 4.60)	4.20 (3.90, 4.60)	4.30 (4.00, 4.70)	4.30(3.90, 4.70)	0.102
Calcium (mg/dL)	8.90 (8.40, 9.30)	9.00 (8.50,9.40)	8.90 (8.50, 9.40)	8.80 (8.40, 9.30)	8.80 (8.30, 9.30)	< 0.001; ***
Creatinine (mg/dL)	1.00 (0.80, 1.50)	0.90 (0.80, 1.20)	1.00 (0.80, 1.40)	1.00 (0.80, 1.50)	1.20 (0.90, 2.10)	< 0.001; ***
Blood urea nitrogen (mg/dL)	20.00 (14.00, 30.00)	17.00 (13.00, 24.00)	19.00 (14.00, 26.00)	20.50 (14.00, 32.00)	24.00 (14.00, 42.00)	< 0.001; ***
Bicarbonate (mmol/L)	26.00 (23.00, 28.00)	26.00 (24.00, 28.00)	26.00 (24.00, 28.00)	26.00 (24.00, 28.00)	26.00 (24.00, 28.00)	0.261
Chloride (mmol/L)	101.00 (98.00, 104.00)	100.00 (97.00, 103.00)	101.00 (98.00,104.00)	101.00 (98.00,104.00)	101.00 (97.00,104.00)	0.004; **
Glucose (mg/dL)	124.00 (97.00, 186.00)	131.00 (99.00,205.00)	121.00 (97.00, 190.50)	121.00 (96.00,177.00)	124.00 (94.00, 175.25)	0.007; **
Hematocrit (g/dL)	36.30 (32.23, 40.10)	37.70 (34.60, 40.90)	37.00(33.34, 40.70)	35.80 (31.98, 39.60)	34.20 (30.08, 38.50)	< 0.001; ***
Red blood cell ($\times 10^6$/μL)	4.06±0.66	4.21±0.58	4.13*pm* 0.64	4.03±0.65	3.89 ±0.74	< 0.001; ***
Mean red blood cell volume (fL)	89.00 (85.00, 93.00)	90.00 (86.00, 93.00)	90.00 (86.00, 93.00)	89.00 (84.00, 93.00)	89.00 (84.00, 95.00)	0.023; *
Mean corpuscular hemoglobin (pg)	29.80 (28.10, 31.30)	30.30 (29.00, 31.50)	29.90 (28.50, 31.40)	29.45 (27.80, 31.10)	29.00 (26.90, 31.00)	< 0.001; ***
White blood cell ($\times 10^3$/μL)	8.80 (6.90, 11.80)	9.00 (7.00, 11.70)	9.00 (7.00, 11.45)	8.70 (6.70, 12.10)	8.70 (6.80, 11.90)	0.937
Platelet ($\times 10^3$/μL)	258.00 (199.00, 332.00)	266.00 (205.00, 333.00)	261.00(204.00, 332.00)	251.50 (199.00, 326.23)	253.00 (184.75, 338.75)	0.097

(Continued)

Table 1. (Continued)

Characteristics	All	Q1	Q2	Q3	Q4	*p*-value
Hemoglobin (g/dL)	12.10 (10.60, 13.40)	12.80 (11.50, 14.00)	12.50 (11.10, 14.00)	11.50 (10.40, 13.20)	11.10 (9.60, 12.60)	< 0.001; ***
Interventions (1st 24 h), n (%)						
Mechanical ventilation	205 (7.6)	18 (2.6)	38 (6.0)	50 (7.3)	99 (14.2)	< 0.001; ***
Hemodialysis	192 (7.1)	8 (1.2)	19 (3.0)	46 (6.7)	119 (4.4)	< 0.001; ***
Vasopressor administration	392 (14.5)	38 (5.5)	62 (9.8)	94 (13.8)	198 (28.4)	< 0.001; ***
Clinical outcomes						
Length of hospitalized stay, days	7.79 (4.92, 12.88)	6.83 (4.25, 10.58)	7.17 (4.79, 11.79)	8.06 (5.13, 13.04)	9.04 (5.58, 17.34)	< 0.001; ***
In-hospital mortality, n (%)	106 (3.9)	2 (0.3)	12 (1.9)	17 (2.5)	75 (10.7)	< 0.001; ***
30-day post-admission mortality, n (%)	144 (5.3)	2 (0.3)	16 (2.5)	28 (4.1)	98 (14.0)	< 0.001; ***
90-day post-admission mortality, n (%)	288 (10.7)	12 (1.7)	39 (6.2)	67 (9.8)	170 (24.4)	< 0.001; ***

Data are expressed as mean ± standard deviation, median (interquartile range), or number (%). Analysis of variance (or the Kruskal-Wallis test) and Chi-square (or Fisher's exact) tests were used for comparisons among groups. Statistical significance was set at $p < 0.05$. Red cell distribution width was grouped as follows: Q1: RDW ≤ 13.5, Q2: 13.5 < RDW ≤ 14.6, Q3: 14.6 < RDW ≤ 16.1, Q4: 16.1 < RDW.

*$p < 0.05$;

**$p < 0.01$;

***$p < 0.001$.

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(71.9%) were White, and the median hospital stay was 7.79 days. In-hospital, 30-day and 90-day post-admission mortality rates were 3.9%, 5.3% and 10.7%, respectively. The highest quartile RDW group was older, more often male, and had more comorbidities such as CHF, MI, chronic lung disease, rheumatic disease, and malignancy compared to all other groups. Importantly, the highest quartile RDW group had a longer length of stay, and significantly higher in-hospital, 30-day and 90-day post-admission mortality rates ($p < 0.001$).

RDW was an independent risk factor for in-hospital, 30-day post-admission, and 90-day post-admission all-cause mortality

According to Table 2, unadjusted RDW was significantly associated with in-hospital, 30-day post-admission, and 90-day post-admission all-cause mortality. After adjusting for confounders in the multivariate Cox regression, RDW remained associated with in-hospital all-cause mortality (*p*-values less than 0.05), 30-day post-admission all-cause mortality ($p < 0.05$), and 90-day post-admission all-cause mortality ($p < 0.05$).

ROC analysis, RCS curves and Kaplan-Meier curves

We plotted the ROC curves for RDW and each all-cause mortality rate (Fig 2), which showed that RDW was significantly effective in predicting in-hospital all-cause mortality (AUC: 0.791, 95% CI: 0.750–0.832), 30-day post-admission all-cause mortality (AUC: 0.794, 95% CI: 0.760–0.829), and 90-day post-admission all-cause mortality (AUC: 0.760, 95%CI: 0.731–0.788). The RCS curve results (Fig 3) indicate a positive association between increasing RDW levels and a higher risk of all-cause mortality during hospitalization, as well as at 30 and 90 days post-admission. The Kaplan-Meier survival curves (Fig 4) showed significantly higher mortality rates in the high RDW group compared to the low RDW group at all observed time points: in-hospital, 30 days post-admission, and 90 days post-admission ($p < 0.001$).

Table 2. Multivariate Cox or logistic regression analyses for categorized RDW and clinical outcomes in patients with osteomyelitis.

Outcomes		Model 1	*p*-value	Model 2	*p*-value	Model 3	*p*-value
In-hospital mortality	Q1	Reference	< 0.001; ***	Reference	< 0.001; ***	Reference	< 0.001; ***
	Q2	6.62 (1.48, 29.69)	0.014; *	6.16 (1.37, 27.68)	0.018; *	4.64 (1.02, 21.05)	0.047; *
	Q3	8.76 (2.02, 38.04)	0.04; *	7.65 (1.76, 33.32)	0.007; **	4.51 (1.02, 19.97)	0.047; *
	Q4	41.23 (10.08, 168.62)	< 0.001; ***	35.87 (8.75, 147.12)	< 0.001; ***	14.98 (3.56, 63.03)	< 0.001; ***
30-day post-admission mortality	Q1	Reference	< 0.001; ***	Reference	< 0.001; ***	Reference	< 0.001; ***
	Q2	8.78 (2.02, 38.17)	0.004; **	7.87 (1.81, 34.23)	0.006; **	6.42 (1.47, 27.96)	0.013; *
	Q3	14.35 (3.42, 60.24)	< 0.001; ***	11.69 (2.78, 49.12)	< 0.001; ***	7.99 (1.89, 33.76)	0.005; **
	Q4	51.91 (12.80, 210.50)	< 0.001; ***	41.94 (10.33, 170.28)	< 0.001; ***	22.53 (5.47, 92.87)	< 0.001; ***
90-day post-admission mortality	Q1	Reference	< 0.001; ***	Reference	< 0.001; ***	Reference	< 0.001; ***
	Q2	3.61 (1.89, 6.89)	< 0.001; ***	3.20 (1.68, 6.12)	< 0.001; ***	2.69 (1.41, 5.14)	0.003; **
	Q3	5.86 (3.17, 10.83)	< 0.001; ***	4.70 (2.54, 8.69)	< 0.001; ***	3.28 (1.76, 6.10)	< 0.001; ***
	Q4	16.00 (8.91, 28.73)	< 0.001; ***	12.84 (7.14, 23.09)	< 0.001; ***	7.18 (3.93, 13.14)	< 0.001; ***

Model results are shown as hazard ratios or odds ratios with 95% confidence intervals. Red cell distribution width was grouped as follows: Q1: ≤ 13.5, Q2: 13.5–14.6, Q3: 14.6–16.1, Q4: > 16.1.

Model 1: Categorized red cell distribution width without adjustment.

Model 2: Model 1 adjusted by age, gender, race.

Model 3: Model 2 additionally adjusted for comorbidities (chronic heart failure, myocardial infarction, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, paraplegia, diabetes, liver disease, cancer, renal disease) and interventions (mechanical ventilation, hemodialysis and vasopressor administration).

Statistical significance was set at $p < 0.05$.

*$p < 0.05$;

**$p < 0.01$;

***$p < 0.001$.

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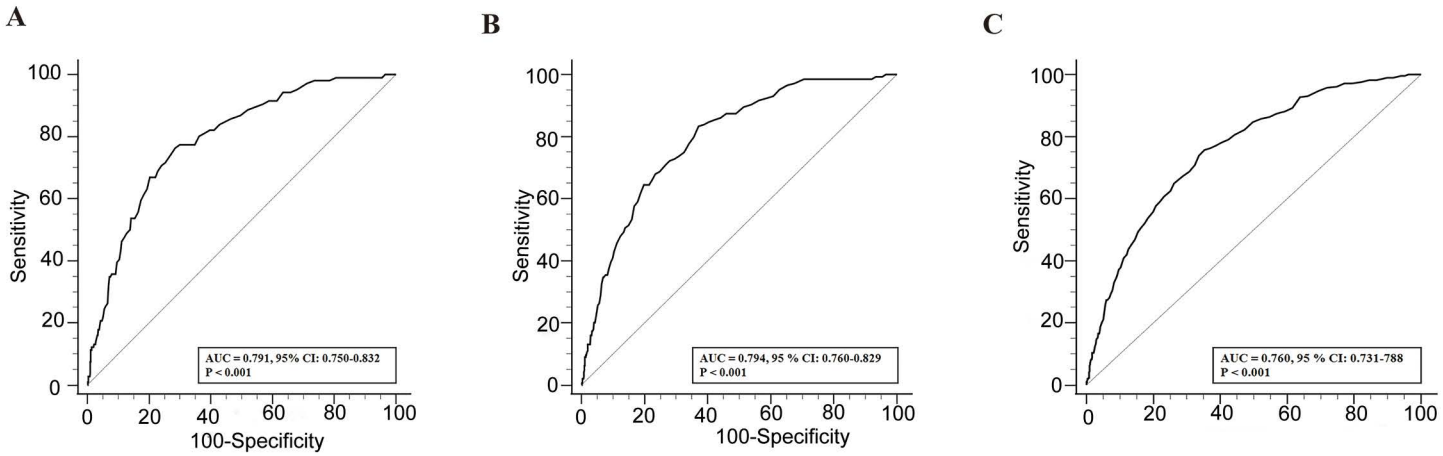

Fig 2. ROC curves for RDW and each all-cause mortality rate. (A) In-hospital all-cause mortality; **(B)**. 30-day post-admission all-cause mortality; **(C)**. 90-day post-admission all-cause mortality.

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Subgroup analysis

Table 3 highlights the consistent association between RDW levels and all-cause mortality across different subgroups, including in-hospital, 30-day, and 90-day post-admission periods. When stratified by sex, CHF, diabetes, and myocardial

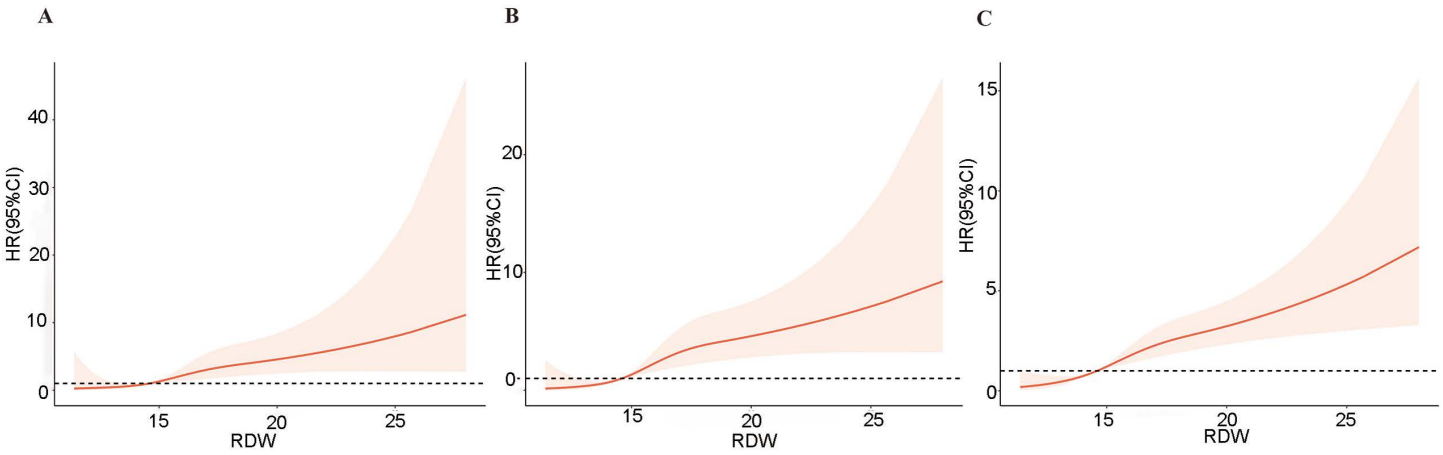

Fig 3. The results of the RCS curve. (A) In-hospital all-cause mortality; **(B)**. 30-day post-admission all-cause mortality; **(C)**. 90-day post-admission all-cause mortality.

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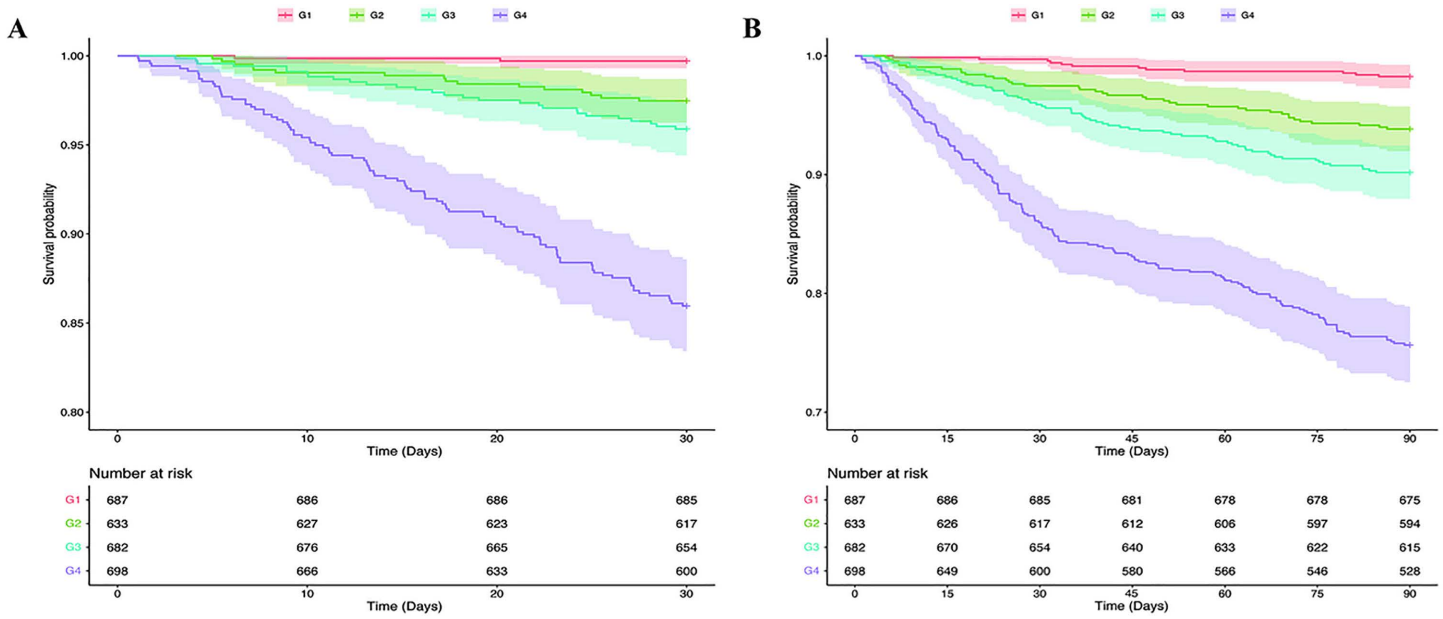

Fig 4. The Kaplan-Meier survival analysis curve. (A) The high RDW group; **(B)** The low RDW group.

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infarction, no significant interaction was observed between RDW and any subgroup (*p*: 0.254–0.920). In conclusion, RDW is an independent prognostic factor.

Discussion

To the best of our knowledge, this retrospective observational study is the first to investigate the association between initial-day RDW levels and overall mortality in adult patients with osteomyelitis admitted to the ICU. Our findings suggest that RDW levels may serve as a reliable and independent predictive biomarker for overall mortality in ICU patients with

Table 3. Multivariate Cox or logistic regression analyses for categorized RDW and clinical outcomes in patients with osteomyelitis in different subgroups according to the fully adjusted model (Model 3).

Subgroups		Results [HR/OR, (95% CI), *P* value]					
		In-hospital mortality	*p*-value for interaction	30-day post-admission mortality	*p*-value for interaction	90-day post-admission mortality	*p*-value for interaction
Gender (male)	Q1	Reference	0.592	Reference	0.915	Reference	0.757
	Q2	4.17 (0.49, 35.80), 0.193		8.96 (1.15, 69.76), 0.036		3.18 (1.37, 7.35), 0.007	
	Q3	5.70 (0.71, 45.47), 0.101		10.25 (1.35, 77.68), 0.024		3.96 (1.76, 8.90), < 0.001	
	Q4	18.74 (2.47, 142.30), 0.005		29.06 (3.93, 214.66), < 0.001		8.19 (3.70, 18.13), < 0.001	
Gender (female)	Q1	Reference		Reference		Reference	
	Q2	5.48 (0.64, 47.12), 0.122		4.57 (0.53, 39.36), 0.166		2.42 (0.86, 6.83), 0.094	
	Q3	2.50 (0.28, 22.42), 0.413		5.56 (0.70, 44.18), 0.105		2.60 (0.97, 6.96), 0.058	
	Q4	9.18 (1.18, 71.65), 0.034		17.13 (2.30, 127.68), 0.006		6.61 (2.60, 16.79), < 0.001	
CHF (-)	Q1	Reference	0.254	Reference	0.543	Reference	0.872
	Q2	4.41 (0.51, 38.45), 0.179		8.04 (1.02, 63.65), 0.048		2.70 (1.21, 6.00), 0.015	
	Q3	6.51 (0.81, 52.68), 0.079		12.84 (1.70, 97.15), 0.013		3.44 (1.59, 7.48), 0.002	
	Q4	19.68 (2.58, 150.34), 0.004		26.60 (3.58, 197.65), 0.001		7.22 (3.38, 15.42), < 0.001	
CHF (+)	Q1	Reference		Reference		Reference	
	Q2	4.10 (0.47, 35.59), 0.200		4.25 (0.52, 34.65), 0.176		2.33 (0.76, 7.10), 0.137	
	Q3	2.04 (0.24, 17.35), 0.512		3.40 (0.44, 26.47), 0.243		2.66 (0.93, 7.58), 0.068	
	Q4	7.26 (0.94, 56.04), 0.057		11.86 (1.63, 86.55), 0.015		6.10 (2.22, 16.73), < 0.001	
Diabetes (-)	Q1	Reference	0.823	Reference	0.920	Reference	0.433
	Q2	5.36 (0.63, 45.86), 0.126		6.73 (0.84, 54.17), 0.073		2.57 (1.02, 6.47), 0.046	
	Q3	4.26 (0.50, 35.97), 0.184		7.93 (1.03, 61.30), 0.047		2.89 (1.19, 7.05), 0.019	
	Q4	12.56 (1.62, 97.62), 0.016		22.31 (3.00, 165.70), 0.002		6.10 (2.56, 14.53), < 0.001	
Diabetes (+)	Q1	Reference		Reference		Reference	
	Q2	4.41 (0.51, 37.91), 0.177		6.25 (0.78, 50.23), 0.085		2.81 (1.12, 7.02), 0.027	
	Q3	4.15 (0.51, 33.88), 0.184		7.87 (1.03, 60.07), 0.047		3.56 (1.49, 8.51), 0.004	
	Q4	17.07 (2.24, 129.96), 0.006		23.49 (3.19, 172.89), 0.002		8.72 (3.76, 20.26), < 0.001	

(Continued)

Table 3. (Continued)

Subgroups		Results [HR/OR, (95% CI), *P* value]					
		In-hospital mortality	*p*-value for interaction	30-day post-admission mortality	*p*-value for interaction	90-day post-admission mortality	*p*-value for interaction
MI (-)	Q1	Reference	0.357	Reference	0.297	Reference	0.576
	Q2	7.65 (0.96, 61.30), 0.055		9.26 (1.19, 71.91), 0.033		2.53 (1.27, 5.02), 0.008	
	Q3	8.74 (1.13, 67.69), 0.038		14.57 (1.96, 108.57), 0.009		3.22 (1.67, 6.20), < 0.001	
	Q4	25.40 (3.42, 188.71), 0.002		38.29 (5.25, 279.53), < 0.001		6.56 (3.47, 12.41), < 0.001	
MI (+)	Q1	Reference		Reference		Reference	
	Q2	1.19 (0.11, 13.47), 0.887		2.07 (0.23, 18.88), 0.518		3.32 (0.40, 27.56), 0.266	
	Q3	1.02 (0.09, 11.23), 0.985		2.26 (0.26, 19.98), 0.462		4.23 (0.54, 33.36), 0.171	
	Q4	4.59 (0.51, 41.63), 0.176		7.64 (0.98, 59.72), 0.053		13.65 (1.82, 102.51), 0.011	

RDW was grouped as follows: Q1: ≤ 13.5, Q2: 13.6–14.6, Q3: 14.7–16.1, Q4: > 16.1.

Model 3: Categorized red cell distribution width adjusted for age, gender, race, and comorbidities and interventions mentioned in the statistical analysis section.

Statistical significance was set at $p < 0.05$.

HR: Hazard Ratio; OR:Odds Ratio; CI:Confidence Interval; CHF:Congestive Heart Failure; MI:Myocardial Infarction.

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osteomyelitis. This association remained significant even after adjusting for potential confounding factors. Furthermore, our subgroup analysis revealed that RDW levels continued to predict all-cause mortality in ICU patients with osteomyelitis.

RDW is a measure of the degree of heterogeneity in red blood cell (RBC) volume [18]. Li et al. found a significant and independent positive correlation between RDW and inflammatory biomarkers, such as high-sensitivity C-reactive protein (hsCRP) and erythrocyte sedimentation rate (ESR) [21]. Several studies have identified that certain inflammatory cytokines (TNF-α, interleukin-1, IL-6, and interferon-γ [INF-γ]) disrupt the response to erythropoietin, inhibit RBC production and lifespan, resulting in variations in RBC volume and subsequently elevated RDW [22–24]. Furthermore, inflammatory cytokines can impair iron metabolism, leading to irregular RBC size and shape, which contributes to elevated RDW levels [22,25].

Osteomyelitis is an inflammatory condition caused by the invasion of bone tissue by bacterial pathogens, with *Staphylococcus aureus* being the most common causative agent [26]. Among its virulence factors, *Staphylococcus aureus* produces β-hemolysin (Hlb), which reduces red blood cell count, and α-toxin, which induces the production of inflammatory cytokines such as IFN-γ[27]. It can be inferred that in osteomyelitis cases caused by *Staphylococcus aureus*, the resulting inflammatory response alters red blood cell quantity and size, thereby contributing to elevated RDW levels.

Although no previous studies have examined the relationship between RDW levels and all-cause mortality in osteomyelitis, associations between RDW and all-cause mortality have been reported in other diseases. In other bone-related diseases, Wang et al. reported that elevated RDW levels were significantly associated with mortality in elderly patients with hip fracture (HR: 1.03, 95% CI: 1.02 to 1.05, $p < 0.0001$, after adjustment) [28]. Similarly, a meta-analysis by Zhu et al. showed that RDW could serve as a predictor of mortality following hip fracture (HR: 3.14, 95% CI: 1.38 to 7.14, $p < 0.001$) [29]. In the ICU setting, Deniz et al. demonstrated that elevated RDW levels (> 16.5%) were significantly associated with all-cause mortality in patients (OR: 3.27, 95% CI: 2.58 to 4.14, $p < 0.001$, after adjustment) [30].

This study fills a gap in the literature by demonstrating that RDW is a significant predictor of all-cause mortality in ICU patients with osteomyelitis.

The main strength of our study is that it demonstrates elevated RDW levels as a strong, independent predictor of all-cause mortality in critically ill patients with osteomyelitis. However, this study also has several limitations. Firstly, this was a retrospective study, and therefore, retrospective bias could not be avoided. Secondly, although we adjusted for a number of confounding variables and performed subgroup analyses, unmeasured confounders may still have influenced the results. Thirdly, this was a single-centre study, and thus, further rigorous prospective studies are needed to validate our conclusion. Fourthly, our study population was predominantly White, so whether these findings apply to other ethnic groups require further investigations. Fifthly, due to the limitation in the available literature and data, the relationship between anemia and RDW remains unclear, and further research is needed to explore this association. Given that RDW is commonly elevated in anemic states and that the Q4 group (with higher RDW) also exhibited lower hematocrit and hemoglobin levels along with a higher mean age, the presence of anemia in this subgroup is plausible. The lack of adjustment for anemia may have influenced the observed association between RDW and mortality. Future studies should incorporate anemia status as a covariate to further elucidate the independent prognostic value of RDW in this population. Finally, the variability of RDW cannot be definitively determined; it may fluctuate over time, and its stability remains uncertain. [31] Although current data indicate an association between RDW and osteomyelitis, further research is needed to clarify this relationship.

Conclusion

A significant association between RDW and increased all-cause mortality has been observed in patients with osteomyelitis. These findings suggest that RDW may serve as a useful marker for identifying individuals at higher risk of mortality during hospitalization. However, further prospective studies are required to clarify the causal relationship and validate the clinical utility of RDW in this population.

Supporting information

S1 Table. The original data for analysis.
(XLSX)

Author contributions

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Visualization: Zongyun He.

Writing – original draft: Likai Liang.

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References

1. Maffulli N, Papalia R, Zampogna B, Torre G, Albo E, Denaro V. The management of osteomyelitis in the adult. Surgeon. 2016;14(6):345–60. https://doi.org/10.1016/j.surge.2015.12.005 PMID: 26805473
2. Schmitt SK. Musculoskeletal Infections: Meeting the Challenge. Infect Dis Clin North Am. 2017;31(2):ix–x. https://doi.org/10.1016/j.idc.2017.03.001 PMID: 28483046
3. Yagdiran A, Otto-Lambertz C, Lingscheid KM, Sircar K, Samel C, Scheyerer MJ, et al. Quality of life and mortality after surgical treatment for vertebral osteomyelitis (VO): a prospective study. Eur Spine J. 2021;30(6):1721–31. https://doi.org/10.1007/s00586-020-06519-z PMID: 32613398
4. Aagaard T, Roed C, Dahl B, Obel N. Long-term prognosis and causes of death after spondylodiscitis: A Danish nationwide cohort study. Infect Dis (Lond). 2016;48(3):201–8. https://doi.org/10.3109/23744235.2015.1103897 PMID: 26484577
5. Gornitzky AL, Kim AE, O'Donnell JM, Swarup I. Diagnosis and Management of Osteomyelitis in Children: A Critical Analysis Review. JBJS Rev. 2020;8(6):e1900202. https://doi.org/10.2106/JBJS.RVW.19.00202 PMID: 33006465
6. Michail M, Jude E, Liaskos C, Karamagiolis S, Makrilakis K, Dimitroulis D, et al. The performance of serum inflammatory markers for the diagnosis and follow-up of patients with osteomyelitis. Int J Low Extrem Wounds. 2013;12(2):94–9. https://doi.org/10.1177/1534734613486152 PMID: 23667102
7. Van Asten SA, Nichols A, La Fontaine J, Bhavan K, Peters EJ, Lavery LA. The value of inflammatory markers to diagnose and monitor diabetic foot osteomyelitis. Int Wound J. 2017;14(1):40–5. https://doi.org/10.1111/iwj.12545 PMID: 26634954
8. Buttarello M. Laboratory diagnosis of anemia: are the old and new red cell parameters useful in classification and treatment, how? Int J Lab Hematol. 2016;38 Suppl 1:123–32. https://doi.org/10.1111/ijlh.12500 PMID: 27195903
9. Eoh K-J, Lee T-K, Nam E-J, Kim S-W, Kim Y-T. Clinical Relevance of Red Blood Cell Distribution Width (RDW) in Endometrial Cancer: A Retrospective Single-Center Experience from Korea. Cancers (Basel). 2023;15(15):3984. https://doi.org/10.3390/cancers15153984 PMID: 37568799
10. Li N, Zhou H, Tang Q. Red Blood Cell Distribution Width: A Novel Predictive Indicator for Cardiovascular and Cerebrovascular Diseases. Dis Markers. 2017;2017:7089493. https://doi.org/10.1155/2017/7089493 PMID: 29038615
11. Owoicho O, Tapela K, Olwal CO, Djomkam Zune AL, Nganyewo NN, Quaye O. Red blood cell distribution width as a prognostic biomarker for viral infections: prospects and challenges. Biomark Med. 2022;16(1):41–50. https://doi.org/10.2217/bmm-2021-0364 PMID: 34784758
12. Aulakh R, Sohi I, Singh T, Kakkar N. Red cell distribution width (RDW) in the diagnosis of iron deficiency with microcytic hypochromic anemia. Indian J Pediatr. 2009;76(3):265–8. https://doi.org/10.1007/s12098-009-0014-4 PMID: 19205647
13. Mutlu NM, Peker TT, Soyal ÖB, Akçaboy ZN, Akçaboy EY, Titiz AP, et al. Red Cell Distribution Width in Diagnosis of Brain Death. Transplant Proc. 2019;51(7):2189–91. https://doi.org/10.1016/j.transproceed.2019.04.072 PMID: 31371213
14. Montagnana M, Danese E. Red cell distribution width and cancer. Ann Transl Med. 2016;4(20):399. https://doi.org/10.21037/atm.2016.10.50 PMID: 27867951
15. Liu S, Zhang H, Zhu P, Chen S, Lan Z. Predictive role of red blood cell distribution width and hemoglobin-to-red blood cell distribution width ratio for mortality in patients with COPD: evidence from NHANES 1999-2018. BMC Pulm Med. 2024;24(1):413. https://doi.org/10.1186/s12890-024-03229-w PMID: 39187816
16. Li X, Xu H, Gao P. Increased red cell distribution width predicts severity of drug-induced liver injury: a retrospective study. Sci Rep. 2021;11(1):773. https://doi.org/10.1038/s41598-020-80116-4 PMID: 33436893
17. Tao Y, Zhou Y, Chen H, Qin Y, He X, Liu P, et al. Prognostic role of red blood cell distribution width and platelet/lymphocyte ratio in early-stage classical Hodgkin lymphoma. Future Oncol. 2022;18(15):1817–27. https://doi.org/10.2217/fon-2021-1398 PMID: 35179068
18. 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. https://doi.org/10.3109/10408363.2014.992064 PMID: 25535770
19. Szygula-Jurkiewicz B, Szczurek W, Skrzypek M, Nadziakiewicz P, Siedlecki L, Zakliczynski M, et al. Red Blood Cell Distribution Width in End-Stage Heart Failure Patients Is Independently Associated With All-Cause Mortality After Orthotopic Heart Transplantation. Transplant Proc. 2018;50(7):2095–9. https://doi.org/10.1016/j.transproceed.2018.02.141 PMID: 30177116
20. Perlstein TS, Weuve J, Pfeffer MA, Beckman JA. Red blood cell distribution width and mortality risk in a community-based prospective cohort. Arch Intern Med. 2009;169(6):588–94. https://doi.org/10.1001/archinternmed.2009.55 PMID: 19307522
21. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med. 2009;133(4):628–32. https://doi.org/10.5858/133.4.628 PMID: 19391664
22. Ganz T. Anemia of Inflammation. N Engl J Med. 2019;381(12):1148–57. https://doi.org/10.1056/NEJMra1804281 PMID: 31532961
23. Kario K, Matsuo T, Nakao K, Yamaguchi N. The correlation between red cell distribution width and serum erythropoietin titres. Clin Lab Haematol. 1991;13(2):222–3. https://doi.org/10.1111/j.1365-2257.1991.tb00274.x PMID: 1934934
24. Jelkmann W. Proinflammatory cytokines lowering erythropoietin production. J Interferon Cytokine Res. 1998;18(8):555–9. https://doi.org/10.1089/jir.1998.18.555 PMID: 9726435
25. Yang Y, Wang Q, Gao L, Liu S, Zhao J, Liu G, et al. Promising applications of red cell distribution width in diagnosis and prognosis of diseases with or without disordered iron metabolism. Cell Biol Int. 2023;47(7):1161–9. https://doi.org/10.1002/cbin.12029 PMID: 37092585

26. Urish KL, Cassat JE. Staphylococcus aureus Osteomyelitis: Bone, Bugs, and Surgery. Infect Immun. 2020;88(7):e00932-19. https://doi.org/10.1128/IAI.00932-19 PMID: 32094258

27. Chen H, Zhang J, He Y, Lv Z, Liang Z, Chen J, et al. Exploring the Role of Staphylococcus aureus in Inflammatory Diseases. Toxins (Basel). 2022;14(7):464. https://doi.org/10.3390/toxins14070464 PMID: 35878202

28. Wang N-J, Zhang Y-M, Zhang B-F. The Association Between Red Cell Distribution Width (RDW) and All-Cause Mortality in Elderly Patients with Hip Fractures: A Retrospective Cohort Study. Int J Gen Med. 2023;16:3555–66. https://doi.org/10.2147/IJGM.S417079 PMID: 37609519

29. Zhu X-F, Weng H-Y, Huang S-F. Red cell distribution width as a predictor of mortality after hip fracture: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2023;27(15):6996–7004. https://doi.org/10.26355/eurrev_202308_33271 PMID: 37606108

30. Deniz M, Ozgun P, Ozdemir E. Relationships between RDW, NLR, CAR, and APACHE II scores in the context of predicting the prognosis and mortality in ICU patients. Eur Rev Med Pharmacol Sci. 2022;26(12):4258–67. https://doi.org/10.26355/eurrev_202206_29063 PMID: 35776025

31. Dugdale AE, Badrick T. Red blood cell distribution width (RDW)—a mechanism for normal variation and changes in pathological states. J Lab Precis Med. 2018;3:73–73. https://doi.org/10.21037/jlpm.2018.08.03