ORIGINAL ARTICLE

IS RED CELL DISTRIBUTION WIDTH CORRELATED WITH MORTALITY IN GERIATRIC PATIENTS UNDERGOING HIP FRACTURE SURGERY: A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Introduction: Our study aimed to determine the impact of preoperative red blood cell distribution width on length of intensive care unit and hospital stays, and short- and long-term mortality in elderly patients undergoing hip fracture surgery.

Materials and Method: This prospective cohort study included 414 patients aged 65 and older who presented with hip fractures between November 2021 and November 2022. Patients' demographic characteristics, American Society of Anesthesiologists score, Revised Cardiac Risk Index, comorbidities, and preoperative complete blood counts (hemoglobin, red blood cell distribution width, platelet count, etc.) were recorded at the preoperative visit. Length of intensive care unit and hospital stays were documented postoperatively. Patients were followed for one year after surgery in terms of mortality.

Results: Patients with high red blood cell distribution width levels (≥14.25%) were older, had more comorbidities, and had higher American Society of Anesthesiologists score and Revised Cardiac Risk Index scores ($p<0.001$). In the high red blood cell distribution width group, length of hospital stays was longer ($p<0.001$). There was no significant difference between red blood cell distribution width groups in terms of intensive care unit stay duration and readmissions ($p=0.304$ and $p=0.664$, respectively). According to the multivariate logistic regression analysis, an red blood cell distribution width of ≥14.25 was found to increase the risk of 30-day mortality by 4.7 times and 1-year mortality by 2.74 times.

Conclusion: Red blood cell distribution width is a useful, practical, and cost-effective indicator of short- and long-term mortality in elderly patients undergoing hip fracture surgery.

Keywords: Aged; Anemia; Hip fracture; Mortality.

INTRODUCTION

Hip fracture, a common problem in geriatric patients, is linked to significant mortality and morbidity rates (1). Over 1 million hip fractures occur annually, imposing a burden on society (1). Even with treatment, 1-year mortality after hip fracture is between 8.4% and 36.0% (2). Therefore, a definitive prognostic parameter is crucial for effective risk stratification. Comorbidities, age, perioperative complications, and various risk prediction models (such as the Charlson Comorbidity Index and the orthopedic version of the Physiologic and Operative Severity Score) are recognized factors influencing mortality in hip fracture patients (3). Nevertheless, these models are time-consuming, requiring further calculations, so a need exists for a simple, cost-effective laboratory parameter associated with postoperative mortality (1).

Red cell distribution width (RDW) measures heterogeneity in erythrocyte sizes and is a routine parameter of a complete blood count (CBC) test. It is calculated automatically or manually with this formula: (standard deviation of mean corpuscular volume / mean corpuscular volume) × 100 (4). Generally used to investigate hematological disorders, RDW has recently been proposed as a long-term inflammatory biomarker (5). An association between increased RDW and mortality has been reported in many diseases, such as diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), acute pancreatitis, and sepsis (6). In this study, evaluate the impact of RDW on 30-day and 1-year mortality in geriatric patients undergoing hip fracture surgery.

MATERIALS AND METHOD

The hospital ethics committee approved the research on October 4, 2021 (reference no: 121/05), and a prospective observational study was planned to include patients aged 65 and older with a diagnosis of hip fracture confirmed by imaging examinations from November 1, 2021, to November 1, 2022. Written consent was obtained from all patients. The exclusion criteria included declining participation in the study, absence of preoperative CBC test, indefinite fracture time, and recent history of blood transfusion, as exogenous red blood cells could alter the RDW (7). The patients in the study were visited preoperatively by an anesthesiologist, and their demographic data (age, gender, body mass index [BMI]) comorbidities (such as DM, HT, congestive heart failure [CHF], and chronic renal failure [CRF]), American Society of Anesthesiologists (ASA) score, and Revised Cardiac Risk Index (RCRI) were recorded.

Blood samples were collected from the patients, and CBC parameters were analyzed (hemoglobin, RDW, platelet count, etc.). The CBC was conducted with the Symex XN-550 automated hematology analyzer (Sysmex Corp., Kobe, Japan), with reference values for RDW coefficients of variation ranging between 12.2% and 16.5%. Other biochemical tests were performed using standard techniques with the Beckman Coulter LH 780 device (Beckman Coulter Inc., Brea, New York, USA). Anemia was classified as follows: mild (11.0-11.9 g/dL for women, 11.0-12.9 g/dL for men), moderate (8.0-11.0 g/dL), and severe anemia (< 8.0 g/dL) (5). At the time of discharge, records were taken of the anesthesia method (general or local anesthesia), surgery duration, postoperative first-day CBC (RDW and hemoglobin levels), in-hospital complications (including hypoxemia, pneumonia, acute coronary syndrome, arrhythmia, stroke, severe bleeding, infection, and acute renal failure), and length of intensive care unit (ICU) and hospital stays. Patients were contacted by phone 1 year after discharge. The last phone call was conducted on November 1, 2023. The primary endpoint of the study was to investigate the impact of RDW on 30-day and 1-year mortality, and the secondary endpoint focused on the effect of RDW on readmission and length of ICU and hospital stays.

Statistical analysis

The data were statistically analyzed using IBM SPSS Statistics for Windows, version 20.0. The study examining the effect of RDW on mortality used as a reference the study of Wei-Hsiang et al. (1). The sample size to detect a significant difference of 1 unit in RDW averages between deceased and surviving groups was calculated with a 5% error level and a minimum 80% power using the two-sided t-test. Accordingly, the study was planned with a minimum of 87 patients in the mortality group and 114 patients in the surviving group over 1 year.

To determine the statistical methods to be applied, the Shapiro-Wilk normality test was initially conducted. If the assumption of normality was not met in any of the groups, non-parametric test methods were selected. In this context, Student's t-test and/or the Mann-Whitney U test were used to compare variables obtained through measurements between two independent groups. Mean, standard deviation, and median (minimum–maximum) values were provided to summarize continuous variables, and Fisher's exact test and chi-squared test results were presented as frequency distributions and percentages for categorical variables.

The area under the receiver operating characteristic (ROC) curve provides an estimate of the overall accuracy of alternative tests. An area of 0.50 indicates that the variable adds no information. For an alternative test, areas under the ROC and 95% confidence intervals (CIs) were calculated as defined by Hanley and McNeil (8). For the variables whose diagnostic powers were found to be statistically significant, the cutoff points determined according to the Youden index are given together with the relevant sensitivity and selectivity points. All variables with statistical significance in the univariate analyses were considered eligible for inclusion in the multiple analysis and were tested for collinearity. Cutoff points determined by the Youden index for variables with statistically significant diagnostic power are provided along with relevant sensitivity and specificity scores. Multiple logistic regression analyses were conducted using the backward logistic regression approach. Variables that remained significant ($p < .05$) in the multivariate model were considered independent predictors. Hosmer-Lemeshow goodness-of-fit statistics were used to evaluate the model fit. Odds ratios (ORs) and 95% CIs were calculated for each predictor.

RESULTS

Figure 1 illustrates the flowchart of patient selection. A total of 414 geriatric patients with hip fractures, 165 males and 249 females, were included in the study. The mean age of the patients was 76.37 ± 8.52 years, and mean RDW was 14.5 ± 2.07%. Table 1 presents the patients' basic characteristics.

Table 2 summarizes the study group's clinical characteristics, comorbidities, and complications according to RDW levels. Patients with higher RDW levels were older and had higher ASA and RCRI scores ($p < .001$). The percentage of anemia in the RDW ≥14.25% group was higher than in the RDW <14.25% group (79.13% vs. 48.28%, respectively; $p < .001$). The most common complications in-hospital were acute kidney injury and pneumonia in the group with high RDW (4/182, 2.19%, for both). The length of hospital stays was longer for patients in the high RDW group ($p<.001$). No statistically significant difference was observed between the two groups regarding the length of ICU stay and readmissions within the 1-year hospital ($p= .304$, $p=.664$, respectively).

The area under the curve (AUC) for both 30-day and 1-year mortality were found to be statistically significant in higher RDW patients ($p < .001$). The AUC was 0.732 (95% CI: 0.671–0.793) for 30-day mortality and 0.709 (95% CI: 0.654–0.765) for 1-year mortality. Accordingly, RDW values of ≥14.25 were determined to predict 30-day mortality, whereas values of ≥14.05 were found to predict mortality at 1 year. Figure 2 shows ROC curves illustrating the AUC for both mortality rates.

Figure 1. Study cohort flow diagram

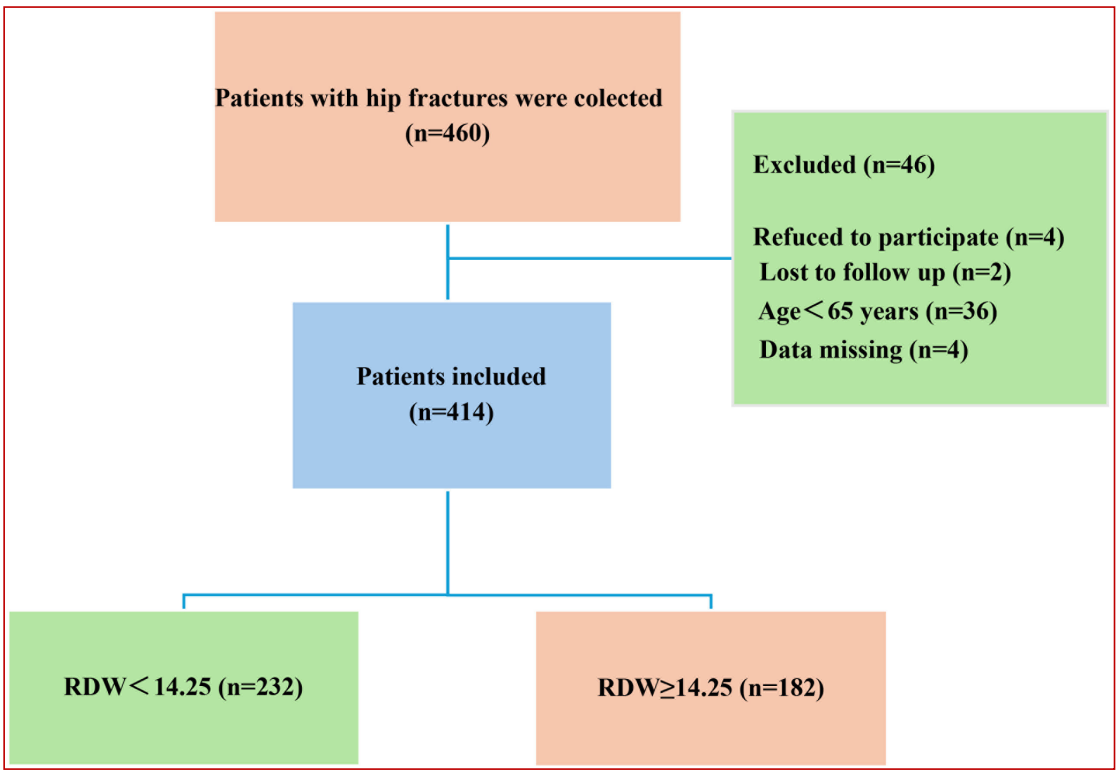

Table 1. Demographic and Clinical Characteristics of Patients

Preoperative characteristics of patients (n = 414)	Values
Age (year)	76.37±8.52
Sex, male, n (%)	165 (39.86)
BMI (kg/m2)	26.99±3.37
RDW (%)	14.5±2.07
Length of hospital stay (days)	5.78±8.85
Length of ICU stay (days)	2.14±6.86
Readmission n (%)	22 (5.31)
30-day mortality n (%)	65 (15.7)
1 year mortality n (%)	94 (22.71)

Values are given as mean ± SD or number (percentage). BMI, body mass index; RDW, red blood cell distribution width; ICU, intensive care unit

Table 2. Characteristics of the study population by RDW group (n = 414)

RDW value		RDW <14.25% (n=232)	RDW ≥14.25% (n=182)	p value
Age (years)		75.03±7.97	78.08±8.91	<0.001
Male n (%)		93 (40.08)	72 (39.56)	0.914
BMI (kg/m^2)		26.82±3.3	27.2±3.46	0.261
Comorbidity n (%)		152 (65.51)	151 (82.96)	<0.001
	Diabetes mellitus	59 (25.43)	70 (38.46)	0.004
	Systemic Hypertension	115 (49.56)	105 (57.69)	0.1
	Hyperlipidemia	8 (3.44)	4 (2.19)	0.452
	Heart failure	5 (2.15)	13 (7.14)	0.014
	Coronary artery disease	37 (15.94)	45 (24.72)	0.026
	Peripheral artery disease	1 (0.43)	2 (1.09)	0.585
	Atrial fibrillation	14 (6.03)	25 (13.73)	0.008
	Asthma	14 (6.03)	10 (5.49)	0.815
	COPD	11 (4.74)	15 (8.24)	0.145
	Cerebrovascular disease	18 (7.75)	17 (9.34)	0.566
	History of malignancy	5 (2.15)	15 (6.5)	0.004
	Chronic renal failure	8 (3.44)	18 (8.24)	0.007
	Alzheimer's disease	16 (6.89)	21 (11.53)	0.1
	Thyroid dysfunction	18 (7.75)	21 (11.53)	0.191
	Chronic liver disease	0	3 (1.64)	0.084
	Rheumatoid arthritis	6 (2.58)	7 (3.84)	0.466
	Parkinson's disease	7 (3.01)	2 (1.09)	0.309
	Heart valve disease	0	2 (1.09)	0.193
	Epilepsy	2 (0.86)	1 (0.54)	1
Anesthesia type n (%)	General anesthesia	96 (53.33)	84 (46.67)	0.331
	Regional anesthesia	136 (58.12)	98 (41.88)	
Complication n (%)		15 (6.46))	17 (9.34)	0.565
	Acute kidney failure	1 (0.43)	4 (2.19)	
	Acute coronary syndrome	2 (0.86)	3 (1.64)	
	Infection	5 (2.15)	3 (1.64)	
	Pneumonia	3 (1.29)	4 (2.19)	
	Atrial fibrillation	2 (0.86)	0	
	Embolism	1 (0.43)	1 (0.54)	
	Bleeding	0	1 (0.54)	
	Hypoxemia	1 (0.43)	1 (0.54)	
RCRI n (%)	Low risk	142 (61.20)	72 (39.56)	<0.001
	Medium risk	60 (25.86)	64 (35.16)	
	High risk	30 (12.93)	46 (25.27)	

Table 2. *Continued*

RDW value		RDW <14.25% (n=232)	RDW ≥14.25% (n=182)	p value
ASA physical status n (%)	1	67 (28.87)	24 (13.18)	<0.001
	2	111 (47.84)	85 (46.70)	
	3	47 (20.25)	55 (30.21)	
	4	7 (3.01)	18 (9.89)	
Preoperative anemia n (%)	No anemia	120 (51.72)	38 (20.87)	<0.001
	Mild anemia	106 (45.68)	121 (66.48)	
	Moderate anemia	4 (1.72)	8 (4.39)	
	Severe anemia	2 (0.86)	15 (8.24)	
Hemoglobin (g/dL)		12.39±1.82	10.91±2.05	<0.001
Hematocrit, %		36.94±5.33	33.64±5.72	0.001
Platelet (10^9/L)		222.91±76.87	250.95±101.05	<0.001
MCV (fL)		88.03±4.24	83.97±8.95	0.168
WBC (10^9/L)		10.06±4.15	10.61±4.62	<0.001
Lymphocyte (10^9/L)		1.61±0.82	1.38±0.85	0.001
Monocytes (10^9/L)		0.64±0.27	0.72±0.3	0.040
Neutrophil (10^9/L)		7.74±3.94	8.5±4.24	0.004
RBC (10^9/L)		4.22±0.67	4.02±0.74	<0.001
MCH (pg)		29.64±1.56	27.35±3.55	<0.001
MCHC (g/dL)		33.67±1.39	32.42±1.58	<0.001
Albumin (g/dL)		39.81±9.8	34.95±9.8	0.034
Alkaline phosphatase (IU/L)		97.33±42.74	120.28±76.19	<0.001
C reactive protein (mg/dL)		38.95±67.85	83.22±88.29	0.001
Urea (mg/dl)		41.43±21.71	49.95±29.68	0.009
Serum creatine (umol/L)		0.87±0.37	1.13±1.08	0.314
Sodium (mEq/L)		138.73±3.78	138.7±3.71	0.243
Potassium (mEq/L)		4.26±0.45	4.34±0.55	0.009
Calcium (mg/dL)		8.79±0.72	8.59±0.83	<0.001
INR		1.04±0.1	1.17±0.49	<0.001
Length of hospital stay (days)		4.55±3.78	7.34±12.49	<0.001
Length of ICU stay (days)		1.24±2.56	3.27±9.83	0.304
Readmission n (%)		10 (45.45)	12 (54.55)	0.664
Operation duration (min)		75.47±27.15	74.07±22.44	0.664
30-day mortality n (%)		14 (21.54)	51 (78.46)	<0.001
1 Year mortality n (%)		29(30,85)	65(69,15)	<0.001

Values are given as mean ± SD or number (percentage). RDW, Red blood cell distribution width; BMI, Body mass index; COPD, chronic obstructive pulmonary disease; RCRI, Revised Cardiac Risk Index, ASA, American Society of Anesthesiologists; MCV, Mean corpuscular volume, WBC, White blood count, RBC, Red blood cells; MCH, Mean corpuscular hemoglobin, MCHC, Mean corpuscular hemoglobin concentration, INR, International normalized ratio; ICU, Intensive care unit

Figure 2. Receiver Operating Curve of Red Blood Cell Distribution Width in predicting 30-day mortality (A) and 1-year mortality (B)

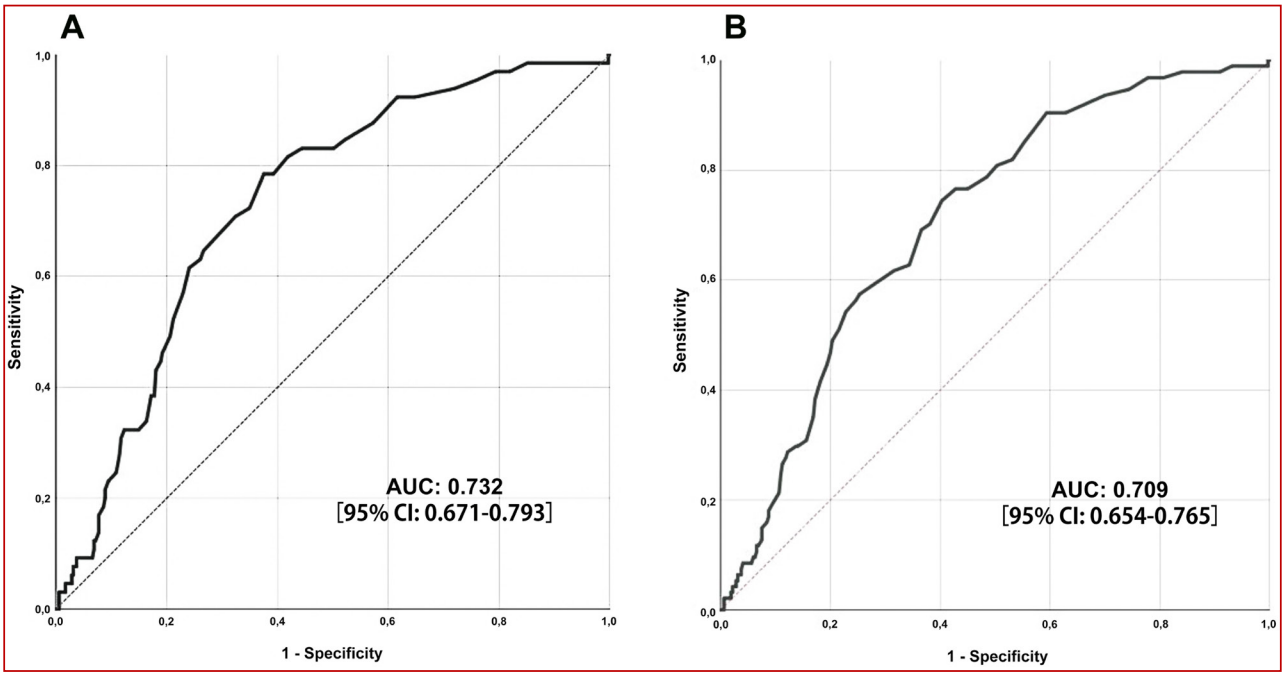

Table 3. Multivariate analysis to identify factors associated with 30–day mortality

	OR (95% C.I.) (Univariate)	p	OR (95% C.I.) (Multivariate)	p
RDW ≥14,25	6.06 (3.22-11.38)	<0.001	4.68 (2.35-9.33)	<0.001
Age	1.18 (1.08-1.15)	<0.001	1.09 (1.05-1.14)	<0.001
Atrial fibrillation	3.55 (1.76-7.29)	0.001	2.64 (1.14-6.11)	0.023
Alzheimer's disease	5.10 (2.49-10.43)	<0.001	2.98 (1.27-6.97)	0.012
CRF	3.78 (1.63-8.76)	0.002	3.42 (1.30-9.03)	0.013

RDW, Red blood distribution width; Chronic renal failure, CRF

According to the multivariate logistic regression analysis, high preoperative RDW levels were independent risk factors for postoperative 30-day and 1-year mortality. A RDW of ≥14.25 increased the risk of death within 30 days by approximately 4.7 times; for 1-year mortality, it increased the risk by 2.74 times. Other independent determinants of 30-day mortality included advanced age (OR 1.09 [1.05–1.14], p<.001), atrial fibrillation (OR 2.64 [1.14–6.11], p=.023), Alzheimer's disease (OR 2.98 [1.27–6.97], p=.012), and chronic kidney disease (OR 3.42 [1.30–9.03], p=.013), (Table 3). Other independent determinants of 1-year mortality included advanced age (OR 1.09 [1.05–1.13], p<.001), Alzheimer's disease (OR 5.35 [2.29–12.46], p=.012), high RCRI (OR 3.02 [1.45–6.30], p=.003), and uremia (OR 1.01 [1.00–1.02], p=.01).

DISCUSSION

Our study demonstrated that high RDW (>14.25%) in aged patients who have hip surgery correlates with age and comorbidity burden. This condition did not increase the duration of ICU stay or risk of readmission. Nevertheless, we observed an independent increase in mortality risk over both short and long periods in patients with a postoperative RDW >14.25%.

It is claimed that RDW levels increase by approximately 1% per year in individuals aged 60 and above (9). In our study, patients with RDW >14.25 were older compared to those with RDW ≤14.25. Therefore, the age distribution between our groups confirms the association between high RDW and age. This phenomenon is explained by the natural decline in the physiological functions of erythropoiesis with aging (10). Yet, it remains uncertain whether the elevated RDW in these patient groups is a result of aging itself or a consequence of critical illness. Therefore, we are inclined to believe that the reason for high RDW in these patients is not attributable to age alone.

The causes of elevated RDW are multifactorial. Several studies suggest that RDW can serve as a biomarker for assessing mortality risk in comorbidities such as heart disease and cancer (5,11). Nevertheless, it remains unclear whether the relationship between elevated RDW and mortality is causal or consequential. In light of all these findings, we believe that RDW to be an indicator that reflects the prognosis of frail patients. Therefore, we emphasize the importance of clinicians considering RDW when assessing prognosis during preoperative examinations.

In our study, comorbidities such as DM, CRF, and CHF were more frequently observed in patients with high RDW values. Our findings, in conjunction with previous studies, support the potential relationship of RDW with adverse outcomes in chronic diseases (12,13). Although the pathophysiological mechanisms between high RDW and poor prognosis remain uncertain, it has been proposed that various systemic factors such as oxidative stress, inflammation, and inadequate nutrition (deficiencies in iron, folate, vitamine B12, etc.) could explain this relationship (6,14). Oxidative stress occurring in chronic illnesses may lead to increased production of reactive oxygen radicals, disruption of erythrocyte homeostasis, and an increase in mortality (15). Additionally, inflammation can affect bone marrow function and disrupt iron metabolism, thereby influencing the erythropoiesis process (5).

Although we found an association between high RDW and length of hospital stay, we did not observe a difference in terms of postoperative complications, length of ICU stays, or risk of readmission. In this regard, our findings contradict previous studies (6,16). In our study, patients with elevated RDW were older than in other studies, and they had a higher burden of comorbidities. This may have affected the clinical decision-making process of clinicians and created a reflex to keep patients in the hospital for a longer period (17). However, we observed that more objective decisions, such as ICU stay duration and readmission, were not influenced by RDW values. Although we could not demonstrate the significance of RDW in terms of complications, pneumonia was the most frequently observed complication in the high RDW group. This also supports the findings of previous studies (18,19).

In our study, we showed that high RDW is independently correlated with postoperative mortality at both 30-day and 1-year periods. Hung Wei-Hsiang et al. reported that RDW>13.35% caused an increase in the risk of 30-day mortality in patients (1). However, this increase in 30-day mortality is quite slight and contradicts our findings. This difference may be attributed to variations in the composition of populations or matching disparities between the two studies. Similarly, in a randomized

controlled trial involving heart failure patients, Felker and colleagues report a twofold increase in the risk of mortality with RDW values above 15.8% compared to those with RDW values below 13.3% (20). Tonelli et al., meanwhile, reported a twofold higher probability of mortality in patients with CAD with RDW greater than 13.8% compared to those with RDW less than 12.6% (21). However, Michael Berry and colleagues assessed the effect of RDW on mortality in emergency laparotomy patients aged 65 and older and could not establish an association between anisocytosis and 30-day mortality (14). In our study, it was observed that an RDW >14.25 was correlated with 4.7 times increased 30-day mortality and 2.74 times increased 1-year mortality. The selection of younger patients in comparison to our study and the inclusion of patients with specific comorbidities in these studies may have caused these differences. However, none of these studies considered robust adjustment factors such as nutritional status, immune status, hemoglobin levels, and multiple diseases that reduce the risk of confusing factors based on a conceptual model. Finally, although studies support the relationship between high RDW and mortality, the difference in RDW cut-off values affected the mortality risk prediction rate. This is because there is currently no standardized threshold value to define high RDW levels. Formun AltıTherefore, despite the indication of clinically significant associations between high RDW and mortality, we believe that future studies are needed to determine an optimal threshold value.

While attempting to predict postoperative mortality rates following hip fracture surgery, there is a need for tests that clinicians can easily apply. Previous studies have found an association between high RCRI scores and 30-day mortality in patients undergoing hip fracture surgery (22). Additionally, Yin et al. suggested that evaluating RDW and ASA scores together may provide a more powerful and effective strategy for predicting mortality in hip fracture patients (23). The findings of our study suggest that mortality increases as ASA and RCRI scores increase. However, the availability of RDW in automated CBC results is a factor that increases its value. Additionally, RDW assessment is practical and cost-effective. Nevertheless, there are various factors that can affect RDW values. Therefore, we believe that RDW alone may not be used as an effective and independent factor in predicting prognosis. However, combining RDW with other known prognostic indicators may enhance the power of risk models. Therefore, in preoperative assessment, RDW, when used in conjunction with other scoring systems, can facilitate resource allocation, potentially providing a practical contribution to the current risk classification strategy.

The strengths of this study are its prospective design, unbiased inclusion criteria, and long-term follow-up of patients. However, various potential limitations should be considered. Firstly, patients were treated and followed up in a single tertiary center, which may not represent other healthcare centers and ethnicities. Secondly, while the assessment of RDW is quick, straightforward, and doesn't demand specialized skills or equipment, there are various methods available for measuring red cell size (e.g., impedance or optical techniques) and RDW (24). This can lead to variations in reference values depending on the device and population. Finally, there was no common opinion on the optimum threshold value for the prognostic aim of RDW (25).

This prospective study revealed a strong association between preoperative RDW and short-term and long-term mortality in geriatric patients who have hip surgery. Due to its routine reporting in CBC, lack of additional cost, and easy interpretability, RDW may provide a practical contribution to predicting patient prognosis.

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