European Journal of Therapeutics pISSN: 2564-7784 eISSN: 2564-7040

Original Research

Red Cell Distribution Width Is an Independent Predictor of 1-Year Mortality in a Turkish Patient Population with Acute Decompensated Heart Failure

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Received: 2023-08-19 / Accepted: 2023-11-26 / Published Online: 2023-11-26

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ABSTRACT

Objective: Heart failure (HF) is a significant public health issue in Turkey. The goal of this study was to look into how red cell distribution width (RDW) affected patients with acute decompensated HF (ADHF) patients' prognoses.

Methods: A total of 101 ADHF patients above the age of 18 were enrolled in the study. Venous blood was drawn to measure the serum rdw. After a year of follow-up, the patients' survival status was determined.

Results: The patients' mean age was 72. Forty-nine patients had heart failure (HF) with a reduced ejection fraction (EF), 8 had HF with a mildly reduced EF, and 44 had HF with a preserved EF. The median RDW value was 15.9%. In the hospital, nine patients passed away, and 92 others were discharged. 14 patients were lost to follow-up after one year, 87 patients completed the trial, and 40 patients passed away. Inotropic medication use, and serum RDW value were identified as independent predictors of 1-year death in ADHF patients by multivariate logistic regression analysis. According to this data, there was a 44% increase in 1-year mortality for every 1% increase in RDW.

Conclusion: In Turkish patients hospitalized for ADHF, red cell distribution width represents an independent prognostic predictor for 1-year mortality.

Keywords: Red cell distribution width, mortality, heart failure

INTRODUCTION

Heart failure (HF) is still a clinical illness with a significant morbidity and mortality rate in the twenty-first century. In a study on the prevalence of HF in Turkey, it was shown that among 4650 persons above the age of 35, absolute HF prevalence was 2.9%, compared to a predicted prevalence of 6.9%, and absolute asymptomatic left ventricular dysfunction prevalence was 4.8%, compared to a predicted prevalence of 7.9% [1]. HF thus remains a significant public health issue in Turkey. Despite the most recent developments in evidence-based therapies and

device technology being employed in HF, fatality rates are still significant. In a more recent study, the mortality rate for Turkish HF patients at one year was 19.9% (13.7% for patients with chronic heart failure and 32.6% for those with acute heart failure) [2]. In comparison to HF mortality in European nations, this is a little higher. The Heart Failure Long-Term Registry (ESC-HF-LT) of the European Society of Cardiology enrolled 12440 HF patients from 211 clinics in 21 countries. According to this study, the 1-year all-cause mortality rate was 14.5% for chronic HF and 23.6% for acute HF [3].

It's critical to pay closer attention to high-risk individuals in order to identify the factors that predict mortality in HF patients and lower morbidity and mortality in this patient population. Numerous prognostic models have been suggested for this purpose [4-6]. However, there is a limited application of these models in clinical settings. 39372 individuals with HF from 30 cohort studies were included in one of these models, the MAGGIC meta-analysis [4]. Age, lower ejection fraction (EF), NYHA functional class, serum creatinine, diabetes, no prescription for a beta-blocker, lower systolic blood pressure, lower body mass, time since diagnosis, being a current smoker, chronic obstructive pulmonary disease, male gender, and no prescription for an angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) were found to be independent predictors of mortality in HF in this analysis [4]. This meta-analysis's authors created an integer score to gauge the probability of HF mortality.

In the past 15 years, it has been discovered that red blood cell distribution width (RDW), an easily measured hemogram parameter representing the change in erythrocyte volume, is a prognostic marker in HF patients [7–10]. RDW demonstrated the strongest association with morbidity and mortality among the laboratory indicators of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) study program, according to the researchers [7]. Several more studies followed this one in showing the predictive importance of RDW in HF patients [8–11]. This study looked into how RDW affected prognosis in a group of Turkish patients with acute decompensated HF (ADHF).

Main Points;

- Heart failure represents a significant public health issue in Turkey with high morbidity and mortality.
- Identifying factors influencing morbidity and mortality is important to lower the risk in high-risk patients.
- Red blood cell distribution width is a prognostic marker in Turkish patients with acute decompensated HF.
- One percent increase in RDW is associated with a 44% increase in 1-year mortality in this patient population.

MATERIALS AND METHODS

One hundred and one individuals hospitalized at the cardiology clinic with ADHF were included in the study. Patients above 18 years of age with a diagnosis of acute HF met the inclusion criteria. Patients with all varieties of HF were included. Only those under the age of 18 were excluded. In order to participate in the study, the patients gave their informed consent. The study was approved by the regional clinical studies ethics committee (Kırıkkale University, date: 2012/12/17, approval number: 12/14-01). The 1964 Helsinki Declaration and its following amendments, as well as other related ethical norms, guided every procedure carried out for this study. A single-center prospective cohort kind of observational study was intended for the investigation.

Both the heart rate and blood pressure were taken upon admission. At the time of discharge, the patients' pulse rates were also noted. Additionally, the patients' HF Killip status was noted during the physical examination. When an electrocardiogram (ECG) was obtained, conditions such as left bundle branch block and atrial fibrillation were identified. All patients had venous blood collected at the time of admission for biochemistry and a full blood count. RDW and other hemogram parameters were measured using an automated haematology analyzer (Abbott Cell-Dyn 2700; Abbott Laboratory, Abbott Park, Illinois, USA). A Vivid 3 Pro Echocardiography device (General Electric Corp, Milwaukee, WI, USA) was used for transthoracic echocardiography. HF with reduced ejection fraction (HFrEF) was defined as HF with $EF \leq 40\%$, HF with mildly reduced EF (HFmrEF) was defined as HF with EF between 41-49%, and HF with preserved EF (HFpEF) was defined as HF with $EF \ge 50\%$. We kept track of cardiac issues such as arrhythmias (atrial fibrillation, ventricular arrhythmias, etc.), cardiogenic shock, and the requirement for inotropic assistance while in the hospital.

One-year all-cause mortality was the study's primary outcome. After a year of follow-up, the patients' survival status was ascertained either directly during cardiology outpatient appointments, over the phone with their relatives, or by consulting their medical files.

Statistical Analysis

The study's statistical analysis was conducted using the statistical package for the social sciences (SPSS) 17.0 software from SPSS Inc. in Chicago, Illinois, USA. The distributional characteristics of the continuous variables were determined using the

Kolmogorov-Smirnov test. In contrast to categorical variables, which were compared between groups using chi-square and Fischer's exact tests, continuous variables were compared using the Student-t test and the Mann-Whitney U test (for normally distributed and non-normally distributed variables, respectively). The chi-square test was once more used to compare categorical variables among the three RDW groups, and the Kruskal-Wallis test was used to compare continuous variables among the three RDW groups.

To determine the factors influencing one-year mortality, we conducted a univariate logistic regression analysis. After that, multivariate logistic regression analysis was used to identify the independent determinants of acute decompensated HF mortality at one year. Based on their statistical significance as a single variable, we included variables in the multivariable logistic regression analysis, considering a p-value less than 0.05 as significant.

RESULTS

One hundred and one ADHF patients were enrolled in the study. 56 (55%) of the patients were men, and 45 (45%) were women. The range of patient ages was 24-90, with a mean age of 72 and the median age was 74. The length of hospitalization varied from 1 to 19 days, with 4 days serving as the median. 49 (48.5%) individuals had HFrEF, 8 (8%) had HFmrEF, and 44 (43.5%) had HFpEF out of the total. Regarding the patients' Killip classification, 77 (76%) had Killip Class 2, 18 (18%) had Killip Class 3, and 6 (6%) had Killip Class 4 HF. 46 (45%) of the patients were on sinus rhythm, while 55 (55%) had atrial fibrillation. On the ECG, 15 (15%) patients showed left bundle branch block. At the time of hospital admission, the median heart rate of the patients was 84 beats per minute (bpm). The patients' median heart rate at discharge was 78 bpm. According to the patients' hemogram data, the mean RDW value was 16.1% (13.0-27.2%) whereas the median value was 15.9%. Seventy individuals (69%) reported RDW values that were high (RDW \geq 15%). Table 1 lists the fundamental characteristics of the entire patient population.

During their stay in the hospital, 38 (38%) patients received positive inotropic treatment, 18 (18%) patients had cardiogenic shock, 2 (2%) patients developed acute renal insufficiency, and 1 (1%) patient developed new atrial fibrillation. Nine (9%) patients passed away while they were hospitalized, and 92 (91%) patients were discharged. At the end of the 1-year follow-up period, 87 patients had finished the follow-up term, 14 (14%) patients had lost follow-up, and 40 (39.6%) patients had passed away.

In this HF population, cardiogenic shock, usage of inotropic drugs, serum creatinine, RDW, and potassium values were found to be associated with 1-year mortality (Table 2). All of these variables were taken into account in the multivariate logistic regression analysis. According to the results of this analysis, serum RDW value and inotropic medication use were independent predictors of 1-year mortality in ADHF patients (Table 3). Additionally, this investigation showed that in decompensated HF patients, a 1% rise in RDW value corresponded to a 44% increase in 1-year all-cause death.

Table 1	 Basal 	l c	haracteristics	of	the	total	pati	ent	po	pul	ati	on
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Characteristic						
Heart failure type						
HFrEF (n,%)	49 (48.5%)					
HFmrEF (n,%)	8 (8%)					
HFpEF (n,%)	44 (43.5%)					
Age (median, 25th-75th percentile)	74 (66-79)					
Ejection fraction (%) (median, 25th-75th percentile)	45 (30-52.5)					
Hospitalization days (median, 25th-75th percentile)	4 (3-6)					
Systolic blood pressure (mmHg) (median, 25th-75th	120 (110-					
percentile)	140)					
Diastolic blood pressure (mmHg) (median, 25th- 75th percentile)	70 (70-80)					
Heart rate at hospital admission (beats per minute)	84 (77-100)					
(median, 25th-75th percentile)	04 (77-100)					
Serum creatinine (mg/dl) (median, 25th-75th	1.0 (0.80-					
percentile)	1.40)					
Serum haemoglobin (g/dl) (mean±SD)	12.7 ± 2.3					
Serum range of distribution width (RDW) (%)	15.9 (14.6-					
(median, 25th-75th percentile)	16.9)					
Killip classification						
2 (n,%)	77 (76%)					
3 (n,%)	18 (18%)					
4 (n,%)	6 (6%)					
Mitral regurgitation						
None (n,%)	5 (5%)					
Mild (n,%)	23 (23%)					
Medium (n,%)	41 (41%)					
Serious (n,%)	32 (31%)					
Atrial fibrillation on ECG (n,%)	46 (45%)					
Cardiogenic shock (n,%)	18 (18%)					
Inotropic drug use (n,%)	38 (38%)					

According to RDW values, we separated the entire group into three subgroups. RDW values in the first group were less than 15.0%, in the second group ranged from 15.0 to 16.9%, and in the third, RDW values were equal to or higher than 17%. When clinical and laboratory traits were evaluated between these three categories, it was found that the extremely high RDW group (RDW \geq 17%) had serum hemoglobin values that were lower than those of the other two groups, but the other traits were comparable between the three subgroups (Table 4). Patients in the highest RDW group had a 2.5-fold higher one-year mortality rate than those in the normal RDW group. The first and second RDW groups' 1-year mortality rates did not significantly differ from one another.

Variables	P value	OR value	95% Cl	n valuo	
variables	D value		Lower	Upper	p-value
Inotropic drug use	1.488	4.428	1.762	11.126	0.002
Cardiogenic shock	1.644	5.176	1.529	17.525	0.008
Serum creatinine	1.366	3.918	1.415	10.850	0.009
Serum potassium	0.818	2.266	1.110	4.628	0.025
Serum RDW	0.468	1.597	1.142	2.233	0.006

Table 2. Univariate logistic regression analysis for 1-year mortality prediction in patients with decompensated heart failure

*Univariate logistic regression analysis found significant associations with inotropic drug use, cardiogenic shock, serum creatinine, serum potassium, serum rdw values and 1-year mortality in decompensated heart failure patients. †B: Logistic regression coefficient, OR: Odds ratio, CI: Confidence interval, RDW: Red cell distribution width

Table 3. Multivariate logistic regression analysis for 1-year mortality prediction in patients with decompe	pensated heart failure
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Variables	D volue	OR value	95% CI	n voluo	
variables	D value		Lower	Upper	p-value
Inotropic drug use	1.150	3.159	1.168	8.542	0.023
Serum RDW	0.365	1.440	1.023	2.027	0.036

*Cardiogenic shock, inotropic drug use, serum creatinine, rdw, and potassium were entered into the multivariate logistic regression analysis. †B: Logistic regression coefficient, CI: Confidence interval, OR: Odds ratio, RDW: Red cell distribution width

Table 4. The comparison of the clinical and laboratory characteristics among the subgroups with normal, high and very high rdw values

	Normal rdw group	High rdw group	Very high rdw	
Characteristic	(rdw<15%)	(rdw 15-16.9%)	group (rdw≥17%)	n voluo
	n=31	n=46	n=24	p-value
Heart failure type				
HFrEF (n,%)	18 (37%)	21 (43%)	10 (20%)	
HFmrEF (n,%)	0 (0%)	6 (75%)	2 (25%)	
HFpEF (n,%)	13 (30%)	19 (43%)	12 (27%)	0.118
Age (median, 25th-75th percentile)	77 (68-80)	74 (63-78)	72 (67.5-78)	0.511
Ejection fraction (%) (median, 25th-75th percentile)	40 (30-50)	45 (30-55)	48 (31.25-50)	0.861
Hospitalization days (median, 25th-75th percentile)	4 (3-6)	4 (3-6)	4 (3-5)	0.676
Systolic blood pressure (mmHg) (median, 25th-75th percentile)	130 (110-140)	120 (110-140)	125 (110-130)	0.936

Diastolic blood pressure (mmHg) (median, 25th-75th percentile)	70 (70-80)	75 (60-82.5)	80 (70-80)	0.985
Heart rate at hospital admission (beats per minute) (median, 25th-75th percentile)	84 (80-92)	86 (75.5-102.5)	81 (72-106)	0.668
Serum creatinine (mg/dl) (median, 25th-75th percentile)	0.9 (0.8-1.1)	1.0 (0.8-1.3)	1.1 (0.8-1.7)	0.267
Serum haemoglobin (g/dl) (mean±SD)	13.2±1.4	13.1±2.1	11.3±3.1	0.002
Killip classification				
2 (n,%)	25 (33%)	34 (44%)	18 (23%)	
3 (n,%)	4 (22%)	10 (56%)	4 (22%)	
4 (n,%)	2 (33%)	2 (33%)	2 (33%)	0.843
Mitral regurgitation				
None (n,%)	2 (40%)	1 (20%)	2 (40%)	
Mild (n,%)	6 (26%)	11 (48%)	6 (26%)	
Medium (n,%)	13 (32%)	17 (41%)	11 (27%)	
Serious (n,%)	10 (31%)	17 (53%)	5 (16%)	0.774
Atrial fibrillation on ECG (n,%)	15 (27%)	26 (47%)	14 (26%)	0.710
Cardiogenic shock (n,%)	4 (22%)	10 (56%)	4 (22%)	0.602
Inotropic drug use (n,%)	9 (24%)	17 (45%)	12 (31%)	0.279

* ECG: Electrocardiography, HFmrEF: Heart failure with mildly reduced ejection fraction, HFpEF: Heart failure with preserved ejection fraction, HFrEF: Heart failure with reduced ejection fraction, RDW: Red cell distribution

DISCUSSION

Nearly all HF patients have their red cell distribution width assessed using an easily accessible hemogram test. RDW was first identified as a prognostic factor in HF patients according to the CHARM trial [7]. In both acute and chronic HF patients, higher RDW values increase the risk of death [7-11]. In HF patients, elevated RDW values were also linked to a higher probability of the combined end-point of death or rehospitalization [12]. In HF patients, a 1% rise in RDW value was linked to a 10% increase in the chance of death in the future and a 9% increase in the probability of hospitalization, according to a meta-analysis on the topic [13]. Additionally, elevated RDW values raise the risk of death and the onset of HF in a group with baseline coronary artery disease but no HF [14]. Numerous studies also demonstrate the superior value of serial RDW monitoring in hospitalized HF patients compared to baseline RDW measurement. A higher risk of future death or rehospitalization is implied by an increase in RDW during hospitalization than by baseline RDW values [15, 16]. Another study in HF found that RDW has additive predictive value for B-type natriuretic peptide (BNP), a prognostic marker with a long history [17]. Furthermore, it has been demonstrated that the bio-width index, which is created by multiplying BNP by RDW and then dividing the result by 10, improves the accuracy of BNP and RDW in predicting mortality in HF patients with anemia [18].

Red blood cell size variation in peripheral blood is measured by RDW. A decline in RDW value is not clinically significant. Anisocytosis, another name for an elevated RDW value, has numerous critical consequences for cardiovascular outcomes in both the general population and HF patients [19]. Ageing, inflammation, oxidative stress, renal dysfunction, nutritional issues, beta-thalassemia, hemolytic anemia, hereditary spherocytosis, sickle cell anemia, after blood transfusion, chronic liver disease, folate deficiency anemia, vitamin B12 deficiency anemia, and myelodysplastic syndrome are just a few conditions that can cause an increase in RDW value [20]. The precise mechanism underlying the elevated risk of HF patients with anisocytosis is unknown. There are numerous proposed mechanisms, though. Anisocytosis and inflammation interact, according to one suggested mechanism. Anisocytosis may develop from abnormally early erythrocyte production, which is recognized to be a contributing factor to bone marrow dysfunction [21]. It is well known that inflammation has a role in the onset and development of HF [22].

Additionally, various forms of anaemia may present with anisocytosis. Anaemia is also a well-known prognostic marker in patients with heart failure [23]. Nevertheless, after accounting for haemoglobin values, certain studies [11, 24] discovered that higher RDW values were predictors of death in HF patients. Another theory is that the prognostic effect of anisocytosis in HF is caused by oxidative stress, which can lead to defective erythropoiesis and unfavorable cardiac remodeling. Patients with anisocytosis may have abnormal erythrocytes that deoxygenate cardiomyocytes, leading to cardiac death or fibrosis [25]. Furthermore, lower heart rate variability was associated with higher RDW in HFrEF patients, which may have negative effects on these patients' prognoses [26]. Elevated RDW was discovered to be related to worse LV deformation, as measured by LV global longitudinal strain in speckle tracking echocardiography, in a different study conducted in HF patients with EF < 50%, which is another unfavorable prognostic marker in the HF population [27].

This study proved that RDW, in a Turkish group of ADHF patients (HFpEF, HFrEF, and HFmrEF patients), is a distinct predictive marker of 1-year mortality. The use of inotropic medications while hospitalized was the other additional predictive factor found in the study. In our investigation, serum RDW values and serum hemoglobin values were correlated. Serum hemoglobin levels were lower in the subgroup of patients with the highest RDW values ($\geq 17\%$) than they were in the patients with lower RDW values (< 17%). This was seen in HF patients in numerous previous studies [24,28], and various types of anemia are also linked to elevated RDW values [20]. The three RDW subgroups did not differ in any other clinical or laboratory measures. The mortality in the subgroup with the highest RDW values was 2.5 times higher at 1 year compared to the cohort with normal RDW values. Patients' 1-year mortality in the usual RDW group (RDW< 15%) and the slightly enhanced RDW group (RDW between 15 and 16.9%) did not differ from one another. When RDW rose above 14.7% in the CHARM program, HF mortality began to rise; similarly, when RDW rose above 15.3% in the Duke Databank dataset [7]. RDW was linked to mortality in a subset of patients with RDW values $\geq 16.6\%$ in a smaller AHF study, which is consistent with the findings of the current analysis [9]. Therefore, this disparity may be explained by the patient numbers included in the study and also in the RDW subgroups. In the current study, a 1% increase in serum RDW value led to a 44% increase in the 1-year mortality rate of these HF patients. This result is a little higher than the results of other research, which revealed that a 1% increase in RDW values was associated with a 10-12% increase in mortality [10, 13, 29]. A 39% all-cause mortality rate within a year indicated a substantial mortality risk for the study's patient cohort. The baseline RDW value for 69% of the cohort was high ($\geq 15\%$). This may help to

explain the present study's higher mortality risk associated with higher RDW values. We should point out that this is a modest, one-center study. The study's small sample size may have also overstated the impact of RDW on population's overall mortality. In Turkey, HF is still a serious health issue. Understanding the high-risk category of patients with HF requires the identification of mortality predictors. In ADHF patients, RDW is an easily obtainable hemogram measure. It might offer crucial prognostic data. Additionally, repeated measurements might even be more useful in identifying these patients' risk for mortality and morbidity.

Limitations

The present study had several important drawbacks, including a limited sample size and a single-center design. The high percentage of patients who were lost to follow-up may be another drawback, especially for a study of this small scale. Last but not least, the endpoint's inclusion of solely all-cause mortality and exclusion of cardiovascular mortality and HF rehospitalization may be considered as a restriction.

CONCLUSIONS

In conclusion, red cell distribution width is an independent prognostic marker for 1-year mortality in Turkish patients hospitalized for acute decompensated heart failure. The data from this study shows that a 1% increase in serum RDW value leads to a 44% increase in 1-year mortality among these patients.

Acknowledgments: Dr. Filiz Akin and Dr. Serkan Ordu kindly contributed to this study.

Informed Consent: The patients provided informed consent to participate in the study.

Conflict of interest: The author declares that he has no conflicts of interest.

Funding: No funding source was used for this study.

Ethical Approval: The local clinical studies ethics committee approved the study (Kırıkkale University, Date: 12/17/2012, Approval number: 12/14-01). All procedures performed in this study were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Author Contributions: Conception: Y,U – Design: Y,U – Materials: Y,U – Data Collection and/or Processing: Y,U – Analysis and/or Interpretation: Y, U – Literature: Y,U – Review: Y, U – Writing: Y,U – Critical Review: Y, U

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How to Cite;

Yuksek, U. (2023) Red Cell Distribution Width Is an Independent Predictor of 1-Year Mortality in a Turkish Patient Population with Acute Decompensated Heart Failure. Eur J Ther. 29(4):829-837. <u>https://doi.org/10.58600/</u> eurjther1803