The importance of hematologic indices in the risk stratification of patients with acute decompensated systolic heart failure

Akut dekompanse sistolik kalp yetersizliği olan hastaların risk sınıflamasında hemogram parametrelerinin önemi

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ABSTRACT

Objectives: In patients with heart failure, a variety of hemogram parameters are known to be of prognostic significance. This study aimed to investigate which of these parameters is/are useful in predicting one-year all-cause mortality in patients with acute decompensated heart failure (ADHF).

Study design: Patients who were hospitalized between September 2012-March 2013 in our hospital with systolic-ADHF with ejection fraction ≤40%, symptoms, and findings of congestion were enrolled retrospectively in the study. The study population was divided into two groups based on one-year-mortality.

Results: 119 patients with ADHF (mean-age 67±14 years; 55% male) were enrolled in the study. One-year-mortality occurred in 29% of patients. Hemoglobin levels, platelet, basophil and lymphocyte counts were significantly lower, while red-cell distribution width (RDW) was found to be significantly higher in the one-year-mortality group. Neutrophil, monocyte, and eosinophil counts were similar in the two groups. Furthermore, lower estimated glomerular-filtration-rate (eGFR) and unused angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) were associated with mortality. Age, presence of hypertension, right-ventricular diameter, eGFR, ACE/ARB treatment, hemoglobin levels, RDW and platelet, leukocyte, lymphocyte, basophil, neutrophil, monocyte, and eosinophil-counts were found to have prognostic significance in univariate analysis. In multivariate analysis, decreased platelet, lymphocyte-counts and hemoglobin level on admission and unused ACE/ARB treatment at discharge ($p<0.05$) were found to be independent factors predicting one-year-mortality.

Conclusion: Among hematological indices; hemoglobin level, platelet and lymphocyte counts are readily available, useful and inexpensive markers for the prediction of one-year all-cause mortality in ADHF patients.

ÖZET

Amaç: Kalp yetersizliğinde bakılan çeşitli hemogram parametrelerinin prognostik önemi olduğu bilinmektedir. Bu çalışmada bu parametrelerden hangilerinin akut dekompanse kalp yetersizliği (ADKY) olan hastalarda 1 yıllık tüm nedenlere bağlı ölümü öngörmede yararlı olduğunu araştırmayı amaçladık.

Çalışma planı: Eylül 2012 ile Mart 2013 tarihleri arasında ADKY tanısıyla hastanemize yatırılan ve ejeksiyon fraksiyonu ≤%40, semptom ve konjesyon bulgusu olan ardışık hastalar geriye dönük olarak çalışmaya alındı. Bir yıl içinde ölüm gözlenen ve gözlenmeyen olarak hastalar iki gruba ayrıldı.

Bulgular: Çalışmaya 119 hasta (ortalama yaş 67±14 yıl; %55 erkek) dahil edildi. Bir yıl sonunda hastaların %29'unun öldüğü saptandı. Ölüm gözlenen grupta hemoglobin, hemotokrit değeri ile trombosit, bazofil ve lenfosit sayısının anlamlı olarak düşük, eritrosit dağılım genişliğinin (EDG) anlamlı olarak yüksek olduğu saptandı. Nötrofil, monosit ve eozinofil sayılarını iki grupta benzer bulduk. Bunun yanında hesaplanmış glomerül filtrasyon hızı (hGFH) düşüklüğü ve anjiyotensin-dünüştürücü enzim inhibitörü/anjiyootensin reseptör blokeri (ADEİ/ARB) kullanmama 1 yıllık ölümle ilişkili bulundu. Tek değişkenli regresyon analizinde, yaş, hipertansiyon, sağ ventrikül çapı, hGFH, ADEİ/ARB tedavisi, hemoglobin, EDG değeri ile trombosit, lökosit, nötrofil, lenfosit, bazofil, eozinofil ve monosit sayısı anlamlı bulundu. Çok değişkenli regresyon modelinde, 1 yıllık mortalite ile ilişkili bağımsız risk faktörleri olarak lenfosit, trombosit sayısı ve hemoglobin değeri düşüklüğü ile çıkış tedavisinde ACEİ/ARB tedavisi kullanmama parametreleri saptandı ($p<0.05$).

Sonuç: Hemogram parametrelerinden lenfosit ve trombosit sayısı ile hemoglobin değeri ADKY olan hastalarda tüm nedenlere bağlı 1 yıllık mortaliteyi ön görmede basit, ucuz ve kolay ulaşılabilir bir parametre olarak kullanılabilir.

Received: April 01, 2014 *Accepted:* August 26, 2014

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Heart failure (HF) is among the common causes of mortality and re-hospitalization in developed countries.[1] Despite advances in diagnosis and treatment, heart failure is still associated with high patient mortality.[1] Identification of high-risk patients is important for treatment, and development of new therapeutic modalities. Many studies have been published on predicting prognosis in HF using hemogram parameters.[2-5] Anemia is known to be a strong and independent predictor of mortality, and red cell distribution width (RDW) has also been associated with mortality, independent of anemia.[3,4,6] Further examples include high leukocyte and low relative lymphocyte counts[7] and absolute eosinophil,[5] which have been shown to be predictors of mortality in acute HF. A variety of hematologic parameters is known to be of prognostic significance in patients with heart failure. This study aimed to investigate which of these parameters is/are useful in predicting one-year all-cause mortality in patients with acute decompensated heart failure (ADHF).

PATIENTS AND METHODS

Patients hospitalized between September 2012 and March 2013 in our hospital with systolic ADHF were enrolled retrospectively in the study. Systolic HF was defined as a left ventricular ejection fraction (LVEF) ≤40%, as determined by transthoracic echocardiography. Specific eligibility criteria for trial enrolment were as follows: older than 18 years of age; hospitalized for worsening HF; EF ≤40%; and two or more signs or symptoms of fluid overload (e.g., dyspnea, orthopnea, pretibial edema, or jugular venous distension), and discharge alive from the hospital.

The following were excluded: Those patients with malignant diseases; in receipt of medications known to affect complete blood count; with severe renal failure (estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m^2), active hepatic disease, or chronic obstructive pulmonary disease; who had given birth in the last month; who had peripartum cardiomyopathy, chronic inflammatory disorders, or acute infectious disease; and those who had had coronary revascularization/MI or heart surgery within the last month. The end point of the study was all-cause mortality. The study was approved by the institutional ethics committee.

Abbreviations:

ACEI	*Angiotensin-converting enzyme inhibitors*
ADHF	*Acute decompensated heart failure*
ARB	*Angiotensin receptor blockers*
CAD	*Coronary artery disease*
CI	*Confidence interval*
DM	*Diabetes mellitus*
eGFR	*Estimated glomerular filtration rate*
HF	*Heart failure*
HL	*Hypercholesterolemia*
HT	*Hypertension*
LVEF	*Left ventricular ejection fraction*
MDRD	*Modification of diet in renal disease*
RDW	*Red cell distribution width*
WBC	*White blood cell*

On admission, we assessed each patient's medical history. Each patient completed a questionnaire to obtain data on lifestyle and risk factors. Hypertension (HT) was defined as previous use of antihypertensive medications, a systolic pressure higher than 140 mmHg, or a diastolic pressure higher than 90 mmHg on at least two separate measurements. Diabetes mellitus (DM) was defined as a previous diagnosis if a patient followed a diet or used anti-diabetic medicines, or if a previously untreated patient had a fasting venous blood glucose level of 126 mg/dL on two occasions. Hypercholesterolemia (HL) was defined as the use of cholesterol-lowering therapy or as total cholesterol of at least 200 mg/dL. Smoking was defined as the current regular use of cigarettes. Anemia was defined as a baseline hemoglobin concentration of less than 13 mg/dL in men and of less than 12 mg/dL in women.[8]

The estimated glomerular filtration rate was calculated using the modification of diet in renal disease (MDRD) formula.[9]

On admission, venous blood was obtained from all study patients. Hemoglobin (Hbg), hematocrit (Hct) values, RDW values, platelet counts, and white blood cell (WBC), neutrophil, lymphocyte, basophil, monocyte and eosinophil counts were obtained using an automated hematology analyzer (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, Illinois). Biochemistry measurements were performed by the biochemistry department using standard methods.

Echocardiographic examinations were performed on all patients within 24 hours of admission. All examinations were evaluated via Vivid 5 system (GE healthcare; Wauwatosa, WI) using a 2.5-5 MHz probe. The modified Simpson method was used in LVEF and chamber size measured according to recent American Society of Echocardiography guidelines.

One year survival status was ascertained either

during the patient's hospitalization, by phone contact with the patient or family members, or by routine clinic visits. At the end of one year, the patients were divided into two groups based on mortality and compared.

Statistics

The distributions of continuous variables were determined using the Kolmogorov-Smirnov test. Between-group comparisons were performed using the chi-square test or Fischer's exact test for categorical variables, Student's t-test for continuous variables with normal distributions, and the Mann-Whitney U test for continuous variables with abnormal distributions and ordinal variables. For correlation analysis, scatter plots were drawn. There was no linear correlation between pairs of variables, so Spearman's correlation test was performed.

We used univariate analysis to quantify the association of variables with all-cause one-year mortality. Variables found to be statistically significant ($p<0.25$) in univariate analysis were used in a multivariate logistic regression with backward stepwise method in order to determine the independent prognostic factors of all-cause one year mortality in patients with hospitalized with systolic ADHF.

Table 1. Patients' clinical characteristics and medications at discharge

	Alived patients (n=84)			Deceased patients (n=35)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (y)			66±13			70±17	0.127
Male sex	47	56		18	51		0.652
Diabetes mellitus	34	40		12	34		0.527
Hypertension	57	68		18	54		0.160
Coronary artery disease	41	49		19	57		0.407
Hyperlipidemia	31	37		10	29		0.383
History of smoking	20	24		11	31		0.408
Atrial fibrillation	30	36		9	26		0.290
Pacemaker/AICD	12	14		5	14		1.000**
Left ventricular ejection fraction (%)			28.5±7.6			27.8±7.9	0.621
Right ventricular diameter (cm)			2.7±0.47			3.0±0.52	0.009
Valvular heart disease	17	20		8	23		0.749
Systolic blood pressure (mmHg)			127±24			122±29	0.432
Diastolic blood pressure (mmHg), median (IQR)	76	13		70	32		0.489*
Heart rate (beats/min)			94±21			90±18	0.382
Pedal edema	54	64		27	77		0.170
Jugular venous distension	45	54		23	66		0.223
Rales on lung examination	73	87		30	86		0.862
Medications at discharge							
β-blocker	81	96		33	94		0.595
ACEI/ARB	80	95		27	77		0.003
Diuretics	65	77		27	77		0.977
Spirinolactone	52	63		18	51		0.257
Digoxin	24	29		9	26		0.751
Statins	23	27		8	23		0.608
Acetylsalicylic acid	57	68		26	74		0.487

Data are presented as number (%), or mean±standard deviation. *Data are expressed as median (interquartile range). **Fisher's exact test. IQR: Interquartile range; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; AICD: Automatic implantable external defibrillator.

The results are provided as odds ratio (OR) and 95% confidence interval (CI). All statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois). P value less than 0.05 was considered statistically significant.

RESULTS

119 patients with ADHF (mean-age 67±14 years; 55% male) were included in the study. The one-year mortality rate was 29% in the study population. Of the patients, 51.3% had coronary artery disease (CAD); 63.9% HT; 38.7% DM; 34.5% HL; 26.1% history of cigarette smoking; 32.8% atrial fibrillation (AF); 21% a severe valvular problem; and 13.4% had a coronary artery bypass graft (CABG). Additionally, 14% of the patients had a pacemaker or automatic implantable external defibrillator (PM/AICD) devices. Approximately half of the patients (47.1%) were anemic.

The one-year mortality rate was 29% in the study population. The mean age of the mortality group was higher than that of the survivor group, but the difference was not statistically significant. Clinical features and treatment at discharge of the two groups are shown Table 1. The present risk factors (HT, DM, HL, AF, CAD, and smoking prevalence) were similar for the two groups. At one year, patients in the mortality

Table 2. Patients' hemogram parameters and other biochemical parameters

	Alive patients (84)			Deceased patients (35)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
WBCs (x10^9 L^{-1})			9.43±2.47			7.83±2.63	0.002
Hemoglobin (g/dL)			12.79±1.79			11.55±1.73	0.001
Hemotocrite (%)			37.64±5.22			34.59±5.33	0.005
Presence of anemia	32	38		24	69		0.002
RDW (%)			17.20±2.15			18.45±2.58	0.008
Platelets (x10^9 L^{-1})			248.37±61.00			208.85±73.18	0.003
Neutrophils (x10^9 L^{-1})			6.65±2.33			5.75±2.32	0.057
Lymphocytes (x10^9 L^{-1}), median (IQR)	1.53	1.02		1.24	0.66		<0.001*
Basophils, (x10^9 L^{-1}), median (IQR)	0.07	0.04		0.06	0.04		0.017*
Monocytes, (x10^9 L^{-1}), mean (SD)			0.71±0.26			0.62±0.30	0.104
Eosinophiles,(x10^9 L^{-1})			0.14±0.12			0.10±0.09	0.102
Lymphocytes (%)			20.64±8.48			17.70±8.04	0.083
Neutrophils (%)			69.20±9.48			72.08±10.20	0.141
Eosinophils (%)			1.49±1.31			1.43±1.53	0.818
Glucose, (mg/dl), median (IQR)	115	77		109	46		0.892*
Urea, (mg/dl)			56.11±27.12			79.82±48.17	0.009
Creatinine (mg/dL)			1.02±0.34			1.25±0.58	0.032
eGFR (mL/min/1.73 m^2)			76.5±23.4			64.6±25.5	0.017
Sodium (mmol/L)			136.48±4.04			135.14±5.53	0.146
Aspartate transaminase (U/L), median (IQR)	27	23		29	19		0.506*
Alkaline phosphatase (U/L), median (IQR)	23	22		17	25		0.424*
Lactate dehydrogenase (U/L)			324.95±172.64			343.62±147.73	0.582
Total bilirubin (mg/dl), median (IQR)	1	0.6		0.7	0.95		0.818*
Direct bilirubin, (mg/dl), median (IQR)	0.3	0.40		0.3	0.45		0.152*
Uric acid (mg/dl)			8.67±7.53			8.43±2.68	0.892

*Data are expressed as median (interquartile range). IQR: Interquartile range; WBC; White blood cell; RDW: Red blood cell distribution width; eGFR: Estimated glomerular filtration rate.

group had significantly higher anemia rates (41.7% and 68.6%, respectively; p=0.007). There were no significant differences between the drug treatments of the two groups, except that angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) therapy was significantly lower in the survivor group (p=0.002).

On analysis of the patients' hemogram parameters, hemoglobin level, platelet, basophil and lymphocyte counts were significantly lower while RDW was significantly higher in dead patients. Neutrophil, monocyte, and eosinophil counts were similar in both groups. Furthermore, lower eGFR and unused ACEI/ARB were associated with mortality. Glucose, AST, ALT, bilirubin (total, direct, and indirect bilirubin), and uric acid values were similar in both groups. Laboratory values are shown in Table 2.

Age, presence of hypertension and right ventricular diameter, eGFR, ACE/ARB treatment and hemoglobin levels, RDW values and platelet, leukocyte, lymphocyte, basophil, neutrophil, monocyte, and eosinophil counts were found to have prognostic significance in univariate Cox proportional hazards analysis (Table 3). In the multivariate Cox proportional-hazards

Table 3. Univariate logistic regression analysis for predictive one-year all-cause mortality in patients with acute decompensated systolic heart failure

	p	OR	95.0% CI	
			Lower	Upper
Baseline characteristics				
Age (year)	0.170	1.022	0.991	1.053
Gender	0.652	1.200	0.544	2.645
Diabetes mellitus	0.528	1.303	0.572	2.967
Hypertension	0.163	0.563	0.251	1.261
Coronary artery disease	0.408	0.715	0.323	1.583
Hyperlipidemia	0.385	1.462	0.621	3.445
Atrial fibrillation	0.292	1.605	0.666	3.868
Laboratory findings at admission				
Left ventricular ejection fraction (%)	0.582	0.986	0.936	1.038
Right ventricle diameter (cm)	0.014	1.080	1.016	1.149
Hemoglobin (g/dl)	0.001	0.667	0.520	0.855
Red blood cell distribution width (%)	0.011	1.249	1.052	1.485
Platelets (x10^9 L^{-1})	0.005	0.990	0.983	0.997
Neutrophils (x10^9 L^{-1})	0.061	0.841	0.702	1.008
Lymphocytes (x10^9 L^{-1})	<0.001	0.253	0.118	0.543
Basophils (x10^9 L^{-1})	0.048	0.987	0.974	1.000
Eosinophils (x10^9 L^{-1})	0.107	0.031	0.000	2.115
Monocytes (x10^9 L^{-1})	0.107	0.267	0.053	1.332
White blood cells (x10^9 L^{-1})	0.003	0.769	0.645	0.917
Estimated glomerular filtration rate (ml/min/1.73 m^2)	0.019	0.980	0.963	0.997
Medication at discharge				
B-blocker	0.599	1.636	0.261	10.246
ACEI/ARB	0.006	5.926	1.653	21.251
Spirinolactone	0.259	1.584	0.713	3.520
Statin	0.609	1.273	0.505	3.204

WBC: White blood cell; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CI: Confidence interval; OR: Odds ratio.

Table 4. Multivariate logistic regression analysis for predictive one-year all-cause mortality in patients with acute decompensated systolic heart failure

	p	OR	95.0% CI	
			Lower	Upper
Hemoglobin (g/dl)	0.028	0.707	0.519	0.963
Platelets (x10^9 L^{-1})	0.023	0.990	0.982	0.999
Lymphocytes (x109 L^{-1})	0.045	0.377	0.145	0.978
ACEI/ARB unused at discharge	0.020	9.097	1.414	58.550

Age, presence of hypertension and right ventricular diameter, eGFR, ACE/ARB treatment and hemoglobin levels, RDW values and platelet, leukocyte, lymphocyte, basophil, neutrophil, monocyte, and eosinophil counts were entered into the multivariate logistic regression with the backward stepwise method. ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; eGFR: Estimated glomerular filtration rate; CI: Confidence interval; OR: Odds ratio.

model with backward stepwise method, decreased hemoglobin level on admission (p=0.028, hazard ratio [HR] 0.707, 95% CI 0.519-0.963), decreased platelet counts (p=0.023, HR 0.990, 95% CI 0.982-0.999), decreased lymphocyte counts (p=0.045, HR 0.377, 95% CI 0.145-0.978), and unused ACE/ARB treatment at discharge (p=0.020, HR 9.097, 95% CI 1.414-58.550) were found to be independent factors predicting one-year all-cause mortality (Table 4).

Correlation analysis revealed that the lymphocyte count had a significant negative correlation with proBNP (r=-0.464, p=0.003) and right ventricle diameter (r=-0.263, p=0.008). RDW positively correlated with proBNP (r=0.315, p=0.050) and creatinine (r=0.258, p=0.005).

In the anemic patients, the number of lymphocytes (p=0.001) and basophils (p=0.001), sodium level (p=0.044), CRP level (p=0.011), RV diameter (p=0.030), and mortality (p=0.002) were significantly higher compared to the non-anemic patients. Low lymphocyte count was associated with low WBC count (p=0.027), low basophil count (p=0.04), low eGFR (p=0.006), high creatinine level (p=0.002), an increase in right ventricle diameter (p=0.026), and high mortality rate (p=0.001) when compared to patients with high lymphocyte counts. There were only 39 patients with proBNP values. Low lymphocyte count was associated with significantly higher proBNP (Z=-2,804, p=0.005). According to the MDRD formula,[9] 32.8% of the patients had eGFR values less than 60 ml/min/1.73 m^2. In patients with impaired renal function, RDW values (p=0.011) and occurrence rates of DM (p=0.048), HT (p=0.013), CAD (p=0.019), and mortality (Fischer's exact test, p=0.043) were significantly higher, while serum sodium levels were significantly lower, compared to patients with good renal function.

DISCUSSION

In the present study, one-year mortality among the ADHF patients was high. In the patients, anemia and renal dysfunction were found to be frequent. Complete blood count parameters, especially hemoglobin level, platelet and lymphocyte count were found to be independent predictors of one-year mortality in the patients.

Some studies have shown that a decrease in platelet count without thrombocytopenia is associated with increased mortality especially in critically ill patients.[10-12] The exact cause of thrombocytopenia in these patients is unknown. Westenbrink BD et al. demonstrate that CHF patients exhibit a profound and general bone marrow dysfunction, which simultaneously affects multiple haematopoietic lineages,[13] and that NYHA functional class and NT-proBNP were independent predictors of reduced clonogenic potential, indicating that extent of bone marrow dysfunction is related to severity of heart failure.[13] In this study, although LVEF was similar between the two groups, hemogram parameters were lower in the group in which mortality occurred. This situation may be a reflection of hypoperfusion at tissue level. The lower platelet count in the mortal group may be due to bone marrow suppression caused by oxidative stress and inflammation or increased apoptosis. Because there is not more data, we cannot further comment on this

issue. There is a need for comprehensive studies on this topic.

In previous studies, lymphocyte impairment has been found to be common in patients with ADHF, and lymphocyte impairment is known to be associated with increased mortality.[2,14-16] Similarly, in the present study, observed mortality was significantly higher in the group with lower lymphocyte counts. Impaired lymphocytes due to splenic congestion is known to be associated with loss of lymphocytes in ADHF patients, and regression of congestion is associated with a return to normal lymphocyte levels.[17] In our study, lymphocyte count was negatively correlated with proBNP and right ventricle diameter, suggesting that impairment may be associated with congestion. In addition, passage of bacterial endotoxins into the bloodstream,[18] long-term increased sympathetic activity,[19] immune activation release of cytokines[20] and apoptotic mechanisms[21] are the causes of decreased lymphocyte counts.

Decreased lymphocyte counts may be associated with the severity of heart failure, and accordingly with increased mortality rates. Pro-inflammatory markers in heart failure (such as TNF-alpha, IL-6, and CRP) are associated with severity of the disease and have been shown to provide more prognostic information than the traditional clinical or other markers.[22] In a study by von Haehling et al.,[20] lymphocyte count was found to be significantly correlated with TNF-alpha. Lymphocyte count in patients with heart failure was identified as a possible indication of inflammation. However, in the present study, low lymphocyte count was associated with worse renal function in patients. Thus, renal dysfunction may contribute to increased mortality. Previously, Vaduganathan et al.[14] found that patients with low lymphocyte counts had worse renal function. Additional studies are needed to explain the relationship between renal dysfunction and impaired lymphocytes.

It is known that the use of ACEI and ARB decrease mortality.[1,23] In the present study, use of ACEI/ARB therapy was found to be associated with a lower mortality rate. Renal dysfunction is common in patients with HF and is associated with increased mortality.[24,25] A systematic review and meta-analysis showed that more than half of all patients with HF had a degree of renal impairment.[24] According to this study, patients with moderate-to-advanced renal dysfunction had approximately twice the mortality rate of those without renal dysfunction (51% versus 26%, respectively).[23] In the present study, patients who had end-stage renal failure or were undergoing hemodialysis were excluded. The incidence of renal dysfunction (eGFR <60 ml/min/1.73 m^2) was determined to be 33%. Those with impaired renal function had a significantly higher mortality rate than those with normal and mild renal dysfunction. The progressive deterioration in renal function in HF patients results from multiple mechanisms, including increased renal venous and intra-abdominal pressure, renal hypoperfusion, neurohormonal and inflammatory activation, adenosine release, and drug therapy for HF.[25]

In patients with heart failure, increased RDW, independent of anemia, is a marker for predicting mortality.[4] Functional capacity has a prognostic importance for patients with heart failure. In our earlier study, RDW was detected as an independent predictor of functional capacity in patients with chronic HF.[26] In a different study, RDW was determined to be associated with the GRACE risk score in patients with acute coronary syndrome.[27] In patients with HF, increased RDW might be associated with nutritional anemia, inflammation, renal insufficiency, ineffective erythropoiesis, and oxidative stress.[28,29] In addition, neurohormonal activation seems to be associated with increased erythropoiesis, thus increasing RDW values.[30] In this study, RDW was positively correlated with proBNP and creatinine values. Therefore, the increase in renal dysfunction and neurohormonal activation may contribution to increased RDW values.

In patients with heart failure, anemia or decreased Hgb is often observed for different reasons. A comprehensive review found an anemia incidence of 37.2% in patients with HF that was correlated with increased observed mortality.[3] The prevalence of anemia is higher in HF populations with comorbid kidney disease, advanced age, and more severe symptoms (range, 30% to 61%) when compared to less symptomatic ambulatory populations (range, 4% to 23%).[31] In our study group of patients with anemia, the mean age and serum creatinine value were higher but the eGFR was lower. Most likely due to the small number of patients, the difference was not statistically significant. In the present study, the prevalence of anemia was 47%, according to WHO criteria. A study conducted by Yılmaz et al. reported an incidence of

anemia similar to our study.[32] Patients with signs of congestion, as in our patients, due to hemodilution may have increased the incidence of anemia. In a previous study, HF patients with anemia were very frequently found to have hemodilution.[33]

Anemia in patients with heart failure occurs for various reasons. Iron deficiency; renal failure; RAS and sympathetic nervous system activation as a result of increased plasma volume from hemodilution; decreased body mass index; RAS inhibition; secretion of pro-inflammatory cytokines; decreased erythropoietin production due to renal failure and bone marrow dysfunction can cause anemia in patients with HF.[31,34] In our study, CRP levels in anemic patients were high, suggesting that inflammation may contribute to the development of anemia.

Anemia in patients with HF is known to be a predictor of mortality. The potential mechanisms linking anemia to increased mortality risk in HF have not been characterized, but may be related to changes in ventricular loading conditions and cardiac structure, comorbidity with renal dysfunction, altered neurohormonal activation, or reduced free radical scavenging capacity. Anemia may be a marker of more severe underlying myocardial disease.[6,7,31]

Study limitations

The most important limitation of the study is its retrospective design and the limited number of patients included in the study and hence, larger and multi-centered studies are needed to draw certain conclusions. Even though medications were generally similar after discharge, patients were not monitored for change in medication and doses during the follow-up. Hence, this may constitute a potential confounder for the study results.

In conclusion, decreased hemoglobin level, and lymphocyte and platelet count which can be calculated automatically are especially associated with an increased risk for one-year all-cause mortality in patients admitted with ADHF. Among hematological indices; hemoglobin level, platelet and lymphocyte counts are readily available, useful and inexpensive markers that can be helpful in risk stratification of patients with ADHF.

Conflict-of-interest issues regarding the authorship or article: None declared

REFERENCES

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:147-239. CrossRef
2. Núñez J, Núñez E, Miñana G, Sanchis J, Bodí V, Rumiz E, et al. Effectiveness of the relative lymphocyte count to predict one-year mortality in patients with acute heart failure. Am J Cardiol 2011;107:1034-9. CrossRef
3. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, et al. Anemia and mortality in heart failure patients a systematic review and meta-analysis. Anemia and mortality in heart failure patients a systematic review and meta-analysis. J Am Coll Cardiol 2008;52:818-27.
4. Pascual-Figal DA, Bonaque JC, Redondo B, Caro C, Manzano-Fernandez S, Sánchez-Mas J, et al. Red blood cell distribution width predicts long-term outcome regardless of anaemia status in acute heart failure patients. Eur J Heart Fail 2009;11:840-6. CrossRef
5. Cikrikcioglu MA, Soysal P, Dikerdem D, Cakirca M, Kazancioglu R, Yolbas S, et al. Absolute blood eosinophil count and 1-year mortality risk following hospitalization with acute heart failure. Eur J Emerg Med 2012;19:257-63. CrossRef
6. Silverberg DS, Wexler D, Iaina A. The importance of anemia and its correction in the management of severe congestive heart failure. Eur J Heart Fail 2002;4:681-6. CrossRef
7. Varat MA, Adolph RJ, Fowler NO. Cardiovascular effects of anemia. Am Heart J 1972;83:415-26. CrossRef
8. World Health Organization. Nutritional Anemia: Report of a WHO Scientific Group World Health Organization. Geneva, Switzerland: World Health Organization; 1968.
9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70. CrossRef
10. Hui P, Cook DJ, Lim W, Fraser GA, Arnold DM. The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. Chest 2011;139:271-8. CrossRef
11. Moreau D, Timsit JF, Vesin A, Garrouste-Orgeas M, de Lassence A, Zahar JR, et al. Platelet count decline: an early prognostic marker in critically ill patients with prolonged ICU stays. Chest 2007;131:1735-41. CrossRef
12. Akca S, Haji-Michael P, de Mendonça A, Suter P, Levi M, Vincent JL. Time course of platelet counts in critically ill patients. Crit Care Med 2002;30:753-6. CrossRef
13. Westenbrink BD, Voors AA, de Boer RA, Schuringa JJ, Klinkenberg T, van der Harst P, et al. Bone marrow dysfunction in chronic heart failure patients. Eur J Heart Fail

2010;12:676-84. CrossRef
14. Vaduganathan M, Ambrosy AP, Greene SJ, Mentz RJ, Subacius HP, Maggioni AP, et al. Predictive value of low relative lymphocyte count in patients hospitalized for heart failure with reduced ejection fraction: insights from the EVEREST trial. Circ Heart Fail 2012;5:750-8. CrossRef
15. Rudiger A, Burckhardt OA, Harpes P, Müller SA, Follath F. The relative lymphocyte count on hospital admission is a risk factor for long-term mortality in patients with acute heart failure. Am J Emerg Med 2006;24:451-4. CrossRef
16. Charach G, Grosskopf I, Roth A, Afek A, Wexler D, Sheps D, et al. Usefulness of total lymphocyte count as predictor of outcome in patients with chronic heart failure. Am J Cardiol 2011;107:1353-6. CrossRef
17. Battin DL, Ali S, Shahbaz AU, Massie JD, Munir A, Davis RC Jr, et al. Hypoalbuminemia and lymphocytopenia in patients with decompensated biventricular failure. Am J Med Sci 2010;339:31-5. CrossRef
18. Peschel T, Schönauer M, Thiele H, Anker SD, Schuler G, Niebauer J. Invasive assessment of bacterial endotoxin and inflammatory cytokines in patients with acute heart failure. Eur J Heart Fail 2003;5:609-14. CrossRef
19. Maisel AS, Knowlton KU, Fowler P, Rearden A, Ziegler MG, Motulsky HJ, et al. Adrenergic control of circulating lymphocyte subpopulations. Effects of congestive heart failure, dynamic exercise, and terbutaline treatment. J Clin Invest 1990;85:462-7. CrossRef
20. von Haehling S, Schefold JC, Jankowska E, Doehner W, Springer J, Strohschein K, et al. Leukocyte redistribution: effects of beta blockers in patients with chronic heart failure. PLoS One 2009;4:e6411. CrossRef
21. Castro A, Bemer V, Nóbrega A, Coutinho A, Truffa-Bachi P. Administration to mouse of endotoxin from gram-negative bacteria leads to activation and apoptosis of T lymphocytes. Eur J Immunol 1998;28:488-95. CrossRef
22. Petersen JW, Felker GM. Inflammatory biomarkers in heart failure. Congest Heart Fail 2006;12:324-8. CrossRef
23. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-847. CrossRef
24. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, et al. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol 2006;47:1987-96. CrossRef
25. Metra M, Cotter G, Gheorghiade M, Dei Cas L, Voors AA. The role of the kidney in heart failure. Eur Heart J 2012;33:2135-42. CrossRef
26. Polat N, Oz F, Baykız D, Cizgici AY, Altun I, Buğra Z, et al. Predictors of functional capacity in younger and elderly chronic heart failure patients: an observational study. Anadolu Kardiyol Derg 2013;13:778-83.
27. Polat N, Yildiz A, Oylumlu M, Kaya H, Acet H, Akil MA, et al. Relationship Between Red Cell Distribution Width and the GRACE Risk Score With In-Hospital Death in Patients With Acute Coronary Syndrome. Clin Appl Thromb Hemost 2013;20:577-82. CrossRef
28. Douglas SW, Adamson JW. The anemia of chronic disorders: studies of marrow regulation and iron metabolism. Blood 1975;45:55-65.
29. Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352:1011-23. CrossRef
30. Kato H, Ishida J, Imagawa S, Saito T, Suzuki N, Matsuoka T, et al. Enhanced erythropoiesis mediated by activation of the renin-angiotensin system via angiotensin II type 1a receptor. FASEB J 2005;19:2023-5.
31. Tang YD, Katz SD. Anemia in chronic heart failure: prevalence, etiology, clinical correlates, and treatment options. Circulation 2006;113:2454-61. CrossRef
32. Yılmaz MB, Zorlu A, Bektaşoğlu G, Yontar OC, Tandoğan I. The product of eGFR and hemoglobin may help predict mortality in systolic heart failure patients without severe anemia and renal failure. Turk Kardiyol Dern Ars 2012;40:9-15. CrossRef
33. Androne AS, Katz SD, Lund L, LaManca J, Hudaihed A, Hryniewicz K, et al. Hemodilution is common in patients with advanced heart failure. Circulation 2003;107:226-9. CrossRef
34. Westenbrink BD, Voors AA, de Boer RA, Schuringa JJ, Klinkenberg T, van der Harst P, et al. Bone marrow dysfunction in chronic heart failure patients. Eur J Heart Fail 2010;12:676-84. CrossRef

Key words: Blood platelets; heart failure; hemoglobins; mortality; predictive value of tests.

Anahtar sözcükler: Trombositler; kalp yetersizliği; hemoglobin; mortalite; testlerin öngörü değeri.