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Preoperative Red Cell Distribution Width as a Predictor of Mortality in Patients After Coronary Artery Bypass Grafting

Koroner Arter Baypas Cerrahisi Sonrası Hastalarda Mortalite Belirteci Olarak Preoperatif Kırmızı Küre Dağılım Hacmi

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ABSTRACT

Introduction: *We hypothesized that the red cell distribution width (RDW) would predict the outcome of surgical revascularization of patients with coronary artery disease.*

Materials and Methods: *Ninety four patients with severe coronary artery disease who underwent coronary artery bypass grafting were included in this study. A total of 94 patients were divided into tertiles based on their preprocedural RDW (mean RDW: tertile 1, 12.68 ± 0.60; tertile 2: 13.64 ± 0.49; tertile 3, 16.47 ± 2.04).*

Results: *There were a total of 18 (19.1%) deaths over a mean follow-up of 51 months. Patients with a high RDW showed the highest mortality (34%) as compared to patients with medium (10%) and low RDW (13%). In multivariable regression modeling, RDW > 14.6 was a significant independent predictor of five year outcome in mortality.*

Conclusion: *In conclusion, elevated preprocedural RDW in patients undergoing coronary artery bypass grafting is associated with increased risk of long-term mortality.*

Key Words: *Coronary artery bypass grafting; mortality; morbidity; red cell distribution width.*

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ÖZET

Giriş: *Biz kırmızı küre dağılım hacmi (RDW)'nin koroner arter hastalarında cerrahi revaskülarizasyon sonrası sonuçlarda belirleyici olduğunu düşündük.*

Gereç ve Yöntem: *Ciddi koroner arter hastalığı olan koroner baypas cerrahisi geçirmiş 94 hasta çalışmaya dahil edildi. Toplam 94 hasta RDW değerlerine göre üç gruba ayrıldı (mean RDW: tertile 1, 12.68 ± 0.60; tertile 2: 13.64 ± 0.49; tertile 3, 16.47 ± 2.04).*

Bulgular: *Ortalama 51 aylık takipte toplam 18 (%19.1) ölüm gözlendi. Yüksek RDW'li hastalar orta (%10) ve düşük (%13) RDW'li hastalara kıyasla yüksek mortalite gösterdi. Değişkenli regresyon analizinde RDW > 14.6 beş yıllık sonuçlar için önemli bağımsız risk faktörüdür.*

Sonuç: *Sonuç olarak, koroner baypas cerrahisi geçirmiş hastaların preoperatif yüksek RDW değeri artmış uzun dönem mortalite riski ile ilişkilidir.*

Anahtar Kelimeler: *Koroner arter baypas; mortalite; morbidite; kırmızı küre dağılım hacmi.*

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INTRODUCTION

The profile of patients candidate for coronary artery bypass grafting (CABG) is continuously changing and older patients share a large part with associated comorbidities, such as diabetes mellitus, hypertension, smoking, and peripheral vascular disease. Although several methods of risk assessment, such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE), are widely used, they are imperfect[1]. There remains, therefore, a need for additional methods for risk stratification, particularly if easily obtained and widely available. Especially in the last decade it was shown that red cell distribution width (RDW) had an important effect on congestive heart failure, coronary artery disease, morbidity and mortality after percutaneous intervention[2-4]. The potential use of preoperative RDW in the risk stratification of patients with coronary artery disease to identify postoperative mortality has not been studied yet.

We aimed to investigate the relation between preoperative RDW and postoperative all cause mortality in patients with coronary artery disease along with other initial parameters.

MATERIALS and METHODS

We randomized widespread coronary artery disease patients for our study because RDW in coronary artery disease is closely related to mortality, cardiovascular events and the progress of coronary atherosclerosis.

Between March 2003 and April 2009, 108 individuals underwent concomitant coronary artery bypass grafting. Demographic characteristics, medical records, laboratory studies and outcome data were collected by the research team using a standardized database (Table 1). The local ethics committee approved the study protocol.

Exclusion criteria included being 85 years or older, emergent surgery, additional major cardiac procedure, previous treatment for anemia, recent transfusion, clinical evidence of active infection, hematologic proliferative diseases, steroid therapy or chemotherapy around the index diagnosis or unavailable complete blood cell count or medical records. According to these criteria, 14 patients were excluded. Thus 94 patients were included the study.

Patients were followed up in outpatient clinics following discharge. The primary end point, all-cause five year mortality, was obtained from electronic medical records and the Social Security Death Index.

Laboratory

All analyses used the blood sample obtained immediately before surgery. Levels of hemoglobin (Hb), RDW, and white blood cells (WBC) were measured using a Siemens Advia 2120 analyzer.

The normal reference range for RDW in our laboratory was 11.5% to 14.5%. Anemia was defined as hemoglobin < 13 g/dL in men and < 12 g/dL in women.

Statistics

The primary end-point was death from any cause within five years of surgery. The effect of RDW on outcome was studied by constructing a receiver operating characteristic (ROC) curve with all cause mortality as the primary variable (Figure 1). Continuous data were presented as mean ± SD. The study population was grouped into tertiles according to the admission RDW value. Comparison between patient groups were made using chi-square tests for categorical variables, independent-samples Student's t tests for normally distributed continuous variables, and Mann-Whitney U tests when the distribu-

Table 1. Patient demographic, clinical and hematochemical characteristics. Baseline characteristics of patients, divided according to red blood cell distribution width

Risk factors	Tertile 1 12.0-13.0 n= 31	Tertile 2 13.0-14.6 n= 31	Tertile 3 14.6-22.0 n= 32	p
Age (year)	57.2 ± 9.6	61.5 ± 8.51	61.6 ± 13.05	0.184
Male	27 (88%)	26 (94%)	20 (63%)	0.057
Current smoke	10 (32%)	8 (25%)	7 (21%)	0.65
Diabetes mellitus	10 (32%)	4 (12%)	15 (46%)	**0.013**
Hypertension	16 (51%)	11 (35%)	16 (50%)	0.38
Obesity	2 (6%)	1 (3%)	2 (6%)	0.82
Hyperlipidemia	7 (22%)	6 (19%)	6 (18%)	0.92
Stable angina pectoris	18 (58%)	1 (3%)	13 (40%)	0.31
Unstable angina pectoris	1 (3%)	2 (6%)	3 (9%)	0.82
Previous myocardial infarction	4 (12%)	6 (19%)	6 (19%)	0.61
Presence of anemia	1 (3%)	4 (12%)	14 (44%)	**< 0.001**
Estimated LVEF %	57.3 ± 12.0	58.4 ± 4.0	7 (21%)	0.48
NYHA I or II	11 (35%)	13 (42%)	14 (44%)	0.32
NYHA III or IV	20 (65%)	18 (58%)	18 (56%)	0.39
EuroSCORE	4 (2-6)	4 (2-6)	6 (4-8)	**< 0.001**
Congestive heart failure	9 (29%)	8 (25%)	11 (34%)	0.93
Operative data				
Postoperative intraaortic balloon pump	3 (9%)	1 (3%)	5 (15%)	0.33
LMCA disease	1 (3%)	0 (0%)	1 (3%)	0.33
No. of bypass grafts	2.6 ± 0.62	2.6 ± 0.59	2.8 ± 0.65	0.61
Cross-clamp time (min)	60.21 ± 32.41	61.34 ± 27.38	50.52 ± 23.73	0.14
Bypass time (min)	87.21 ± 50.61	96.93 ± 36.68	84.58 ± 49.92	0.51
Internal mammary artery used	28 (90%)	28 (90%)	30 (93%)	0.48
Postoperative data				
Drainage (mL)	665.48 ± 386.39	702.5 ± 398.291	731.25 ± 702.50	0.89
ICU time (hour)	12.93 ± 16.64	12.46 ±10.37	18.03 ± 24.53	0.20
Mechanical ventilation (hour)	5.03 ± 11.8	2.03 ± 3.8	2.4 ± 2.1	0.18
Hospital time (day)	13.03 ± 19.01	7.3 ± 8.4	7.5 ± 4.3	0.11
Hospital exitus	3 (9%)	1 (3%)	2 (6%)	0.59
Totally exitus	4 (12%)	3 (9%)	11 (34%)	**0.02**
Preoperative laboratory				
RDW (%)	12.68 ± 0.60	13.64 ± 0.49	16.47 ± 2.04	**< 0.001**
Hemoglobin (mg/dL)	14.54 ± 1.22	13.76 ± 2.25	12.04 ± 2.03	**< 0.001**
WBC (10^3/mm^3)	7.8 ± 2.1	8.54 ± 2.5	9.1 ± 3.01	0.14
Creatinine (mg/dL)	0.87 ± 0.14	1.07 ± 1.1	1.25 ± 1.27	0.83
Urea (mg/dL)	40 ± 8.07	44.4 ± 26.8	50.3 ± 27.65	0.2

Percentages refer to patients with data available. LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; LMCA: Left main coronary artery; LAD: Left anterior descending coronary artery; RCA: Right coronary artery, ICU: Intensive care unit, RDW: Red cell distribution width, WBC: White blood count.

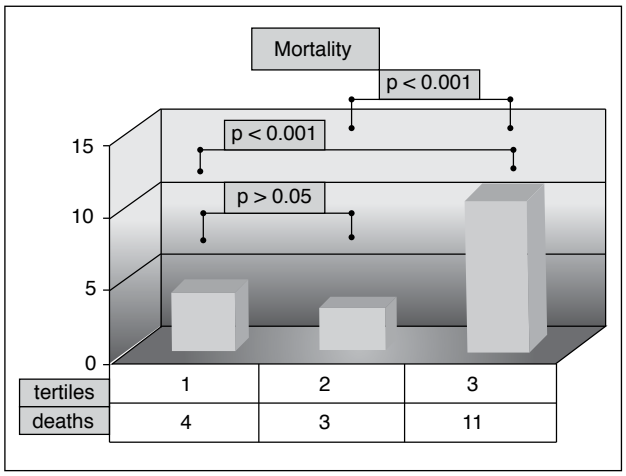

Figure 1. Red blood cell distribution width measures as a function of mortality at five year after CABG.

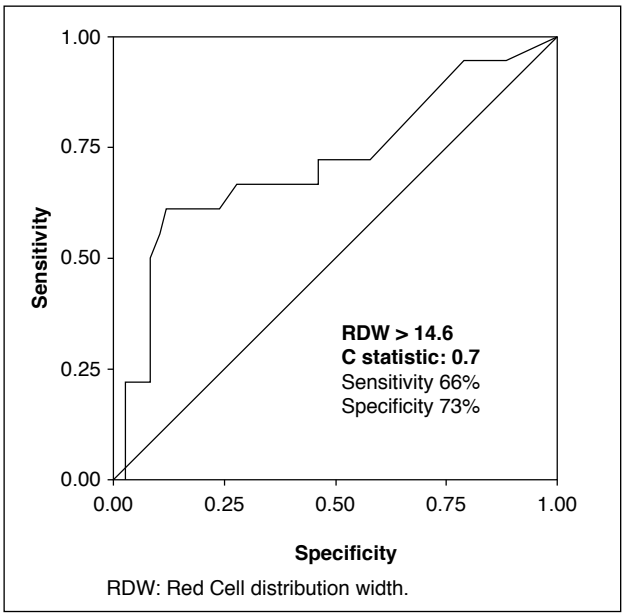

Figure 2. A receiver operating characteristic curve for red cell distribution width versus mortality.

tion was skewed. Categorical variables were summarized as percentages. Correlations between mortality and other continuous variables were studied using Pearson's and Spearman's correlation.

Potential prognostic factors were entered into univariate logistic regression models of five year mortality. Significant univariate correlates were then entered into a reverse stepwise multivariate logistic regression model to test for independence.

Multivariable logistic regression analysis was applied to identify whether RDW level on admission was independently associated with any cause mortality. Analyses were performed using SPSS.

RESULTS

The study cohort was predominantly male (%77) with a median age of 59 ± 10.3 years (Table 1). Patients included in this study have atherosclerosis documented with coronary angiography in 3.2 ± 1.8 coronary vessels; 2.7 ± 1.3 are grafted and one of these vessels had always severe atherosclerosis.

Overall, there were a total of 18 (19.1%) deaths from any cause within five years of surgery, and patients with a high RDW showed the highest mortality (n= 11, 34%) as compared to patients with medium (n= 3, 10%) and low RDW (n= 4, 13%) (Table 1, p= 0.02). Furthermore, the difference between mortality in high RDW with intermediate and low RDW was also statistically significant (Figure 2).

Baseline characteristics of patients divided according to three tertiles of RDW are presented in Table 1. There were no statistical differences in age and gender between groups.

No difference was observed between groups with respect to the risk factors, medical history, and preoperative, operative, and postoperative data, but diabetes mellitus (p= 0.013), presence of anemia (p < 0.001), EuroSCORE (p < 0.001), Hb (p < 0.001), RDW (p < 0.001) were higher in tertile 3.

In our patients, all cause mortality was correlated with admission (first ever obtained) RDW > 14.6 (r= 0.405, p< 0.001), Hb (r = -0.292, p= 0.004), presence of anemia (r= 0.393, p< 0.001), urea (r= 0.322, p= 0.002), and age (r= 0.279, p= 007). There were no significant correlations between all cause mortality and the other data (p > 0.05).

In univariate logistic regression, age, preoperative Hb, preoperative RDW > 14.6 and, EuroScore were all significantly associated with five year mortality. In multivariate regression modeling, EuroSCORE and preoperative RDW > 14.6 independently predicted survival in 5 years. In multivariable regression modeling, RDW > 14.6 was a significant independent predictor of five year outcome in mortality (HR = 3.7 per 1% increase in RDW; 95% CI: 1.08-12.8; p= 0.03) (Table 2).

DISCUSSION

RDW reflects the variability in size of circulating red blood cells and, when elevated, defines the state of anisocytosis. Recently, RDW, a recently described novel risk marker, has been shown to be predictive of morbidity and mortality in variety of cardiovascular settings, includ-

Table 2. Results of multivariate logistic regression models

	Multivariate analysis		
Variable	**HR**	**95% CI**	**p**
Age	1.05	0.9-1.1	0.1
Hemoglobin (g/dL)	0.9	0.6-1.2	0.4
RDW > 14.6	3.7	1.08-12.8	**0.03**
EuroSCORE	5.1	1.2-20.2	**< 0.001**

HR: Hazard Ratio, CI: Confidence interval, RDW: Red cell distribution width.

ing heart failure, stable coronary artery disease, and acute myocardial infarction[2-4]. We assessed the effect of RDW on all-cause mortality in patients after CABG.

Very importantly, we found a significant association between RDW and all cause mortality in CABG, and showed for the first time, to our knowledge, that this remained significant even in the presence of other powerful markers, such as EuroSCORE, whereas hemoglobin was not an independent predictor when RDW was in the model.

We found a graded, independent association between baseline RDW level and the risk of all-cause death. Higher levels of baseline RDW (RDW > 14.6) were associated with increased risk of all-cause death. This association remained significant even after adjustment for a wide variety of clinically relevant covariates. These covariates included not only important laboratory and clinical parameters, but also operative and post operative variables which are known to be powerful determinants of mortality.

Recently, RDW has been demonstrated to be associated also with cardiovascular and pulmonary diseases[3,5]. In the context of cardiac diseases, RDW retains remarkably strong prognostic power in chronic heart failure and coronary artery disease[3,6]. Initially, Felker et al. showed that increased RDW was a strong independent predictor of outcome in patients with chronic heart failure[6]. Tonelli et al. reported findings from a randomized controlled trial of patients with coronary artery disease and indicated that mortality was twice as likely in patients with an RDW > 13.8% compared to those with an RDW < 12.6%[4]. Several studies have shown the relation between RDW and coronary artery disease[1,7,8]. Sandip et al. showed that a higher RDW was a powerful independent predictor of future coronary artery disease risk[3]. Zorlu et al. showed that RDW value was an independent predictor of early mortality in patients with acute pulmonary embolism due to any reason[5]. However, there is no report about RDW-CABG mortality relation. Thus, we studied the effect of RDW on late mortality of CABG.

The mechanism by which elevated values of RDW are associated with increased mortality is unknown. Identification of a putative mechanism is hampered by the lack of epidemiological studies demonstrating factors that are associated with anisocytosis. Overtly elevated RDW may represent nutritional deficiency (such as iron deficiency anemia, vitamin B_{12} and folic acid deficiency) or recent blood transfusion[9-12]. Therefore, we do not think that either of these is a plausible explanation for our findings, although we did not directly assess nutritional status. The presence of systemic atherosclerosis is associated with a low-grade systemic inflammatory response in which leucocytes play a key role. Consequently, inflammatory markers such as C-reactive protein correlate with outcome in patients with atherosclerotic disease[13,14]. We speculate that higher levels of RDW may reflect a chronic background inflammatory state, which is associated with adverse clinical outcomes. In inflammatory state, cytokines might affect bone marrow function; and, erythrocyte maturation, induced by erythropoietin, is inhibited and RDW therefore becomes elevated[5,15]. Elevated levels of RDW could show the inflammation due to the perioperative myocardial injury. Certainly, perioperative myocardial damage is associated with adverse clinical outcomes. Likewise, cardiopulmonary bypass itself is associated with inflammatory state which may accentuate the effects of elevated preoperative levels which is known to be associated with long-term adverse outcome[16-18]. However, these hypotheses will require confirmation in future studies, and more work is needed to explore determinants of RDW in populations with cardiovascular disease.

Study Strengths and Limitations

The strength of our study is that as our patients have severe coronary artery disease, effect of coronary atherosclerosis is more likely to be manifested at the results.

The limitations of our study include the possibility of selection bias, the relatively small number of patients with a highly prevalent disease, lack of data for other adverse outcomes during the follow-up period (heart failure, myocardial infarction, the need for revascularization subsequently and stroke), and the possibility of missing medical records to assess the survival status (however, our mortality rate is similar to that in the literature).

Data are also lacking regarding pre and postoperative medication, which may have influenced the outcome of patients and possibly the RDW itself. Lastly, our analysis is retrospective in nature and may be only viewed as hypoth-

esis-generating; prospective data regarding the prognostic value of RDW in patients with CABG are awaited.

In conclusion, we demonstrate an independent relation between preoperative higher levels of RDW and all-cause death in CABG. This prognostic utility is independent of other well-recognized individual risk factors and the Euro-SCORE. It appears that RDW > 14.6 holds considerable promise as a powerful predictor of survival after CABG; particularly attractive is that these data are widely available (as a part of the complete blood count) to the clinician at no extra cost. Further studies are required to determine the explanation for the association between RDW and adverse clinical outcomes.

CONFLICT of INTEREST

None declared.

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