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Red Blood Cell Distribution Width as New Biomarker in Predicting Outcomes after Aortic Valve Replacement: A Retrospective Cohort Study

Calogera Pisano, Paolo Nardi, Fabio Bertoldo, Claudia Altieri and Giovanni Ruvolo*

Department of Cardiac Surgery, Tor Vergata University Hospital, Rome, Italy

Abstract

Objective: Red Blood Cell Distribution Width (RDW) is a measurement of the size variation as well as an erythrocyte heterogeneity index used in combination with the mean corpuscular volume for anemia diagnosis. It's emerging as a useful predictor biomarker of mortality and morbidity of cardiovascular diseases. Until now no literature data there are about the RDW role in predicting mortality after Aortic Valve Replacement (AVR). Thus, in this pilot study biological significance of elevated RDW values in early outcome following AVR was evaluated.

Methods: We enrolled 75 patients (mean age 73.5 ± 7.9 years) after isolated AVR. Demographics, comorbidities, clinical presentations, and laboratory parameters were collected. Multivariate and univariate analysis were performed in determine associations between preoperative RDW values and postoperative outcome.

Results: Preoperative higher RDW values had a prevalence of 41% (31 patients) in AVR cases studied. These 31 patients were older (76 ± 5.5 years *vs*. 71.6 ± 8.9 years, p=0.02) with higher platelet count (p=0.005) than the other 44 cases. In addition, they represented the patients that should have likely required renal replacement therapy (13% *vs*. 0%, p=0.026), and prolonged ventilation (16% *vs*. 0%, p=0.01) after surgery. Multivariate adjustment analysis also demonstrated significant associations between higher preoperative RDW values with high BMI values (p=0.05) and renal failure (p=0.06 and p=0.02).

Conclusion: Increased RDW values seem to be a good predictor biomarker of early outcome after AVR, particularly in patients with high BMI, renal impairment and postoperative prolonged ventilation.

Keywords: Red cell distribution width; Aortic valve replacement; Mortality and morbidity

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Correspondence:

Calogera Pisano, Department of Cardiac Surgery, Tor Vergata University Hospital, Viale Oxford 81, 00133 Rome, Italy, Tel: +39-3283297692; Fax: +39(06)20903538; E-mail: bacalipi@libero.it

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Introduction

Aortic valve disease is a major cardiovascular problem in developed countries that is likely to grow the population ages [1-5]. Aortic Valve Replacement (AVR) is the standard treatment even for very elderly patients despite its elevated risk in this age group [6]. Accurate prediction of surgical risk for patients undergoing AVR remains therefore a relevant issue. Many models to assess risk of operative mortality in cardiac surgery are currently available, and they are used to provide internal and/or external benchmark comparisons. However, these risk models, such as the European System for Cardiac Operative Risk Evaluation (EuroSCORE), have shown several limitations, including poor performance in the elderly and overestimated mortality [7,8].

As consequence, there is imperative to identify risk biomarkers in this setting. Accordingly, complete blood cell count parameters, such as hemoglobin, have been shown to predict outcomes in patients with cardiovascular disease, even if none of them has been incorporated into surgical risk scores. In particular, the preoperative hemoglobin has been investigated as a risk biomarker for mortality and morbidity following AVR [9]. However, among the clinical parameters routinely associated with erythrocyte counts, Red Blood Cell Distribution Width (RDW), a measurement of the size variation as well as an erythrocyte heterogeneity index (i.e., anysocytosis), used in combination with the mean corpuscular volume for anemia diagnosis, is emerging as a strong predictor biomarker of both morbidity and mortality of cardiovascular diseases. Highly significant associations have been described between RDW value and all-cause, non-cardiac and cardiac

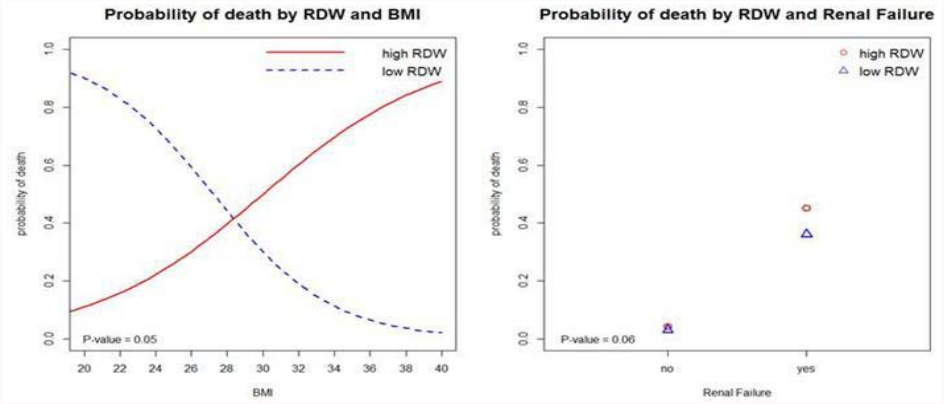

Figure 1: Multivariate analysis: higher preoperative RDW values were combined predictor biomarkers of mortality with higher BMI and renal failure.

mortality in patients with coronary artery disease, acute and chronic heart failure, peripheral artery disease, stroke, pulmonary embolism and pulmonary arterial hypertension [10-13]. It is, however, still unclear whether anisocytosis might be the cause, or a simple epiphenomenon of an underlying disease, such as inflammation, impaired renal function, under-nutrition, oxidative damage, or perhaps an element of both. Nevertheless, RDW is an easy, inexpensive, routinely reported test, whose assessment might allow the acquisition of significant diagnostic and prognostic information in patients with cardiovascular and thrombotic disorders. Its role in predicting mortality and morbidity of AVR patients has not been investigated yet. Thus, in pilot study, we sought to evaluate biological significance of elevated RDW values in early outcome following AVR.

Materials and Methods

Patient population

This is a retrospective review of prospectively collected data on a group of patients who underwent non-emergency isolated AVR (n=75) in the Cardiac Surgery Unit of Palermo University. Preoperative, operative and postoperative data were prospectively collected by medical staff. All patient data from the present study were de-identified; as such, individual patient consent was waived by Research Ethics Board.

Definition of preoperative red blood cell distribution width

Baseline RDW values were measured after overnight fasting using an XE-5000 automated hematology analyzer (Sysmex, XE 2100). To evaluate associations between RDW and clinical outcome, patients were divided into 2 groups according to the median baseline RDW value. Patients with a RDW >48 fL (RDW% >15%) were classified into the high RDW group and those with a RDW <38 (RDW% <11%) were classified into the low RDW group.

Outcome definitions

Patients were followed for a minimum of 30 days after discharge from the hospital. Death was defined as mortality occurring in hospital at any time during the index hospitalization or within 30 days of operation. Perioperative morbidity is defined as the presence of any of the following major complications, alone or in combination.

Perioperative Myocardial Infarction (MI), stroke, renal failure requiring renal replacement therapy, deep sternal wound infection and prolonged ventilation.

Perioperative MI was clinically diagnosed using a combination of electrocardiographic (new Q-waves), biochemical (significant elevations in cardiac enzymes) and echocardiographic (presence of new wall motion abnormalities) criteria. Stroke was defined as a permanent new focal neurological deficit occurring with focal or lateralizing signs on physical examination and confirmed by computerized tomographic study or magnetic resonance imaging. Postoperative renal failure was defined as requirement for renal replacement therapy. Prolonged mechanical ventilation was defined as the need of mechanical ventilation for >24 h. Deep sternal wound infection was diagnosed if the surgical wound had purulent discharge, positive wound cultures or required debridement and involved deep layer including subcutaneous tissue, fascia or an organ space infection. Composite morbidity was defined as patients having one or more of the following adverse outcomes: stroke, MI, renal failure, prolonged ventilation or deep sternal wound infection.

Operative technique

All procedures were performed via median sternotomy with standard anesthetic and surgical and perioperative protocols. All procedures were carried out with Cardiopulmonary Bypass (CPB) and mild systemic hypothermia (32°C to 34°C). Cardiac arrest was achieved with cold crystalloid cardioplegia. Coronary artery bypass grafting was performed whenever necessary.

Statistical methods

All analysis was conducted using R software. To find a relationship between RDW and clinical or outcome variables a univariate analysis was performed using t test or Wilcoxon rank sum test for continuous variables according to the normality of data; Pearson X^2 test or exact Fisher test were computed for categorical variables. To analyze the relationship between post-operative outcomes (such as death or morbidity) and RDW a logistic regression model was performed. In this context we adjusted the relationship considering in the model BMI and renal failure.

Results

Study population

This study included 75 non-emergent patients (mean age 73.5 ± 7.9 years) who underwent isolated AVR in our Cardiac Unit from July 2015 to July 2016. Of these 31 patients (41%) presented preoperative high RDW value. There were no differences in preoperative high RDW values between males and females. The demographic and preoperative characteristics are listed in Table 1. Univariate analysis showed that patients with high RDW value were older (76 ± 5.5 years

Table 1: Preoperative patient's characteristics.

Clinical characteristic	Low RDW	Hight RDW	P -value
Age	71.1 (8.9)	76.0 (5.5)	0.02
Height (cm)	163.9 (7.2)	161.5 (8.8)	0.189
Weight (Kg)	69.7 (13.9)	74.1 (11.2)	0.126
Preoperative Platelet	193.5 (59)	242.7 (79.6)	0.005
Preoperative INR	0.98 (0.075)	0.99 (0.088)	0.721
Preoperative Creatinine (mg/dl)	0.983 (0.35)	1.34 (0.44)	0.103
Recent MI (<6 week)	3 (6.8%)	1 (3.2%)	0.638
NYHA III/IV	18 (41%)	16 (51.6%)	0.496
Preoperative Cardiogenic Shock	1 (2.3%)	0 (0%)	>0.999
Redo Surgery	1 (2.3%)	1 (3.2%)	>0.999
Diabetes	15 (34.1%)	7 (22.6%)	0.412
Hypertension	36 (81.8%)	21 (67.7%)	0.258
Operative Priority (% urgenty)	2 (4.6%)	1 (3.2%)	>0.999
Vascular Peripheral Diseases	7 (15.9%)	6 (19.3%)	0.937
Normal LV	37 (84%)	25 (80.6%)	0.937
ECC time (min)	92.4 (19.1)	91.3 (18.2)	0.853
Cross clamp time (min)	76.9 (19.4)	72 (16.5)	0.48

RDW: Red Blood Cell Distribution Width; INR: International Normalized Ratio; MI: Myocardial Infarction; NYHA: New York Heart Association classification; Normal LV: Ejection Fraction ≥ 60%; ECC time: Extracorporeal Circulation

Table 2: Postoperative outcomes.

Unadjusted Outcomes	Low RDW	Hight RDW	P -value
Mortality within 30 days	1 (2.3)	3 (9.7%)	0.3
In hospital mortality	3 (6.8%)	3 (9.7%)	0.687
Stroke	1 (2.3%)	1 (3.2%)	>0.999
Renal Failure	0 (0%)	4 (12.9%)	0.026
Prolonged Ventilation	0 (0%)	5 (16.1%)	0.01
Deep sternal Infection	2 (4.6%)	1 (3.2%)	>0.999
Composite Morbidity	4 (9%)	5 (16.1%)	0.475

RDW: Red Blood Cell Distribution Width

vs. 71.6 ± 8.9 years, p=0.02) with higher platelet levels (p-value 0.005) than the other 44 cases.

Hospital outcomes

Univariate analysis established a negative association between high RDW levels and hospital outcome. Mortality and composite morbidity was higher in patients with higher RDW value than in patients with lower RDW levels, although not significantly. In particular in hospital and within 30 days mortality in patient with higher RDW was 9.7% (causes of mortality: renal failure, cardiac failure, multi-organ failure), in patient with lower RDW was respectively 6.8% (causes of mortality: cardiac arrest, cardiac failure, respiratory failure) and 2.3% (causes of mortality: cardiac arrest) Patients with higher RDW values should have likely required renal replacement therapy (13% *vs.* 0%, P=0.026), and prolonged ventilation (16% *vs.* 0%, P=0.01) than other cases (Table 2).

Multivariate analysis

Since preoperative higher RDW vales were significantly associated with other variables likely predictive of morbidity and mortality, we performed a multivariate analysis adjusted for those characteristics. It demonstrated that higher preoperative RDW values were combined predictor biomarkers of mortality and morbidity with higher BMI (p=0.05) and renal failure (p=0.06 and p=0.02) (Figure 1 and 2).

Table 3: Analysis of sensitivity and specificity between red blood cell distribution width values and haemoglobin values.

		RDW	Hb	p-value
Death	Sensitivity	43%	43%	>0,999
	Specificity	59%	46%	0.1
Morbidity	Sensitivity	50%	60%	0.65
	Specificity	60%	48%	0.13

RDW: Red Blood Cell Distribution Width; Hb: Hemoglobin

RDW sensitivity and specificity

In our study we found that RDW- values and hemoglobin had similar sensitivity in predicting mortality and morbidity, but RDW- values are more specific. In fact, the specificity of mortality is 58.8% for RDW-values and 45.6% for hemoglobin-values (p-value 0.10), the specificity of morbidity is 60% for RDW-values and 47.7% for hemoglobin values (p-value 0.13) (Table 3).

Discussion

Risk stratification in patient requiring AVR is a very important issue. According to the European professional practice guidelines "The risk assessment should mostly rely on the clinical judgment of the heart team in addition to the combination of scores" [14]. Different score systems have been assessed to optimize risk stratification including: European System for Cardiac Operative Risk Evaluation (EuroSCORE), EuroSCORE II, Society of Thoracic Surgeons (STS) score, and an Australasian model (Aus-AVR score) [15]. However, these scoring systems seem to have a lot of limitations, related to the differences among the variables used and to their respective weights-a source of major discordance among the various models. Thus, new prognostic biomarkers are essential.

Our study showed that elevated RDW values seem to be a good predictor biomarker of early outcomes in patients subjected to AVR. In particular, patients with higher RDW values should seem likely required renal replacement therapy and prolonged ventilation. In addition, according to our results, mortality and composite morbidity were higher in patients with elevated RDW values than in patients with lower RDW values. Increased RDW values indicate the presence of anisocytosis, an increased variability in red blood cell size caused by ineffective erythrocyte production. The major causes associated with an increased RDW include hemolytic and thrombotic conditions, B12/iron deficiency, liver and kidney diseases, which are also linked to anemia. In the case of cardiovascular disease, it is, however, still unclear whether anisocytosis might be the cause, or a simple epiphenomenon of an underlying disease, such as inflammation, impaired renal function, under-nutrition, oxidative damage, or perhaps an element of both. Nevertheless, RDW is an easy, inexpensive, routinely reported test, whose assessment might allow the acquisition of significant diagnostic and prognostic information in patients with cardiovascular and thrombotic disorders.

In our study, the frequency of anemia was not different among patients with higher and low RDW values. This leads us to hypothesize that other mechanisms might contribute to higher RDW levels.

As above mentioned, in some relevant studies theories related to oxidative stress and inflammatory reactions have led the way [16]. Because of their higher antioxidant capacity, erythrocytes are more

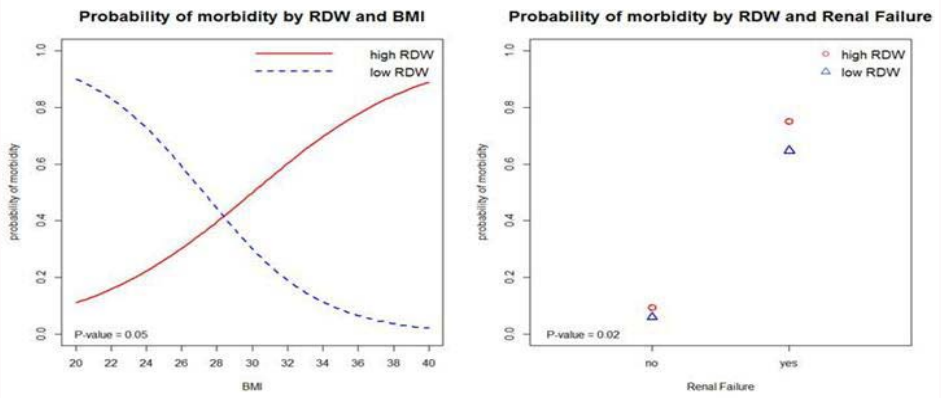

Figure 2: Multivariate analysis: higher preoperative RDW values were combined predictor biomarkers of morbidity with higher BMI and renal failure.

vulnerable to the effects of oxidative damage. Oxidative stress and chronic inflammation decrease production of erythropoietin and aggravates destructive process of erythrocytes leading to ineffective production of red blood cells. Semba et al., [17] investigated the effect of serum antioxidants on RDW in community-dwelling elder women. In this study, selenium, as a marker of antioxidant levels, was an independent predictor of RDW, suggesting that antioxidant status might influence RDW and play a role in the relationship between increased RDW and worsened clinical prognosis. Lippi et al., [18] demonstrated a correlation between RDW and indices of inflammation, such as elevated Erythrocyte Sedimentation Rate (ESR) and hotshot C-Reactive Protein (s-CRP), identifying strong, graded increases in both ESR and hs-CRP across RDW quartiles. In addition, increased RDW is associated with increased levels of pro-inflammatory cytokines such as tumor necrosis factor α and interleukin 6 [19]. These cytokines attenuate the activity of erythropoietin and cause production of ineffective red blood cells, leading to elevated RDW. Based on these observations, in our study, patients with higher RDW values seem to be older and to have lower weight. As consequence, RDW might reflect multiple pathophysiologic processes including nutritional deficiencies, ineffective erythrocyte production and shortened erythrocyte lifespan via chronic inflammation and oxidative stress, which might result in increasing morbidity and mortality of cardiovascular diseases.

Numerous study have indicated that that RDW is an applicable parameter in the predictions of risk and determining prognosis in numerous cardiovascular diseases including heart failure, myocardial infarction, angina pectoris, disease of peripheral arteries and lung. In particular and higher value of RDW is seems to be a risk factor for unfavorable outcomes.

Felker et al., [20] have demonstrated that in the prediction of mortality and morbidity of chronic heart failure, RDW is an important marker. They also indicated that RDW also complies with widely accepted risk assessment tools as ejection fraction, functional classification of heart failure, and renal functions with comparable statistical level of significance and concluded that RDW is a potential prognostic factor in heart failure.

Tonelli et al., [21] investigated the relationship between RDW values and the risk of death due to all causes and development of cardiovascular event in coronary artery patients without heart failure and observed a significant correlation between the baseline RDW levels and all-cause mortality in patients followed up for 60 months. Besides, risk of newly-developed cardiovascular event and mortality was higher in patients with increased RDW values. In addition, an association between higher RDW levels on the one hand and newly developed myocardial infarction and symptomatic heart failure and stroke was revealed. In a study, which investigated prognostic value of RDW following percutaneous coronary interventions, after an average of 4 years of follow-up, RDW was revealed as a robust predictive marker of mortality [22]. At the same time, RDW seems to be a potentially important prognostic marker in congenital heart surgery in that RDW reveals the clinical status of a patient after a major operation such as congenital heart surgery, which exposes the patient to a greater amount of oxidative stress [23].

Warwick et al., [24] investigated the significance of RDW in patient's candidate for coronary bypass surgery and analyzed in-hospital mortality, long-term survival rates, lengths of hospital, and ICU stay. They found that RDW is an important factor in the prediction of in-hospital mortality and long-term survival but an insignificant factor for the determination of lengths of ICU and hospital stay. We analyze the relationship between RDW and clinical outcome after AVR. Interestingly, the multivariate analysis showed that high RDW was a combined predictor of mortality and morbidity with higher BMI and renal failure. Finally, in our study we found that RDW- value and hemoglobin have similar sensitivity in predicting mortality and morbidity but RDW-value is more specific. We think that RDW may be an earlier marker of prognosis than hemoglobin, as it may reflect early steps in the complex processes of anemia, when ineffective production and increased destruction of red cells are occurring, but hemoglobin is still within the normal range. Increased RDW could affect outcomes irrespective of anemia status, maybe because the pathophysiologic mechanism might be due to chronic subclinical inflammation which precedes de novo cardiovascular events, and can affect erythropoiesis by means of direct myelosuppression of erythroid precursors, reduced renal erythropoietin production and bioavailability of iron, increased erythropoietin resistance in erythroid precursor cell lines, and promoted cell apoptosis.

Limitations

This study has some potential limitations. First of all, it is a single-centered retrospective study which included a small number of patient populations. Residual confounding factors might have thus affected the results, regardless of the adjusted analysis. Secondly, information about other clinical markers was not provided. Further

studies explaining the mechanism of relationship between mortality and morbidity are needed.

Conclusion

In conclusion, RDW might be useful as a marker for risk stratification in patient's candidate for isolated AVR. Increased RDW, in fact, seems to be a good predictor of early outcome after AVR, particularly in patients with high BMI, renal impairment and postoperative prolonged ventilation. In addition RDW-value might be an earlier biomarker of prognosis than hemoglobin. It might reflect early steps in the complex processes of anemia, when ineffective production and increased destruction of red cells are occurring, but hemoglobin is still within the normal range.

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