Association between Red Cell Distribution Width and Mortality after Cardiac Resynchronization Therapy

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ABSTRACT: **Background:** Cardiac resynchronization therapy (CRT) is a non-pharmacological option for patients with heart failure and interventricular dyssynchrony. Elevated red cell distribution width (RDW) reflects higher size and heterogeneity of erythrocytes and is associated with poor outcome in patients with chronic heart failure.

Objectives: To examine the association between RDW levels and outcomes after CRT implantation.

Methods: We conducted a cohort analysis of 156 patients (126 men, median age 69.0 years) who underwent CRT implantation in our institution during 2004–2008. RDW was measured at three time points before and after implantation. Primary outcome was defined as all-cause mortality, and secondary outcome as hospital re-admissions. We investigated the association between RDW levels and primary outcome during a median follow-up of 61 months.

Results: Ninety-five patients (60.9%) died during follow-up. Higher baseline RDW levels were associated with all-cause mortality (unadjusted HR 1.35, 95%CI 1.20–1.52, $P < 0.001$). On multivariate analysis adjusted for clinical, electrocardiographic and laboratory variables, baseline RDW levels were associated with mortality (HR 1.33, 95%CI 1.16–1.53). RDW levels 6 months and 12 months post-implantation were also associated with mortality (HR 1.22, 95%CI 1.08–1.38, $P = 0.001$; and HR 1.15, 95%CI 1.01–1.32, $P = 0.02$, respectively). Patients who were re-admitted to hospital during follow-up (n=78) had higher baseline RDW levels as compared to those who were not (14.9%, IQR 14.0, 16.0% vs. 14.3%, IQR 13.7, 15.0%, respectively, $P = 0.03$).

Conclusion: An elevated RDW level before and after CRT implantation is independently associated with all-cause mortality.

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KEY WORDS: cardiac resynchronization therapy (CRT), red cell distribution width (RDW), congestive heart failure (CHF), re-hospitalization, mortality

Cardiac resynchronization therapy (CRT) is a non-pharmacological treatment for patients with congestive heart failure (CHF) who have electrical interventricular dyssynchrony. Although CRT reduces morbidity and mortality [1-4], about 30% of patients who undergo CRT implantation do not benefit from it and are defined as "non-responders" [5,6]. Patients who benefit more from CRT are those with non-ischemic cardiomyopathy, left bundle branch block (LBBB), a wider QRS on electrocardiogram (ECG), and women [2,4,7,8]. Other potential predictors of clinical outcomes after CRT implantation could be important.

Red cell distribution width (RDW) is a quantitative measure of anisocytosis that describes the variability in erythrocyte size on complete blood count. In recent years several studies have demonstrated that an elevated RDW level is associated with poor outcome in patients with cardiovascular diseases including CHF, coronary artery disease (CAD) and post-myocardial infarction [9-13]. Two recent trials demonstrated that RDW levels are inversely associated with a positive response after CRT implantation, as defined by an improvement in echocardiographic parameters [14,15]. However, sparse data on the association between RDW levels before and after CRT implantation and between clinical outcomes are available. We therefore conducted a study aiming to examine the association between RDW levels and outcome in patients undergoing CRT implantation.

PATIENTS AND METHODS

A total of 174 patients underwent CRT implantation at Rabin Medical center during the years 2004–2008. Eighteen of them had incomplete data and were excluded from the analysis. Demographic, laboratory and outcome data were derived from our facility's computerized database. Mortality data were confirmed by the Israel Central Bureau of Statistics. During the follow-up, all-cause mortality was the primary endpoint, and re-admission rates to the hospital the secondary endpoint. For re-admission etiologies we included: decompensated CHF, angina, stroke, shock from defibrillator (either appropriate or inappropriate), and assist device implantation. We also assessed which prognostic clinical, ECG and echocardiographic characteristics were associated with worse outcome in patients who underwent

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CRT implantation. Data collection was approved by the hospital ethics committee, with a waiver for individual informed consent. The follow-up ended on 31 December 2013 for mortality data and on 30 October 2012 for hospitalization data.

VARIABLE DEFINITION AND CLASSIFICATION

Baseline characteristics at the time of CRT implantation were obtained from the patients' files. Functional capacity was classified according to the New York Heart Association (NYHA) and was determined at the time of CRT implantation. Chronic renal failure was defined as glomerular filtration rate < 60 ml/min.

RDW and other laboratory tests were analyzed in a single central laboratory using standardized automated kits (Advia 2120, Siemens, Erlangen, Germany) at three time points: within 1 month prior to CRT implantation (baseline RDW), within 6 months post-implantation (range 4–8 months), and within 12 months post-implantation (range 10–14 months). The normal reference for RDW in our laboratory is defined as 11.5%–14.5%. Baseline RDW levels were further subdivided into tertiles: RDW ≤ 14.0%, 14.0% < RDW ≤ 15.0%, and RDW > 15.0%.

STATISTICAL ANALYSIS

Categorical variables were described using frequency and percentages. Continuous variables were evaluated for normal distribution using the Kolmogorov-Smirnov test and Q-Q plot. Normal distributed variables were described using mean ± standard deviation, and abnormal distributed variables were described using median and interquartile range. Chi-square test was used to compare categorical variables between RDW tertiles. Normally distributed continuous variables were compared between RDW tertiles using ANOVA and abnormal distributed variables using the Kruskal-Wallis test. Survival curves were calculated by the Kaplan-Meier method and comparison between tertiles was performed with the log-rank test. Univariate Cox regression was used to evaluate the crude hazard ratio for mortality. Variables with $P < 0.2$ in the univariate Cox regression were included in the multivariate analysis (using the backward method). The results of multivariate analysis are presented as the hazard ratio (HR) with 95% confidence interval (CI). Spearman's correlation coefficient was used to evaluate the correlation between RDW at baseline, 6 months post-implantation and 12 months post-implantation. Friedman's test was used to compare RDW levels at the three time points. A two-sided P value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS-21 software (Chicago, IL).

RESULTS

The study group included 156 patients with a median age of 69.0 years (IQR 61.0, 76.0 years), of whom 126 (80.8%) were men. Most of the patients had ischemic cardiomyopathy (70.5%) and NYHA functional class III-IV (93.6%). Patients' characteristics are depicted in Table 1. Median baseline RDW levels were 14.5% (IQR 13.8, 15.6%). Patients were divided into tertiles accord-

Table 1. Characteristics of study patients

Clinical characteristics	Tertile 1 RDW ≤ 14.0%	Tertile 2 14.0% < RDW ≤ 15.0%	Tertile 3 RDW > 15.0%	*P* value	Total (n=156)
Age (years), median	67.0 (60.0,75.0)	71.0 (64.5, 76.0)	69.0 (56.5,77.0)	0.32	69.0 (61.0,76.0)
Men, n (%)	38 (71.7)	41 (87.2)	47 (83.9)	0.11	126 (80.8)
Comorbidities					
Dislipidemia, n (%)	36 (67.9)	37 (78.7)	41 (73.2)	0.48	
Ischemic cardiomyopathy, n (%)	31 (58.5)	35 (74.5)	44 (78.6)	0.06	114 (73.1)
Hypertension, n (%)	39 (73.6)	31 (66.0)	36 (64.3)	0.55	110 (70.5)
CRF, n (%)	13 (25.0)	26 (55.3)	31 (55.4)	0.002	106 (67.9)
Diabetes mellitus, n (%)	22 (41.5)	20 (42.6)	22 (40.7)	0.98	70 (45.2)
AF, n (%)	15 (28.3)	24 (51.1)	25 (44.6)	0.06	64 (41.6)
COPD, n (%)	7 (13.2)	10 (21.3)	9 (16.1)	0.55	64 (41.6)
Before CRT implantation					
LBBB, n (%)	36 (67.9)	35 (74.5)	36 (64.3)	0.54	107 (68.6)
RBBB, n (%)	6 (11.3)	6 (12.8)	7 (12.5)	0.97	19 (12.2)
QRS duration (ms), median	120 (140,160)	160 (140,160)	140 (120,160)	0.06	140 (120,160)
LVEF (%), mean ± SD	27.2 ± 8.0	26.1 ± 7.3	26.0 ± 7.2	0.3	26.6 ± 7.5
NYHA III/IV, n (%)	51 (96.2)	42 (89.4)	53 (94.6)	0.31	146 (93.6)
ACE/ARB, n (%)	45 (84.9)	41 (87.2)	45 (80.3)	0.26	131 (84.0)
BB, n (%)	36 (67.9)	34 (72.3)	37 (66.1)	0.79	107 (68.6)
Diuretic, n (%)	32 (60.4)	31 (66.0)	47 (83.9)	0.02	110 (70.5)
Hemoglobin (g/dl), mean ± SD	13.2 ± 1.7	13.0 ± 1.6	12.5 ± 1.6	0.11	12.9 ± 1.6
WBC (cells/µl), median	8.0 (7.0, 9.7)	7.8 (6.5, 9.4)	7.9 (6.8,9.2)	0.61	7.9 (6.8, 9.4)
Baseline RDW (%), median	13.6 (13.2,13.8)	14.4 (14.3,14.8)	16.1 (15.5,17.2)	NR	14.5 (13.8,15.6)
Mortality rate, n (%)	23 (43.4)	28 (59.6)	44 (78.6)	< 0.001	95 (60.1)
Hospitalizations, n (%)	20 (37.8)	22 (46.8)	36 (64.3)	< 0.001	78 (50.0)

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, AF = atrial fibrillation, CRF = chronic renal failure, CRT = cardiac resynchronization therapy, LBBB = left bundle branch block, LVEF = left ventricular ejection fraction, NYHA = New York Heart Association, RBBB = right bundle branch block, RDW = red blood cell distribution width, WBC = white blood cells

Table 2. Independent predictors for mortality as assessed by Cox regression analysis (unadjusted and adjusted hazard ratios and 95% CI)

Variable	Non death (n= 61)	Death (n=95)	Unadjusted HR (95%CI)	Adjusted HR (95%CI)*
Age (years), median	65.0 (53.5,74.5)	72.0 (65.0,77.0)	1.04 (1.02-1.06)	1.06 (1.03-1.08)
Men, n (%)	42 (68.9)	84 (88.4)	2.17 (1.15-4.08)	3.45 (1.67-7.13)
Ischemic cardiomyopathy, n (%)	33 (54.1)	77 (81.1)	2.29 (1.37-3.84)	0.80 (0.40-1.58)
Chronic renal failure, n (%)	14 (23.3)	56 (58.9)	2.40 (1.59-3.63)	1.17 (0.68-2.02)
Atrial fibrillation, n (%)	21 (34.4)	43 (45.3)	1.52 (1.01-2.29)	1.28 (0.77-2.14)
COPD, n (%)	7 (11.5)	19 (20.0)	1.68 (1.01-2.80)	2.01 (1.11-3.66)
RBBB, n (%)	3 (4.9)	16 (16.8)	1.88 (1.09-3.22)	1.74 (0.84-3.63)
Hemoglobin (g/dl), mean ± SD	13.2 ± 1.7	12.7 ± 1.6	0.84 (0.74-0.96)	0.84 (0.72-0.98)
Baseline RDW (%), median	14.1 (13.5,14.7)	15.0 (14.1, 16.1)	1.35 (1.20-1.52)	1.33 (1.16-1.53)

*Adjusted for age, gender, ischemic cardiomyopathy, CRF, AF, COPD, hemoglobin, RBBB and QRS duration
COPD = chronic obstructive pulmonary disease, RBBB = right bundle branch block, RDW = red cell distribution width

ing to levels of baseline RDW [Table 1]. Patients in the third tertile had chronic renal failure more often ($P = 0.002$) and were treated more commonly with diuretics ($P = 0.02$). However, they did not differ in age, gender or other comorbidities as compared to patients in the lower tertiles, as shown in Table 1. Echocardiography before CRT implantation was available for all patients with a mean ejection fraction of 26.6% ± 7.5%. Echocardiography post-CRT implantation was available for only 53 patients. In these patients, baseline RDW levels were not associated with change in ejection fraction, left ventricular end-systolic and end-diastolic diameters after implantation, as assessed by echocardiography (data not shown).

RDW AND MORTALITY

During a median follow-up of 61 months (IQR 28.3, 82.8 months) 95 patients (60.9%) died. Median baseline RDW levels of patients who survived during follow-up were 14.1% (IQR 13.5%, 14.7%) as compared to 15.0% (IQR 14.1, 16.1%) in patients who died during follow-up. Higher baseline RDW levels were associated with all-cause mortality (unadjusted HR 1.35, 95%CI 1.20–1.52, $P < 0.001$). Other factors associated with mortality were male gender ($P = 0.02$), age at implantation ($P < 0.001$), chronic renal failure ($P < 0.001$), ischemic cardiomyopathy ($P = 0.002$), atrial fibrillation ($P = 0.045$), chronic obstructive pulmonary disease (COPD) ($P = 0.045$), right bundle branch block (RBBB) ($P = 0.02$) and low baseline hemoglobin level ($P = 0.009$) [Table 2]. In multivariate analysis adjusted for age, gender, chronic renal failure, ischemic cardiomyopathy, atrial fibrillation, COPD, hemoglobin, RBBB and QRS duration, the factors independently associated with mortality were male gender (HR 3.45, 95%CI 1.67–7.13), older age (HR 1.06, 95%CI 1.03–1.08), COPD (HR 2.01, 95%CI 1.11–3.66) and baseline RDW level (HR 1.33, 95%CI 1.16–1.53). Patients in the third tertile of baseline RDW levels had significantly higher Kaplan-Meier mortality rates [Figure 1]. On multivariate analysis, the HR for mortality in the second and third tertiles of baseline RDW levels, as compared to the first tertile, were 1.12 (95%CI 0.62–2.05) and 2.94 (95%CI 1.64–5.28), respectively.

CORRELATION BETWEEN RDW POST-IMPLANTATION AND MORTALITY

RDW levels 6 months post-implantation were available for 111 patients (median RDW levels 14.8%, IQR 13.9, 16.1%), whereas at 12 months post-implantation RDW levels were available for 107 patients (median RDW levels 14.4%, IQR 13.3, 15.6%). RDW levels 6 months and 12 months post-implantation were correlated with baseline RDW levels (correlation coefficient 0.581 and 0.489, respectively, $P < 0.001$ for both). Both RDW

Figure 1. Kaplan-Meier survival curves for baseline tertiles of RDW

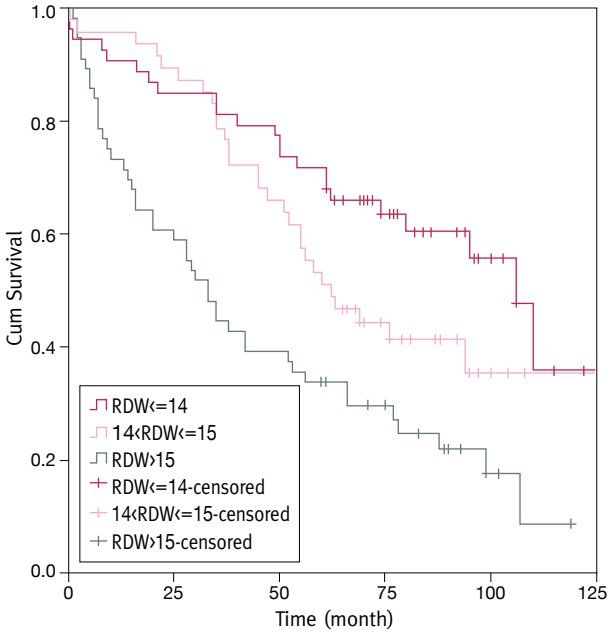
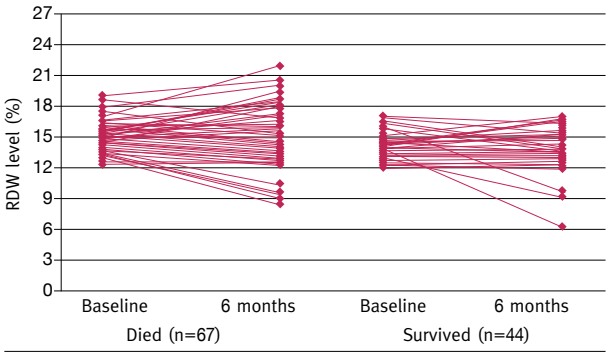


Figure 2. RDW levels at baseline and 6 months post-CRT implantation in patients who died and those who survived during follow-up (n=111)



levels 6 months and 12 months post-implantation were associated with all-cause mortality (HR 1.22, 95%CI 1.08–1.38, P = 0.001; and HR 1.15, 95%CI 1.01–1.32, P = 0.02, respectively).

ASSOCIATION BETWEEN CHANGE IN RDW LEVELS AND MORTALITY

We examined the association between the change in RDW levels 6 months post-CRT implantation and mortality. The change in RDW levels was defined by the difference between RDW levels 6 months post-implantation and between baseline RDW levels. Although the mean difference was found to be higher in patients who died vs. patients who were alive during follow-up (mean difference of +0.3 vs. +0.007, respectively) [Figure 2], this difference was not associated with mortality (P = 0.85).

CORRELATION BETWEEN RDW AND RE-ADMISSIONS

The median baseline RDW levels of patients who were re-admitted to the hospital during follow-up (n=78) were higher as compared to those who were not (14.9%, IQR 14.0, 16.0% vs. 14.3%, IQR 13.7, 15.0%, respectively, P = 0.03) [Table 1]. Among patients who were re-admitted to hospital during follow-up, higher baseline RDW levels were also associated with a higher number of re-admissions (P = 0.03).

DISCUSSION

The main finding of our study is that higher baseline RDW levels, as well as RDW after CRT implantation, are independently associated with mortality in patients who undergo CRT implantation. CRT is a well-established treatment used in patients with CHF. It remains a challenge to predict which patients will benefit most from CRT. Most trials focused on cardiac characteristics such as left ventricular dyssynchrony, ejection fraction and ECG parameters; the data on non-cardiac characteristics in patients undergoing CRT implantation are sparse. RDW is a numeric parameter that describes the variation in the size of red blood cells in the blood circulation. It is a routine component of a complete blood count and is readily available. Although it is not a cardiac-specific marker, elevated RDW has been associated with poor short and long-term outcomes in patients with cardiovascular diseases including CHF, CAD, pulmonary hypertension and stroke [9-13]. In a sub-study of the CHARM trial, which examined candesartan in patients with heart failure, RDW levels were independently associated with cardiovascular death and heart failure hospitalization [9]. Nevertheless, this association has never been addressed before in CHF patients undergoing CRT implantation.

We demonstrated the association between RDW and mortality in patients undergoing CRT implantation. The exact mechanism by which RDW is associated with poor outcome is not well established. It is not clear whether RDW is simply a marker of more advanced disease or a marker of a complex interplay between several pathologies associated with CHF, including anemia, chronic renal failure, nutritional deficiencies, oxidative stress, and inflammation. Indeed, we have demonstrated that patients with elevated RDW levels have more renal failure, suggesting a higher systemic burden associated with CHF. However, even after adjusting for CRF and other factors, RDW was still associated with worse outcome. Therefore, we assume that an elevated RDW level is a marker of a more advanced CHF disease associated with systemic organ damage. As a byproduct, patients with elevated RDW who are undergoing CRT implantation have higher mortality rates.

To our knowledge, only two studies have investigated the association between RDW levels and clinical outcomes in patients undergoing CRT implantation [14,15]. Rickard et al. [14] demonstrated a direct correlation between elevated RDW levels and impaired left ventricular reverse remodeling and worse outcomes. Celikyurt et al. [15] found an inverse correlation between RDW levels and positive response to CRT as defined by a relative increase in ejection fraction ≥ 15% measured by echocardiography [15]. To our knowledge, our study is the first to examine, as a primary endpoint, the association between baseline and post-implantation RDW levels and mortality. An additional finding that was not addressed in previous studies is the association between the difference between RDW levels post- and pre-implantation and its association with mortality. Our findings suggest that RDW levels, rather than the change in RDW levels over time, are associated with mortality in these patients. Therefore, RDW levels might be considered as a tool to predict risk and follow-up in patients undergoing CRT implantation.

Some limitations in our analysis must be noted. First, due to the study's observational nature it cannot be determined whether the relationship between RDW levels and mortality is causal. Still, it is unique in its long-term clinical follow-up and it represents the experience of a single tertiary medical center in consecutive patients referred for CRT implantation.

Echocardiography data were not available for all patients during follow-up and therefore this was not a pre-defined outcome. Since we have no systematic data collection of functional class or quality of life post-procedure, we only examined clinical outcomes such as mortality and hospitalizations. We had data only on all-cause mortality and not on specific causes of death such as cardiovascular death. RDW data following CRT implantation were missing. This could be due to mortality which we did not account for. Finally, this study is based on a single RDW measurement at each time point. RDW levels are subject to variation which was not addressed in the present analysis.

CONCLUSIONS

An elevated RDW level before and after CRT implantation is independently associated with all-cause mortality.

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References

1. Cleland JG, Daubert JC, Erdmann E, et al., Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005; 352 (15): 1539-49.
2. Bristow MR, Saxon LA, Boehmer J, et al., Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; 350: 2140-50.
3. Wells G, Parkash R, Healey JS, et al. Cardiac resynchronization therapy: a meta-analysis of randomized controlled trials. *CMAJ* 2011; 183 (4): 421-9.
4. Rinkuniene D, Bucyte S, Ceseviciute K, et al. Predictors of positive response to cardiac resynchronization therapy. *BMC Cardiovasc Disord* 2014; 14: 55.
5. Abraham WT, Fisher WG, Smith AL, et al., MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002; 346 (24): 1845-53.
6. Farwell D, Patel NR, Hall A, Ralph S, Sulke AN. How many people with heart failure are appropriate for biventricular resynchronization? *Eur Heart J* 2000; 15: 1246-50.
7. Auricchio A, Stellbrink C, Butter C, et al., Pacing Therapies in Congestive Heart Failure II Study Group; Guidant Heart Failure Research Group. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J Am Coll Cardiol* 2003; 42 (12): 2109-16.
8. Moss AJ, Hall WJ, Cannom DS, et al., MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009; 361 (14): 1329-38.
9. Felker GM, Allen LA, Pocock SJ, et al., CHARM Investigators. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. *J Am Coll Cardiol* 2007; 50 (1): 40-7.
10. Tonelli M, Sacks F, Arnold M, Moye L, Davis B, Pfeffer M, for the Cholesterol and Recurrent Events (CARE) Trial Investigators. Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. *Circulation* 2008; 117 (2): 163-8.
11. Dabbah S, Hammerman H, Markiewicz W, Aronson D. Relation between red cell distribution width and clinical outcomes after acute myocardial infarction. *Am J Cardiol* 2010; 105 (3): 312-17.
12. Cavusoglu E, Chopra V, Gupta A, et al. Relation between red blood cell distribution width (RDW) and all-cause mortality at two years in an unselected population referred for coronary angiography. *Int J Cardiol* 2010; 141 (2): 141-6.
13. Kim J, Kim YD, Song TJ, et al. Red blood cell distribution width is associated with poor clinical outcome in acute cerebral infarction. *Thromb Haemost* 2012; 108 (2): 349-56.
14. Rickard J, Kumbhani DJ, Gorodeski EZ, et al. Elevated red cell distribution width is associated with impaired reverse ventricular remodeling and increased mortality in patients undergoing cardiac resynchronization therapy. *Congest Heart Fail* 2012; 2: 79-84.
15. Celikyurt U, Agacdiken A, Sahin T, Kozdag G, Vural A, Ural D. Association between red blood cell distribution width and response to cardiac resynchronization therapy. *J Interv Card Electrophysiol* 2012; 35 (2): 215-18.