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Prognostic significance of red cell distribution width and its relation to increased pulmonary pressure and inflammation in acute heart failure

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Abstract

Background: *Red cell distribution width (RDW) in acute heart failure (AHF) is accepted as a prognostic indicator with unclear pathophysiological ties. The aim of this study was to evaluate the prognostic value of RDW in AHF patients in relation to clinical and echocardiographic data.*

Methods: *170 patients with AHF were retrospectively studied. All patients had laboratory testing and an echocardiogram performed within 24 h of admission to the Cardiology Department.*

Results: *During the mean 193 ± 111 days of follow-up, 33 patients died. More advanced age, high RDW and low peak early diastolic velocity of the lateral mitral annulus (MVe') were independent predictors of all-cause mortality with hazard ratios of: 1.05 (95% CI 1.02–1.09), $p < 0.005$, 1.40 (95% CI 1.22–1.60), $p < 0.001$, and 0.77 (95% CI 0.63–0.93), $p < 0.007$, respectively. In a stepwise multiple linear regression model, RDW was correlated with hemoglobin concentration (standardized $\beta = –0.233$, $p < 0.001$), mean corpuscular volum (standardized $\beta = –0.230$, $p < 0.001$), mean corpuscular hemoglobin concentration (standardized $\beta = –0.207$, $p < 0.007$), the natural logarithm of C-reactive protein (CRP) (standardized $\beta = 0.184$, $p < 0.004$) and tricuspid regurgitation peak gradient (TRPG) values (standardized $\beta = 0.179$, $p < 0.006$), whereas MVe' was correlated with atrial fibrillation (standardized $\beta = 0.269$, $p < 0.001$).*

Conclusions: *The present data demonstrates a novel relation between higher levels of RDW and elevated TRPG and high sensitivity CRP values in patients with AHF. These findings suggest that RDW, the most important mortality predictor, is independently associated with elevated pulmonary pressure and systemic inflammation in patients with AHF. Moreover, in AHF patients, more advanced age and decreased MVe' are also independently associated with total mortality risk.* (Cardiol J XXXX; XX, X: xx–xx)

Key words: acute heart failure, red cell distribution width, anemia, MVe', tricuspid regurgitation peak gradient, high sensitivity C-reactive protein

Introduction

Heart failure (HF) is becoming one of the most important cardiovascular syndromes due to its increasing prevalence, high mortality and increasing cost of care. Despite progress in therapeutic methods for acute heart failure (AHF), it still carries a grim prognosis and that is why searching for reliable predictors of mortality is of utmost importance [1]. Among them, red cell distribution width (RDW) was found to be the cheapest and most widely available indicator. The RDW was established to be a strong predictor of mortality in the general population above 45 years of age [2], as well as during sepsis, trauma and in critically ill patients [3–5]. Several studies confirmed that RDW predicts mortality in acute and chronic heart failure (CHF) [5–9]. It was reported that an increasing

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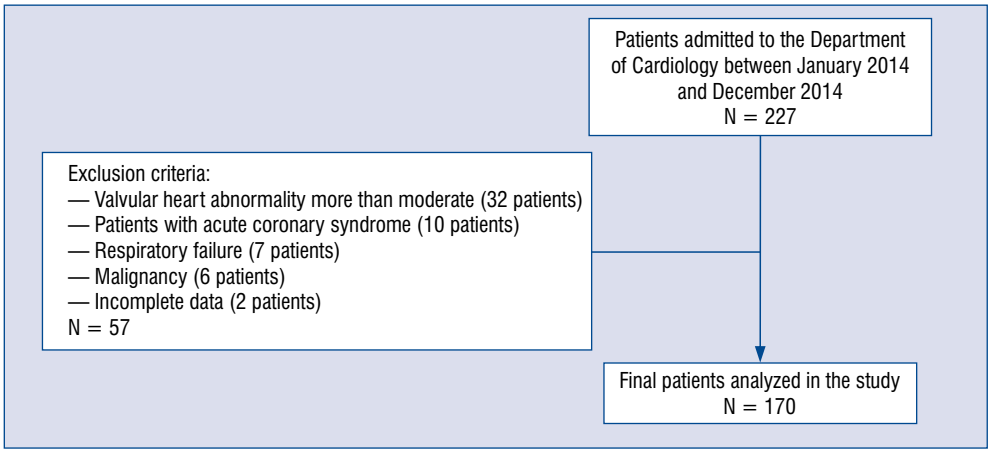

Figure 1. The flow chart of case enrolment of our study according to the inclusive and exclusive criteria.

RDW value is associated with cytokine activation, impaired iron mobilization and decreased hemoglobin (Hb) levels [10–12]. Furthermore, impaired deformability of erythrocytes (RBC) caused by proinflammatory cytokines can also be manifested as increased RDW [4]. The exact mechanism of how elevated RDW is associated with an adverse prognosis has not been entirely elucidated and its relation to clinical findings has not been fully explained. Recently, it was documented that high RDW values were independently associated with increased left ventricular (LV) end diastolic pressure [13]. Data concerning the association of RDW with echocardiographic findings in AHF are scarce and ambiguous [5, 6, 14]. The aim of the present study was to evaluate the mid-term prognostic value of RDW in AHF with regards to clinical and echocardiographic data.

Methods

The retrospective study included 170 patients chosen from 237 consecutive patients admitted to the hospital due to recent resting dyspnea caused by decompensation of CHF. All patients had N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasma levels that were above 300 units and signs of systolic and/or diastolic LV dysfunction in resting transthoracic echocardiography (ECHO) performed within 24 h of admission. The following exclusion criteria were applied: age younger than 18 years, valvular heart abnormality higher than moderate, acute coronary syndrome, dyspnea due to concomitant respiratory failure, malignancy and incomplete data (Fig. 1). All patients were treated according to the current guidelines for congestive heart failure (HF). Pharmacotherapy on admission was presented in Tables 1 and 2. Each patient underwent a standard echocardiogram (Vivid 5, GE Vingmed) using an adaptive 1.3–4.0 MHz transducer. Left atrial diameter (LAd), LV end-diastolic diameter (LVEDD) and right ventricular end-diastolic diameter (RVEDD) were assessed. The tricuspid regurgitation peak gradient (TRPG) was calculated according to the simplified Bernoulli formula, and was measured using a continuous wave Doppler in the modified apical 4-chamber view. The transmitral early diastolic velocity (E) was assessed from the mitral inflow velocity. The LV ejection fraction (LVEF) was measured using the Simpson biplane method. Tissue Doppler myocardial imaging (TDI) was used to assess the peak early diastolic velocity of the lateral mitral annulus (MVe') by placing the Doppler sample volume over the lateral side of the mitral annulus at the posterior leaflet. Venous blood samples were taken for determination of serum creatinine, sodium level, high sensitivity C-reactive protein (hsCRP), D-dimer, NT-proBNP and a complete blood count. Laboratory analysis was performed using a COBAS C-6000 Analyzer (Roche Diagnostic GmGH, Mannheim, Germany). Baseline hematologic analyses were performed using SYSMEX XT 1800i. The reference range for RDW was 11.5–14.5%. The glomerular filtration rate (GFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) formula. Follow-up began on of the day of admission to the Cardiology Department due to AHF. The endpoint of this study was all-cause mortality, including in-hospital and post-discharge deaths. The study protocol was approved by the Warmia

Table 1. Baseline characteristics and treatments in patients who died or survived

Variable	Survivors (n = 137)	Non-survivors (n = 33)	P
Age [years]	73.9 ± 12.5	78.3 ± 9.4	0.1
Sex, male	75 (54.7%)	14 (42.42%)	0.2
Diabetes mellitus	44 (32.12%)	16 (48.48%)	0.08
Hypertension	92 (67.15%)	21 (63.64%)	0.7
CAD	20 (14.60%)	9 (27.27%)	0.08
COPD	23 (16.79%)	7 (21.21%)	0.6
History of DVT	9 (6.57%)	6 (18.18%)	0.04
Acute infection	50 (36.5%)	9 (27.27%)	0.3
Heart rate [bpm]	78.42 ± 17.03	85.6 ± 15.89	0.03
BP systolic [mmHg]	136.8 ± 26.5	133.3 ± 21.7	0.5
BP diastolic [mmHg]	80.8 ± 15.2	82.0 ± 14.4	0.7
Weight [kg]	83.1 ± 19.5	77.6 ± 11.8	0.1
BMI [kg/m^2]	30.9 ± 6.5	28.3 ± 4.2	0.03
NT-proBNP [pg/mL]	2539 [1431-5496]	4240 [2028-9090]	0.03
Hb [g/dL]	12.8 ± 2.3	11.8 ± 2.7	0.04
RDW [%]	15.0 ± 1.8	16.9 ± 2.9	0.00003
Ht [%]	39.07 ± 6.27	37.03 ± 7.84	0.1
MCV [fL]	90.78 ± 6.88	90.66 ± 9.44	0.9
MCHC [g/dL]	32.87 ± 1.69	32.44 ± 1.46	0.2
Leukocytes [G/mL]	8.3 ± 3.3	7.7 ± 3.2	0.3
PLT [G/mL]	217.8 ± 126.9	186.1 ± 92.3	0.2
Na [mmol/L]	139.2 ± 4.3	137.9 ± 5.1	0.1
Creatinine [mg/dL]	1.2 ± 0.4	1.3 ± 0.6	0.3
eGFR [mL/min/1.73 m^2]	62.5 ± 26.5	58.5 ± 23.6	0.4
CRP [mg/L]	3.7 [1.5-12.7]	14.0 [5.0-34.8]	0.0005
D-dimer [μg/mL]	0.9 [0.5-1.5]	1.7 [0.7-3.1]	0.02
LBBB	12 (8.76%)	3 (9.09%)	1.0
RBBB	6 (4.38%)	3 (9.09%)	0.3
AF	68 (49.64%)	16 (48.49%)	0.91
LAd [cm]	4.9 ± 0.8	4.9 ± 0.6	0.8
LVEDD [cm]	5.6 ± 0.9	5.5 ± 1.0	0.9
RVEDD [cm]	3.3 ± 0.7	3.3 ± 0.7	0.9
EF [%]	43.1 ± 15.2	41.6 ± 17.2	0.6
TRPG [mmHg]	35.9 ± 13.6	42.2 ± 14.4	0.02
E [cm/s]	94.9 ± 29.4	84.7 ± 26.6	0.07
MVe' [cm/s]	8.5 ± 2.6	7.3 ± 1.7	0.01
E/MVe'	12.4 ± 4.7	12.5 ± 2.7	0.8
Mitral regurgitation	24 (17.52%)	5 (15.15%)	0.8
ACEI/ARB	129 (94.16%)	27 (81.82%)	0.02
Spironolactone	74 (54.01%)	23 (69.70%)	0.1
Furosemide	103 (75.18%)	26 (78.79%)	0.7
Chlortalidone	44 (32.12%)	6 (18.18%)	0.1
Hydrochlorothiazide	24 (17.52%)	5 (15.15%)	0.8
Oral anticoagulant	89 (64.96%)	18 (54.55%)	0.3
Statins	76 (55.47%)	13 (39.39%)	0.1
Beta-blockers	118 (86.13%)	25 (75.76%)	0.1

Data are shown as mean ± standard deviation/median [IQR]/patients' number (%); IQR — range from 1st to 3rd quartile; CAD — coronary artery disease; COPD — chronic obstructive pulmonary disease; DVT — deep vein thrombosis; BP — blood pressure; BMI — body mass index; NT-proBNP — N-terminal pro-B-type natriuretic peptide; Hb — hemoglobin; RDW — red blood cell distribution width; Ht — hematocrit; MCV — mean corspuscular volume; MCHC — mean corpuscular hemoglobin concentration; PLT — platelet count; eGFR — estimated glomerular filtration rate; CRP — C-reactive protein; LBBB — left bundle branch block; RBBB — right bundle branch block; AF — atrial fibrillation; LAd — left atrium diameter; LVEDD — left ventricular end-diastolic diameter; RVEDD — right ventricular end-diastolic diameter; EF — ejection faction; TRPG — tricuspid regurgitation peak gradient; E — early diastolic mitral inflow velocity; MVe' — peak early diastolic velocity of the mitral annulus lateral portion; ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin receptor blocker

Table 2. Total mortality in relation to clinical measures.

Variable	Univariate Cox proportional survival analysis (n = 170)				Multivariate Cox proportional survival analysis (n = 170)			
	HR	95% CI		P	HR	95% CI		P
Age [years]	1.034	1.000	1.070	0.05	1.050	1.015	1.087	0.005
Sex, male	0.658	0.330	1.313	0.2				
Diabetes mellitus	1.698	0.858	3.361	0.1				
Hypertension	0.834	0.410	1.696	0.6				
CAD	2.169	0.895	5.257	0.09				
COPD	1.328	0.576	3.062	0.5				
History of DVT	2.169	0.895	5.257	0.09				
Acute infection	1.420	0.660	3.055	0.4				
Heart rate [bmp]	1.022	1.006	1.038	0.007				
Systolic BP [mmHg]	0.978	1.007	0.317	1.0				
Diastolic BP [mmHg]	1.003	0.980	1.026	0.8				
Weight [kg]	0.983	0.964	1.003	0.1				
BMI [kg/m^2]	0.934	0.882	0.989	0.02				
NT-proBNP [pg/mL]	1.629	1.161	2.285	0.005				
Hb [g/dL]	0.880	0.771	1.005	0.06				
RDW [%]	1.348	1.194	1.522	< 0.001	1.396	1.221	1.596	< 0.001
Ht [%]	0.966	0.919	1.016	0.2				
MCV [fL]	0.991	0.947	1.036	0.7				
MCHC [g/dL]	0.855	0.700	1.043	0.1				
Leukocytes [G/mL]	1.030	0.895	1.185	0.7				
PLT [G/mL]	0.997	0.992	1.001	0.2				
Na [mmol/L]	0.962	0.894	1.034	0.3				
Creatinine [mg/dL]	1.544	0.810	2.945	0.2				
eGFR [mL/min/1.73 m^2]	0.994	0.980	1.009	0.4				
CRP [mg/L]	1.476	1.184	1.841	0.001				
D-dimer [μg/mL]	1.195	1.076	1.326	0.001				
LBBB	1.074	0.328	3.520	0.9				
RBBB	2.346	0.715	7.694	0.2				
AF	0.996	0.503	1.971	1.0				
LAd [cm]	0.965	0.647	1.439	0.9				
LVEDD [cm]	0.987	0.681	1.431	0.9				
RVEDD [cm]	0.881	0.532	1.459	0.6				
EF [%]	0.993	0.972	1.015	0.5				
TRPG [mmHg]	1.023	1.001	1.046	0.04				
E [cm/s]	0.985	0.971	0.999	0.03				
MVe' [cm/s]	0.846	0.746	0.958	0.009	0.767	0.632	0.931	0.007
E/MVe'	1.016	0.941	1.097	0.7				
Mitral regurgitation	0.996	0.503	1.971	1.0				
ACEI/ARB	0.339	0.140	0.822	0.02				
Spironolactone	1.614	0.768	3.395	0.2				
Furosemide	1.156	0.502	2.664	0.7				
Chlortalidone	0.459	0.189	1.112	0.09				
Hydrochlorothiazide	1.013	0.390	2.633	1.0				
Oral anticoagulant	0.670	0.338	1.330	0.3				
Statins	0.537	0.267	1.079	0.08				
Beta-blockers	0.468	0.211	1.040	0.06				

HR — hazard ratio; CI — confidential interval. The meaning of other abbreviations are the same as in Table 1.

and Masuria Medical Chamber Ethics Committee (no. 435/06).

Statistical analysis

Normally distributed variables were reported as mean and standard deviation. Variables that did not have a normal distribution were reported as median and interquartile range. Depending on the type of distribution of the variables, the groups were compared using the Student t test or the Mann-Whitney test. The χ^2 test was used to compare qualitative variables between groups. A value of $p < 0.05$ was considered statistically significant.

Variables selected to be tested in multivariate analysis were those with $p < 0.1$ in the univariate model. Multivariate survival analysis was performed using the Cox proportion hazard model to determine which factors were significantly associated with death after adjustment for the other variables. A stepwise selection was done using a p to remove and a p to enter into the model ≤ 0.05 with both prior backward selection after inclusion of all selected variables and then forward selection.

For the receiver operator characteristic (ROC) Youden Index was used to find the optimal cut-off points for the best discrimination of death risk. Kaplan-Meier survival curves analysis for the optimal cut-off point of RDW was created and statistical comparison between survival curves was done using the log-rank test.

Linear regression analysis was used to evaluate association between clinical variables and the most important independent death predictors. Identified variables ($p < 0.1$) were considered to enter in a stepwise manner to the multivariate linear regression model. The variable retention criterion was set at ≤ 0.05.

All statistical analysis was performed using STATSTICA 12 software.

Results

The study included 170 patients (males 47.7%). The mean observation time was 193 ± 111 days. Within the follow-up period, 33 (19.4%) patients died.

The baseline characteristics of the survivor and non-survivor groups are presented in Table 1. For survivors, the mean age was 73.9 ± 12.5 and for non-survivors the mean age was 78.3 ± 9.4 years ($p = 0.1$). A history of deep vein thrombosis was more frequent in the non-survivors group (18.2% vs. 6.6%, $p < 0.04$). There was a similar prevalence of reported comorbidities and acute infections in both studied groups. The number of subjects with anemia in survivors and non-survivors in the study group was 56 (40.88%) and 19 (57.58%), respectively ($p = 0.08$). After exclusion of anemic subjects, the median value of RDW in survivors and non-survivors was 14.4 (13.8–15.5) and 15.7 (14.6–17.30), respectively ($p = 0.03$). Treatment with angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) was significantly more frequent in the survivors group. Biochemical and clinical analyses revealed significantly higher concentration of NT-proBNP, CRP, D-dimer, and higher RDW and TRPG values in non-survivors (Table 1). In the non-survivors group, significantly lower Hb concentration and diminished MVe' values were found.

The univariate relative risk of mortality in relation to clinical variables is listed in Table 2. The presence of advanced age, higher values of NT-proBNP, CRP, D-dimer, RDW, TRPG, and lower values of mitral E and MVe' were related to total mortality.

The multivariate relative risk of mortality in relation to clinical variables is presented in Table 2. Advanced age, increased RDW value and decreased lateral MVe' velocity were retained as independent predictors for all-cause mortality with hazard ratios of 1.05 (95% CI 1.02–1.09), $p < 0.005$, 1.40 (95% CI 1.22–1.60), $p < 0.001$, and 0.77 (95% CI 0.63–0.93), $p < 0.007$, respectively.

In the univariate linear regression analysis, RDW was positively correlated with the natural logarithm of CRP (LnCRP), TRPG, NT-proBNP and RVEDD. Negative RDW correlation was found with Hb, hematocrit, mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) values. In the stepwise multiple linear regression model, RDW was correlated with Hb, MCV, MCHC, LnCRP and TRPG values (Table 3).

In the stepwise multiple linear regression model, MVe' was correlated with the presence of atrial fibrillation (AF) (standardized $\beta = 0.269$, $p < 0.001$).

In the whole study group the ROC curve analysis for RDW revealed that area under curve (AUC) was 0.72 (95% CI 0.62–0.82; $p < 0.0001$). The ROC curve analysis in the subgroup without anemia revealed AUC of 0.69 (95% CI 0.53–0.84; $p < 0.02$). RDW value ≥ 14.6 was found to be the optimal cut-off point for the discrimination of death risk. The same value of optimal cut-off point was found for non-anemic patients. RDW value ≥ 14.6 in the whole study group was found to have sensitivity and specificity of 86% and 51% and for non-anemic patients 78.6% and 56.0%, respectively.

Table 3. Univariate and multivariate analysis of association of patient characteristics with RDW

Variable	Univariate linear regression analysis			Multivariate linear regression analysis		
	β unstandarised ± SD	β standarised	P	β unstandarised ± SD	β standarised	P
Age [years]	–0.014 ± 0.014	–0.078	0.3			
Sex, male	0.175 ± 0.168	0.080	0.3			
Diabetes mellitus	0.140 ± 0.175	0.062	0.4			
Hypertension	–0.289 ± 0.175	–0.126	0.1			
CAD	0.275 ± 0.224	0.095	0.2			
COPD	–0.348 ± 0.217	–0.123	0.1			
DVT history	0.001 ± 0.265	0	1.0			
Acute infection	–0.064 ± 0.177	–0.028	0.7			
Heart rate [bpm]	0.018 ± 0.010	0.143	0.06			
Systolic BP [mmHg]	–0.0003 ± 0.007	–0.003	1.0			
Diastolic BP [mmHg]	–0.006 ± 0.011	–0.038	0.6			
Weight [kg]	–0.002 ± 0.009	–0.016	0.8			
BMI [kg/m^2]	–0.028 ± 0.027	–0.079	0.3			
NT-proBNP [pg/mL]	0.000 ± 0.000	0.181	0.02			
Hb [g/dL]	–0.356 ± 0.065	–0.392	< 0.001	–0.212 ± 0.065	–0.233	0.001
Ht [%]	–0.108 ± 0.024	–0.331	< 0.001			
MCV [fL]	–0.108 ± 0.021	–0.369	< 0.001	–0.067 ± 0.02	–0.23	0.001
MCHC [g/dL]	–0.557 ± 0.092	–0.425	< 0.001	–0.271 ± 0.099	–0.207	0.007
Leukocytes [G/mL]	–0.042 ± 0.051	–0.064	0.4			
PLT [G/mL]	0.002 ± 0.001	0.094	0.2			
Na [mmol/L]	–0.053 ± 0.037	–0.109	0.2			
Creatinine [mg/dL]	0.572 ± 0.347	0.127	0.1			
eGFR [mL/min/1.73 m^2]	0.004 ± 0.006	0.051	0.5			
LnCRP [mg/L]	0.330 ± 0.109	0.229	0.003	0.266 ± 0.092	0.184	0.004
D-dimer [μg/mL]	0.160 ± 0.085	0.143	0.06			
LBBB	–0.267 ± 0.297	–0.069	0.4			
RBBB	0.603 ± 0.374	0.123	0.1			
AF	0.142 ± 0.169	0.065	0.4			
LAd [cm]	0.335 ± 0.209	0.123	0.1			
LVEDD [cm]	0.167 ± 0.179	0.072	0.4			
RVEDD [cm]	0.523 ± 0.238	0.168	0.03			
EF [%]	–0.010 ± 0.011	–0.073	0.3			
TRPG [mmHg]	0.035 ± 0.012	0.227	0.003	0.028 ± 0.01	0.179	0.006
E [cm/s]	0.004 ± 0.006	0.057	0.5			
MVe' [cm/s]	0.003 ± 0.003	0.078	0.3			
E/MVe'	0.051 ± 0.039	0.101	0.2			
Mitral regurgitation	0.286 ± 0.223	0.098	0.2			

SD — standard deviation; the meaning of all abbreviations are the same as in Table 1 and Table 2.

When Kaplan-Meier survival curves for 1-year mortality were constructed, patients with RDW ≥ 14.6 had a 1-year cumulative survival probability of 65% compared with 92% for those with RDW < 14.6 ($p < 0.001$ in log-rank test) (Fig. 2). Number of patients at risk in the group assessed with RDW ≥ 14.6 was 97 and in the group with RDW < 14.6 was 73 subjects.

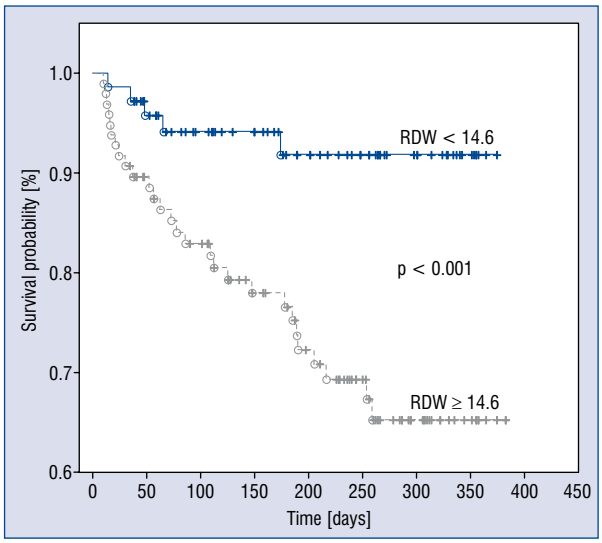

Figure 2. Kaplan-Meier survival curves for total mortality in 170 patients with acute heart failure with red cell distribution width (RDW) ≥ 14.6 (n = 97) and RDW < 14.6 (n = 73).

Discussion

Elevated RDW on admission is the most powerful independent predictor of all-cause mortality in AHF patients. A 1% RDW increase predicted an almost 40% increase in total mortality risk, which is consistent with previously reported data in AHF [6, 7, 15–17].

There are numerous reasons for RDW elevation under different clinical conditions. Traditionally, an isolated rise in RDW is the first abnormality seen in early iron deficiency and coupled with a low MCV is regarded as being diagnostic of absolute iron deficiency [16, 17]. Hemoglobin concentration and automatically measured red cell indices are considered sensitive indicators of systemic iron status [18]. It was found that iron deficiency is an ominous finding in CHF [17]. As the deficit worsens, the MCHC falls with a further reduction in MCV. In the present study, increased RDW was independently correlated with a low Hb level, as well as decreased MCV and MCHC values. Similar correlations have been described by other authors [8, 19] in AHF patients. In a recent study by Senthong et al. [13] this correlation was observed in patients who underwent elective coronary angiography. Moreover, van Kimmenade et al. [8] found no correlation between increased RDW and serum iron, TIBC, serum transferin saturation and ferritin level. Allen et al. [10] demonstrated similar findings in CHF patients. They additionally found a correlation between elevated RDW and high eyrthropoetin levels, normal iron binding capacity and ferritin levels. All results are consistent with a state of impaired iron mobilization and the inhibition of erythropoietin-induced erythrocyte maturation, the hallmark of anemia in chronic diseases [20]. There is an increasing recognition that in the AHF population, the ability to mobilize and use existing iron stores may be impaired even in the setting of adequate overall total body iron [21]. This is sometimes referred to as "reticuloendothelial block", and it is mediated in part by the overexpression of hepcidin; a peptide hormone secreted by the liver which is upregulated by inflammation and acts as a regulator of human iron metabolism [10, 22].

In the entire study group, an association between lower MCV, MCHC and Hb concentration with higher RDW may indicate an underlying iron deficiency, but it cannot be excluded that the RDW value is also modified by erythrocyte destruction and ineffective iron utilization for red cell production [23]. In rodent models of sepsis, decreases in Hb content and erythrocyte deformability resulting in RDW elevation was shown to be most profound in the second-oldest subpopulation of cells accounting for 20% of total circulating erythrocytes [24]. On the other hand, it was demonstrated that RDW elevation is caused by a rise of immature erythrocyte forms [11].

In the present study group, increased RDW was independently positively correlated with hs-CRP level. Lippi et al. [23] demonstrated a similar correlation in an unselected population between high RDW and elevated CRP concentration. It was reported that inflammation alters erythropoiesis by direct myelosuppression of erythroid precursors, promotion of red cell apoptosis, reduction of erythropoietin production, reduced iron bioavailability, and erythropoietin resistance in erythroid precursor cell lines. CRP contributes to stimulating the secretion of cytokines and tissue factor, it also induces the expression of adhesion molecules from endothelial cells [25]. Inflammatory cytokines also suppress erythrocyte maturation, allowing newer, larger reticulocytes to enter the circulation and skew the RDW distribution [4]. An inverse correlation between RDW and MCV, MCHC and Hb values indicate that proliferation and new erythrocytes entering into circulation are less important than erythrocyte destruction in the study group. The median hsCRP value in the non-survivors group was 14.0 (5.0–34.8) mg/L. The elevation of hsCRP above 10 mg/L should be evaluated for noncardiovascular etiologies, most likely resulting from an infection [26]. The prevalence of acute

infection was similar for both the survivors and non-survivors group. Therefore, it seems that in AHF patients studied, destruction of erythrocytes is associated not only with HF related vascular inflammation but probably also with severity of the superimposed infection.

The inflammatory process, particularly accompanying HF, is an important pro-thrombotic factor. In the present study, D-dimer concentration was significantly higher in the non-survivors group in univariate regression analysis and a significant positive correlation between D-dimer and RDW was observed. No patients had clinical symptoms of recent deep vein thrombosis or acute coronary syndrome, so activated fibrinolysis is rather connected with other vascular territories. Itani et al. [7] found that a higher DIC score was independently associated with risk of death in AHF patients. Interestingly, it was reported that in patients with hypoxemia and pulmonary hypertension due to HF, endothelial dysfunction and ongoing intravascular coagulation was associated with the occurrence of ischaemic and thrombotic pulmonary events [27]. In a mixed etiology pulmonary hypertension population, it was demonstrated that elevated RDW levels were inversely correlated with Hb and MCV values which is in line with the present results [12]. Tandon et al. [28] described extensive thrombotic pulmonary vascular changes at various stages of organization with pulmonary iron deposits seen in 70% of cases in patients with severe pulmonary hypertension due to isolated mitral stenosis. Similar abnormalities were described in HF and pulmonary hypertension [29].

According to available research, the current study provides the first data evaluating the relationship between the RDW and TRPG values in AHF. An independent direct positive correlation between RDW with TRPG values in the present study group may indicate the role of elevated pulmonary artery pressure on the modification of RDW values. It has been proven that blood stasis, due to low cardiac output, passive vascular distension, and systemic inflammation leads to endothelial dysfunction by means of neurohormonal activation [30]. Costello et al. [31] have described disruption of some or all layers of the alveolar-capillary unit by elevated capillary hydrostatic pressures, a phenomenon they referred to as pulmonary capillary stress failure. When all of the layers are disrupted, RBCs may be seen traversing the alveolarcapillary membrane. It was found that RBC destruction releases free Hb, and these react with nitric oxide to form inactive nitrate and methemoglobin, thus leading to endothelial dysfunction [32]. Recently in a murine model of hemolysis, a significant reduction in nitric oxide bioavailability due to free Hb was shown to be accompanied by platelet activation and the activation of a coagulation pathway resulting in thrombosis, pulmonary hypertension, right ventricular failure and eventually death [32]. The impact of increased pulmonary pressure on vascular endothelial cells in AHF may lead to erythrocyte damage and serve as an important modifier of the RDW. Free Hb leads to further microcirculation damage and creation of a self-perpetuating vicious circle. It has been demonstrated that unfractionated heparin treatment in cardio-renal syndrome and peripheral vein thrombosis without pulmonary embolism resulted in lowering pulmonary arterial hypertension and increased plasma anticoagulants indicating the thrombotic nature of the underlying pathology which plays an important role in pulmonary circulation of AHF patients [33].

Results herein demonstrate that decreased MVe', unlike LVEF and other echocardiographic data including the E/MVe' ratio in AHF patients, independently predicts risk of death. Gandhi et al. [34] first described that the impairment of diastolic dysfunction in patients with sinus rhythm is associated with the development of acute pulmonary edema with normal and unchanged LVEF. The MVe' value is a key indicator of diastolic function because it reflects both relaxation and restoration forces [35]. It is commonly assumed that in the failing heart, MVe' is modified by diastolic pressure but is less load dependent than transmitral flow velocities [35]. However, AF changes the ventricular diastolic filling profile from double to single phase, leading to a significant increase of maximal MVe' velocity, falsely denotes a better LV diastolic function. The prevalence of AF in the survival and nonsurvival groups was similar; therefore, AF is not likely to be a factor affecting MVe' predictability of death in the present study group. It was demonstrated that early diastolic mitral annulus velocity in patients with LV systolic dysfunction and sinus rhythm was found to be a powerful predictor of cardiac mortality. Moreover, MVe' emerged as the best prognosticator for long-term follow-up and was even more accurate than the E/e' ratio, incremental to other clinical or echocardiographic variables in patients with impaired LV systolic function [36]. It was also reported that the presence of diastolic dysfunction provides important prognostic insights in patients with HF, especially preserved ejection fraction and sinus rhythm [36, 37]. According to available research, there is no published data concerning the prog-

nostic impact of MVe' in AHF groups consisting of patients with preserved as well as reduced ejection fraction. However, further analysis of a larger mixed HF population with and without AF are needed to establish absolute predictive values separately for patients with AF and those with sinus rhythm.

Limitations of the study

The present study has several limitations.

Firstly, the study was performed at a single center with a small, retrospective sample size, which raises a concern of whether the sample is representative. However, demographic, clinical, and biological characteristics of the present study collectively correspond with the respective characteristics reported from other studies of AHF [6, 19].

Secondly, analysis of precise indices of iron metabolism, transfusion status or nutritional deficiency was not carried out.

Thirdly, analysis of TRPG was performed instead of a direct invasive pulmonary pressure estimation.

Conclusions

The present data demonstrates a novel relation between higher levels of RDW, elevated TRPG and elevated hsCRP values in patients with AHF. These findings suggest that RDW, the most important mortality predictor, is independently associated with elevated pulmonary pressure and systemic inflammation in patients with AHF. Moreover, more advanced age and a decreased MVe' are also independently associated with total mortality risk in AHF patients.

Conflict of interest: None declared

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