ORIGINAL ARTICLE

Red blood cell distribution width, relative lymphocyte count, and type 2 diabetes predict all-cause mortality in patients with advanced heart failure

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KEY WORDS

diabetes, heart failure, prognosis

ABSTRACT

INTRODUCTION Early identification of patients with advanced heart failure (HF) who are at higher risk of poor outcome is an important element of patient management, both from the medical and economic standpoint.

OBJECTIVES We sought to determine the association between hematologic parameters assessed on admission and within a 3-year follow-up in consecutive patients with advanced HF. We also investigated the association between baseline demographic and clinical data and mortality.

PATIENTS AND METHODS We analyzed the data of consecutive patients with advanced HF from the single-center registry COMMIT-HF. Patients with hematologic and autoimmune disorders, acute or chronic inflammatory diseases, malignant diseases, incomplete clinical and laboratory data, and those receiving glucocorticoids were excluded from the study.

RESULTS We analyzed 785 patients with advanced HF out of the total number of 1798 patients included in the COMMIT-HF registry between 2009 and 2013. The mean (SD) age of the patients was 61.9 (12.4) years, and 76.8% of them were male. Diabetes (hazard ratio [HR], 1.46; 95% CI, 1.15–1.86; $P = 0.002$), elevated red blood cell distribution width (RDW; HR, 1.05; 95% CI, 1.04–1.07; $P < 0.0001$), and a low relative lymphocyte count (RLC%; HR, 0.942; 95% CI, 0.928–0.956; $P < 0.0001$) were shown to be independent predictors of death.

CONCLUSIONS Our study showed that diabetes is a strong independent predictor of death in patients with advanced HF. RDW and RLC% are simple, accurate, and widely available markers predicting mortality at 3 years in patients with advanced HF.

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INTRODUCTION Advanced heart failure (HF) is one of the most severe cardiovascular disorders, associated with high incidence, morbidity, and mortality rates.[1] Early identification of patients who are at higher risk of poor outcome is an important element of patient management, both from the medical and economic standpoint.[2,3] There are several risk stratification models that can be used to predict the prognosis of patients with advanced HF. The 2 most commonly used scores include the Heart Failure Survival Score and the Seattle Heart Failure Model.[4] The first score includes such clinical data as mean blood pressure, resting heart rate, left ventricular ejection fraction, interventricular conduction defects, serum sodium levels, mean wedge

pressure, ischemic etiology of HF, and peak oxygen consumption. The second score is calculated on the basis of 24 variables including common clinical parameters obtained at baseline, as well as the use of medications and devices. Recently, another score has been gaining popularity, namely, the Model for End-stage Liver Disease, which is used for the assessment of multisystem dysfunction (renal, cardiac, and hepatic) and coagulopathy.[5]

It should be noted, however, that prognostic factors in patients with chronic HF are still being investigated, because their type and prognostic value change with time as a result of medical progress, as reflected by modifications in management standards for patients with HF. Furthermore, the most useful stratification tools in daily clinical practice should include noninvasive, simple, repeatable, and readily available tests.

Considering the underlying pathophysiological mechanisms of HF, we analyzed the parameters reflecting the 2 key processes that affect the development and progression of the disease: neurohumoral activation and inflammation. These are hematologic parameters that can be easily measured with modern cell counters used for assessing complete blood count. Because complete blood count is a routine test performed in patients with HF, these hematologic indices can be used in the assessment of prognosis at no additional costs. Therefore, in the present study, we sought to determine the association between hematologic parameters assessed on admission to the hospital and within a 3-year follow-up in consecutive patients with advanced HF. We also investigated the association between baseline demographic and clinical data and mortality of these patients.

PATIENTS AND METHODS We analyzed the data of consecutive patients with advanced chronic systolic HF (New York Heart Association [NYHA] functional classes III and IV), who were included in a single-center registry—COMMIT-HF.[6] The registry included 1798 patients with symptomatic chronic systolic HF (left ventricular ejection fraction <35%) who were hospitalized in a tertiary referral cardiology center between January 2009 and December 2013. The exclusion criteria were age below 18 years and acute coronary syndrome as the cause of index hospitalization. The current study was a subanalysis of patients with advanced HF included in the COMMIT-HF registry. Patients with hematologic disorders (including anemia) and autoimmune disorders, acute or chronic inflammatory diseases, malignancies, incomplete clinical and laboratory data, and those receiving glucocorticoids, blood transfusions, erythropoietin therapy, or intravenous iron therapy at the time of enrollment were excluded from the study.

HF was diagnosed by the attending physician on the basis of guideline recommendations on inclusion to the study. The ischemic etiology of HF was diagnosed in cases with confirmed coronary revascularization procedure or previous myocardial infarction. In patients with an unknown etiology of HF, coronary angiography was performed. Diabetes was diagnosed when one of the following criteria was met: 1) diabetes was previously diagnosed and documented in the patient's medical records; 2) the patient had a current prescription for oral hypoglycemic medication or insulin. The estimated glomerular filtration rate was calculated with the Modification of Diet in Renal Disease formula; the value of less than 60 ml/min/1.73 m^2 was diagnostic for chronic kidney disease. The definition of anemia was based on a report by the World Health Organization (hemoglobin levels <12 g/dl for women and <13 g/dl for men).[7,8]

Venous blood samples were collected on admission into standardized dipotassium EDTA tubes. The samples were tested within 30 minutes of collection to minimize variations due to sample aging. The complete blood count of patients, as well as hematologic parameters such as hemoglobin concentration, hematocrit, mean corpuscular volume (MCV), platelet-to-lymphocyte ratio (PLR), relative lymphocyte count (RLC%), mean platelet volume (MPV), and red blood cell distribution width (RDW) were analyzed using automated blood cell counters (Sysmex XS1000i and XE2100, Sysmex Corporation, Kobe, Japan). The intra-assay and interassay coefficients of variation of the blood samples were 5% and 4.5%, respectively. RDW was calculated using the following formula: RDW = (SD of red blood cell corpuscular volume) / MCV × 100 [%]. RLC% was calculated as the ratio between the lymphocyte count and the total white blood cell count.

During the 3-year follow-up, mortality was assessed. Data on survival were obtained from the national health care provider. Both the registry and the current study conformed to the Declaration of Helsinki.

Statistical analysis The statistical analysis was performed using the SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina, United States). Continuous variables were expressed as median (25th–75th percentiles), and categorical variables—as percentages. Continuous variables were compared using the Wilcoxon–Mann–Whitney test due to nonnormal distribution, and categorical variables were compared using the χ^2 test. A univariable Cox proportional hazards regression analysis was used to select the potential independent predictive factors of death for inclusion in a multivariable analysis. The examined covariables included clinical and demographic data (age, sex, obesity, ischemic etiology of HF, chronic kidney disease, diabetes, atrial fibrillation, and hypertension), as well as hematologic parameters (PLR, RLC%, RDW, MCV, and MPV). The univariable predictors of death with a *P* value of less than 0.1 were entered in the multivariable Cox regression model with

TABLE 1 Baseline characteristics of the study groups according to the survival or death status

Parameter	Survival (n = 422)	Death (n = 363)	*P* value
Age, y, median (IQR)	60.9 (52.8–69.4)	63.1 (55.6–74.7)	<0.001[a]
Male sex, n (%)	312 (73.9)	291 (80.2)	0.04[b]
Chronic kidney disease, n (%)	126 (29.9)	153 (42.1)	<0.001[b]
Diabetes, n (%)	170 (40.3)	197 (54.3)	<0.001[b]
Ischemic etiology of HF, n (%)	262 (62.1)	249 (68.6)	0.05[b]
ICD/CRT-D, n (%)	316 (74.9)	222 (61.2)	<0.001[b]
Arterial hypertension, n (%)	235 (56.04)	182 (50.4)	0.12[b]
Atrial fibrillation, n (%)	120 (28.6)	135 (37.4)	0.009[b]
LVDD, mm, median (IQR)	64.5 (59.0–70.0)	63.0 (58.0–70.5)	0.19[a]
RV, mm, median (IQR)	31.0 (28.0–34.0)	30.0 (28.0 – 34.0)	0.29[a]
LA, mm, median (IQR)	45.0 (41.0–50.0)	45.0 (40.0–50.0)	0.72[a]
LVEF, %, median (IQR)	26.0 (21.0–30.0)	27.0 (21.0–31.0)	0.18[a]
MVR (%)	119 (28.2)	108 (29.8)	0.63[b]

a Wilcoxon-Mann-Whitney test; **b** χ^2 test

Abbreviations: ICD/CRT-D, implantable cardioverter–defibrillator/cardiac resynchronization therapy device; HF, heart failure; IQR, interquartile range; LA, left atrium; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MVR, mitral valve regurgitation; RV, right ventricle

TABLE 2 Baseline laboratory parameters in the study groups according to the survival or death status according to the survival or death status

Parameter	Survival (n = 422)	Death (n = 363)	*P* vaule*
Leukocytes, $10^3/mm^3$	7.5 (6.1–9.1)	7.4 (6.0–9.11)	0.43
Hemoglobin, mmol/l	8.8 (8.0–9.4)	8.7 (8.0–9.3)	0.44
Bilirubin, μmol/l	13.0 (9.3–20.4)	15.3 (9.3–26.3)	0.02
Creatinine, μmol/l	91.0 (75.7–111.2)	101.5 (80.0–128.2)	<0.001
Uric acid, μmol/l	421.6 (341.0–505.0)	457.3 (364.0–578.8)	<0.001
Glucose, mmol/l	5.7 (5.1–6.7)	5.80 (5.2–7.4)	0.02
HbA_{1c}, %	6.4 (6.0–7.1)	6.6 (6.0–7.1)	0.52
Total cholesterol, mmol/l	4.3 (3.6–5.4)	4.00 (3.3–5.2)	0.002
Triglycerides, mmol/l	1.3 (1.00–1.8)	1.2 (0.9–1.6)	<0.001
eGFR, ml/min/1,73 m^2	73.0 (57.0–89.4)	64.0 (50.00–84.2)	<0.001
Sodium, mmol/l	137. (135.0–139.0)	136.3 (133.2–139.0)	0.002
Platelets, $10^3/mm^3$	197.0 (161.0–240.0)	215.0 (172.0–259.0)	0.002
Lymphocytes, $10^3/mm^3$	25.5 (19.9–31.3)	19.6 (15.1–27.9)	<0.001
PLR	92.7 (72.6–120.6)	150.9 (114.5–200.9)	<0.001
RLC%	26.9 (21.5–32.7)	19.2 (14.1–26.2)	<0.001
MCV, fl	90.6 (87.0–93.4)	90.1 (86.2–93.8)	0.55
RDW, fl	45.2 (42.9–49.1)	48.7 (45.2–53.2)	<0.001
MPV, fl	11.1 (10.4–11.6)	11.9 (10.9–12.6)	<0.001
NT-proBNP, pg/ml	3050.5 (1518.0–5214.0)	3307.0 (1772.0–5728.0)	0.03

Data are presented as median (IQR).

Abbreviations: eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin A_{1c}; MCV, mean corpuscular volume; MPV, mean platelet volume; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PLR, platelet-to-lymphocyte ratio; RDW, red blood cell distribution width; RLC%, relative lymphocyte count; others, see **TABLE 1**

stepwise backward elimination. The tolerance and variance inflation factor was used to assess the correlation between explanatory variables and to assess multicollinearity. Schoenfeld residuals were used to check the proportional hazards assumption. A *P* value of less than 0.05 was considered significant. The results were presented as hazard ratios with 95% CIs.

RESULTS We analyzed 785 patients with advanced HF out of the total number of 1798 patients included in the COMMIT-HF registry between 2009 and 2013. NYHA class III was reported for 612 patients, of whom 500 were classified as the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile 6, while 112 patients—as INTERMACS profile 7. There were 173 patients in NYHA class IV, of whom 101 were classified as INTERMACS profile 4 and 72—as INTERMACS profile 5.

Baseline demographic and clinical characteristics according to the survival or death status are presented in **TABLE 1**. Baseline laboratory characteristics according to the survival or death status are summarized in **TABLE 2**. During the 3-year follow-up, death was reported for 363 patients (45%). The multivariable Cox regression analysis confirmed that RDW, RLC%, and diabetes were significant independent predictors of death (**TABLE 3**). Data on pharmacotherapy at baseline according to the survival or death status are summarized in **TABLE 4**.

DISCUSSION The main finding of our study on this large unselected population of hospitalized patients with advanced HF is that the 2 hematologic parameters—RDW and RLC%—are associated with all-cause mortality during the 3-year follow-up. Moreover, our data support prior findings on the association between diabetes and an increased risk of death during a long-term follow-up.

In accordance with previous reports, we observed that RDW—a numerical measure of the variability in the size of circulating erythrocytes (anisocytosis)—independently predicted mortality in patients with chronic HF.[9-12] The exact mechanisms underlying the association between RDW and mortality observed in our study remain unknown. It is postulated that inflammation may explain the relationship between a higher RDW and a poorer prognosis in patients with HF. It is also well documented that the inflammatory response plays an important role in the development of HF.[13] On the other hand, it is known that inflammation inhibits erythrocyte maturation and accelerates the migration of reticulocytes into the peripheral circulation, thereby increasing RDW.[14] Forhecz et al[12] documented a positive relationship between RDW and inflammatory indices, and observed that higher RDW values were associated with significantly lower serum iron and ferritin levels. Additionally, they showed that

TABLE 3 Results of a multivariable Cox regression analysis

Parameter	HR	95% CI	*P* value
Diabetes	1.46	1.15–1.86	0.002
RDW	1.05	1.04–1.07	<0.001
RLC%	0.94	0.93–0.96	<0.001

Abbreviations: HR, hazard ratio; others, see **TABLE 2**

TABLE 4 Pharmacotherapy at baseline in the study groups according to the survival or death status

Medication	Survival (n = 422)	Death (n = 363)	*P* value[a]
B-blocker	410 (97.2)	335 (92.3)	0.002
ACEI	313 (74.3)	230 (65.3)	0.006
ARB	40.0 (9.6)	20.0 (5.7)	0.05
Loop diuretic	378 (89.8)	320 (90.4)	0.8
Digitalis	123 (29.4)	117 (33.3)	0.2
Allopurinol	136 (32.6)	144 (41.3)	0.01
Warfarin	162 (38.7)	139 (39.5)	0.8
Oral hypoglycemic drug	120 (28.8)	136 (38.6)	0.004
Insulin	64 (15.4)	74 (21.3)	0.04

Data are presented as the number (percentage) of patients.

a χ^2 test

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker

an increased RDW is associated with ineffective erythropoiesis and a decrease in renal function.[12] Finally, they observed a strong correlation with RDW also for markers of nutritional deficiency, such as total cholesterol and albumin levels.[12]

Westenbrink et al[15] reported that a higher RDW in patients with HF is associated with elevated levels of proinflammatory cytokines and C-reactive protein. Inflammatory cytokines may directly inhibit erythropoietin-induced erythrocyte maturation, which leads to an increase in RDW.[16] It is also known that inflammatory cytokines upregulate hepcidin, which regulates iron homeostasis by inhibiting iron absorption from the intestine and iron release from reticuloendothelial stores.[17]

Considering the above findings, it could be speculated that increased RDW reflects inflammatory changes in erythropoiesis. Moreover, increased RDW is associated with reduced erythrocyte deformability, which can impair blood flow through microcirculation.[18] Based on the current evidence, it appears that increased RDW may be an important marker of poor stem cell mobilization and bone marrow dysfunction in advanced HF.[15,19] Although the underlying mechanisms of bone marrow dysfunction in these patients have not bee elucidated, the possible explanation is that apoptosis is triggered by proinflammatory cytokines and blunted response of hematopoietic stem cells to erythropoietin.[15] These data suggest that RDW may be an integrative measure of the main pathophysiological processes that occur in HF. Additionally, it has been shown to be independent of N-terminal pro-B-type natriuretic peptide, which is a prognostic marker in patients with HF.[9,20] Furthermore, the lifespan of red blood cells is approximately 100 days, which is much longer than that of natriuretic peptides.[21] Therefore, RDW may be subject to biological variation to a lesser extent, which may make its clinical interpretation much easier than that of the standard laboratory parameters evaluated in patients with HF.

The current study demonstrated that another hematologic parameter, RLC%, is an independent predictor of mortality in patients with advanced HF. Importantly, our results confirm previous findings in other populations with HF.[22] Furthermore, RLC% is a component of the Seattle Heart Failure Model. Several hypotheses explain the association of low RLC% with mortality in patients with HF. Lymphocytopenia may reflect neurohormonal activation and is a marker of the physiological stress response mediated by an increased release of cortisol and catecholamines in HF.[22] Cortisol and catecholamines can induce lymphocyte apoptosis and downregulate lymphocyte proliferation and differentiation.[23] It is well documented that inflammation and immune activation play a critical role in the development and progression of HF.[24] Moreover, a chronic activation of lymphocytes and monocytes by high levels of cytokines is observed in advanced HF.[25] It has been postulated that during episodes of decompensation and systemic congestion, bacterial endotoxin translocation from the gut into the circulation may occur.[26] Endotoxin levels increase especially in patients with HF with volume overload and low cardiac output.[27] Endotoxin induces cytokine release and lymphocyte apoptosis, which appear to be the main mechanisms implicated in the pathogenesis of lymphopenia in HF.[28] Additionally, lymphopenia may predispose patients with HF to infections, which are a well-known cause of death.

Our data support prior analyses that have shown the association between diabetes and an increased risk of death during long-term follow-up.[29-33] The main metabolic abnormalities in diabetes include hyperglycemia, hyperlipidemia, and inflammation. They stimulate the generation of reactive oxygen species, which leads to diabetic complications such as diabetic cardiomyopathy, coronary artery disease, and cardiac autonomic neuropathy.[34] The latter affects blood flow in the coronary arteries and alters the contractile function of the myocardium. Patients with cardiac autonomic neuropathy were found to have reduced vascular elasticity and an increased peripheral vascular resistance due to abnormal sympathetic tone.[34] Therefore, HF complicates the treatment of diabetes by altering the pharmacokinetics of antidiabetic medications. The results of 2 multicenter randomized trials—SOLVD[29] and CHARM[30]—showed that diabetes was an independent predictor of all-cause mortality in patients with

chronic HF. Cubbon et al[32] observed that patients with HF and type 2 diabetes have a higher risk of all-cause mortality than similar patients without diabetes. In accordance with our report, the Swedish Heart Failure Registry[33] and the Spanish National Registry on Heart Failure (RICA)[35] showed that type 2 diabetes was associated with higher all-cause mortality rates. Furthermore, the EVEREST database[36] of inpatients with HF indicated a close relationship between diabetes and all-cause mortality during a 10-month follow-up. Moreover, the EPICAL study,[37] which has included nearly 500 hospitalized HF patients, showed that one of the predictors of death during a long-term follow-up was diabetes. Our results are in conflict with findings from the Norwegian Heart Failure registry, which did not reveal the association between diabetes and mortality.[38] However, the registry differed from our study because it involved a real-life population treated at outpatient clinics and the patients were older than those in our analysis. Also a Brazilian registry did not show diabetes to be a cardiovascular risk factor.[39] In the OPTIMIZE-HF registry,[40] there was no association between diabetes and mortality rates. The discrepancy may have resulted from the significantly shorter follow-up in that registry.

The above analyses and our findings emphasize the need for active screening of the population with HF for the presence of diabetes. This is especially true because, as recent evidence suggests, HF is one of the most common initial manifestations of cardiovascular disease in type 2 diabetes.[41]

Study limitations Our population was recruited from a single referral center for patients with HF; therefore, the results should be interpreted with caution. Unfortunately, the data on the duration of diabetes, important for all-cause mortality, were unavailable. Furthermore, diabetes was defined on the basis of a previously established diagnosis rather than on routine screening of all individuals. This might have resulted in the inclusion of some patients with diabetes in the nondiabetic cohort, thereby potentially diminishing the effect of diabetes in our analysis. However, the prevalence of diabetes in our cohort remains within the broad range observed in contemporary HF cohorts, and so the impact of crossover is likely to be limited.

Another limitation is the fact that our patients did not undergo routine assessment of the biomarkers reflecting systemic iron status, such as serum iron, ferritin, total iron binding protein, transferrin, vitamin B_{12}, or folic acid. Being aware of that limitation, we excluded patients with anemia. It should be emphasized that there is no universal definiton of anemia that would specify the lower limit of normal blood hemoglobin concentrations. In the present study, the definition was based on the report of the World Health Organization from 1968.[7] Although this definition is widely accepted, it is controversial whether these cutoff values may be still applied today.

Yet another limitation of the study is that although patients did not receive blood transfusions, erythropoietin therapy, or intravenous iron therapy at the time of inclusion, the data on potential iron therapy or the use of erythropoiesis--stimulating agents during the follow-up period are lacking.

A relatively small percentage of patients with an implantable cardioverter–defibrillator (ICD) or cardiac resynchronization therapy device (CRT-D) may be explained by the fact that the COMMIT--HF registry included patients who were hospitalized in our institution for the first time. The reason for hospitalization was decompensation of HF, requiring optimization of pharmacotherapy or coronary revascularization before implantation. This group also included patients who were scheduled to be admitted to our center for ICD or CRT-D implantation.

In conclusion, RDW and RLC% are simple, accurate, and widely available markers that predict mortality in patients with advanced HF during a 3-year follow-up. Because complete blood count is a routine test for patients with HF, and RDW and RLC% are standard hematologic parameters, they may be included in a standard assessment of prognosis in patients with HF at no additional cost. Finally, the present study showed that type 2 diabetes is a strong independent predictor of death in patients with advanced HF.

CONTRIBUTION STATEMENT ŁS and BS-J contributed to the study concept and design, data analysis and interpretation, as well as drafting and revision of the manuscript. ŁP, ER, and PP were involved in data collection and performed statistical analysis. MG was responsible for the critical revision for intellectual concept of the manuscript. All authors approved the final version of the manuscript.

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