ORIGINAL ARTICLE

Mortality risk factors in patients with advanced heart failure and diabetes mellitus

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ABSTRACT

BACKGROUND An accurate assessment of prognosis is an important element of the management of patients with advanced heart failure (HF) and diabetes mellitus, because the cooccurrence of these 2 diseases has a particularly unfavorable effect on their course and treatment efficacy.

AIMS The aim of the study was to determine the prognostic factors affecting survival in patients with HF and diabetes.

METHODS This was a retrospective analysis of clinical and laboratory data of 367 consecutive patients with advanced HF (New York Heart Association classes III–IV) and diabetes, hospitalized in a tertiary referral center for interventional cardiology between 2009 and 2013. Patients with hematologic disorders, those treated with steroids, and those with incomplete clinical data were excluded. The endpoint of the study was all-cause death.

RESULTS The mean (SD) age of patients was 63.3 (10.8) years; men constituted 75.7% of the study group. During a mean (SD) follow-up of 4.4 (1.3) years, the overall mortality rate was 53.7%. In a multivariate analysis, independent risk factors of death included atrial fibrillation (AF) (hazard ratio [HR], 1.57; 95% CI, 1.14–2.17; P <0.01), red blood cell distribution width (RDW) (HR, 1.05; 95% CI, 1.02–1.07; P <0.0001), and platelet-to-lymphocyte ratio (PLR) (HR, 1.01; 95% CI, 1.01–1.01; P <0.0001).

CONCLUSIONS Our study showed that permanent AF and 2 hematologic parameters, RDW and PLR, are associated with an increased risk of death in a long-term follow-up in patients with advanced HF and concomitant diabetes.

INTRODUCTION An early diagnosis and accurate assessment of prognosis is an important element of the management of patients with advanced heart failure (HF) and diabetes mellitus, because the cooccurrence of these 2 diseases has a particularly unfavorable effect on their course and treatment efficacy.

Diabetes is associated with accelerated atherosclerosis and direct myocardial damage.[1] It is postulated that accelerated atherosclerosis in patients with HF and concomitant diabetes is caused by the presence of such factors as low-grade inflammation, hyperglycemia with increased formation of advanced glycation end products, dyslipidemia, hyperinsulinemia, obesity, oxidative stress, and autonomic imbalance.[2] Hyperglycemia is associated with low-grade inflammation, and this association has been found to underlie the development of both diabetes and HF. Chronic hyperglycemia is connected with an increased production of proinflammatory cytokines stimulated by oxidative mechanisms in vascular endothelial cells, leading to endothelial dysfunction [3,4] and imbalance in the production of vasodilators and prothrombotic factors. Elevated platelet activation and increased release of prothrombotic and proinflammatory factors in patients with diabetes is further sustained by overproduction of reactive oxygen species, impaired calcium metabolism, decreased bioavailability of nitric oxide, as well as increased phosphorylation and glycosylation of cellular proteins.[5] The impact of diabetes on HF depends on the degree of metabolic disturbances, the use of antidiabetic drugs, as

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WHAT'S NEW?

This single-center, retrospective study assessed the predictive value of inflammatory markers and prothrombotic activity in patients with advanced heart failure and type 2 diabetes in a long-term follow-up. We demonstrated that the platelet-to-lymphocyte ratio and red blood cell distribution width are predictors of death in patients with concomitant type 2 diabetes and heart failure. The main advantage of these prognostic indicators is that they are based on simple and routinely used laboratory parameters; therefore, their measurement is cost-effective and can be done in each patient admitted to the hospital. Among the analyzed clinical factors, permanent atrial fibrillation was also found to be an independent predictor of mortality in our patients.

well as their side effects and interactions with drugs commonly used in HF.[6,7]

The aim of the study waso to identify factors associated with an increased risk of death in long-term follow-up in patients with advanced HF and concomitant diabetes.

METHODS We analyzed clinical and laboratory data of 367 consecutive patients with advanced HF (New York Heart Association [NYHA] classes III–IV; Interagency Registry for Mechanically Assisted Circulatory Support, 4–6 profile) and type 2 diabetes from the COMMIT-HF registry, admitted to a tertiary referral center for interventional cardiology between 2009 and 2013.[8] Patients with hematologic disorders (including anemia) and autoimmune disorders, acute or chronic inflammatory diseases, known malignancies, or incomplete clinical and laboratory data were excluded from the study. Furthermore, patients receiving intravenous iron or erythropoietin therapy, glucocorticoids, or blood transfusions at the time of inclusion were also excluded from the study. Heart failure was diagnosed based on guideline recommendations at the time of inclusion.[9-11] Diabetes was diagnosed when one of the following criteria was met: 1) the diagnosis of diabetes was previously established and documented in the patient's medical records; and 2) the patient had a current prescription for oral hypoglycemic medication or insulin.

Samples of peripheral venous blood were drawn after 12 hours of fasting from the antecubital vein on admission and studied at the laboratory within 30 minutes of collection. Blood samples were placed in standardized EDTA tubes for a complete blood count. The results, together with hematologic parameters such as mean corpuscular volume (MCV), platelet-to--lymphocyte ratio (PLR), mean platelet volume (MPV), relative lymphocyte count (RLC%), and red blood cell distribution width (RDW), were analyzed using an automated blood cell counter (Sysmex XS1000i and XE2100, Sysmex Corporation, Kobe, Japan). For the calculation of RDW, the following formula was used: RDW = (standard deviation of red blood cell corpuscular volume) / MCV × 100%. The PLR was calculated by dividing the platelet count by the absolute lymphocyte count. The endpoint of the study was death from all causes. Survival within a 3-year follow-up was based on the information obtained from the national healthcare provider.

The present study conforms to the Declaration of Helsinki.

Statistical analysis Continuous data were expressed as a mean (SD) for normally distributed data or median with lower and upper quartiles for skewed data. Categorical variables were presented as a number and percentage. Differences between groups were assessed with the *t* test for normally distributed data, while the Mann–Whitney test was used for nonnormally distributed continuous variables and the χ^2 test was used for categorical variables. The effect of the continuous and dichotomous variables on the incidence of death in long-term follow-up was assessed with a Cox proportional hazards model. A univariate Cox proportional hazards regression analysis was used to select the potential independent predictors of death for inclusion in a multivariate analysis. The variables of univariate analysis with a *P* value of less than 0.2 were entered into a multivariate logistic regression model with stepwise selection. The examined covariates included age, male sex, NYHA class IV, history of arterial hypertension, atrial fibrillation (AF), as well as laboratory parameters (alanine aminotransferase, creatinine, uric acid, sodium, erythrocytes, hemoglobin, hematocrit, platelets, lymphocytes, PLR, RDW, PDW, and MPV). The tolerance and variance inflation factor was used to assess the correlation between explanatory variables as well as to assess multicollinearity. A *P* value of less than 0.05 was considered significant. Calculations were performed using the SAS software (Version 9.4, SAS Institute Inc., Cary, North Carolina, United States).

RESULTS The study was a retrospective analysis of 367 consecutive patients with advanced HF and diabetes, selected out of the total number of 1812 patients with chronic HF hospitalized in our cardiology department between 2009 and 2013. The mean (SD) age of patients was 63.3 (10.8) years; men constituted 75.7% of the study group. During a mean (SD) follow-up of 4.4 (1.3) years, the overall mortality rate was 53.7%.

Patients received maximum tolerated doses of β-blockers (95.1% of the study group), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (80.4%), aldosterone antagonists (80.9%), and loop diuretics (90%). All patients were receiving insulin therapy or oral hypoglycemic drugs. The baseline characteristics of the study population divided into

TABLE 1 Baseline characteristics of the study population divided into patients who survived and failed to survive during follow-up

Parameter	Survival (n = 170 [46.3%])	Nonsurvival (n = 197 [53.7%])	*P* value
Age, y	62.0 (56.0–70.4)	63.2 (56.6–73.7)	0.08
Male sex	121 (71.2)	157 (79.7)	0.06
BMI, kg/m^2	27.85 (25.60–29.76)	27.44 (25.14–29.76)	0.53
Obesity	41 (24.1)	45 (22.8)	0.77
Ischemic etiology of HF	114 (67.1)	138 (70.1)	0.8
NYHA class III	138 (81.2)	139 (70.6)	0.02
NYHA class IV	32 (18.8)	58 (29.4)	0.02
Atrial fibrillation	56 (32.9)	79 (40.3)	0.15
Arterial hypertension	110 (64.7)	114 (58.2)	0.2
Erythrocytes, ×10^{12}/l, mean (SD)	4.53 (0.66)	4.44 (0.64)	0.16
Hemoglobin, mmol/l	8.51 (1.23)	8.32 (1.20)	0.14
Hematocrit, l/l, mean (SD)	0.41 (0.05)	0.40 (0.05)	0.15
Leukocytes, ×10^9/l	7.65 (6.23–9.53)	7.72 (6.28–9.23)	0.88
Lymphocytes, ×10^9/l	2.11 (1.42–3.25)	1.34 (0.81–2.07)	<0.001
Platelets, ×10^9/l	204 (161–248)	232 (194–265)	<0.001
PLR	81.62 (62.90–97.44)	168.22 (132.71–232.31)	<0.001
MCV, fl	90.6 (86.8–93.6)	89.4 (85.7–93.7)	0.16
RDW-SD, fl	46.3 (43.4–49.9)	47.7 (44.7–52.9)	<0.001
PDW, fl	13.5 (12.5–15.4)	13.4 (12.2–14.6)	0.07
MPV, fl	11.1 (10.8–11.7)	12.4 (12.0–13.0)	<0.001
Bilirubin, µmol/l	13.1 (8.9–21.5)	14.1 (9.0–23.0)	0.33
Creatinine, µmol/l	97.0 (79.9–120.0)	102.0 (82.0–126.2)	0.15
AST, U/l	26.0 (19.2–35.0)	25.1 (18.9–38.0)	0.98
ALT, U/l	25.8 (17.6–40.7)	23.0 (15.3–39.0)	0.13
INR	1.11 (1.00–1.28)	1.13 (1.04–1.35)	0.10
Uric acid, µmol/l, mean (SD)	430.4 (132.0)	475.5 (146.9)	<0.05
Glucose, mmol/l	6.4 (5.4–7.9)	6.6 (5.4–8.7)	0.29
HbA_{1c}, %	6.8 (6.3–7.4)	6.7 (6.1–7.2)	0.58
Cholesterol, mmol/l	4.06 (3.23–5.44)	4.00 (3.21–5.09)	0.48
Triglycerides, mmol/l	1.33 (0.98–1.88)	1.16 (0.91–1.62)	<0.05
HDL cholesterol, mmol/l	0.97 (0.84–1.27)	0.94 (0.81–1.23)	0.78
LDL cholesterol, mmol/l	2.28 (1.68–3.38)	2.25 (1.68–3.07)	0.82
Sodium, mmol/l	137 (135–139)	137 (134–139)	0.14
Potassium, mmol/l	4.4 (4.1–4.7)	4.5 (4.1–4.9)	0.19
NT-proBNP, pg/ml	3005 (1548–4757)	3292 (1930–5268)	0.20
LA, mm	43 (40–50)	45 (41–51)	0.16
LVEDd, mm	64 (59–70)	62 (58–70)	0.15
LVEF, %	26 (21–32)	28 (22–31)	0.64
Insulin therapy	95 (55.9)	128 (65)	0.08
Oral hypoglycemic drugs	56 (32.9)	56 (28.4)	0.35
Insulin therapy + hypoglycemic drugs	41 (24.1)	45 (22.8)	0.12

Data are presented as median (interquartile range) or number (percentage) of patients unless otherwise indicated.

SI conversion factors: hemoglobin to g/l, multiply by 1.611 (mmol/l).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HbA_{1c}, glycated hemoglobin A_{1c}; HDL, high-density lipoprotein; INR, international normalized ratio; LA, left atrium; LDL, low-density lipoprotein; LVEDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MCV, mean corpuscular volume; MPV, mean platelet volume; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; NYHA, New York Heart Association; PDW, platelet distribution width; PLR, platelet-to-lymphocyte ratio; RBC, red blood cells; RDW, red blood cell distribution width; RLC, relative lymphocyte count; WBC, white blood cells

TABLE 2 Comparison between patients treated with oral hypoglycemic drugs and insulin therapy

Parameters	Oral hypoglycemic drugs (n = 112)	Insulin therapy (n = 223)	*P* value
Age, y	63.14 (56.34–72.58)	60.65 (53.97–65.76)	0.20
BMI, kg/m^2	27.68 (24.77–29.76)	27.90 (26.03–29.09)	0.50
Leukocytes, ×10^9/l	7.67 (6.22–9.35)	7.73 (6.95–9.2)	0.67
Erythrocytes, ×10^{12}/µl, mean (SD)	4.48 (0.66)	4.47 (0.56)	0.90
Hemoglobin, mmol/l, mean (SD)	8.41 (1.23)	8.39 (1.12)	0.92
Hematocrit, l/l, mean (SD)	0.4 (0.05)	0.4 (0.05)	0.87
Platelets, ×10^9/l	204 (166–245)	193 (164–243)	0.81
INR	1.11 (1.02–1.34)	1.1 (1–1.32)	0.78
AST, U/l	26 (19.1–36.77)	21.5 (18–33)	0.09
ALT, U/l	24.91 (17–40.65)	21.5 (14–34)	0.13
Bilirubin, µmol/l	12.48 (8–22.1)	14.5 (9.55–22.3)	0.09
Creatinine, µmol/l	99 (80.32–123)	102 (78.32–132)	0.77
Uric acid, µmol/l, mean (SD)	459.08 (142.98)	411.53 (123.57)	0.09
Glucose, mmol/l	6.4 (5.4–8.37)	6.65 (5.63–10.39)	0.21
HbA_{1c}, %	6.7 (6.2–7.3)	6.70 (6.2–7.5)	0.92
Cholesterol, mmol/l	4.01 (3.23–5.3)	3.87 (3.22–4.67)	0.34
Triglycerides, mmol/l	1.27 (0.95–1.79)	1.25 (0.95–1.62)	0.80
HDL, mmol/l	0.94 (0.81–1.22)	1.14 (0.86–1.50)	0.06
LDL, mmol/l	2.29 (1.68–3.2)	2.18 (1.79–2.51)	0.50
Sodium, mmol/l	137 (134–139)	136.77 (135–138.5)	0.88
Potassium, mmol/l	4.4 (4.1–4.73)	4.57 (4.23–4.87)	0.15
PLR	123.37 (86.53–184.45)	103.28 (65.79–166.19)	0.06
MCV, fl	90.05 (86.10–93.7)	88.90 (86.40–92.1)	0.63
RDW-SD, fl	47.15 (44–51.2)	46.40 (43.50–50.7)	0.31
PDW, fl	13.50 (12.4–15.1)	13.40 (11.80–15.6)	0.55
MPV, fl	11.90 (11.2–12.6)	11.30 (10.50–12.3)	0.05
NT-proBNP, pg/ml	3232 (1653–5095)	2993.5 (1452.5–5234.5)	0.81
LVEDd, mm	63 (58–70)	64.50 (61–72)	0.18
LA, mm, mean (SD)	45.43 (6.83)	44.19 (6.57)	0.33
LVEF, %	27 (22–31)	27 (21–32)	0.87

Data are presented as medians (IQR) or numbers (percentages) of patients unless otherwise indicated. For conversion factors, see TABLE 1.

Abbreviations: see TABLE 1

groups of patients who survived and those who died are presented in TABLE 1. There were no significant differences between alive and deceased patients in terms of pharmacological therapy of HF and diabetes. Moreover, there were no differences between patients who received insulin therapy and those on oral hypoglycemic drugs in terms of the mortality predictors (TABLE 2). The percentage of patients who received defibrillation and / or resynchronization therapy was similar between alive and deceased patients (71.8% and 69.5%, respectively). The results of the univariate and multivariate Cox proportional hazard regression analyses are presented in TABLES 3 and 4.

DISCUSSION

In this single-center study, we found that PLR and RDW (hematologic parameters obtained by a routine blood test) are predictors of death during long-term follow-up in patients with advanced HF and diabetes. Among the analyzed clinical factors and laboratory parameters, permanent AF and serum sodium levels were found to be independent predictors of mortality.

Importantly, our patients did not suffer from hematologic disorders, bone marrow dysfunction, connective tissue diseases, thyroid or hepatic disorders, and they did not receive blood transfusions, intravenous iron, or erythropoietin therapy. The above disorders can be responsible for RDW and PLR alterations.

To the best of our knowledge, this is the first clinical study assessing the relationship between PLR and outcomes in patients with advanced HF and diabetes. The PLR is a marker of systemic inflammation, which can be calculated from the platelet and lymphocyte counts for each patient admitted to the hospital. Since the indicator is a ratio, its value is relatively more stable than that of the platelet or lymphocyte count alone.[12]

It has been shown that platelets are activated in HF and diabetes through an interplay between inflammation and thrombosis. Activated platelets release proinflammatory markers, a mechanism involved in the pathophysiology of HF and atherothrombotic processes.[13] Our results are consistent with the available literature. Moreover, previous studies also indicated that lymphocytopenia results from increased stress and consequent lymphocyte apoptosis. The pathologic mechanisms underlying these findings are unclear. However, the lymphocyte count can be considered an early marker of physiologic stress and systemic inflammation.[14] Gary et al[15] reported that PLR significantly correlated with inflammatory markers such as C-reactive protein and fibrinogen in patients with limb ischemia.

The RDW is a measure of heterogeneity in the size of circulating erythrocytes. It is calculated using automated hematologic analyzers. It is typically elevated in clinical conditions such as ineffective red cell production, increased red cell destruction, or after blood transfusions. The elevation of RDW has been associated with other disease processes, including liver disorders, malnutrition, occult colon cancer, and bone marrow metastases.[16,17] The RDW is a marker of multiple pathologic processes in HF (nutritional

TABLE 3 Results of the univariate Cox proportional hazard regression analysis

Parameter	HR	95% CI	*P* value
Age	1.01	1.01–1.03	0.04
Male	1.48	1.04–2.09	0.03
NYHA class IV	1.56	1.15–2.13	0.004
Arterial hypertension	0.79	0.59–1.05	0.11
Atrial fibrillation	1.28	0.96–1.70	<0.01
Erythrocytes	0.83	0.67–1.02	0.08
Hematocrit	0.77	0.01–1.01	0.05
ALT	0.99	0.99–1.01	0.16
Creatinine	1.01	1.01–1.02	0.01
Uric acid	1.01	1.01–1.02	0.003
Sodium	0.95	0.91–0.98	0.001
Platelets	1.01	1.01–1.02	0.003
Lymphocytes	0.95	0.93–0.97	<0.0001
PDW	0.94	0.88–1.01	0.07
MPV	2.15	1.87–2.47	<0.0001
PLR	1.01	1.01–1.02	<0.0001
RDW	1.05	1.03–1.07	<0.0001

Abbreviations: HR, hazard ratio; others, see TABLE 1

TABLE 4 Results of the multivariate Cox proportional hazard regression analysis

Parameter	HR	95% CI	*P* value
PLR	1.01	1.00–1.01	<0.0001
RDW	1.05	1.02–1.07	0.0002
Sodium	0.94	0.90–0.98	0.002
Atrial fibrillation	1.61	1.14–2.27	0.01

Abbreviations: see TABLES 1 and 3

deficiencies, renal dysfunction, hepatic congestion), explaining its association with clinical outcomes. Recent studies have demonstrated an association between diabetes and RDW, and RDW has been reported to be a marker of inflammation.[18-20] Importantly, inflammation is a common finding in patients with diabetes, which may explain why diabetes is called a "proinflammatory state."[21]

Atrial fibrillation is another factor influencing the long-term prognosis of patients with HF and diabetes. There is some evidence that the underlying biological link between diabetes and AF is one of the main cardiovascular complications associated with diabetes. An unfavorable effect of hyperglycemia in diabetes is associated with alterations in vascular homeostasis and cardiomyocytes. Increased production of inflammatory cytokines and reactive oxygen species induces the formation of advanced glycosylation end products, which infiltrate the myocardium, leading to myocardial hypertrophy and interstitial fibrosis.[22] All these mechanisms form the basis for anatomic and electrical atrial remodeling.

An important mechanism underlying the development of AF is also low-grade inflammation. It has been shown that inflammation can affect the generation, maintenance, and perpetuation of AF. In atrial biopsies of patients with AF, increased inflammatory infiltrates have been found.[23] Furthermore, in AF patients, the C-reactive protein levels were higher compared with patients without AF.[24]

It should be also emphasized that disturbances in the balance between glucose and insulin levels negatively affect the atrial and ventricular myocardium by maintaining low-grade inflammation and promoting production of free radicals. In conditions of impaired glucose tolerance and inadequate insulin secretion, a gradual left ventricular hypertrophy is observed, which is also a significant risk factor for AF development. An analysis of patients from Framingham Heart Study showed that the worsening of glucose tolerance was associated with an increased left ventricular mass,[25] which can affect the maintenance and perpetuation of AF.

Finally, some studies have also shown that an important factor influencing the initiation and maintenance of AF is the level of activity of the autonomic nervous system. In most patients with organic heart diseases, AF episodes appear to depend more on the sympathetic nervous system activity.[26-30]

Our study demonstrated that the plasma sodium level was another factor influencing prognosis. Hyponatremia remains a common problem and a strong predictor of poor outcome in different populations of patients with HF.[31-34] It is included in many prognostic models used in these patients.[31-34]

Our study has several limitations. First, it was a single-center analysis and the results should thus be interpreted with caution. Unfortunately, data on diabetes duration and the presence of complex ventricular arrythmias on admission and during follow-up, important for all-cause mortality, were unavailable.

In conclusion, our study confirmed that permanent AF, serum sodium levels, and the hematologic parameters RDW and PLR are associated with an increased risk of death in long-term follow-up in patients with advanced HF and concomitant diabetes.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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