Red Blood Cell Distribution Width in End-Stage Heart Failure Patients Is Independently Associated With All-Cause Mortality After Orthotopic Heart Transplantation

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ABSTRACT

Background. Red blood cell markers (RBCM) have been found to be predictors of mortality in various populations. However, there is no information regarding the association between the values of RBCM and long-term outcomes after orthotopic heart transplantation (OHT).

The aim of this study was to assess whether the values of inflammatory markers and RBCM obtained directly before OHT are associated with mortality in patients diagnosed as having end-stage heart failure undergoing OHT.

Methods. We retrospectively analyzed data of 173 nonanemic adult patients diagnosed as having end-stage heart failure undergoing primary OHT between 2007 and 2014. Clinical and laboratory data were obtained at the time of admission for the OHT. RBCM were analyzed using an automated blood counter (Sysmex XS-1000i and XE-2100, Sysmex Corporation, Kobe, Japan).

Results. Mean age of the patients was 54 (41–59) and 72% of them were male. During the observation period, the mortality rate was 32%. Multivariable analysis of Cox proportional hazard confirmed that elevated pretransplantation red blood cell distribution width value (hazard ratio [HR], 1.38 [1.25–1.48], $P < .001$) was the sole independent predictor of death during long-term follow-up. Other red blood cell distribution width such as mean corpuscular volume, mean corpuscular hemoglobin concentration, and mean corpuscular hemoglobin (HR, 0.88 [0.84–0.91]; $P < .001$; HR, 0.75 [0.53–1.05]; $P < .05$; HR, 0.78 [0.64–0.96]; $P < .05$, respectively) had predictive value in univariable analysis.

Conclusions. In summary, we have demonstrated that elevated red blood cell distribution width immediately before OHT is an independent predictor of all-cause mortality in heart transplant recipients. Other factors associated with posttransplantation mortality include lower values of mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

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RED blood cell distribution width (RDW) is a quantitative measure of variation in circulating erythrocyte volume (ie, anisocytosis) recorded during a standard complete blood count [1]. Conditions of ineffective erythropoiesis or increased erythrocyte destruction cause greater heterogeneity in red blood cell size and, thus, higher RDW [2,3]. Increased RDW may reflect iron deficiency, bone marrow depression, or systemic inflammation [4]. Recent studies have suggested that other red blood cell markers—mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC)— are hematologic indices related to iron stores [5]. Therefore, low MCHC represents a gross estimate of the presence of relative hypochromia (defined as low MCHC in the setting of normal hemoglobin level).

Another important marker of bone marrow malfunction is mean corpuscular volume (MCV), a measure of the average size of erythrocytes [6]. Traditionally, MCV is applied as an indicator in the differential diagnosis of anemia. In recent years, RDW and other red blood cell markers have been found to be independent predictors of mortality and morbidity in various populations, including patients diagnosed as having different stages of heart failure (HF), subjects diagnosed as having end-stage renal disease, or critically ill patients [6–10]. However, there is no information regarding the association between the values of red blood cell markers and long-term outcomes after orthotopic heart transplantation (OHT).

The aim of this study was to assess whether the values of inflammatory and red blood cell markers obtained directly before OHT are associated with all-cause mortality in patients diagnosed as having end-stage HF undergoing OHT.

MATERIAL AND METHODS

The data were collected retrospectively in 231 adult patients diagnosed as having end-stage HF undergoing primary OHT at the Silesian Centre for Heart Diseases between 2007 and 2014.

Patients with a previous history of anemia or previous red blood cell transfusion, as well as patients receiving treatment for anemia, such as supplemental iron, folate, or erythropoiesis-stimulating agents at the baseline, were excluded from this study. Based on such criteria, we excluded 58 subjects, leaving a total of 173 patients in the analysis. Laboratory data for the calculation of RDW and other laboratory data were obtained at the time of admission for the OHT.

Venous blood samples were collected on admission in standardized dipotassium EDTA tubes. The samples were tested within 30 minutes of collection to minimize variations due to sample aging. The complete blood counts of patients as well as red blood cell markers were analyzed using an automated blood counter (Sysmex XS-1000i and XE-2100, Sysmex Corporation, Kobe, Japan). The intra-assay and inter-assay coefficients of variation for the blood samples were 5% and 4.5%, respectively.

RDW is defined as a quotient of SD of red blood cell volume and its mean volume and is expressed as a percentage. RDW was calculated according to the following formula: RDW = (SD of red blood cell volume/mean cell volume) × 100. Higher RDW values reflect greater variations in red blood cell volume [1]. The MCV is a measure of the average size of red blood cells; it was calculated using the following formula: MCV = Hematocrit/Red Blood Cell Count [1].

MCHC is the relative amount of hemoglobin content in erythrocytes; it has served as one of several hematologic indices related to iron stores [9].

Anemia was defined using the World Health Organization's criteria: hemoglobin level lower than 12 g/dL in women and 13 g/dL in men [11].

The all-cause mortality status was obtained from direct physical or telephone contact with the patients or their relatives and from hospital information systems. No patient was lost to follow-up.

Statistical Analysis

A statistical analysis was performed using SAS software, version 9.4 (SAS Institute Inc, Cary, NC, United States).

Continuous variables with normal distribution are expressed as means and SD s; those with skewed distribution are expressed as medians (25th-75th percentile). Categorical variables are expressed as percentages. Differences between the study groups were assessed using t test, Mann-Whitney test, or χ^2 test.

The effect of the studied variables on the incidence of death in long-term follow-up was assessed with Cox's proportional hazards model. Cox's univariable proportional analysis was used to select potential independent predictive factors of death for inclusion in the multivariable analysis. The examined covariates included erythrocytes, RDW, MCV, MCHC, MCH, and C-reactive protein. Univariable predictors of death with P value of $< .1$ were entered into the multivariable Cox proportional hazards model with backward stepwise selection. The correlation between explanatory variables was checked, and multicollinearity was evaluated by means of tolerance and variance inflation factor. Results are presented as hazard ratios (HRs) with 95% CI s.

RESULTS

The study population consisted of 173 nonanemic patients diagnosed as having end-stage HF undergoing OHT. Baseline patient characteristics are summarized in Table 1. The average follow-up was 45.5 ± 28.4 months. During the observation period, the mortality rate was 32% (n = 56). Before the OHT, all patients had received optimal pharmacological therapy with the maximum tolerated dose of an angiotensin-converting enzyme inhibitor (or angiotensin II receptor antagonist), a β-receptor antagonist (an extended-release carvedilol or metoprolol preparation), a mineralocorticoid receptor antagonist, furosemide, and defibrillation therapy with or without resynchronization therapy as appropriate.

Immunosuppressive regimen after OHT consisted of 3 drugs, including a calcineurin inhibitor (cyclosporine or tacrolimus), mycophenolate mofetil, and prednisone. Prednisone was discontinued at the end of the first year after OHT.

A multivariable analysis revealed that an elevated RDW value was the sole independent predictor of death during a long-term follow-up. Other red blood cell markers such as red blood cells, MCV, and MCHC showed a prognostic significance in a univariable analysis (Table 2).

DISCUSSION

The present study is the first to demonstrate that higher RDW obtained in patients diagnosed as having end-stage