



Role of circulatory leukocyte based indices in short-term mortality of patients with heart failure with reduced ejection fraction

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Abstract

Background. Pro-inflammatory signaling is mediated by a variety of inflammatory mediators which can cause myocardial apoptosis, hypertrophy, and fibrosis, and also ultimately lead to adverse cardiac remodeling. This study aimed to assess the role of circulating leukocyte-based indices in predicting the short-term mortality in patients with heart failure with reduced ejection fraction (HFrEF).

Methods. In a retrospective study, patients with HFrEF admitted to a tertiary referral center between January 2016 and January 2017 were recruited to this study. The association between neutrophil to lymphocyte ratio (NLR), derived neutrophil to lymphocyte ratio (dLNR = neutrophils/(leukocytes-neutrophils)), monocyte/granulocyte to lymphocyte ratio (MGLR = (white cell count-lymphocyte count) to lymphocyte count), platelet to lymphocyte ratio (PLR) and six-months mortality of patients were assessed.

Results. A total of 197 patients with HFrEF were enrolled in the study. NLR ($P<0.001$), dLNR ($P<0.001$), MGLR ($P<0.001$), PLR ($P=0.006$) and LVEF ($P=0.042$) showed significant difference between survived and died patients. In the Cox multivariate analysis we did not find NLR, dLNR, MGLR or PLR as an independent predictor of short-term mortality in HFrEF patients.

Conclusions. Although High NLR, PLR, MGLR and dLNR was associated with short-term mortality, it failed to independently predict the prognosis of HFrEF patients.

Keywords: heart failure, neutrophils, monocytes, lymphocytes, neutrophil to lymphocyte ratio, survival

Introduction

Heart failure (HF) is correlated with significant morbidity and mortality worldwide. As the population is aging, the incidence of HF is rising quickly and it is particularly due to an increasing rate of chronic ischemia and hypertension. It has a high burden of disease and contributes significantly to increasing health care costs [1].

HF is typically defined as either left ventricular diastolic or systolic dysfunction, otherwise known as HF with preserved ejection fraction (HFpEF) or

reduced EF (HFrEF), respectively. These categories are more than a descriptive issue and provide a treatment guide for patients with chronic HF [2].

Earlier, in the 1990s, cytokine hypothesis became an important link in addition to hemodynamic disorders in the pathogenesis of HF [3]. Nowadays, the role of neurohormones and inflammatory biomarkers in the pathogenesis of HF are well specified [4]. Additionally, the range of circulating inflammatory biomarkers may contribute to the clinical outcome of the patients [5]. Many studies reports

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the value of circulation leukocyte-based indices, such as the neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR), in predicting disease severity and outcomes across a variety of disorders including cardiovascular diseases [6,7], renal disease [8], and malignancy [9].

HF progression is associated with sustained pro-inflammatory signaling stipulated by previous studies. Pro-inflammatory signaling is mediated by a variety of inflammatory mediators which can produce apoptosis, hypertrophic cardiomyopathy, fibrosis, and ultimately lead to adverse cardiac remodeling [3]. Cytokines that have been involved in the pathogenesis of HF are the tumor necrosis factor (TNF)- α [10] and interleukins (ILs). IL-1 and 18 have a negative inotropic effects in the setting of HF [11] and IL-6 induced cardiac fibrosis and hypertrophy resulting in diastolic dysfunction [12]. The neutrophil chemotactic factor is another cytokine that induced chemotaxis, angiogenesis, and phagocytosis in HF. It has been linked to poor clinical outcomes in chronic HF [13]. Anti-inflammatory cytokines signaling act to mitigate hypertrophic cardiac remodeling [14] and stimulate alternative activation of macrophages and proliferation of T lymphocytes to Th2 cells [1].

Neutrophil has a major role in the inflammatory process and the lymphocyte is a marker of regulatory pathways. The NLR as an indicator of systemic inflammation is associated with poor clinical outcomes in cardiovascular diseases such as acute coronary syndrome [15]. Recent evidence showed that high NLR was associated with an increased risk of mortality and complications in post-acute myocardial infarction [16,17]. Turcato et al. [18] showed that the values of NLR and PLR were higher in acute decompensated heart failure patients who died within 30 days

Chen et al. [16] revealed that the inflammatory process plays an important role in the initiation and progression of cardiovascular diseases and Durmus et al. [19] showed that PLR and NLR were higher in HF. But PLR and NLR were not sufficient to confirm the diagnosis of HF. PLR or NLR are not included in the criteria for HF diagnosis. Also Pourafkari et al. [20] pointed out that higher PLR was associated with long-term mortality in acute HF patients, but it failed to be an independent predictor for the prognosis.

Also according to previous findings, inflammatory factors cells like NLR could be considered as a predictor of post-angiographic mortality in coronary artery disease [21].

Herein, the aim of this study was to assess the role of circulating leukocyte-based indices in predicting the short outcome in patients with HFrEF.

Methods

Subjects

A retrospective study on hospitalized HF patients was performed after the Institutional Review Board (IRB)

approval. All patients with HFrEF (ICD 11-th revision code: BD11.2) admitted to Shahid Madani Cardiovascular Hospital of Tabriz University of Medical Sciences between January 2016 and January 2017 were recruited in this study. This study was performed in accordance with the Helsinki humanity research declaration (2008).

All of the patients included in the study had the following inclusion criteria: progressive dyspnea associated with clinical evidence of pulmonary congestion and decreased cardiac output requiring hospitalization and left ventricular ejection fraction (LVEF) <40% and age >20 years.

Patients with acute myocardial infarction (MI), cardiogenic shock, hematologic disease, metastatic neoplastic disease, sepsis, pregnancy, advanced arthritis, inflammatory bowel disease, chronic inflammatory disease, recent corticosteroid use, and patients with fluids retention disease such as hypothyroidism and cirrhosis were excluded.

Clinical and biochemical measurements

Study entry required at least a baseline complete blood count (CBC) with a differential formula. After sampling, blood samples were investigated for total white blood cell (WBC), neutrophil, lymphocyte, and platelets using CBC H1 automated differential counter. All patients were referred to echocardiography examination in the first 24h of admission. Baseline cardiac functional capacities were computed for all patients based on the New York Heart Association (NYHA) classification at the time of hospitalization based on their medical records.

Demographic, clinical, echocardiographic, and laboratory characteristics of patients including age, sex, smoking, underlying diseases, LVEF percentage, cardiac functional capacity evaluated by LVEF values from echocardiography, total WBC count, platelets, neutrophils, and lymphocytes counts, six-month post-discharge hospital readmission and 180-days death, and emergency visits numbers were collected.

We calculated NLR, derived neutrophil to lymphocyte ratio ($dLNR = \text{neutrophils}/(\text{leucocytes} - \text{neutrophils})$), monocyte/granulocyte to lymphocyte ratio ($MGLR = (\text{white cell count} - \text{lymphocyte count}) / \text{lymphocyte count}$), PLR, platelet distribution width (PDW), and red cell distribution width (RDW).

Statistical analysis

Collected data were analyzed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0 software. Also, P values, odds ratio (OR) with 95% CI were calculated. Cox regression multivariable analysis was performed for short-term survival including variables with p values less than 0.05 in univariate analysis.

Results

A total of 197 patients with HFrEF were enrolled in the study. The mean \pm SD age of patients in the survivors and the mortality groups was 65.9 ± 14.64 and 68.63 ± 16.82

years, respectively. The baseline characteristics, echocardiographic findings and laboratory parameters of the HFrEF patients according to the patient's outcome are shown in table I.

There was no statistically significant relationship between the age of patients (OR: 1.013; P= 0.361) and survival in the six-month follow-up, but female gender (OR: 3.03; P <0.001), WBC (OR: 1.001; P <0.001) and absolute neutrophil count (ANC) (OR: 1.001; P <0.001) were significantly higher in the mortality group. As indicated in table I, NLR (OR: 1.259; P<0.001), dNLR

(OR: 1.435; P<0.001), MGLR (OR: 1.264; P<0.001), PLR (OR: 1.005; P= 0.006) and low LVEF (OR: 0.958; P=0.042) were associated with higher mortality.

Following ROC analyses, the optimal cut-off values of dNLR, MGLR, PLR, NLR were found to be 4.5, 8, 150 and 7.5 with a sensitivity of 56.7%, 50%, 51.7% and 50% and a specificity of 89%, 91.7%, 72.3%, and 91.7%, respectively. The corresponding areas under the curve for dNLR, MGLR, PLR, NLR were 0.728 (P <0.001), 0.708 (P <0.001), 0.62 (P=0.041) and 0.708 (P <0.001), respectively (Table II).

Table I. Demographic and laboratory findings of patients for hospital survival.

Variable	Survivors (n=167)	Mortality (n=30)	Odds Ratio [95%CI]	P value
Age (Years)	65.9±14.64	68.63±16.82	1.013 [0.985-1.014]	0.361
Gender (Female)	57 (36.3%)	19 (63.3%)	3.03 [1.347-6.817]	<0.001
Smoking	85 (22.3%)	6 (20%)	0.871 [0.33-2.3]	0.781
Hyperlipidemia	22 (14%)	2 (6.7%)	0.438 [0.097-1.972]	0.282
Hypertension	94 (59.9%)	16 (53.3%)	0.766 [0.349-1.679]	0.506
Diabetes Mellitus	42 (26.8%)	9 (30%)	1.173 [0.498-2.765]	0.715
Positive FH	14 (8.9%)	4 (13.3%)	1.571 [0.479-5.151]	0.456
LVEF (%)	29.97±10.95	25.19±11.04	0.958 [0.919-0.998]	0.042
FC (III, IV)	43 (27.3%)	15 (50%)	1.43 [0.751-2.723]	0.277
White Blood Cells (/μL)	8439.74±3362.9	11750±6057.52	1.001 [1.0007-1.002]	<0.001
ANC (/μL)	5871.79±2990.1	9431.33±6068.21	1.001 [1.0009-1.002]	<0.001
Lymphocyte (/μL)	1958.33±1099.9	1650±902.39	1 [0.999-1.0001]	0.152
Hematocrit (%)	38.87±6.07	38.51±6.07	0.99 [0.928-1.056]	0.762
Hemoglobin (g/dL)	13.39±2.26	12.77±2.85	0.899 [0.712-1.135]	0.370
PDW	13.41±2.25	14.36±2.97	1.038 [0.991-1.358]	0.065
RDW (%)	15.36±4.45	16.39±5.81	1.013 [0.966-1.114]	0.310
Platelet (*10 ³ /μL)	210±84	285±290	1.000003 [1-1.000009]	0.069
MPV	10.21±1.07	10.63±1.11	1.41 [0.971-2.049]	0.071
NLR	3.84±2.82	7.61±5.62	1.259 [1.132-1.399]	<0.001
dNLR	2.64±1.79	4.98±3.57	1.435 [1.214-1.696]	<0.001
MGLR	4.18±2.84	8.1±5.77	1.264 [1.135-1.406]	<0.001
PLR	132.81±81.18	220.72±233.3	1.005 [1.001-1.008]	0.006
Hospitalization (Days)	5.33±4.23	3.6±2.28	0.847 [0.726-0.989]	0.035
Death Time (Days)	180±0	80.7±53.49	1.509 [0-2.851×10 ⁵¹]	0.993
Readmission Rate	0.11±0.368	1.07±0.254	62.44 [17.16-227.14]	<0.001
Emergency Refer Rate	0.25±0.58	1.2±0.407	7.135 [3.597-14.152]	<0.001

ANC, Absolute Neutrophil Count; dNLR, derived Neutrophil to Lymphocyte Ratio; FC, Function Class; FH, Familial History; LVEF, Left Ventricular Ejection Fraction; MGLR, Monocyte/Granulocyte to Lymphocyte Ratio; MPV, Mean Platelet Volume; NLR, Neutrophil to Lymphocyte Ratio; PDW, Platelet Distribution Width; PLR, Platelet to Lymphocyte Ratio; RDW, Red Cell Distribution Width.

Table II. Diagnostic value of dNLR, MGLR, PLR and NLR in predicting the outcome of the patient.

Variable	Cut off	Sensitivity	Specificity	PPV	NPV	Accuracy	AUC	P value
dNLR	4.5	56.7	89	50	91.4	83.7	0.728	<0.001
MGLR	8	50	91.7	53.6	90.5	84.9	0.708	<0.001
PLR	150	51.7	72.3	25.9	88.9	69	0.62	0.041
NLR	7.5	50	91.7	53.6	90.5	84.9	0.708	<0.001

AUC, Area under the ROC Curve; NPV, Negative Predictive Value; PPV, Positive Predictive Value.

Table III. Cox regression multivariable analysis for short-term survival.

Variable	Coefficient	SE	HR [%95CI]	P Value
Gender	2.49	0.86	12.1 [2.21-66.18]	0.004
LVEF	-0.006	0.052	0.994 [0.898-1.099]	0.903
White Blood Cells	0.008	0.004	1.008 [0.999-1.016]	0.071
Absolute Neutrophil Count	-0.008	0.004	0.992 [0.983-1.001]	0.072
Mean Platelet Volume	3.42	1.44	30.63 [1.801-521.32]	0.018
Lymphocyte	-0.009	0.005	0.991 [0.981-1.002]	0.107
NLR	-1.56	6.95	0.209 [0-174756.58]	0.822
dLNR	1.162	0.75	3.198 [0.736-13.9]	0.121
MGLR	1.454	6.43	4.28 [0-1278553.4]	0.821
PLR	0.006	0.008	1.006 [0.99-1.021]	0.487
Readmission Rate	5.69	1.6	297.48 [12.71-6962.38]	0.001
Hospitalization	-0.753	0.281	0.471 [0.271-0.817]	0.007

dNLR, derived Neutrophil to Lymphocyte Ratio; LVEF, Left Ventricular Ejection Fraction; MGLR, Monocyte/Granulocyte to Lymphocyte Ratio; NLR, Neutrophil to Lymphocyte Ratio; PLR, Platelet to Lymphocyte Ratio.

On the other hand, in the Cox multivariate analysis (Table III) we did not find a significant association between the left ventricular ejection fraction, NLR, dLNR, MGLR or PLR and six-month survival. Moreover, smoking (OR: 25.98; $P=0.007$), and positive familial history in heart diseases (HR: 12.14; $P=0.027$) were associated with six-month survival.

Discussion

The predictive role of leukocyte-based circulating indices in cardiovascular diseases has been reported in recent years. Despite progression in HF treatment, the prognosis of patients is poor and it is estimated that the five year estimated mortality of HF patients is over 50% [22]. A better understanding of the HF pathophysiology and the role of inflammatory biomarkers could improve the clinical management of HF patients and reduce the adverse clinical outcomes [5]. The evidence showed a strong relationship between high NLR and increased morbidity and mortality in a wide range of cardiovascular diseases including heart failure [16]. The relationship for NLR in some studies is probably due to that some physiological conditions which affect the absolute number of white blood cells subtypes more than NLR. For example, exercise increases lymphocyte and neutrophil counts, affecting to a lesser degree the NLR ratio [23].

To our knowledge, we did not find studies to investigate the prognostic role of PLR, dNLR or MGLR in the patients' survival prognosis, but there are few studies regarding NLR value significance in cardiovascular diseases including HF. In this study, NLR, dNLR, MGLR, and PLR as parameters showed high specificity, acceptable accuracy, but respectively low sensitivity. Turfan et al. evaluated patients admitted with HF and found that NLR was an independent predictor of in-hospital mortality [24].

Durmus et al. in a case-control study found higher NLR and PLR in HF patients. In their study, NLR was an independent predictor for survival and was related with higher mortality in HF patients, but they could not find an association between the PLR and HF prognosis [19]. In a study on HF patients performed by Yan et al. it was shown that high NLR is associated with a higher rate of major cardiovascular events in elderly patients with HF [25]. Moreover, the prognostic role of increased NLR in HF patients was confirmed by Delcea et al. in a comprehensive review [26]. We found a significant difference in NLR and PLR in HF patients, but in the Cox regression the difference was not significant. Although NLR and PLR were higher in HF patients, they were not sufficient to establish the diagnosis of HF [19]. Furthermore, in the Cox regression multivariable analysis for short-term survival there is a significant association between the mean platelet volume ($P=0.018$) and six-month survival, probably due to the prothrombotic tendency in this vulnerable period of time.

In the development of HF, inflammatory reactions and their affecting factors with which white blood cells count and subtypes could release many inflammatory cytokines, such as TNF- α , IL-6, and CRP, are established and very important [27]. Cortisol level is clearly increased in ischemic events, as a stress marker. Cortisol reduces lymphocytes by apoptosis and CD4+ and CD8 cells sensitivity to TNF- α [28]. As its shown in previous studies, level of pro-inflammatory cytokines may be related to cardiac arrhythmia and myocardial remodeling [29]. Lymphopenia is also associated with decreased survival in patients with HF as it is a prognostic factor [30,31]. We found a higher prevalence of mortality from HF in the female group; it may correlate with the specific hormonal profile (estrogen, menopause) in relation to the status of cortisol-sympathetic stimulation and chronic inflammation.

Involvement of leukocytes and platelets in the pathogenesis and evolution of HF has multiple explanations: hematopoietic bone marrow dysfunction (the two non-red hematopoietic lines coming from the same pluripotent stem cell), sustained sympathetic stimulation, closely related to the presence of inflammation and the generation of cytokines [32,33]. The study by Westenbrink et al. has proven that patients with ischemic HF have a profound and general bone marrow dysfunction affecting simultaneously many cell lines that is correlated to HF severity [34]. Lymphopenia found in patients with acute or chronic HF, irrespective of etiology [35,36], correlates with disease severity [24] and was proven to be a negative prognostic marker, associated with increased mortality [37]. Fărcas et al. showed that the lymphocyte count, NLR and NYHA class are predictors for event-free outcome in patients with HF. Furthermore, after adjusting for NYHA class, they found that the lymphocyte count and NLR remained predictors only in patients with ischemic HF [38]. NLR provides information on two pathophysiologic pathways: neutrophils (linked to rapid immunologic response and increased levels of free radicals, responsible for tissue injury) and lymphocytes (linked to chronic adaptive immune response). Durmus et al. [19] found that in patients with acute decompensated HF the NLR is correlated with left ventricular systolic performance (assessed through ejection fraction). Also, Fărcas et al. [38] found a positive correlation between the NLR and NT-proBNP level.

This study has some limitations such as the small sample size and low predictive sensitivity and specificity levels for indices. Also we evaluated only the short-term survival in our group of HF_rEF patients. Moreover, NT-proB-type natriuretic peptide (BNP) and C-reactive protein were not considered in this study. Although we demonstrated elevated leukocyte-based inflammatory indices in HF_rEF, the mechanism of these indices' role on cardiac remodeling and HF progression is unclear. Therefore, more studies need to take place for better judgments of the inflammatory markers and their influences in HF.

Conclusions

In this study on patients with HF_rEF, although there was a significant association between neutrophil, lymphocyte and platelet based indices and six-month mortality, the high NLR, PLR, MGLR and dNLR have not a role in predicting short-term mortality in the Cox regression analysis.

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