Lymphocytopenia is associated with poor NYHA functional class in chronic heart failure patients with reduced ejection fraction

Lenfositopeni kronik düşük ejeksiyon fraksiyonlu kalp yetersizliği olan hastalarda kötü NYHA fonksiyonel sınıf ile ilişkilidir

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ABSTRACT

Objective: In heart failure (HF) patients, functional capacity has been demonstrated to be a marker of poor prognosis, independent of left ventricular ejection fraction (EF). Lymphocyte count is currently recognized in certain risk stratification scores for chronic HF, and severe HF is associated with lymphocytopenia. However, no data exists on the association between lymphocyte count and functional capacity in patients with stable HF. This study aimed to assess the relationship between lymphocyte count and New York Heart Association (NYHA) functional capacity in systolic HF outpatients.

Methods: The Turkish Research Team-HF (TREAT-HF) is a network which undertakes multi-center observational studies in HF. Data on 392 HF reduced ejection fraction (HFREF) patients from 8 HF centers are presented here. The patients were divided into two groups and compared: Group 1 comprised stable HFREF patients with mild symptoms (NYHA Class I-II), while Group 2 consisted of patients with NYHA Class III-IV symptoms.

Results: Patient mean age was 60±14 years. Lymphocyte count was lower in patients with NYHA functional classes III and IV than in patients with NYHA functional classes I and II, (0.9 [0.6–1.5] x1000 versus 1.5 [0.7–2.2] x1000, p<0.001). In multivariate logistic regression analysis, lymphocyte count (OR: 0.602, 95% CI: 0.375–0.967, p=0.036), advanced age, male gender, presence of hypertension, EF, left atrium size, systolic pulmonary artery pressure, neutrophil and basophil counts, creatinine level, and diuretic usage were associated with poor NYHA functional class in systolic HF outpatients.

Conclusion: The present study demonstrated that in stable HFREF outpatients, lymphocytopenia was strongly associated with poor NYHA function, independent of coronary heart disease risk factors.

ÖZET

Amaç: Kalp yetersizliği (KY) olan hastalarda fonksiyonel kapasite, sol ventrikül ejeksiyon fraksiyonundan (EF) bağımsız şekilde kötü prognozu gösteren bir belirteçtir. Lenfosit sayısı günümüzde kronik KY için risk sınıflandırılması amacıyla kullanılmakta ve lenfositopeni şiddetli KY ile ilişkilendirilmektedir. Ancak, kararlı KY'li hastalarda lenfosit sayısı ve fonksiyonel kapasite arasındaki ilişki hakkında veri mevcut değildir. Bu çalışmada, ayaktan başvuran sistolik KY bulunan hastalarda lenfosit sayısı ve NYHA (New York Heart Association) fonksiyonel kapasitesi arasındaki ilişki araştırıldı.

Yöntemler: Türk Araştırma Ekibi-KY (TREAT-HF), KY merkezleri arasında, KY'de çok merkezli gözlemsel çalışma yapan bir bilgi ağıdır. Burada sekiz KY merkezi, azalmış EF'si olan 392 hastanın bilgilerini topladı ve sundu. Hastalar iki gruba ayrıldı ve gruplar karşılaştırıldı. Grup 1: Azalmış EF'si olup hafif şikayetleri olan KY'li hastalar (NYHA I–II), Grup 2: NYHA III–IV semptomlara sahip olan hastalar.

Bulgular: Hastaların yaşları ortalama 60±14 idi. Lenfosit sayısı NYHA III–IV olanlarda, NYHA I–II olanlara göre daha düşüktü (0.9 [0.6–1.5] x1000 karşı 1.5 [0.7–2.2] x1000, p <0.001). Çok değişkenli lojistik regresyon analizinde, lenfosit sayısı (OR: 0.602, %95 GA: 0.375–0.967, p=0.036), ileri yaş, erkek cinsiyet, hipertansiyon mevcudiyeti, ejeksiyon fraksiyonu, sol atriyum çapı, sistolik pulmoner arter basıncı, nötrofil ve bazofil düzeyleri, kreatinin seviyesi ve diüretik kullanımı ayaktan başvuran sistolik KY'li hastalarda, kötü NYHA fonksiyonel sınıf ile ilişkilidir.

Sonuç: Yaptığımız bu çalışma lenfostipeninin, azalmış EF'si olan ayaktan başvuran kararlı KY'li hastalarda koroner arter hastalığından bağımsız olarak, kötü NYHA fonksiyonu ile ilişkili olduğunu göstermiştir.

Received: September 19, 2014 *Accepted:* January 19, 2015

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Heart failure (HF) is the leading cause of death and hospitalization worldwide, and thus constitutes an important share of health care costs.[1,2] Patients with HF and similar left ventricular systolic dysfunction have varying functional capacity. Independent of left ventricular ejection fraction, exercise intolerance has been demonstrated as a marker of poor prognosis.[3]

Some risk stratification scores now recognize lymphocyte count as a risk for chronic HF, and severe HF is associated with lymphocytopenia.[4,5] Downregulation of proliferation and differentiation of lymphocytes, neurohumoral activation and lymphocyte apoptosis have been suggested as potential mechanisms for lymphocytopenia.[6]

Higher NYHA classification and lymphocytopenia have been associated with adverse cardiac events in patients with chronic HF.[7,8] However, no data exists on the association between lymphocyte count and functional capacity in patients with stable HF. This study evaluated the association between lymphocyte count and NYHA functional capacity in systolic HF outpatients.

METHODS

Patients

This study included 392 HF patients (mean age 60±14 years) with reduced ejection fraction (EF) from 8 HF centers. Patients with left ventricular EF ≤40% were included. Stable systolic HF patients with mild symptoms of NYHA functional class I-II (Group 1) were compared with patients of NYHA functional class III-IV (Group 2). NYHA functional classifications were determined by cardiologists blinded to the patients' clinical data. Exclusion criteria were: hematological disease, cancer, neoplastic metastases to bone marrow, sepsis, ongoing systemic inflammatory conditions, pregnancy, autoimmune disease, glucocorticoid therapy, acute myocardial ischemia and cardiogenic shock. Patients' baseline characteristics and in-hospital data were recorded on case report forms.

All venous blood samples were obtained upon patient presentation. Total white blood cell, neutrophil and lymphocyte counts were obtained on admission using an automated blood cell counter. Written informed consent was obtained from all patients, and the study was approved by the local Ethics Committee.

Echocardiography

Abbreviations:

HF	*Heart failure*
N/L	*Neutrophil/lymphocyte*
NYHA	*New York Heart Association*

Echocardiography examinations were performed by experienced operators. Patients were imaged in the left lateral decubitus position with a commercially available system (VIVID 7, General Electric-Vingmed Ultrasound, Horten, Norway). Doppler tracings and 2-dimensional images were obtained from parasternal long- and short-axes, apical and subcostal views. Two-dimensional guided M-mode measurements of left ventricle internal dimensions, and septum and posterior wall thicknesses were made at the LV minor axis. Left ventricular EF was measured using Simpson's biplane method.[9]

Statistical analysis

Continuous variables were expressed as mean ± SD or median (interquartile range) in the presence of abnormal distribution, and categorical variables as percentages. Comparisons between groups of patients were made using a χ^2 test for categorical variables, an independent samples t test for normally distributed continuous variables, and the Mann-Whitney U test when distribution was skewed. Correlations were evaluated either via Pearson or Spearman correlation tests. We used univariate logistic regression analysis to quantify the association of variables with poor NYHA functional class. Age, male gender, hypertension, coronary artery disease, chronic obstructive pulmonary disease, atrial fibrillation, ejection fraction, left atrium size, left ventricular diastolic diameter, systolic pulmonary artery pressure, right ventricular dilatation, hemoglobin, white blood cell, neutrophil, lymphocyte, neutrophil/lymphocyte (N/L) ratio, monocyte, eosinophil, basophil, creatinine levels, and digoxin, diuretics and beta blocker usage were entered into the multivariate logistic regression model using the backward LR method in order to determine the independent prognostic factors for poor NYHA functional class. All statistical procedures were performed using SPSS software version 14.0 (SPSS Inc., Chicago, IL). A p value of 0.05 was considered statistically significant.

RESULTS

Table 1 presents the patients' baseline clinical characteristics according to NYHA functional class. Groups 1 and 2 consisted of patients with NYHA functional classes I–II and III–IV respectively. The mean age

Table 1. Baseline characteristics of study patients

	NYHA I-II (n=242)	NYHA III-IV (n=150)	*p*
Baseline characteristics			
Age (years)	58±14	63±14	**<0.001**
Male/Female	173/69	98/52	0.200
Hypertension	64 (26%)	49 (33%)	0.186
Diabetes mellitus	35 (15%)	27 (18%)	0.351
Coronary artery disease	116 (48%)	60 (40%)	0.125
Chronic obstructive pulmonary disease	15 (6%)	16 (11%)	0.111
Atrial fibrillation	42 (17%)	56 (37%)	**<0.001**
Echocardiography parameters			
Ejection fraction (%)	35 (28-40)	25 (20-35)	**<0.001**
Left atrium size (cm)	4.5±0.81	4.8±0.87	**<0.001**
Left ventricular diastolic diameter (cm)	57 (50-63)	59 (54-69)	0.018
Systolic pulmonary artery pressure (mmHg)	30 (25-40)	46 (35-57)	**<0.001**
Right ventricular dilatation	57 (25%)	90 (61%)	**<0.001**
Laboratory findings			
Hemoglobin (gr/dl)	13.2±1.95	12.3±2.42	**<0.001**
White blood cell (1000xcells/mm^3)	7.5±2.24	6.9±2.23	0.014
Neutrophil (1000xcells/mm^3)	4.4 (2.3-5.6)	3.8 (1.7-6.0)	0.267
Lymphocyte (1000xcells/mm^3)	1.5 (0.7-2.2)	0.9 (0.6-1.5)	**<0.001**
Neutrophil/lymphocyte ratio	2.7 (2.0-3.9)	3.3 (2.1-5.8)	0.007
Monocyte (1000xcells/mm^3)	0.5 (0.3-0.7)	0.4 (0.1-0.6)	0.027
Eosinophil (1000xcells/mm^3)	0.1 (0.04-0.2)	0.06 (0.01-0.1)	**<0.001**
Basophil (1000xcells/mm^3)	0.04 (0.01-0.2)	0.06 (0.02-0.3)	0.034
Fasting glucose (mg/dl)	107 (90-139)	115 (95-148)	0.156
Creatinine (mg/dL)	1.0 (0.8-1.2)	1.1 (0.9-1.4)	**<0.001**
Medication			
Antiplatelet agents	163 (67%)	103 (69%)	0.787
ACE inhibitors/ARB	192 (79%)	126 (84%)	0.252
Beta blockers	230 (95%)	137 (91%)	0.212
Digoxine	42 (17%)	47 (31%)	**<0.001**
Diuretics	162 (67%)	139 (93%)	**<0.001**
Aldosterone antagonist	137 (57%)	92 (61%)	0.357

ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker.

of patients was 60±14 years. Lymphocyte count was lower in patients with NYHA functional classes III and IV than in patients with NYHA functional classes I and II (0.9 (0.6–1.5) x1000 versus 1.5 (0.7–2.2) x1000, p<0.001, Figure 1).

As shown in Table 2, we performed univariate logistic regression analysis, including lymphocyte count and other variables for poor NYHA functional class. Table 2 also presents the factors associated with poor NYHA functional class which were analyzed in the multivariate logistic regression. Lymphocyte count (OR: 0.602, 95% CI: 0.375-0.967, p=0.036), advanced age, male gender, presence of hypertension, ejection fraction, left atrium size, systolic pulmonary artery pressure, neutrophil and basophil counts, cre-

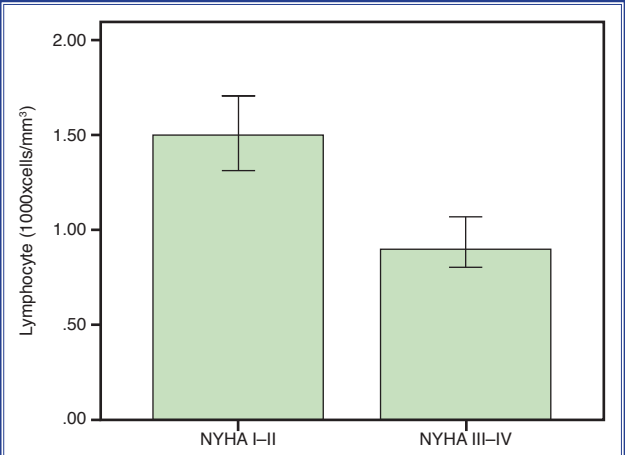

Figure 1. Comparison of lymphocyte levels between the groups.

atinine level, and diuretic usage were associated with poor NYHA functional class in systolic HF outpatients.

DISCUSSION

Systolic HF is a complex syndrome resulting from structural or functional disorders of the heart that impair ventricular ability to eject blood.[10] In addition to high mortality despite optimal medical treatment, hospitalization rates are also consistently high.[11] Worsening of symptoms is a key reason for patients with HF to enter hospital or seek treatment from health care providers. Since hospitalization represents one of the strongest indicators of prognosis in patients

Table 2. Univariate logistic regression analysis for predicting poor NYHA class

	Univariate		
Variable	*p*	OR	(95% CI)
Age (years)	**<0.001**	1.028	1.012-1.044
Male gender	0.200	1.330	0.859-2.059
Hypertension	0.187	1.349	0.865-2.106
Coronary artery disease	0.125	1.381	0.914-2.086
Chronic obstructive pulmonary disease	0.115	1.807	0.866-3.772
Atrial fibrillation	**<0.001**	2.837	1.775-4.535
Ejection fraction (%)	**<0.001**	0.948	0.925-0.971
Left atrium size (cm)	**<0.001**	1.046	1.021-1.073
Left ventricular diastolic diameter (cm)	0.022	1.024	1.004-1.046
Systolic pulmonary artery pressure (mmHg)	**<0.001**	1.049	1.032-1.066
Right ventricular dilatation	**<0.001**	4.791	3.070-7.478
Hemoglobin (gr/dl)	**<0.001**	0.816	0.740-0.901
White blood cell (1000xcells/mm³)	0.015	0.892	0.814-0.978
Neutrophil (1000xcells/mm³)	0.352	0.960	0.880-1.046
Lymphocyte (1000xcells/mm³)	**<0.001**	0.507	0.385-0.668
Neutrophil/lymphocyte ratio	0.030	1.056	1.005-1.109
Monosit (1000xcells/mm³)	0.020	0.448	0.228-0.881
Eizonofil (1000xcells/mm³)	0.026	0.214	0.055-0.835
Bazofil (1000xcells/mm³)	0.088	2.428	0.875-6.738
Creatinine (mg/dL)	**0.002**	1.985	1.288-3.057
Digoxine usage	**0.002**	2.173	1.346-3.509
Diuretics usage	**<0.001**	6.240	3.194-12.192
Beta blocker usage	0.149	1.819	0.807-4.099

All the variables from Table 1 were examined and only those significant at a p<0.25 level and Neutrophil level (associated with Neutrophil/lymphocyte ratio) are shown in univarite analysis. CI: Confidence interval; OR: Odds ratio.

Table 3. Multivariate logistic regression analysis for predicting poor NYHA class

			95% CI		
Variable		*p*	OR	Lower	Upper
Step 1 (Baseline)	Age (years)	0.115	1.022	0.995	1.049
	Male gender	0.155	0.595	0.291	1.217
	Hypertension	0.016	0.391	0.183	0.838
	Coronary artery disease	0.816	0.915	0.431	1.940
	Chronic obstructive pulmonary disease	0.172	0.396	0.105	1.496
	Atrial fibrillation	0.799	0.903	0.410	1.987
	Ejection fraction (%)	**<0.001**	0.905	0.862	0.949
	Left atrium size (cm)	0.054	1.049	0.999	1.101
	Left ventricular diastolic diameter (cm)	0.142	0.966	0.923	1.012
	Systolic pulmonary artery pressure (mmHg)	0.050	1.024	1.000	1.049
	Right ventricular dilatation	0.217	0.586	0.251	1.369
	Hemoglobin (gr/dl)	0.328	0.918	0.773	1.090
	White blood cell (1000xcells/mm^3)	0.236	1.129	0.923	1.381
	Neutrophil (1000xcells/mm^3)	0.096	0.814	0.639	1.037
	Lymphocyte (1000xcells/mm^3)	0.110	0.616	0.340	1.116
	Neutrophil/lymphocyte ratio	0.628	0.981	0.907	1.061
	Monocyte (1000xcells/mm^3)	0.503	0.610	0.144	2.592
	Eosinophil (1000xcells/mm^3)	0.232	0.371	0.073	1.886
	Basophil (1000xcells/mm^3)	0.129	4.516	0.644	31.650
	Creatinine (mg/dL)	0.034	2.710	1.078	6.812
	Digoxine usage	0.470	0.762	0.364	1.593
	Diuretics usage	0.002	0.205	0.076	0.554
	Beta blocker usage	0.587	1.495	0.351	6.369
Step 13 (final)	Age (years)	0.074	1.023	0.998	1.050
	Male gender	0.048	1.969	1.006	3.850
	Hypertension	0.009	2.654	1.272	5.538
	Ejection fraction (%)	**<0.001**	0.928	0.893	0.964
	Left atrium size (cm)	0.071	1.037	0.997	1.080
	Systolic pulmonary artery pressure (mmHg)	0.002	1.032	1.012	1.053
	Neutrophil (1000xcells/mm^3)	0.059	0.857	0.730	1.006
	Lymphocyte (1000xcells/mm^3)	0.036	0.602	0.375	0.967
	Bazofil (1000xcells/mm^3)	0.043	7.240	1.061	49.407
	Creatinine (mg/dL)	0.013	2.873	1.247	6.617
	Diuretics usage	**<0.001**	5.255	2.058	13.421

Age, male gender, hypertension, coronary artery disease, chronic obstructive pulmonary disease, atrial fibrillation, ejection fraction, left atrium size, left ventricular diastolic diameter, systolic pulmonary artery pressure, right ventricular dilatation, hemoglobin, white blood cell, neutrophil, lymphocyte, neutrophil/lymphocyte ratio, monocyte, eosinophil, basophil, creatinine, digoxine, diuretics and beta blocker usage were entered into the multivariate logistic regression model with backward LR method. CI: Confidence interval; OR: Odds ratio.

with chronic HF,[12] it may be important to predict worsening functional capacity in order to recognize impending exacerbation of HF.

White blood cell count and subtypes are of prognostic value in cardiovascular disease.[13] In recent studies, elevated neutrophil levels have been shown to

be associated with worse outcomes in cardiovascular diseases.[14–16] On the other hand, lymphocytopenia is associated with poor prognosis in patients with coronary artery disease and HF.[6–8,17] N/L ratio combines the predictive value of two white blood cell types, and seems to be a strong indicator of systemic inflammation.[18] Several studies have reported increased N/L ratio in rheumatic mitral valve stenosis and pulmonary artery hypertension, and it is associated with increased mortality in patients with acute coronary syndromes, HF, peripheral arterial disease, pulmonary embolism and infective endocarditis.[14–16,19–24] Furthermore, elevated N/L ratio is related to poor functional capacity in patients with HF.[25,26]

In HF patients, neurohumoral activation, downregulation of proliferation and differentiation of lymphocytes and lymphocyte apoptosis have been suggested as underlying mechanisms for lymphocytopenia.[8] Severe HF, and thus higher NYHA functional class, is associated with higher levels of circulating endotoxin.[27] Immune activation and release of cytokines may directly relate to reductions in lymphocyte count.[28,29] In symptomatic HF patients with higher NYHA functional class, elevated biventricular filling pressures and subsequent splanchnic congestion may cause direct enteric losses of lymphocytes.[30] In this respect, patients with lymphocytopenia are likely have more advanced disease with severe presenting congestion. In support of these hypotheses, our study found low lymphocyte count to be associated with higher NYHA functional class.

Independent of left ventricular EF, exercise intolerance has been demonstrated as a marker of poor prognosis.[3] Although introduction of new drugs and use of devices have reduced mortality rates,[10] both hospitalization and readmission rates continue to increase. Prediction of worsening HF may help to reduce hospitalization rates. Therefore, early risk stratification is very important, meaning that early identified high risk patients may be directed toward more intensive and advanced treatment options. This association of low lymphocyte count and higher NYHA functional class suggests that inflammation and congestion may play a pathophysiological role in determining patients at higher risk of hospitalization.

Similarly to other studies, the present study found age, systolic pulmonary artery pressure, diuretic use and creatinine level to be associated higher NYHA functional class. Furthermore, we showed that high neutrophil and basophil levels are associated with poor NYHA functional class in systolic HF patients. To our knowledge, this is the first study to show an association between lymphocyte count and NYHA functional class.

Limitations

Our study has certain limitations. Firstly, other inflammatory markers were not analyzed and compared with lymphocyte count since they were not part of routine evaluation. In addition, only a small number of Turkish patients is represented in the study. A larger prospective study needs to be performed to establish the clinical importance and application of measurements of this simple and widely-available laboratory test in chronic HF patients. Moreover, this study did not evaluate mortality. In addition to NYHA class, the inclusion of objective evaluations of functional status could have potentially improved the value of the findings. Last, but not least, the independent prognostic value of this finding was not evaluated, although this is planned in a future prospective observational cohort study.

Our data suggests that low lymphocyte count is associated with poor NHYA functional class. Our study showed that this simple and widely-available test might help to identify HF patients at a higher risk of hospitalization, and may help in risk stratification of these patients.

Conflict-of-interest issues regarding the authorship or article: None declared

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Key words: Heart failure; lymphocyte; lymphocytopenia; NYHA functional class.

Anahtar sözcükler: Kalp yetersizliği; lenfosit; lenfositopeni; NYHA fonksiyonel sınıfı.