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Relation between the severity of lymphopenia and severity of heart failure in patients with heart failure with reduced ejection fraction in Suez Canal University Hospital

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Abstract

Background: **Inflammatory and hematological factors that contribute to heart failure (HF) are of increasing interest. Our objective is to determine whether the absolute lymphocyte count (ALC) and the level of severity of HF are correlated among subjects with heart failure with reduced ejection fraction.** ***Methods:*** **208 suitable individuals having heart failure with reduced ejection fraction (LVEF<50% by echocardiography) were selected for inclusion in the NYHA class—were thoroughly assessed. The neutrophil-to-lymphocyte ratio (NLR) was computed, and complete blood count with automated differential counts was carried out.** ***Results:*** **The Mean Lymphocyte count was 3.6 x1000, 3.4x1000, 1.8x1000, 1.5x1000 in NYHA class I, II, III and IV respectively (P value < 0.001). A significant positive correlation between BNP levels (r = 0.438, p < 0.001), and NYHA class, indicating higher values with increasing NYHA class. Neutrophil-Lymphocyte ratio (NLR) was elevated in participants with NYHA classes I and II more than participants with NYHA classes III and IV (2.9 versus 1.4, P value < 0.001).** ***Conclusion:*** **Low lymphocytic count and high Neutrophil-Lymphocyte ratio are linked to poor NHYA class and higher BNP levels.**

Keywords: Heart Failure, Lymphocyte Count, Lymphopenia, NYHA Class

Introduction

Heart failure is a complex illness that affect survival rates and patient health seriously. Over the last three decades, there has been an increase in HF cases due to the development of therapies that have successfully reduced mortality [(1)]. In addition to being a cardiovascular condition, chronic heart failure (CHF) also impacts other bodily systems and organs. The excessive production of cytokines and neuroendocrine mediators, which accelerates the course of CHF, is the cause of this systemic involvement. Among other chemicals, elevated catecholamine levels are believed to play a part in this illness [(2)]. Finding easily accessible laboratory indicators that can predict mortality and the chance of hospital readmission has drawn increased attention in HF patients in the previous few years [(3)]. The significance of inflammatory and immune systems in the development of HF has been disclosed by recent research [(4)].

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Neutrophil-to-lymphocyte ratios (NLR) [5,6], platelet-to-neutrophil ratios (PNR) [7,8], monocyte-lymphocyte ratios [9,10], and lymphocyte percentages have all been explicitly studied for their potential as independent indicators of death. Though they have little effect on lymphocytes, these indices can be affected by factors like acute infections or stress that change neutrophil and platelet count. Lymphopenia was linked to poor outcomes in both acute heart failure (AHF) as well as chronic heart failure, as well as it is postulated that it is a basic sign of significant inflammation [11]. Whether particular pathways cause lymphocytopenia in HF is still unknown [12]. One of the postulated pathways that results in cytokine production and systemic endotoxin transfer, which definitely cause direct lymphocyte killing, is portal congestion [13]. Furthermore, elevated cortisol levels brought on by biological stress in HF can drastically lower lymphocyte count and cause white blood cells to redistribute, which in the current instance increases both monocytes and neutrophils [14,15]. Our study intends to find the connection between a low lymphocyte count and the level of severity of heart failure among individuals referred to the Suez Canal University hospital's cardiology department in Ismailia City.

Methods:

The SCU ethics board validated this study, and each patient gave informed and written consent. From April 2024 to December 2024, we screened 321 consecutive patients with CHF (who has ejection fraction (EF) less than 50% (Either mid-range EF~40-50% and reduced EF less than 40%) recruited from various departments in Suez Canal University Hospital in Ismailia city, including the outpatient cardiology clinic, ward, cardiac care unit (CCU), and emergency department. Of the 249 eligible patients invited to participate, 208 agreed to join the study, while 41 declined.

Patients in New York Heart Association classes I–IV who exhibit heart failure signs and symptoms had maintained their existing medication regimen for at least four weeks prior to the assessment, were evaluated. We compared mild-symptom stable heart failure individuals (NYHA class I–II, Group 1) with those who had more severe symptoms (NYHA class III–IV, Group 2). Cardiology physicians who were oblivious to clinical information established NYHA classifications.

Symptoms, clinical measures, and the recorded left ventricular ejection fraction by echocardiography were used to diagnose CHF. Clinical information and baseline patient details were documented on case report files. Every venous specimen of blood was taken when the patient first arrived. The data was gathered prospectively and included complete blood counts with automatic differentiation counts, including total white blood cells (WBCs), neutrophils, and lymphocytes. The neutrophil and lymphocyte count in the same computerized blood sample withdrawn at admission and were used to compute the neutrophil-to-lymphocyte ratio (NLR). At presentation, measurements were also made regarding serum creatinine, lipid profiles, BNP, and hemoglobin levels.

Patients under the age of 18 and those with illnesses recognized to impact both differential and total WBC counts, as those on steroid hormones or non-steroidal anti-inflammatory drugs, or those exhibiting clinical symptoms of rheumatoid arthritis, or infection, cancer, patients with leukemia, lymphoma, myeloma, or other blood disorders, chemotherapy within the past year or a life expectancy of less than 12 months,

Those who had coronary revascularization or an acute myocardial infarction in the prior six months, Liver-induced lymphocyte abnormalities in patients with hepatic inflammatory diseases like hepatitis, liver fibrosis, and liver cirrhosis and pregnant individuals were not included in our analysis.

Statistical Analysis

When continuous variables have normal distribution, they are documented as mean ± SD; when they have a skewed distribution, they are documented as medians and interquartile ranges. Frequencies and percentages are used to express categorical variables. Analysis of variance and Kruskal-Wallis analysis were applied to compare continuous variables with normal and skewed distributions, respectively. Through chi-square testing, Categorical parameters were compared. Using both univariate as well as multivariate Cox regression models, the independent relationship between the NLR tertiles and mortality over the long term was evaluated; the corresponding 95% CIs for the unadjusted and adjusted hazard ratios (HRs) were provided.

Results

Lymphocytes Absolute Counts According to NYHA Classes

The distribution of the lymphocytes' absolute counts across different NYHA classes is presented in figure 1. The mean lymphocyte count was highest in NYHA Class I at 3644.26 cells/µL (SD = 1266.68) while it progressively decreased with higher NYHA classes, with Class II at 3448.36 cells/µL (SD = 1353.50), Class III at 1862 cells/µL (SD = 771.62), and Class IV at 1510.20 cells/µL (SD = 748). Analysis by t-test revealed a statistically significant difference in lymphocyte counts across NYHA classes ($p < 0.001$), establishing an association between lower absolute lymphocyte counts and more severe heart failure features (figure 1). It should be highlighted that the lower the lymphocyte count, the more the NYHA class regardless of the degree of EF.

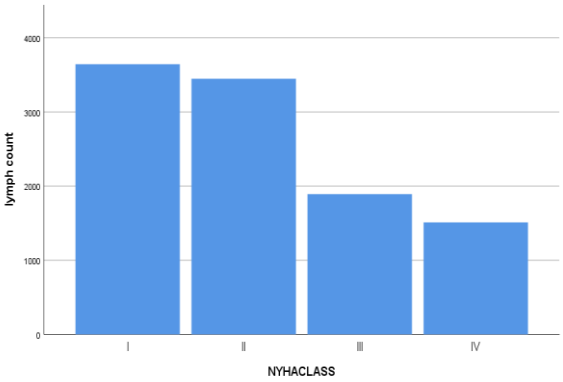

Figure 1: Lymphocytes Absolute Counts According to NYHA Classes

30 days mortality rate in relation to lymphocytes absolute counts

The mean lymphocyte count was lower in patients who died at 30 days (1180 cells/µL (SD = 418.3) while it was significantly higher in survivors (2681.96 cells/µL (SD = 1397.873) with P value=0.002 as shown in table 1.

Table 1: 30-day mortality in relation to lymphocytes absolute counts

	Mortality in 30 days	No.	Mean	Std. Deviation	p-Value
Lymphocytes absolute count	Yes	9	1180.00	418.300	0.002
	No	199	2681.96	1397.873	

*p-Value calculated by ANOVA test with significance level at <0.01

Patients' Characteristics According to NYHA Classes

Table 2 compares the features of individuals of NYHA Classes I–II and III–IV. No difference (p = 0.60) in the mean age of the patients among the two groups, with Class I-II having a mean age of 57.50 years (SD = 12.76) and Class III-IV having a mean age of 58.34 years (SD = 10.40). Likewise, BMI was similar between the groups (28.19 ± 4.94 for Class I-II vs. 27.32 ± 4.05 for Class III-IV, p = 0.16). No noticeable differences in hemoglobin levels (14.45 ± 2.29 g/dl for Class I-II vs. 14.33 ± 1.97 g/dl for Class III-IV, p = 0.66). However, significant differences were observed in white blood cell counts (7821.26 ± 2333.37 cells/µL for Class I-II vs. 6709.57 ± 2529.02 cells/µL for Class III-IV, p = 0.001), lymphocyte counts (3541.35 ± 1290.60 cells/µL for Class I-II vs. 1710.19 ± 780.69 cells/µL for Class III-IV, p < 0.001), and the neutrophil/lymphocyte ratio (NLR) (1.401 ± 1.15 for Class I-II vs. 2.90 ± 1.93 for Class III-IV, p < 0.001). Expectedly, BNP levels were higher115.28 ± 750.22 pg/ml) compared to Class I-II (326.11 ± 198.1 pg/ml, p < 0.001). No significant differences in creatinine levels (p = 0.38), LDL levels (p = 0.46), or 30-day mortality rates (p = 0.170) between the groups. Smoking status didn't differ between the groups (p = 0.878).

Correlation Analysis

Table 3 demonstrates the Pearson correlation coefficients for various parameters with NYHA class. A significant negative correlation between white blood cell counts & NYHA class (r = -0.224, p < 0.001), lymphocyte counts and NYHA class (r = -0.65, p < 0.001), indicating lower counts with higher NYHA class (figure 2). Conversely, A significant positive correlation between NLR (r = 0.43, p < 0.001), BNP levels (r = 0.438, p < 0.001), and NYHA class, indicating higher values with increasing NYHA class. The CBC parameters' correlation with heart failure severity was further confirmed by analyzing the ejection fraction measurement of patients (Table 4).

Regression Analysis

Table 5 presents regression models using white blood cell counts, lymphocyte counts, NLR, and BNP as predictors for NYHA class. The regression model for white blood cell counts showed an R-squared value of 0.05 (adjusted R-squared = 0.04, p = 0.001), indicating a modest explanatory power. The model for lymphocyte counts had a higher R-squared value of 0.428 (adjusted R-squared = 0.425, p < 0.001), suggesting a stronger predictive relationship. The models for NLR (R-squared = 0.182, adjusted R-squared = 0.178, p < 0.001) and BNP (R-squared = 0.133, adjusted R-squared = 0.129, p < 0.001) also demonstrated significant predictive value, though less robust than lymphocyte counts. Similarly, the same CBC parameters can be used to predict left ventricle function measurement by ejection fraction as shown in table 6.

Overall, these analyses indicate that lymphocyte counts, NLR, and BNP levels are significantly associated with NYHA class, with lower lymphocyte counts and higher NLR and BNP levels correlating with more severe heart failure. Also, lower lymphocyte counts are significantly associated with 30 days mortality as shown in table 7.

Table 2: Patients' Characteristics According to NYHA Classes					
Variables	**NYHA Class I, II (n=103)**		**NYHA Class III, IV (n=105)**		***p*-Value**
	Mean	**SD**	**Mean**	**SD**	
Age (yrs)	57.50	12.76	58.34	10.40	0.60
BMI (Kg/m²)	28.19	4.94	27.32	4.05	0.16
Hemoglobin (g/dl)	14.45	2.29	14.33	1.97	0.66
White blood cells count (cell/µL)	7821.26	2333.37	6709.57	2529.02	**0.001**
Neutrophils absolute count (cell/µL)	3978.27	1896.92	4236.19	2163.31	0.36
Lymphocytes absolute count (cell/µL)	3541.35	1290.60	1710.19	780.690	**<0.001**
Neutrophils/Lymphocytes Ratio	1.401	1.15	2.90	1.93	**<0.001**
BNP (pg/ml)	326.11	198.1	1115.28	750.22	**<0.001**
Creatinine (mg/dl)	1.00	0.36	1.05	0.46	0.38
LDL (mg/dl)	96.67	38.28	101.70	52.20	0.46
Mortality within 30 Days **No** **Yes**	 n=101 n=2	 -	 n=98 n=7	 -	0.170
Smoking **No** **Yes** **Ex-smoker**	 n= 60 n= 40 n= 3	 -	 n= 64 n= 36 n= 5	 -	0.878

Table 3: Correlation between WBCs, Lymphocytes Count and NLR and NYHA Class				
Variables	**NYHA I & II Mean**	**NYHA II & IV Mean**	**Pearson Correlation Coefficient**	**p-Value**
White blood cells count (cell/µL)	7821.26	6709.57	-0.224	**<0.001**
Lymphocyte Absolute Count (cell/µL)	3541.35	1710.19	-0.65	**<0.001**
NLR	1.401	2.90	0.43	**<0.001**
BNP (pg/ml)	326.11	1115.28	0.438	**<0.001**

Table 4: Correlation with LV function measured by Ejection Fraction		
Variables	**Pearson Correlation Coefficient**	**p-Value**
White blood cells count (cell/µL)	-0.122	0.079
Lymphocyte Absolute Count (cell/µL)	-0.347	**<0.001**
NLR	0.254	**<0.001**

Table 5: Regression Models Using WBCs, Lymphocytes, and NLR as Predictors for NYHA Class (Dependent)				
Variables	**R**	**R square**	**Adjusted R square**	**p-Value**
White blood cells count (cell/µL)	0.224	0.05	0.04	**0.001**
Lymphocyte Absolute Count (cell/µL)	0.654	0.428	0.425	**<0.001**
NLR	0.427	0.182	0.178	**<0.001**
BNP (pg/ml)	0.365	0.133	0.129	**<0.001**

Table 6: Regression Models Using WBCs, Lymphocytes and NLR as Predictors for LV Function by EF (Dependent)				
Variables	**R**	**R square**	**Adjusted R square**	**p-Value**
White blood cells count (cell/µL)	0.122	0.015	0.010	0.079
Lymphocyte Absolute Count (cell/µL)	0.347	0.120	0.116	**<0.001**
NLR	0.254	0.085	0.06	**<0.001**

Table 7: Regression Models Using Lymphocytes as Predictor of 30-day mortality (Dependent)				
Variables	**R**	**R square**	**Adjusted R square**	**p-Value**
Lymphocyte Absolute Count (cell/µL)	**0.218**	**0.048**	**0.043**	**0.002**

Discussion

Various hematological abnormalities such as elevated neutrophil and reduced lymphocyte counts have been noted among heart failure individuals [16]. These abnormalities can be interpreted as systemic inflammatory markers, as the inflammatory process becomes a crucial component in the pathophysiology of HF [17]. A worse prognosis for heart failure has also been clearly linked to them [18–20]. Traditionally, lymphopenia has been thought to be the direct consequence of increased cortisol levels in the blood during stress reaction. Increased lymphocyte death, down-regulation of lymphocyte proliferation and differentiation; and lymphocyte redistribution in the lymphopoietic systems are likely the causes of this paradigm shift in the leukocyte differential to a smaller fraction of lymphocytes [21]. Pro-inflammatory cytokine activation is seen among individuals suffering an acute aggravation of chronic HF, potentially due to sympathetic as well as renin-angiotensin-aldosterone pathway activation [22]. Decreases in the total number of lymphocytes may be clearly linked to immune activation and cytokine release [15]. Direct intestinal loss of lymphocytes may result from increased biventricular filling pressures and splanchnic congestion in HF individuals with symptoms and a greater NYHA class [23]. Patients with heart failure participated in this trial had lymphocytopenia that was clearly associated with worse NYHA function. The Mean Lymphocyte count was 3.6 x1000, 3.4x1000, 1.8x1000, 1.5x1000 in NYHA class I, II, III and IV respectively (P value < 0.001). The mean lymphocyte count was significantly lower in

patients with 30-day mortality (1180 cells/µL, SD = 418.3) compared to survivors (2681.96 cells/µL, SD = 1397.873) with p value= 0.002. A significant direct positive correlation between BNP levels (r = 0.438, p < 0.001), and NYHA class, indicating higher values with increasing NYHA class. Our study also showed that Neutrophil-Lymphocyte ratio (NLR) was greater in patients with NYHA classes I and II than in patients with NYHA classes III and IV (2.9 versus 1.4, P value < 0.001). In line with our data, Yücel et al. concluded that patients with NYHA classes III and IV had lower lymphocyte counts than subjects with NYHA classes I and II in their research of 392 heart failure patients with reduced ejection fraction, (0.9 [0.6–1.5] x1000 versus 1.5 [0.7–2.2] x1000, P value <0.001 [24]. In 129 subjects suffering chronic heart failure, Huehnergarth et al. found a substantial and inverse relationship in high jugular vein pressure and relative lymphocyte count. [25]. According to earlier research, those suffering from heart failure & coronary artery disease accompanied by lymphocytopenia had a worse prognosis [26,27]. A multicenter study found that lymphocytopenia was positively linked to all-cause death through a median follow-up of 417 days in individuals with acute decompensated heart failure and retained left ventricular ejection fraction [28]. Öztürk et al. have recognized that patients with a lower LVEF had higher NLR score than those having a preserved or slightly lower LVEF (*p* = 0.002) [29]. Despite similar LVEF and independent of inpatient versus outpatient environment, greater NLR was similarly linked to higher NT-proBNP, congestion indicators, and worse NYHA functional class in a multicenter trial assessing patients with new or worsening heart failure [30]. In patients with acute decompensated heart failure, Tamaki et al. discovered that those suffering with high NLR values had higher PASP (p < 0.001), higher NT-proBNP concentrations (p < 0.001), and lesser hemoglobin concentrations (p < 0.001) in comparison to patients with other NLR values [31]. Elevated NLR in acute heart failure participants during index hospitalization was independent predictor of in-hospital as well as post-discharge three-year death in the Korean Acute Heart Failure registry [32]. Based on these data, it can be summarized that NLR and total lymphocyte count may indicate for choosing patients with severe heart failure symptoms and a poor clinical picture. In comparison to BNP, they are also readily accessible, reasonably priced, and exhibit minimal test variability. Additionally, NLR and BNP work well together in a variety of therapeutic contexts.

There are several limitations to this analysis that require further discussion. Notably, a single-location design, and number of participants is few. To ascertain the clinical importance and use of this straightforward and extensively accessible laboratory test in patients with chronic HF, the outcomes of our study must be confirmed in a more thorough examination. Furthermore, as other inflammatory markers were not included in the standard assessment, we did not examine or contrast them with the lymphocyte count. Moreover, catecholamine concentrations were not measured.

Conclusion:

According to our outcomes, a poor NHYA class has been linked to a lower lymphocyte count. Pursuant to our research, this easy-to-use and accessible test may be useful in categorizing risks for individuals suffering from heart failure and in identifying those who are more likely to require hospitalization.

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