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Original article

Utility of the neutrophil to lymphocyte ratio for predicting in-hospital mortality after levosimendan infusion in patients with acute decompensated heart failure

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ABSTRACT

Background: The aim of this study was to investigate the effect of a levosimendan infusion on hematological variables in patients with acute decompensated heart failure (ADHF). The predictive value of these variables for in-hospital mortality was also evaluated.
Methods: A total of 553 patients (368 males; mean age, 63.4 ± 14.9 years) with acute exacerbations of advanced heart failure (ejection fraction ≤35%) and treated with either dobutamine or levosimendan were included in this retrospective analysis. The patients that received levosimendan therapy were divided into two groups according to in-hospital mortality: group 1 (21%) included patients who died during hospitalization ($n = 45$), while group 2 (79%) included patients with a favorable outcome ($n = 174$) after levosimendan infusion. Changes in several hematological variables between admission and the third day after levosimendan infusion were evaluated.
Results: The demographic characteristics and risk factors of the two groups were similar. A comparison of changes in laboratory variables after the infusion of levosimendan revealed significant improvement only in those patients who had not died (group 2) during hospitalization. The neutrophil to lymphocyte (N/L) ratio after levosimendan infusion was an independent predictor of in-hospital mortality (odds ratio: 1.310, 95% CI: 1.158–1.483, $p < 0.001$). In a receiver-operating characteristic curve analysis, a value of 5.542 for the N/L ratio after levosimendan administration was identified as an effective cut-off point for predicting in-hospital mortality (area under the curve = 0.737; 95% confidence interval = 1100–1301; $p < 0.001$).
Conclusions: Levosimendan treatment was associated with significant changes in hematological variables in patients with ADHF. A sustained higher N/L ratio after levosimendan infusion is associated with an increased risk of in-hospital mortality in patients with ADHF.

Introduction

Heart failure (HF) is a complex syndrome rather than an exclusive problem of low cardiac output. Neurohormonal and inflammatory activation, particularly involving polymorphonuclear leukocytes, is thought to play a key role in the pathophysiology of HF [1]. An association between increased white blood cell (WBC) counts and a high incidence of HF-related hospitalization and mortality has been reported [2,3]. Additionally, the neutrophil-to-lymphocyte (N/L) ratio is a well-known prognostic marker in patients with coronary artery disease or in those undergoing coronary angiography, percutaneous coronary intervention, and coronary artery bypass grafting [4,5]. In parallel, neutrophilia has been found to be associated with an increased incidence of acute decompensated HF (ADHF) in patients with acute myocardial infarction [6], while relative lymphocytopenia has been shown to be an independent predictor of mortality in HF patients [7–10]. Recently, a higher N/L ratio on hospital admission was shown to be associated with an increased risk of short- and long-term morbidity and mortality in patients with ADHF [11].

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Levosimendan, a Ca^{2+} sensitizer that increases troponin-C sensitivity to cytoplasmic Ca^{2+} without modifying the intracellular Ca^{2+} density, improves cardiac performance and decreases systemic and vascular resistance and proinflammatory marker levels [12–16]. However, no data exist regarding the effect of a levosimendan infusion on the N/L ratio and its utility in predicting in-hospital mortality for patients with ADHF. The aims of this study were to evaluate the effects of levosimendan infusion on hematological variables and the association between the N/L ratio after levosimendan infusion and in-hospital mortality in patients with ADHF. We also compared the discriminative prognostic efficacy of these hematological variables with that of other variables at baseline and after the infusion of levosimendan. To our knowledge, our study is the first to investigate the effects of levosimendan on the WBC count and the prognostic value of the N/L ratio after levosimendan infusion in ADHF patients.

Materials and methods

Patient population

We retrospectively evaluated a total of 1061 consecutive patients who were admitted (from January 2011 to April 2013) to Bezmialem Foundation University Hospital (Istanbul) and Mehmet Akif Ersoy Thoracic-Cardiovascular Surgery Training and Research Hospital (Istanbul) with ADHF [ejection fraction $\leq$ 35% and New York heart Association (NYHA) Class IV]. Patients were analyzed in two groups according to positive inotropic treatment that they had received such as, levosimendan or dobutamine. Patients with medical conditions known to affect the total and differential WBC counts, such as: disorders of the hematopoietic system, history of cancer and/or previous treatment with chemotherapy, infection, and chronic inflammatory conditions; glucocorticoid therapy and/or histories of glucocorticoid use 3 months before the admission; and acute myocardial infarction or coronary revascularization within the past 6 months; and patients with incomplete data were excluded from the study. Also, patients who did not have both WBC counts before and after levosimendan infusion were excluded (Fig. 1). The study protocol was approved by the hospitals' ethics committees.

Analysis of patient data

Data included demographic characteristics, laboratory data, medications, and echocardiographic parameters collected by the study personnel from the hospitals' medical records. Clinical risk factors such as age, sex, diabetes mellitus (DM), hypertension (HT), hypercholesterolemia, smoking, and history of cardiovascular disease were determined. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. The left ventricular end systolic and diastolic diameters (LVESD, LVEDD), and ejection fraction (LVEF) measured before and after levosimendan therapy with transthoracic echocardiography were recorded. Complete blood counts which included total WBCs, neutrophils, and lymphocytes, and routine biochemical tests results were obtained and N/L ratio was calculated as the ratio of the neutrophil to lymphocytes, from the same automated blood sample before and after levosimendan infusion on the third day. Also, the serum high sensitivity C-reactive protein (hsCRP) levels, which were obtained with the nephelometric method, using a Dade Behring Cardio Phase kit (Dade Behring Inc., Newark, DE, USA) were recorded on admission and after levosimendan infusion. Death from any cause during hospitalization was the primary end point. Association between proportion of changes in hematological variables after levosimendan infusion were evaluated. Additionally, the independent association of different hematological variables with in-hospital mortality was analyzed.

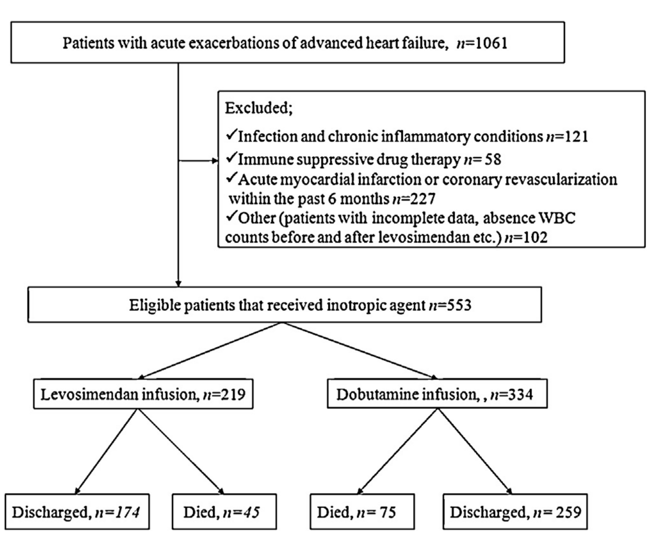

Fig. 1. Flow chart of the patients enrolled in the study. WBC, white blood cell.

Statistical analyses

Categorical variables were expressed as frequencies and percentages. Chi-square tests were used to compare categorical variables. Univariate and a backward stepwise multivariate logistic regression analysis, was performed to evaluate the independent predictors of in-hospital cardiovascular mortality. To analyze the association of ΔN/L ratio with in-hospital mortality, continuous variables were compared using analysis of covariance when baseline variables were presumed as a covariate for those with skewed distributions. A logistic regression model was used to analyze the independent association of ΔN/L ratio. The Kaplan–Meier curve and log-rank test were used to compare time to event distributions. A *p*-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 15.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

A total of 219 consecutive eligible patients (mean age, 63.2 ± 12.7 years; 168 males, 51 females) that received levosimendan were included in this retrospective study. Also, 334 patients that underwent dobutamine therapy were analyzed as a control group. After the levosimendan infusion, a significant increase in the LVEF ($26.7 \pm 5.8\%$ *vs.* $29.2 \pm 5.4\%$, $p < 0.001$) and lymphocyte count ($1.3 \pm 0.7 \times 1000/\mu l$ *vs.* $1.5 \pm 0.7 \times 1000/\mu l$, $p = 0.03$) and significant decreases in the LVESD (49.1 ± 4.9 cm *vs.* 47.1 ± 4.5 cm, $p = 0.02$), WBC count ($9.6 \pm 3.7 \times 1000/\mu l$ *vs.* $9.2 \pm 3.8 \times 1000/\mu l$, $p = 0.02$), neutrophil count ($7.2 \pm 3.6 \times 1000/\mu l$ *vs.* $6.8 \pm 3.7 \times 1000/\mu l$, $p = 0.004$), hsCRP (7.6 ± 4.8 ng/ml *vs.* 5.9 ± 3.1 ng/ml, $p < 0.001$), and creatinine level (1.3 ± 0.5 mg/dl *vs.* 1.2 ± 0.5 mg/dl, $p = 0.005$) were observed (Table 1). However, favorable changes in hematological variables were not seen in patients that received dobutamine therapy (Table 1). The patients that received levosimendan infusion were divided into two groups according to in-hospital mortality: group 1 (21%) included patients who died during hospitalization ($n = 45$), while group 2 (79%) included patients with a favorable outcome ($n = 174$) after levosimendan infusion. The demographic characteristics and risk factors of the two groups were similar (Table 2). There was no significant difference in the medications that the patients received during hospitalization. An analysis of laboratory

Table 1
Effects of levosimendan and dobutamine on hemodynamic, echocardiographic, and laboratory variables.

	Levosimendan $n = 219$			Dobutamine $n = 334$		
	Before infusion	After infusion	p	Before infusion	After infusion	p
Hemodynamic variables						
Heart rate (beats/min)	75.9 ± 16.7	81.5 ± 19.8	0.22	79.1 ± 12.8	78.4 ± 11.9	0.48
Systolic BP (mmHg)	104.6 ± 5.9	104.2 ± 5.5	0.97	108.9 ± 7.6	114.3 ± 8.7	0.23
Diastolic BP (mmHg)	62.5 ± 4.7	62.2 ± 4.0	0.98	69.5 ± 8.4	73.6 ± 9.2	0.31
Echocardiographic variables						
LVEF (%)	26.7 ± 5.8	29.2 ± 5.4	<0.001	27.1 ± 6.1	28.9 ± 5.4	0.04
LVESD (mm)	49.1 ± 4.9	47.1 ± 4.5	0.02	51.5 ± 5.1	50.8 ± 4.9	0.88
LVEDD (mm)	61.4 ± 5.1	60.9 ± 4.8	0.76	62.4 ± 6.1	62.3 ± 6.0	0.81
Laboratory variables						
WBC count (×1000/μl)	9.6 ± 3.7	9.2 ± 3.8	0.02	10.3 ± 3.9	10.5 ± 4.1	0.48
Neutrophil count (×1000/μl)	7.2 ± 3.6	6.8 ± 3.7	0.004	7.2 ± 2.0	7.8 ± 1.6	0.32
Lymphocyte count (×1000/μl)	1.3 ± 0.7	1.5 ± 0.7	0.03	1.7 ± 0.9	1.8 ± 1.0	0.31
Hemoglobin (mg/dl)	11.4 ± 1.9	11.3 ± 2.2	0.34	11.1 ± 2.4	11.4 ± 2.1	0.14
Platelet count (×1000/μl)	246.4 ± 100.2	243.8 ± 95.7	0.56	196.2 ± 69.4	194.3 ± 83.1	0.87
Creatinine (mg/dl)	1.3 ± 0.5	1.2 ± 0.5	0.005	1.3 ± 0.4	1.4 ± 0.4	0.83
hsCRP (ng/ml)	7.6 ± 4.8	5.9 ± 3.1	<0.001	6.9 ± 5.7	8.2 ± 6.2	0.28

BP, blood pressure; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; WBC, white blood cell; hsCRP, high-sensitivity C-reactive protein.

parameters before the infusion of levosimendan demonstrated that being in group 1 was associated with a lower lymphocyte count ($1.3 \pm 0.6 \times 1000/\mu l$ *vs.* $1.4 \pm 0.7 \times 1000/\mu l$, $p = 0.005$) and a higher WBC count, neutrophil count, N/L ratio, and creatinine level ($12.2 \pm 4.8 \times 1000/\mu l$ *vs.* $8.9 \pm 3.1 \times 1000/\mu l$, $p < 0.001$; $9.8 \pm 4.7 \times 1000/\mu l$ *vs.* $6.6 \pm 2.9 \times 1000/\mu l$, $p = 0.001$; 10.2 ± 8.4 *vs.* 6.1 ± 5.3, $p < 0.001$; and 1.5 ± 0.5 mg/dl *vs.* 1.3 ± 0.5 mg/dl, $p = 0.009$, respectively). A comparison of changes in laboratory variables after the infusion of levosimendan demonstrated a meaningful improvement in only those patients who had not died (group 2) during hospitalization (Table 3). The N/L ratio after the infusion of levosimendan was identified as an independent predictor of in-hospital mortality when all hemodynamic, hematological, and biochemical variables associated with mortality were subjected to a multivariate logistic regression analysis [odds ratio: 1.310, 95% confidence interval (CI): 1.158–1.483, $p < 0.001$] (Table 4).

In a receiver-operating characteristic curve analysis, a value of 5.542 for the N/L ratio after levosimendan administration was identified as an effective cut-off point for predicting in-hospital mortality (area under the curve = 0.737, 95% CI = 1100–1301, $p < 0.001$) in patients with ADHF. An N/L ratio value of >5.542 yielded a sensitivity of 67% and a specificity of 66% (Fig. 2). A significant association was noted between a high N/L ratio (≥5.542) and earlier in-hospital all-cause mortality compared to patients with lower N/L ratio (12 ± 7 days *vs.* 22 ± 12 days, respectively, $p = 0.002$; Fig. 3).

Table 2
Baseline demographic characteristics and laboratory values of the study population.

	Group 1 $n = 45$	Group 2 $n = 174$	p
Age (years)	65.4 ± 11.2	62.5 ± 12.9	0.17
Gender (male) (%)	31 (68.9)	137 (78.7)	0.16
BMI (kg/m^2)	23.0 ± 4.6	25.3 ± 3.5	0.41
Current smoker (%)	5 (11.1)	21 (12.0)	0.86
Hypertension (%)	23 (51.1)	87 (50.0)	0.99
Diabetes mellitus (%)	16 (35.5)	53 (30.4)	0.51
Dyslipidemia (%)	15 (33.3)	63 (36.2)	0.12
Previous coronary artery bypass graft (%)	7 (15.5)	20 (11.5)	0.44
Cause of HF (ischemic/nonischemic)	35/10	130/44	0.71
Heart rate (beats/min)	75.9 ± 16.7	81.5 ± 19.8	0.22
Systolic BP (mmHg)	104.6 ± 5.9	104.2 ± 5.5	0.97
Diastolic BP (mmHg)	62.5 ± 4.7	62.2 ± 4.0	0.98
LVEF (%)	25.9 ± 5.8	26.9 ± 5.4	0.31
WBC count (×1000/μl)	12.2 ± 4.8	8.9 ± 3.1	<0.001
Neutrophil count (×1000/μl)	9.8 ± 4.7	6.6 ± 2.9	0.001
Lymphocyte count (×1000/μl)	1.3 ± 0.6	1.4 ± 0.7	0.005
Neutrophil-to-lymphocyte ratio	10.2 ± 8.4	6.1 ± 5.3	<0.001
Serum sodium (mequiv./l)	135 ± 3	133 ± 4	0.29
Creatinine (mg/dl)	1.5 ± 0.5	1.3 ± 0.5	0.009
hsCRP (ng/ml)	8.2 ± 5.2	7.5 ± 4.7	0.46
Medications			
ACEI or ARB (%)	41 (92)	154 (89)	0.62
β blocker (%)	43 (97)	164 (94)	0.73
Digoxin (%)	31 (68)	109 (63)	0.44
Spironolactone (%)	42 (93)	165 (95)	0.40
Furosemide (%)	45 (100)	174 (100)	1.00
Levosimendan (%)	45 (100)	174 (100)	1.00
Nitroglycerine (%)	8 (18)	26 (15)	0.64

BMI, body mass index; HF, heart failure; BP, blood pressure; LVEF, left ventricular ejection fraction; WBC, white blood cell; hsCRP, high-sensitivity C-reactive protein; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers.

Discussion

Our study revealed that an unchanging or increasing N/L ratio after the infusion of levosimendan was associated with in-hospital mortality in patients admitted to the hospital with ADHF. Furthermore, the predictive value of the N/L ratio was superior to that of other hematological variables.

Inflammatory processes are involved in the pathophysiology of HF and portent a worsening functional capacity and poor prognosis; thus, inflammation is currently considered to be a therapeutic target in HF [17]. The WBC count is a marker of systemic inflammation, but data on its association with an increased risk of HF are limited [2,18]. However, cytokines, which are associated with the development, progression, and unfavorable outcomes in HF, are secreted by mainly leukocytes [19–21]. Neutrophilia, lymphocytopenia, and particularly an increase in the N/L ratio, have been shown to be independent predictors of mortality in patients with ADHF [10,11,15]. Downregulation of the proliferation and differentiation of lymphocytes, neurohumoral activation, and lymphocyte apoptosis have been suggested as potential mechanisms of lymphocytopenia [15]. Likewise, in our study, patients with ADHF had a lower lymphocyte count on admission. After the infusion of levosimendan, a dramatic increase was detected in patients with a favorable outcome compared to patients who experienced death. We suggest that a deterioration in the lymphocyte count after the

Table 3
Comparison of hemodynamic, echocardiographic, and laboratory variable changes after levosimendan infusion between two groups.

	Group 1 (n = 45)		Group 2 (n = 174)		F	p
	Before LS	After LS	Before LS	After LS		
Hemodynamic variables						
Heart rate (beats/min)	78.6 ± 6.8	81.9 ± 6.8	77.0 ± 5.2	80.5 ± 5.2	0.1	0.80
Systolic BP (mmHg)	104.7 ± 5.7	98.5 ± 4.4	104.2 ± 5.5	99.3 ± 4.7	1.1	0.29
Diastolic BP (mmHg)	62.5 ± 4.7	61.7 ± 3.6	62.2 ± 4.0	61.1 ± 4.1	1.0	0.31
Echocardiographic variables						
LVEF (%)	25.9 ± 5.8	28.5 ± 5.3	26.9 ± 5.4	29.3 ± 4.7	1.2	0.28
LVESD (mm)	48.2 ± 4.2	45.2 ± 4.1	47.5 ± 4.9	44.3 ± 4.3	2.1	0.15
LVEDD (mm)	62.5 ± 5.1	61.4 ± 4.8	61.2 ± 4.4	60.4 ± 5.1	0.9	0.33
Laboratory variables						
WBC count (×1000/μl)	12.2 ± 4.8	12.1 ± 5.4	8.9 ± 3.1	8.5 ± 2.9	1.8	0.18
Neutrophil count (×1000/μl)	9.8 ± 4.7	10.0 ± 5.4	6.6 ± 2.9	5.9 ± 2.5	17.8	<0.001
Lymphocyte count (×1000/μl)	1.3 ± 0.6	1.2 ± 0.6	1.4 ± 0.7	1.5 ± 0.7	9.5	0.002
Neutrophil-to-lymphocyte ratio	10.2 ± 8.4	12.9 ± 14.3	6.2 ± 5.3	5.1 ± 3.4	24.9	<0.001
Creatinine (mg/dl)	1.5 ± 0.5	1.6 ± 0.7	1.3 ± 0.5	1.2 ± 0.4	15.4	<0.001
hsCRP (ng/ml)	8.2 ± 5.2	6.8 ± 3.0	7.5 ± 4.7	5.6 ± 3.1	5.7	0.02

LS, levosimendan; BP, blood pressure; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; WBC, white blood cell; hsCRP, high-sensitivity C-reactive protein.

infusion of levosimendan can be used to predict in-hospital mortality. Recently, Uthamalingamet al. [11] showed that a higher N/L ratio was associated with an increased risk of mortality in patients with ADHF. Furthermore, the ability of the N/L ratio to predict mortality in these patients was superior to that of the neutrophil count, total WBC count, or a relatively low lymphocyte count. The authors did not mention whether their patients had received levosimendan or the potential effects of levosimendan on hematological variables. Calculation of the N/L ratio is simple and inexpensive compared with the measurement of proinflammatory cytokines, including interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)-α [20,21].

Several studies have suggested that levosimendan causes a marked decrease in the levels of proinflammatory compounds such as brain natriuretic peptide (BNP), IL-6, and TNF-α [22–24]. Levosimendan also provided hemodynamic and clinical improvement in patients with ADHF [22–24]. It has been suggested that the amelioration of hemodynamic parameters may partly explain the decreased expression of these mediators in the myocardium [25]. In another study, superiority of levosimendan over dobutamine in improving hemodynamics was related to its anti-inflammatory and anti-apoptotic effects [26]. Additionally, levosimendan-induced improvements in systolic function and peripheral vasorelaxation may attenuate peripheral tissue hypoperfusion leading to the downregulation of extracardiac cytokine production [27,28]. In our patients, there was a significant decrease in the neutrophil count and N/L ratio, and an increase in the lymphocyte count after the infusion of levosimendan. However, patients on dobutamine therapy did not exhibit similar changes on hemotological parameters. When the study population was divided into two groups on the basis of in-hospital mortality, the lymphocyte count was lower while the WBC count, neutrophil count, and N/L ratio were higher, on admission. In this study, the mortality rate was higher compared to results of the previous similar studies [22,24,29]. Some of the possible explanations for this issue could be increased age of our study population (mean age 63.4 ± 14.9 years old), worst functional status of the patients (all the patients were NYHA Class IV), and ischemic etiology as the underlying pathology in most of the patients (77%). Pereira-Barretto et al. recently published their in-hospital mortality rate as 16% in a similar study group consisting of patients with advanced heart failure (NYHA Class III/IV, mean LVEF 26%) [29]. After the infusion of levosimendan, a significant increase in the lymphocyte count and significant decreases in the

Table 4
Univariate and multivariate logistic regression analysis for variables associated with in-hospital mortality.

	Univariable predictors				Multivariate predictors				
	β coefficient	OR	95% CI	p	β coefficient	OR	95% CI	p	R^2
Age (years)	0.02	1.020	0.992–1.048	0.17	–	–	–	–	
Hypertension (%)	−0.002	0.998	0.518–1.924	0.99	–	–	–	–	
Diabetes mellitus (%)	0.23	1.260	0.631–2.513	0.51	–	–	–	–	
Ischemic cardiomyopathy (%)	0.15	1.158	0.529–2.533	0.71	–	–	–	–	
Baseline									
Neutrophil-to-lymphocyte ratio	0.09	1.092	1.038–1.149	0.001	−0.08	0.921	0.843–1.006	0.07	
Creatinine (mg/dl)	0.80	2.235	1.205–4.147	0.01	−1.21	0.299	0.055–1.637	0.16	
hsCRP (ng/ml)	0.02	1.022	0.955–1.093	0.54	–	–	–	–	
Heart rate (beats/min)	0.05	1.050	0.992–1.111	0.92	–	–	–	–	
Systolic BP (mmHg)	0.02	1.015	0.956–1.077	0.63	–	–	–	–	0.41
Diastolic BP (mmHg)	0.02	1.018	0.941–1.102	0.65	–	–	–	–	
LVEF (%)	−0.03	0.969	0.913–1.030	0.31	–	–	–	–	
Final									
Neutrophil-to-lymphocyte ratio	0.18	1.198	1.114–1.288	<0.001	0.27	1.310	1.158–1.483	<0.001	
Creatinine (mg/dl)	1.42	4.125	2.201–7.729	<0.001	1.38	3.975	1.841–8.582	0.001	
hsCRP (ng/ml)	0.13	1.136	1.021–1.265	0.02	0.09	1.091	0.951–1.252	0.21	
Heart rate (beats/min)	0.06	1.065	1.007–1.131	0.03	0.12	1.129	1.045–1.220	0.002	
Systolic BP (mmHg)	−0.04	0.960	0.888–1.038	0.31	–	–	–	–	
Diastolic BP (mmHg)	0.05	1.045	0.959–1.137	0.32	–	–	–	–	
LVEF (%)	−0.03	0.966	0.902–1.035	0.32	–	–	–	–	

CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; BP, blood pressure.

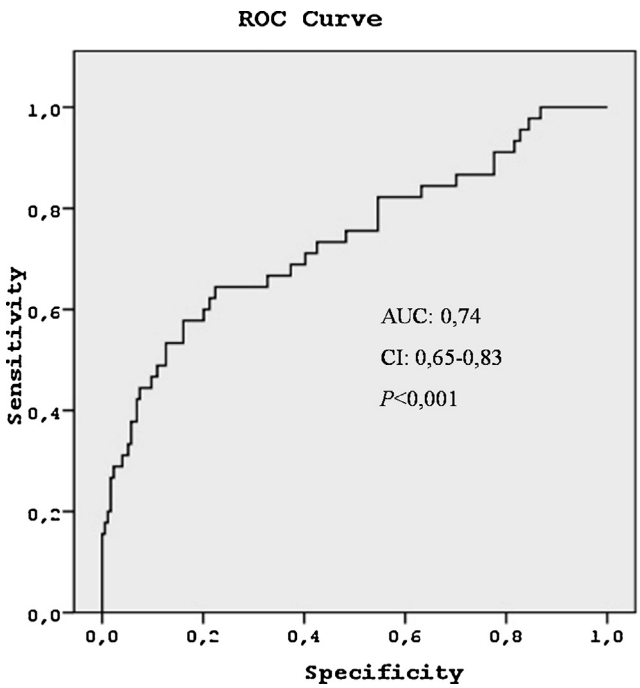

Fig. 2. The receiver-operating characteristic (ROC) curve for the neutrophil to lymphocyte ratio (N/L ratio) after levosimendan infusion, for predicting in-hospital mortality [area under the curve (AUC) = 0.737, 95% confidence interval (CI): 0.65–0.83; $p < 0.001$]. A N/L ratio value of at least 5.542 yielded a sensitivity of 67%, a specificity of 66%.

neutrophil count and N/L ratio were observed only in patients who recovered (group 2) after the infusion of levosimendan. However, the lymphocyte count was decreased, while the N/L ratio and neutrophil count were significantly increased, in patients who died during hospitalization. In addition, significant amelioration of the creatinine levels and serum hsCRP levels were detected in patients with a good clinical outcome after the infusion of levosimendan. Experimental and clinical studies have shown that levosimendan improves renal function with a decline in serum creatinine levels [30,31]. Zemljic et al. [31] reported that levosimendan improved long-term renal function in patients with advanced chronic HF. In their study, an improvement in creatinine to ≥0.5 mg/dL occurred in 50% of patients in the levosimendan group, compared with 10% of the controls ($p = 0.005$). In our study, a significant decrease in baseline creatinine levels was identified after the infusion of levosimendan (1.3 ± 0.5 mg/dL *vs.* 1.2 ± 0.5 mg/dL; $p = 0.005$). The

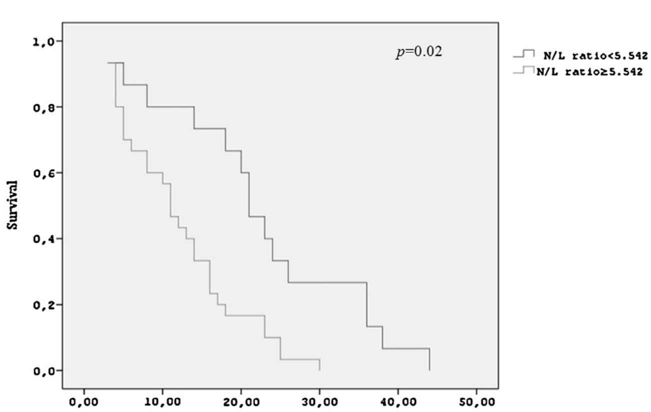

Fig. 3. Kaplan–Meier estimates for survival according to the N/L ratio after levosimendan therapy. N/L ratio, neutrophil to lymphocyte ratio.

underlying mechanisms of the potential renoprotective effects of levosimendan remain undefined. Both improved cardiac output and vasodilatation could lead to enhanced renal perfusion and improved kidney function. Similarly, cardiac decompensation and sustained damage to other organs because of a low cardiac output and venous congestion can induce IL-6 production, which activates hsCRP and complement resulting in amplification of the inflammatory response through TNF-α production. This in turn may lead to a worsening of HF and unfavorable outcomes [32].

Our study demonstrated that increased N/L ratio after levosimendan infusion was an independent predictor of poor outcomes in patients with ADHF. Furthermore, the predictive value of increased N/L ratio was superior to other hematological parameters which were previously demonstrated as predictors of morbidity and mortality in these patients. In our study, higher N/L ratio after levosimendan therapy was associated with increased heart rate, elevated serum creatinine and hsCRP levels, which were suggested as independent predictors of mortality in patients with ADHF previously [33–35].

In light of these findings, the N/L ratio, which is an inexpensive and readily obtainable parameter, could be used in clinical practice as a useful marker of risk stratification in patients admitted with ADHF. Additional randomized, controlled trials are needed to determine the prognostic role of the N/L ratio in ADHF patients.

Limitations

The major limitation of this study was the small population size. Additionally, this was not a randomized and controlled study; no detailed comparison with patients who received a placebo or dobutamine was performed. Further, well known pro-inflammatory and prognostic markers such as BNP, IL-6, IL-1β, TNF-α, and cardiac troponin were not analyzed and compared with the N/L ratio [20,21,36]. Thus, the results of this study should be confirmed in larger, prospective, randomized trials.

Conclusion

In conclusion, a high N/L ratio may be used as a novel marker of inflammation in the risk stratification of patients with ADHF. Our results demonstrate that a high N/L ratio on admission and a lack of a decrease in the N/L ratio after levosimendan infusion are associated with an increased risk of in-hospital mortality in patients with ADHF. In addition to its favorable effects on cardiac and hemodynamic measures, levosimendan could help to normalize the impaired WBC composition in these patients.

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