

Neutrophil to lymphocyte ratio as noninvasive predictor of pulmonary vascular resistance increase in congestive heart failure patients: Single-center preliminary report

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Abstract

Background. Nowadays, heart failure (HF) is a significant health problem due to steady increase in diagnosis, unpredictable acute decompensations and high mortality rate. Early risk stratifications of clinical deterioration are essential in preventing life-threatening events and ensuring proper patients management. Increased neutrophil to lymphocytes ratio (NLR) above 6 is associated with the risk of re-hospitalizations and increased mortality.

Objectives. To compare NLR and clinical, laboratory and hemodynamic results obtained from patients re-hospitalized within six-month intervals due to HF decompensation.

Material and methods. We evaluated 41 patients (n = 36 males (87%) and n = 5 females (13%), mean age 50 ± 10 years) admitted to our hospital at least twice within six-month interval due to decompensation of chronic heart failure (CHF) between 2017 and 2019. All patients were divided into 2 groups depending on the NLR values.

Results. There was no death in presented group during the observational time. We observed a significant difference in cardiac index (CI) – 2.4 ± 0.5 compared to 2.6 ± 0.6 L/m²/min – between the 1st and 2nd admission (p = 0.0356). The right ventricle systolic pressure (RVSP) results related to NLR level revealed significant difference (43 ± 14 mm Hg compared to 59 ± 21 mm Hg, p = 0.0438). We observed a significant increase of pulmonary vascular resistance (PVR) values (175 ± 106 compared to 438 ± 300 dyn*s*cm⁻⁵, p = 0.0386) in patients with NLR above 6.

Conclusions. Neutrophil to lymphocyte ratio may be an easy and suitable tool for monitoring of the HF progression. According to our study, the ratio correlates with PVR and RVSP increase.

Key words: neutrophils, heart failure, pulmonary hypertension, pulmonary vascular resistance

Background

Nowadays, heart failure (HF) is a significant health problem due to steady increase in diagnosis, unpredictable acute decompensations and high mortality rate.¹ Early risk stratifications of clinical deterioration are essential in preventing life-threatening events and ensuring proper patient management.² Pulmonary hypertension secondary to HF is a factor of poor prognosis and has a significant influence on the severity of the disease.³

Increased neutrophil to lymphocytes ratio (NTLR) above 6 is associated with the risk of re-hospitalizations and increased mortality.⁴ In response to a variety of signals, neutrophils produce several cytokines and other inflammatory factors, including neutrophil serine proteases, peroxidases, proteinases, gelatinases, NADPH oxidase, and pentraxin 3.^{5,6} Cytokine hypothesis involving serum elevation levels of interleukin 1 (IL-1), tumor necrosis factor α (TNF- α), transmembrane suppression of tumorigenicity-2 receptor (ST2), IL-6, and galectin-3 in HF patients support inflammatory contribution of disease progression.⁷

We analyzed the clinical status, laboratory results and hemodynamic parameters in patients suffering from chronic

heart failure (CHF), re-hospitalized within 6 months in our hospital.

Material and methods

We evaluated 41 patients ($n = 36$ men (87%) and $n = 5$ women (13%), mean age 50 ± 10 years) admitted to our hospital at least twice within a six-month interval due to decompensation of CHF due to HF with reduced ejection fraction (HFrEF) between 2017 and 2019. Twenty of them were diagnosed with dilated cardiomyopathy (DCM) and 21 with ischemic cardiomyopathy (ICM). Mean body mass was 85 ± 15 kg compared to 87 ± 16 kg on 1st and 2nd admission, respectively, and the mean height was 176 ± 8 cm. Concomitant diseases included diabetes mellitus (DM; 3 patients), chronic obstructive pulmonary disease (COPD; 2 patients), kidney dysfunction (2 patients), and a history of stroke (1 patient).

On admission and during hospitalization, laboratory tests, echocardiography, right catheterization, and 6-minute walking test (6MWT) were performed (Table 1). We analyzed baseline patients' demographics, change in functional class according to World Health Organization

Table 1. Differences in laboratory, echocardiographic and RHC parameters between 1st and 2nd hospitalization

Parameters	1 st admission	2 nd admission	p-value
Whole blood count			
Leukocyte count [$10^9/L = 10^9/L$]	7.3 [6.3–8.4]	7 [5.8–8.3]	0.0593
Neutrophil count [$10^9/L = 10^9/L$]	4.9 [4.1–5.9]	4.8 [3.9–5.8]	0.1561
Lymphocyte count [$10^9/L = 10^9/L$]	1.4 [1.2–1.8]	1.5 [1–2]	0.2461
NTLR	3.5 [2.5–4.7]	3.3 [2.2–4.4]	0.7216
Hemoglobin [mmol/L]	9.2 [8.7–9.6]	8.9 [8.5–9.5]	0.3724
Albumin [mg/dL]	40.3 [38.5–42.8]	40.5 [38.5–41.9]	0.4476
AST [IU/L]	136 [31–140]	136 [34–139]	0.8174
Creatinine [mg/dL]	101.4 [85.9–128.2]	94 [83.3–122.9]	0.8055
CRP [mg/L]	2 [1.0–6.2]	2.8 [1.1–8.8]	0.2256
BNP [pg/mL]	310 [133.4–645.1]	360 [131.9–567.0]	0.2158
proBNP [pg/mL]	1652 [743–2618]	1467 [831–2627]	0.4661
Echocardiographic parameters			
LVD [mm]	75 [67–80]	73 [65–82]	0.8561
RVD [mm]	35 [32–39]	35 [31–37]	0.4461
RVSP [mm Hg]	40 [34–55]	45 [35–50]	0.9652
LVEF [%]	20 [15–25]	20 [15–25]	0.5888
Right heart catheterization			
PAPm [mm Hg]	32.5 [23–44]	29.5 [21.5–40.0]	0.3626
CO [L/min]	4.7 [3.9–5.5]	5.3 [4.6–6.0]	0.0534
CI [$L/m^2/min$]	2.3 [2–2.7]	2.6 [2.4–2.9]	0.0356
PVR [$dyn*s*cm^{-5}$]	151.5 [113–270]	150 [106.0–218.5]	0.1401

Data presented as median [LQ–UQ]; LQ – lower quartile; UQ – upper quartile; AST – aspartate aminotransferase; BNP – natriuretic brain peptide; CI – cardiac index; CO – cardiac output; CRP – C-reactive protein; EF – ejection fraction; LVD – left ventricle diameter; LVEF – left ventricle ejection fraction; NTLR – neutrophil to lymphocyte ratio; NT-proBNP – N-terminal prohormone natriuretic brain peptide; PAPm – mean pulmonary artery pressure; PVR – pulmonary vascular resistance; RHC – right heart catheterization; RVSP – right ventricle systolic pressure.

(WHO) classification, results of 6MWT, and vital signs on admission (including heart rate, blood pressure). Laboratory data included brain natriuretic peptide (BNP), N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP), blood morphology, C-reactive protein (CRP), creatinine, alanine aminotransaminase (ALT), aspartate transaminase (AST), and NTLR. Echocardiography was performed in each patient at the admission, including left and right ventricle and atrial diameters, left ventricle ejection fraction (LVEF), presence of pericardial effusion, right atrial pressure (RAP) estimated by evaluating the inferior cava (IVC) size and change with respiration, and right ventricle systolic pressure (RVSP). The estimation of RVSP was based on the peak tricuspid regurgitation velocity (TRV) taking into account RAP as described by the simplified Bernoulli equation.

Right heart catheterization was performed in the catheterization lab. Pressure measurements were obtained, including mean RAP, right ventricle pressure (systolic, diastolic and end-diastolic), pulmonary artery pressure (systolic, diastolic and mean), and wedge pressure. Cardiac output (CO) was measured with thermodilution with cold saline. The cardiac index (CI), pulmonary vascular resistance (PVR), systemic vascular resistance (SVR), and transpulmonary gradient (TPG) were estimated.

All patients were divided into 2 groups depending on the NTLR values obtained from blood samples taken on admission. The values above or below 6 determined the division according to previous reports.⁷

Statistical analysis

Mean body mass, weight, 6MWT results and drugs daily dosages were presented as mean values and standard deviations (SD). The analyzed parameters were presented as medians and interquartile range (IQR), since data did not follow according to normal distribution (Shapiro–Wilk test); therefore, non-parametric tests were used. The comparison between data obtained during the 1st and 2nd admission was performed with Wilcoxon matched pairs test. Parameters between patients with NTLR value lower or greater than 6 were compared with Mann–Whitney test. Statistical analysis was performed using STATISTICA v. 13.3 (StatSoft Inc., Tulsa, USA). All tests were considered significant at $p < 0.05$.

Results

There was no death in the presented group during the observational time (2017–2019). The clinical evaluation of severity of HF decompensation was based on the New York Heart Association (NYHA) classification with mean NYHA functional class on the 1st and 2nd admissions 2.5 ± 0.5 and 3.2 ± 0.5 , respectively. The indications for 2nd admission were based on worsening in clinical symptoms

regarding shortness of breath in 41 (100%), easy fatigue in 35 (85%) and lower extremities swellings in 38 (93%) patients. Five (12%) patients reported persistent cough.

There was neither a statistically significant difference in NYHA stage nor a correlation between NYHA stage and NTLR between both admissions. Moreover, the differences in BNP and NT-pro-BNP serum levels between both admissions were non-significant. The BNP serum levels were 435 ± 409 pg/mL compared to 485 ± 537 pg/mL on the 1st and 2nd admission, respectively. The NT-pro-BNP serum levels were 2103 ± 1942 pg/mL compared to 2171 ± 2239 pg/mL on the 1st and 2nd admission, respectively. The results of BNP serum levels related to NTLR were still insignificant (413 ± 418 pg/mL compared to 566 ± 263 pg/mL, respectively, $p = 0.0736$). The results of NT-pro-BNP serum levels related to NTLR were not significant (1961 ± 1982 pg compared to 2938 ± 1979 pg/mL, respectively, $p = 0.0933$). Detailed data is presented in Table 1.

There was no significant difference in echocardiographic parameters between both admissions including RSPV results (45 ± 16 mm Hg compared to 45 ± 13 mm Hg, respectively). The RVSP results related to NTLR subgroups revealed a significant difference (43 ± 14 mm Hg compared to 59 ± 21 mm Hg, $p = 0.0438$). Detailed data is presented in Table 2.

The clinical evaluation was also performed with 6MWT before discharge. The mean values of achieved distances on 1st and 2nd hospitalization were 356 ± 41 m compared to 361 ± 52 m, respectively. The results of 6MWT during the 2nd hospitalization in 2 NTLR subgroups were significantly different: 331 ± 42 compared to 378 ± 39 m, in patients with NTLR ratio above and below 6, respectively.

We observed a significant difference in CI (2.4 ± 0.5 compared to 2.6 ± 0.6 L/m²/min) between the 1st and 2nd admission ($p = 0.0356$). However, there was no relationship between NTLR level and CI.

There was no statistical difference in PVR values between admissions in studied group (212 ± 170 compared to 190 ± 117 dyn*s*cm⁻⁵). However, we observed a significant increase in PVR values (175 ± 106 compared to 438 ± 300 dyn*s*cm⁻⁵), $p = 0.0386$ in patients with NTLR above 6.

Pharmacotherapy on 1st admission included β -blockers, diuretics, eplerenone, and angiotensin-converting-enzyme inhibitors (ACE-I). The doses of diuretics and ACE-I were optimized increased during 1st hospitalization. Pharmacotherapy regimes between both admissions are compared in Table 3.

Discussion

To the best of our knowledge, this is the first study presenting the correlation between NTLR and PVR and RVSP increase in patients with CHF. Heart failure is a challenging clinical problem with high mortality risk, exceeding 50% within 5 years.⁸ Therapy is focused on clinical improvement

Table 2. Differences in laboratory, echocardiographic and RHC parameters between NTLR subgroups

Parameter	NTLR ≤ 6	NTLR > 6	p-value
Laboratory results			
Leukocyte count [$10^9/L = 10^9/L$]	7.1 [6.2–8]	9.9 [8.4–10.6]	0.0036
Hemoglobin [mmol/L]	9.2 [8.7–9.6]	9.1 [8.5–9.4]	0.5922
Albumin [mg/dL]	40.7 [38.4–43.0]	39.4 [38.6–40.4]	0.5444
AST [IU/L]	136 [30–140]	137 [31–140]	0.9410
Creatinine [mg/dL]	93.9 [81.8–125.3]	125.4 [111.9–134.4]	0.0797
CRP [mg/L]	1.8 [1.0–5.2]	8.9 [6.2–10.2]	0.0676
BNP [pg/mL]	240 [122.1–574.4]	519.4 [356.1–650.4]	0.0736
NT-proBNP [pg/mL]	1293 [674–2590]	2775.5 [1763–4626]	0.0933
Echocardiography			
LV [mm]	73 [64–80]	80 [75–84]	0.0930
RV [mm]	34 [31–39]	35 [35–37]	0.3952
EF [%]	20 [15–25]	20 [15–23]	0.7930
RVSP [mm Hg]	40 [32–49]	60 [40–65]	0.0438
Right catheterization			
PAPm [mm Hg]	28.5 [21.5–42.5]	44 [33.0–57.5]	0.1005
CO [L/min]	4.9 [4.2–5.5]	3.7 [3.6–4.6]	0.2244
CI [L/m ² /min]	2.4 [2.1–2.7]	2 [1.8–2.4]	0.1227
PVR [dyn*s*cm ⁻⁵]	142 [99.5–244.3]	407 [186–690]	0.0386

Data presented as median [LQ–UQ]; LQ – lower quartile; UQ – upper quartile; AST – aspartate aminotransferase; BNP – natriuretic brain peptide; CI – cardiac index; CO – cardiac output; CRP – C-reactive protein; EF – ejection fraction; LVD – left ventricle diameter; LVEF – left ventricle ejection fraction; NTLR – neutrophil to lymphocyte ratio; NT-proBNP – N-terminal pro hormone natriuretic brain peptide; PAPm – mean pulmonary artery pressure; PVR – pulmonary vascular resistance; RHC – right heart catheterization; RVSP – right ventricle systolic pressure.

Table 3. Pharmacology during both hospitalizations

Pharmacotherapy	1 st admission (n = 41 patients)	2 nd admission (n = 41 patients)
β-blockers:		
Metoprolol [mg/daily]	100 ± 37.5	100 ± 25
number of patients	4 (10%)	4 (10%)
Bisoprolol [mg/daily]	10 ± 2.5	10 ± 2.5
number of patients	2 (5%)	2 (5%)
Carvedilol [mg/daily]	25 ± 12.5	25 ± 6.25
number of patients	35 (85%)	35 (85%)
Diuretics:		
Furosemide [mg/daily]	120 ± 80	180 ± 40
number of patients	41 (100%)	41 (100%)
Eplerone [mg/daily]	50 ± 1.25	50 ± 0.25
number of patients	41 (100%)	41 (100%)
Torsemide [mg/daily]	10 ± 3	20 ± 4
number of patients	4 (10%)	6 (15%)
ACE-I:		
Ramipril [mg/daily]	3.3 ± 1.6	4.8 ± 1.2
number of patients	41 (100%)	41 (100%)

ACE-I – angiotensin-converting-enzyme inhibitors.

by blocking neurohormonal and sympathetic systems activation.⁹ In different types of cardiomyopathies, the trigger insult may be of inflammatory etiology with secondary immune system activation in response. The blood-recruited monocytes infiltrate the myocardium, causing further deterioration of the heart function.^{10,11} The persistence of inflammation after acute phases promotes adverse heart

remodeling.¹² In our study, we focused on a possible risk prognosis for future clinical deterioration assessed with NTLR. Neutrophils are known to be important effector cells in the immune system responding to multiple signals by producing inflammatory factors.^{13,14} They are involved in cell activation at the inflammatory sites.¹⁵ The link between HF development and clinical progression is strong and complementary to neurohormonal activation.¹⁶ Neutrophil to lymphocyte ratio above 6 is a known predictor for in-hospital mortality among patients with acute decompensations.¹⁷

In our study, there was a correlation noticed between NTLR and PVR values. Hence, the NTLR could be a possible prognostic factor for future clinical status deterioration among patients requiring readmission within a six-month time interval. Right heart catheterization (RHC) is a definitive tool for accurate hemodynamic monitoring.¹⁸ We found the PVR increased from $175 \pm 105 \text{ dyn*s*cm}^{-5}$ to $438 \pm 300 \text{ dyn*s*cm}^{-5}$ in the subgroup of patients with elevated NTLR. Although the BNP and NT-pro-BNP values were insignificant, the progression of the failing heart was noticed by hemodynamic results of heart function. In our study, we present the results confirming NTLR as a significant marker for future heart function deterioration. There was no statistically significant difference in RVSP between admissions, but an increase was noted ($42 \pm 14 \text{ mm Hg}$ compared to $59 \pm 21 \text{ mm Hg}$) regarding NTLR.

Although the population did not differ in NYHA stage between both admissions, the clinical symptoms requiring hospitalizations may be related to increase in pulmonary hypertension evaluated easily using RSVP results in echocardiographic imaging. Among predictors in patients with left ventricular dysfunction, impaired function of right ventricle is believed to be an independent predictor of less than 30% survival within 5 years.¹⁹ Echocardiography of right ventricle hemodynamics is focused on its function and on risk estimation of pulmonary hypertension. Both parameters are significant for patients' prognosis including disease severity and survival.²⁰ We present the results of the study, indicating NTLR as an easy laboratory tool of parallel significance related to RHC results.

We noticed that despite clinical deterioration, heart catheterization revealed an increase in CI. The initial results were 2.4 ± 0.5 and 2.6 ± 0.6 L/m²/min and changed to 2.6 ± 0.6 L/m²/min ($p = 0.0356$). The differences may be explained by pharmacotherapy optimization including diuretics and ACE-I doses increase. However, there was no relationship between NTLR level and CI.

The most significant result of the study is connected to the NTLR to PVR estimation with RHC. Pulmonary vascular resistance is a lone predictor of poor outcomes according to previous studies in patients suffering from HF.²¹ Moreover, the PVR increase indicates ominous disease progression.^{22,23} The results of our study suggest that NTLR can be a suitable, quick and easy tool for assessing the risk of PVR progression stratification in patients suffering from circulatory insufficiency.

Conclusions

Neutrophil to lymphocyte ratio may be an easy and suitable tool for monitoring HF progression. According to our study, the ratio correlates with PVR and RVSP increase.

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