Predictive value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in decompensated heart failure
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Objective
Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which are new inflammatory markers, inexpensive, widely available, and obtained from routinely used test (complete blood count), have proved to be potential predictors of outcome in many cardiovascular diseases. The aim of this study was to investigate the predictive value of NLR and PLR in detecting HF and their effect on morbidity and mortality of patients with heart failure (HF).

Patients and methods
This prospective study included 60 patients diagnosed with acute decompensated HF and 40 age-matched and sex-matched healthy controls. Echocardiography was done for all participants to assess cardiac function. All participants were tested for biochemical parameters (urea, creatinine, and liver function tests). Complete blood count with calculation of NLR and PLR was done for all participants. Then all cases were followed up for occurrence of cardiovascular, cerebrovascular complications, history of hospitalization, and death during the period of the study.

Results
NLR and PLR of patients were significantly higher than controls (P < 0.02 and <0.03, respectively). There was an inverse correlation between both PLR and NLR and left ventricular ejection fraction of the study population (P < 0.01 and <0.02, respectively). PLR had 70% sensitivity and 47% specificity for prediction of HF with cutoff point more than 186, whereas NLR had 97% sensitivity and 47% specificity for prediction of HF with cutoff point more than 3.56. Moreover, PLR had 83% sensitivity and 58% specificity for prediction of mortality in those patients with decompensated HF with cutoff point more than 175, whereas NLR had 92% sensitivity and 33% specificity for prediction of mortality in those patients with decompensated HF with cutoff point more than 3.56, with average 1-year follow-up.

Conclusion
NLR and PLR are cheap, widely available inflammatory biomarkers that can be used to predict morbidity and mortality in patients with HF.

Keywords: heart failure, lymphocyte, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio

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Introduction
Heart failure (HF) is a clinical syndrome that represents the most frequent complication of all cardiac diseases, and it is the main cause of morbidity, mortality, and hospitalization in this group of patients [1]. The estimated prevalence of HF is 23 million worldwide. Despite the introduction of many emerging therapeutic modalities, the survival rate in HF is still poor [2].

Chronic inflammatory reactions have been observed to play an important role in the pathogenesis of cardiovascular diseases and cancer [3]. Recently, increased white blood cell (WBC) count has been observed to be a predictive biomarker of cardiovascular diseases which acts independently of other well known risk factors [4]. In response to inflammation, WBCs and their subtypes release proinflammatory cytokines which lead to destruction of the myocardium, affecting left ventricular function and leading to HF [5].

However, different WBC subtypes, especially lymphocytes, neutrophils, and monocytes, are believed to have a stronger role in predicting the risk of cardiovascular disease than total WBC count [3].

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are relatively novel biomarkers of inflammation. Both have shown prognostic value in different cardiovascular conditions [6].
The aim of this study was to investigate the predictive value of NLR and PLR in detecting HF and prediction of morbidity and mortality in patients with HF.

Patients and methods
This prospective nonrandomized study included 60 patients with acute decompensated HF in addition to 40 age-matched and sex-matched controls without HF between 2016 and 2018. Patients were recruited from critical care unit and cardiology outpatient clinic of Internal Medicine department, Assiut University Hospital, according to European Society of Cardiology guidelines [7]. Patients with acute infection, those with autoimmune diseases, those with acute and chronic renal diseases, and patients with acute coronary syndrome were excluded. All patients and controls were evaluated by history taking, clinical examination, complete blood count with calculation of NLR and PLR, complete liver functions, renal function tests, and prothrombin time and concentration in addition to chest X-ray and transthoracic echocardiography to assess cardiac function. Then all patients were followed up for occurrence of cardiovascular and cerebrovascular complications, history of hospitalization, and death during the period of the study. Written informed consents were taken from all participants. This study was approved by the ethical committee of Assiut University.

Statistical analysis
Data were collected and analyzed using statistical package for the social science, version 20 (IBM Corp., Armonk, New York, USA). Continuous data were expressed in the form of mean±SD or median (range), whereas nominal data were expressed in the form of frequency (percentage). \( \chi^2 \)-test was used to compare the nominal data of different groups in the study, whereas Student’s \( t \)-test was used to compare means of two different groups and analysis of variance test for more than two groups. Pearson’s correlation was used to determine the correlation between NLR and PLR with other continuous variables. Receiver operating characteristic curve was used to determine the diagnostic accuracy of NLR and PLR for prediction of decompensated HF. Predictors of mortality in patients with decompensated HF were determined by multivariate regression analysis. \( P \) value was considered significant if less than 0.05, \( \chi^2 \)-test was used to compare the nominal data of different groups in the study, whereas paired \( t \)-test was used to compare means of different variables before and after therapy. \( P \) value was significant if less than 0.05.

Results
This study included 60 patients with decompensated HF with mean age of 59.20±10.33 years and 40 healthy controls with mean age of 57.03±7.98 years. Diabetes mellitus, hypertension, and dyslipidemia presented in 19 (31.7%), 41 (68.3%), and 31 (52.5%) patients, respectively, and presented in four (10%), six (15%), and 10 (25%) of the control group. It was noticed that the frequency of diabetes mellitus, hypertension, and dyslipidemia was significantly higher in those patients with decompensated HF \( (P<0.001) \), as shown in Table 1.

Patients with decompensated HF had significantly higher total leukocytic count \( (8.01±1.79) \) versus the control group \( (6.62±1.42×10^6/ml) \); \( P<0.001 \). Moreover, neutrophil count was significantly higher in the study group \( (5.72±1.76×10^6/ml) \) than the control group \( (4.32±1.15×10^6/ml) ; \) \( P<0.001 \). NLR was significantly higher in the study group than the control group \( (4.60±1.22 \) vs. \( 3.04±1.41; \) \( P=0.02 \) ). PLR was significantly higher in the study group than the control group \( (193.09±15.98 \) vs. \( 140.87±40.07; \) \( P=0.03 \) ). However, the control group had significantly higher platelet count \( (307.60±40.07\) in comparison with the study group \( (276.95±65.61×10^9/ml) ; \) \( P=0.02 \) ), as shown in Table 2.

It was noticed that all of echocardiographic findings such as left ventricular end diastolic diameter, left ventricular end systolic diameter, interventricular septal defect, right ventricular diameter, and left atrial diameter had no significant correlations with NLR and PLR \( (P<0.05) \). NLR and PLR had significant inverse correlations with ejection fraction \( (r=-0.46, P=0.01 \) with PLR and \( r=-0.44, P=0.02 \) with NLR), as shown in Table 3 and Figs 1 and 2.

Both PLR and NLR were significantly higher in those patients with cardiovascular complications in

| Table 1 Baseline characteristics of studied groups |
|----------------------------------------------|
| Study group \( (n=60) \) & Control group \( (n=40) \) & \( P \) value |
| Age (years) & 59.20±10.33 & 57.03±7.98 & 0.08 |
| Sex & | | 0.44 |
| Male & 38 (63.3) & 24 (60) & |
| Female & 22 (36.7) & 16 (40) & |
| Diabetes mellitus & | | <0.001 |
| Hypertension & 19 (31.7) & 4 (10) & |
| Dyslipidemia & 41 (68.3) & 6 (15) & <0.001 |
| Data are expressed as mean±SD and frequency (%). \( P<0.05 \), significant. |
comparison with those without complications (194.63 ±34.98 vs. 181.33±44.87, P=0.01 for PLR and 6.67 ±1.23 vs. 3.21±1.22, P=0.02 for NLR), but both of them had no significant differences between different types of cardiovascular complications, as shown in Tables 4–6.

Both PLR and NLR had no significant differences in those patients with cerebrovascular complications in comparison with those without complications (195.613 ±34.01 vs. 185.93±41.23, P=0.34, for PLR and 5.17 ±0.99 vs. 4.21±1.91, P=0.12 for NLR), as shown in Table 7.

It was noticed that PLR had 70% sensitivity and 47% specificity for prediction of HF with area under the curve of 0.63 at a cutoff point more than 186, whereas NLR had 97% sensitivity and 47% specificity for prediction of HF with area under the curve of 0.74 at a cutoff point more than 3.56, as shown in Table 8 and Fig. 3.

Multivariate regression analysis for prediction of mortality in patients with decompensated HF showed that raised NLR and PLR were independent risk factors for mortality in patients with decompensated HF (P=0.04 and 0.01, respectively), as shown in Table 9.

During the period of follow-up, 43 patients needed rehospitalization with a range of one and three times. It was noticed that both of NLR and PLR were

### Table 2 Baseline laboratory data of studied groups

| Data                      | Study group (n=60) | Control group (n=40) | P value |
|---------------------------|--------------------|----------------------|---------|
| Liver function tests      |                    |                      |         |
| Bilirubin (μmol/l)        | 8.12±2.14          | 8.99±1.34            | 0.12    |
| Direct bilirubin (μmol/l) | 2.33±1.34          | 1.98±0.97            | 0.22    |
| Serum albumin (mg/dl)     | 41.20±7.35         | 40.10±5.70           | 0.73    |
| Alanine transaminase (U/l)| 15.09±9.11         | 16.68±3.22           | 0.46    |
| Aspartate transaminase (U/l)| 13.01±3.13       | 16.01±4.56           | 0.99    |
| Total protein (mg/dl)     | 85.70±12.48        | 81.96±10.68          | 0.93    |
| Kidney function tests     |                    |                      |         |
| Blood urea nitrogen (mg/dl)| 15.16±4.09      | 9.98±3.02            | 0.09    |
| Serum creatinine (mg/dl)  | 1.0±0.54           | 0.8±0.65             | 0.07    |
| Complete blood picture    |                    |                      |         |
| TLC (×10⁹/ml)             | 8.01±1.79          | 6.62±1.42            | <0.001  |
| Neutrophil (×10⁶/ml)      | 5.72±1.76          | 4.32±1.15            | <0.001  |
| Lymphocyte (×10⁶/ml)      | 1.93±0.94          | 1.63±0.63            | 0.09    |
| Platelets (×10⁹/ml)       | 276.95±65.61       | 307.60±63.77         | 0.02    |
| Hemoglobin (g/dl)         | 11.20±1.33         | 12.60±1.91           | 0.06    |
| PLR                       | 193.09±15.98       | 140.87±40.07         | 0.03    |
| NLR                       | 4.60±1.22          | 3.04±1.41            | 0.02    |
| PT (%)                    | 91.07±7.87         | 95.90±3.01           | 0.45    |
| INR                       | 1.01±0.09          | 1.02±0.09            | 0.09    |
| Serum electrolytes        |                    |                      |         |
| Sodium (μmol/l)           | 132.1±5.04         | 136.33±6.65          | 0.09    |
| Potassium (μmol/l)        | 3.03±0.95          | 3.87±0.63            | 0.45    |

Data are expressed as mean±SD and frequency (%). INR, international randomized ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PT, prothrombin time; TLC, total leukocytic count. P<0.05, significant.

### Table 3 Correlation of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with echocardiographic findings

|                    | PLR       | NLR       |
|--------------------|-----------|-----------|
|                    | r        | P         | r        | P         |
| LVEDD (cm)         | -0.11    | 0.48      | -0.04    | 0.08      |
| LVESD (cm)         | -0.10    | 0.43      | -0.06    | 0.69      |
| LAD (cm)           | 0.14     | 0.95      | 0.06     | 0.11      |
| RVD (cm)           | -0.01    | 0.36      | -0.09    | 0.43      |
| IVSD (cm)          | 0.12     | 0.96      | 0.31     | 0.08      |
| Ejection fraction (%)| -0.46  | 0.01      | -0.44    | 0.02      |

IVSD, interventricular septal defect; LAD, left atrial diameter; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; r, strength of correlation; RVD, right ventricular diameter. P<0.05, significant.
significantly higher in those with rehospitalization (204.74±23.09 vs. 155.31±55.80, \(P=0.04\) for PLR and 5.07±2.11 vs. 3.27±1.09, \(P=0.02\) for NLR), as shown in Table 10.

Discussion
The prevalence of HF is increasing owing to improving survival rates and aging population, which is associated with increased short-term and long-term morbidity [8].

One of the classical markers of systemic inflammation and cardiovascular disease is increased levels of total WBCs. High neutrophil concentrations have been proved to be a predictor of cardiovascular risk as they respond to inflammation releasing cytokines as C-reactive protein, tumor necrosis factor \(\alpha\), and interleukin-6, causing direct damage to the myocardium and affecting ventricular function [9].

Lymphopenia was observed in different cardiovascular diseases and was a predictor of mortality in patients with HF. It can be explained by neurohormonal activation with increased levels of cortisol and catecholamines in patients with HF which induce apoptosis, downregulation of proliferation, and differentiation of lymphocytes [8].

NLR and PLR, which are new inflammatory markers, inexpensive, widely available, obtained from routinely used test (complete blood count), have proved to be potential predictors of outcome in many cardiovascular diseases.
diseases. The aim of this study was to investigate the predictive role of these biomarkers in patients of HF. Although many studies tested the relation between total WBC counts and different cardiovascular diseases, only very few studies explored the predictive value of WBCs subtypes such as NLR and PLR in HF.

In this study, total leukocytic counts and neutrophil counts were significantly higher in cases than controls; however, there was no significant difference observed in lymphocytic counts between both groups. Durmus et al. [5] also observed a similar significant increase in neutrophil count in cases, but this increase was associated with a significant decrease in lymphocytic count in cases than controls. Engstrom et al. [9] previously proved that high leukocytic counts are associated with increased incidence of HF. In contrast, Haim et al. [4] had observed that increased WBC counts in patients with pre-existing coronary heart disease were associated with increased long-term all-cause mortality risk but that risk was eliminated after adjustment for baseline cardiovascular risk factors.

Significant inverse correlations between ejection fraction and both NLR and PLR were observed in this study. This can be explained by the release of proteolytic enzymes by activated neutrophils that lead to destruction of the myocardium [10]. Similar results were observed by Durmus et al. [5], but the correlation was only significant with NLR and not PLR.

This study proved that NLR has 97% sensitivity and 47% specificity for prediction of HF with cutoff point more than 3.56 and that PLR has 70% sensitivity and 47% specificity with cutoff point more than 186. This agreed with previous study which proved 86.3% sensitivity and 77.5% specificity for NLR with cutoff value of 3 and 70% sensitivity, 60% specificity for PLR with cutoff value of 137.3 [5].

This study observed that NLR and PLR are independent predictors of hospitalization and mortality in patients with HF. Similar results were observed by Durmus et al. [5], but they showed that NLR not PLR was associated with higher mortality in HF.

Turfan et al. [11] proved that high NLR was a strong predictor of mortality in acute HF independent of other risk factors in a study including 167 consecutive patients with acute HF. Moreover, Uthamalingam et al. [10] observed that high NLR was associated with increased risk of mortality in acute

### Table 4 Platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio based on the presence of cardiovascular complications

| Presence of cardiovascular complication (n=48) | Absence of cardiovascular complication (n=12) |
|---------------------------------------------|---------------------------------------------|
| PLR 194.63±34.98                             | 181.33±44.87                                |
| NLR 6.67±1.23                                | 3.21±1.22                                   |

Data are expressed as mean±SD. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

### Table 5 Level of platelet-to-lymphocyte ratio based on types of cardiovascular complications

| Type of complications       | Platelet-to-lymphocyte ratio (mean±SD) |
|-----------------------------|----------------------------------------|
| Arrhythmias                 | 5.21±1.01                              |
| Pulmonary edema             | 4.99±2.01                              |
| Cardiogenic shock           | 4.22±1.11                              |
| Intraventricular thrombus   | 5.61±1.90                              |
| Cardiac ischemia            | 6.07±1.13                              |

One-way analysis of variance test was used. 

### Table 6 Level of neutrophil-to-lymphocyte ratio based on types of cardiovascular complications

| Type of complications       | Neutrophil-to-lymphocyte ratio (mean±SD) |
|-----------------------------|----------------------------------------|
| Arrhythmias                 | 5.21±1.01                              |
| Pulmonary edema             | 4.99±2.01                              |
| Cardiogenic shock           | 4.22±1.11                              |
| Intraventricular thrombus   | 5.61±1.90                              |
| Cardiac ischemia            | 6.07±1.13                              |

One-way analysis of variance test was used. 

### Table 7 Level of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio based on types of cerebrovascular complications

| Presence of cerebrovascular complication (n=10) | Absence of cerebrovascular complication (n=50) |
|-----------------------------------------------|---------------------------------------------|
| PLR 195.613±34.01                             | 185.93±41.23                                |
| NLR 5.17±0.99                                 | 4.21±1.91                                   |

Data are expressed as mean±SD. NLR, neutrophil-to-lymphocytes ratio; PLR, platelet-to-lymphocyte ratio.

### Table 8 Diagnostic accuracy of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in prediction of decompensated heart failure

| PLR 194.63±34.98 | NLR 6.67±1.23 |
|------------------|---------------|
| Sensitivity (%)  | 70            |
| Specificity (%)  | 47            |
| Positive predictive value (%) | 67          |
| Negative predictive value (%) | 41       |
| Area under the curve | 0.63     |
| Cutoff point     | >168          | >3.56         |
| P value          | 0.001         | 0.001         |

NLR, neutrophil-to-lymphocytes ratio; PLR, platelet-to-lymphocyte ratio.
decompensated HF and that high NLR was also associated with higher rates of hospital readmission. In a recent study, Kim et al. [3] proved that NLR was associated with all-cause mortality in prospective cohorts of coronary heart disease and HF. They also observed that NLR rates vary with time reaching maximum around the time of event as death.

In contrast, in a previous study by Pourafkari et al. [2], neither PLR nor NLR showed significant association with hospital mortality in acute HF. Moreover, Nagarajan et al. [12] did not show any significant association for PLR with mortality in patients with advanced HF.

However, in a recent meta-analysis by Wang et al. [13], it was proved that NLR was associated with all-cause mortality and renal dysfunction in patients with HF stating that 1% increase in baseline NLR was associated with 28% increased risk of all-cause mortality.

The heterogeneity of results of different studies may be owing to differences in sample sizes, and also different demographic characteristics of study samples.

**Conclusion and recommendations**

NLR and PLR are inexpensive, widely available inflammatory biomarkers that can be used to predict morbidity and mortality in patients with HF. More studies with a larger number of patients are recommended.

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Nil.
Conflicts of interest
There are no conflicts of interest.

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