Lymphocytopenia has long been associated with poor prognosis in heart failure (HF). Several studies over the past few decades have demonstrated the potential of neutrophil-to-lymphocyte ratio (NLR), a widely available hematologic marker of oxidative stress damage, to serve as a good prognostic marker of mortality in cardiac and noncardiac diseases. In this study, we evaluated the association between NLR and future risk of mortality or cardiac transplantation in a large contemporary cohort of patients with advanced HF.

Methods

We analyzed 549 consecutive patients presented to the Cleveland Clinic (Cleveland, Ohio) from 2007 to 2010 for evaluation of advanced HF therapies and consideration for heart transplantation or mechanical circulatory assist devices. Electronic medical records were used to obtain demographic variables (age, gender, and race), clinical variables, laboratory values, and medications. Among this cohort, 527 patients had documented values of NLR within the time frame and clinical stability to complete the comprehensive evaluation for advanced HF therapeutics and were included in this study. Mortality data were obtained from social security death index (until 2012) and timing of death and heart transplantation were confirmed by review of the electronic medical records. The construction of the database was conducted by an independent researcher who was not involved in the care of patients. Data were collected retrospectively and the study was approved by the Institutional Review Board of the Cleveland Clinic.

NLR was calculated as the ratio between neutrophil count and lymphocyte count obtained at the time of evaluation. Participants were categorized in NLR tertiles low (<3.0), intermediate (3.0 to 5.4), and high (>5.4). The primary outcome was a composite of all-cause mortality or heart transplantation. Information on heart transplantation was extracted from the electronic records.

Continuous variables were described as mean and SD or median with interquartile range. Categorical variables were expressed as frequencies and percentages. Continuous variables were compared among NLR tertiles with the analysis of variance or Kruskal-Wallis tests; categorical variables were compared with the chi-square test. The Kaplan-Meier method was used to evaluate survival or freedom from events, and the log-rank test was used to evaluate differences among NLR tertiles. Univariate and multivariate Cox regression models were used to assess the association between tertiles of NLR and the primary outcome or its components. We reported crude and adjusted hazard ratios.
(HRs) with their 95% confidence intervals (CIs). Variables with \( p < 0.2 \) in univariate analysis were considered candidates to enter into the multivariate model along with age, gender, and race. The variable mechanical circulatory assist device was analyzed as a time-dependent variable. Analyses were conducted in STATA version 11.0 (StataCorp LP, College Station, Texas).

### Results

Of the 527 patients, 176, 177, and 174 patients were in the lowest, intermediate, and higher NLR tertiles, respectively. Baseline characteristics of the patients across NLR tertiles are listed in Table 1. Overall, NLR correlated directly with B-type natriuretic peptide (\( r = 0.14 \), \( p < 0.01 \)). There was no correlation between NLR and left ventricular ejection fraction, peak oxygen consumption, and hemodynamic variables. The distribution of the logarithm of NLR is presented in Figure 1, stratified according to gender (mean \( \pm SD \), NLR men 5.9 \( \pm 6.3 \) vs women 5.5 \( \pm 8.4 \), \( p = 0.6 \)).
Over a median follow-up period of 11.3 (interquartile range 3.4 to 21.1) months, the primary outcome occurred in 263 patients (50%), 121 patients were transplanted (23%), and 158 patients died during follow-up (30%). In univariate analysis, NLR was associated with the primary end point ($p < 0.01$, Figure 2). In comparison to the lowest tertile, the intermediate and high tertiles of NLR had higher risk for the primary outcome. In multivariate analysis, and compared with the lowest tertile, the intermediate and highest NLR tertiles were associated with the primary outcome (HR = 1.61, 95% CI 1.10 to 2.37 and HR = 1.55, 95% CI 1.02 to 2.36, respectively; Table 2). No association between NLR and heart transplantation was observed in univariate analysis or multivariate analysis (Table 2, Figure 4). We did not find an association between lymphocyte or neutrophil counts with all-cause mortality in models using the same set of confounders of our primary analyses (Table 3).

**Discussion**

The key finding of this analysis is that patients with advanced HF and higher levels of NLR portend higher mortality or heart transplantation risk. This association was
mainly driven by higher all-cause mortality risk, as we did not find association between NLR and heart transplantation after multivariate adjustments. Although NLR may link to mortality like several other conditions, the potential contributory role of NLR in disease progression is not supported by our analysis. Thus, it appears that NLR is more likely a risk marker than the altered composition of leukocytes being a risk mediator for advanced HF.

Several studies of NLR have been carried out in recent years in cardiac and noncardiac diseases. Ommen et al.2,3,4 NLR has been studied in acute coronary syndromes in which an increased risk of outcomes was observed in patients with higher values of NLR. Earlier studies in acute coronary syndromes suggested strong prognostic value of NLR associated with mortality risk,5,6,7 whereas short- and long-term prognostic value also extended to those who underwent percutaneous coronary intervention.8,9,10,11,12,13 Independently, either neutrophilia11,21,22 or lymphopenia14,23,24 have been associated with increased mortality in acute coronary syndromes and HF, respectively. Indeed, percent lymphocyte is an independent predictor of mortality in the Seattle Heart Failure Model.25,26 Interestingly, NLR has been shown to be a better predictor of mortality than independent absolute neutrophil and lymphocyte counts in patients with acute decompensated HF.27 There is still no consensus on the cutoff points to define the levels of NLR as most studies categorized into tertiles as we did in our study. In studies of acute cardiac diseases, the median values for the higher tertile of NLR ranged between 6 and 9, where the median of our higher tertile range was found. Why is NLR a better marker of mortality than absolute lymphocyte and neutrophil count separately? We attribute the strength of the NLR to the fact that it combines 2 different immune pathways: neutrophils are involved with a much quicker response, whereas lymphocytes are related to more adaptive long-term response of the immune system, a synonymous of physiological stress.9 Neutrophils produce the enzyme myeloperoxidase that is involved in promoting phagocytic function of neutrophils, but when the levels of this enzyme are high, an excess of free radicals is produced that is responsible for tissue injury and elevated in HF.27 As complete blood count is commonly ordered in patients with HF and often includes automated distributions of leukocyte subsets, the ability to risk stratify a patient population with advanced HF without additional testing is attractive.

Although ejection fraction, peak oxygen, and other hemodynamic variables are classic risk factors on mortality in HF,28,29 we did not find associations of these variables with NLR. This may mean that the risk of death from NLR is independent of hemodynamic variables.

Our study has several limitations. First, only baseline measurements of NLR were available that made it impossible to evaluate NLR values over time and their effect on clinical outcomes. Second, we did not have information on exact causes of death, therefore we cannot further determine if inflammation is the primary driver of disease progression leading to mortality. Third, we did not have information on some potential confounders such as nutritional status or concomitant inflammatory conditions or acuity of disease; however, we had a large number of other relevant confounding variables that served for adjustment in multivariate models. Finally, this study was conducted at a single center with high expertise in the management of severe HF and our experience may not necessarily translate to those without our wide range of advanced therapeutic options.

Table 3

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Tertiles</th>
<th>Neutrophil Crude HR (95% CI)</th>
<th>Neutrophil Adjusted HR (95% CI)</th>
<th>p value</th>
<th>Lymphocyte Crude HR (95% CI)</th>
<th>Lymphocyte Adjusted HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause Mortality or Heart Transplantation†</td>
<td>Higher</td>
<td>1.15 (0.83-1.60)</td>
<td>1.10 (0.74-1.62)</td>
<td>0.65</td>
<td>0.45 (0.33-0.62)</td>
<td>0.53 (0.35-0.81)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>1.42 (1.05-1.94)</td>
<td>1.47 (1.04-2.08)</td>
<td>0.03</td>
<td>0.57 (0.42-0.77)</td>
<td>0.63 (0.44-0.90)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Lower</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>All-cause Mortality†</td>
<td>Higher</td>
<td>1.44 (0.97-2.14)</td>
<td>1.39 (0.84-2.31)</td>
<td>0.20</td>
<td>0.59 (0.39-0.89)</td>
<td>0.96 (0.54-1.69)</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>1.16 (0.78-1.75)</td>
<td>1.05 (0.65-1.69)</td>
<td>0.85</td>
<td>0.68 (0.46-0.99)</td>
<td>0.96 (0.60-1.55)</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>Lower</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Heart Transplantation†</td>
<td>Higher</td>
<td>0.67 (0.38-1.17)</td>
<td>0.56 (0.31-1.00)</td>
<td>0.05</td>
<td>0.46 (0.28-0.76)</td>
<td>0.45 (0.26-0.80)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>1.59 (1.03-2.47)</td>
<td>1.64 (1.04-2.58)</td>
<td>0.03</td>
<td>0.60 (0.38-0.94)</td>
<td>0.64 (0.33-0.87)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Lower</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>–</td>
</tr>
</tbody>
</table>

* Adjusted for: Age, sex, black race, cigarette smoker, diabetes, coronary artery disease, atrial fibrillation, ventricular assist device, albumin, bilirubin, blood urea nitrogen, sodium, brain natriuretic peptide, platelets, aspirin, beta-blocker, angiotensin-converting enzyme inhibitors and hydralazine.
† Adjusted for: Age, sex, black race, diabetes, hypertension, No ischemic failure, chronic obstructive pulmonary disease, coronary artery disease, stroke, atrial fibrillation, ventricular assist device, creatinine, estimated glomerular filtration rate albumin, blood urea nitrogen, brain natriuretic peptide, platelets and beta-blocker.
‡ Adjusted for: Age, black race, cigarette smoker, hypertension, dyslipidemia, No ischemic failure, chronic obstructive pulmonary disease, stroke, ventricular assist device, albumin, sodium, mean platelet volume, aspirin, beta-blocker, angiotensin-converting enzyme inhibitors and hydralazine. Model stratified by gender.

2. Ommen SR, Hodge DO, Rodeheffer RJ, McGregor CG, Thomson SP, Gibbons RJ. Predictive power of the relative lymphocyte


