Clinical Investigation

The Neutrophil-Lymphocyte Ratio and Survival During Left Ventricular Assist Device Support

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ABSTRACT

Background: Systolic heart failure (HF) is a low-grade systemic inflammatory state. Neutrophil-lymphocyte ratio (NLR) is a nonspecific inflammatory marker with prognostic value in HF. We aimed to determine the relationship between NLR and mortality during left ventricular assist device (LVAD) support.

Methods and Results: We retrospectively reviewed LVAD recipients implanted in the years 2010−2018. NLR was recorded before LVAD implantation and at intervals during LVAD support; pre-LVAD and 90-day LVAD NLRs were compared. Cox proportional hazard models were constructed to study the impact of NLR, both before LVAD implantation and at 90 days with LVAD, on mortality during subsequent LVAD support. Among 301 subjects, the median pre-LVAD NLR was 4.7 (interquartile range 3.0−8.0). Higher pre-LVAD NLR was independently associated with increased mortality during a median 324 days of LVAD support (adjusted hazard ratio [HR] 1.03, 95% confidence interval [CI] 1.01−1.06; $P = .012$, adjusted for pre-LVAD age, HF etiology, white blood count, hemoglobin, blood urea nitrogen, and sodium). After LVAD implantation, the NLR rose initially and then plateaued lower by day 90. Despite the mean decrease, higher 90-day LVAD NLR remained independently associated with increased mortality (adjusted HR 1.06, 95% CI 1.01−1.13; $P = .033$, stratified by early infection events).

Conclusions: Higher pre-LVAD NLR is independently associated with mortality during LVAD support. NLR improves during LVAD support, but even accounting for early infections, a higher NLR at day 90 remains associated with subsequent mortality. (*J Cardiac Fail 2019;25:188−194*)

Key Words: Heart Failure, ventricular assist device, inflammation, leucocytes.

Systolic heart failure (HF) is a low-grade systemic inflammatory state. Inflammation has been implicated in the progression of HF and is associated with myocardial remodeling, hypertrophy, and poorer HF outcomes.[1] The ratio between peripheral neutrophils and lymphocytes can be altered by inflammation, resulting in an elevated neutrophil-lymphocyte ratio (NLR). The NLR has become established as an inexpensive and accessible nonspecific biomarker of low-grade systemic inflammation, showing prognostic utility in several cardiac settings, including after acute coronary syndromes,[2] after coronary artery bypass grafting,[3] after cardiac resynchronization therapy,[4] in acutely decompensated HF,[5] and in patients with advanced systolic HF.[6] NLR also has additive value to the Framingham risk score for prediction of coronary heart disease deaths,[7] and value in differentiating between pulmonary infection and HF as a cause of dyspnea.[8]

Patients with the most advanced systolic HF may proceed to left ventricular assist device (LVAD) implantation to improve symptoms and survival. There are preliminary data indicating that higher NLR remains prognostic in this population, with logistic regression showing a significant association between NLR and post-LVAD mortality or right-side heart failure.[9] We sought to determine whether NLR is independently associated with mortality during LVAD support, whether NLR improves after LVAD implantation, and

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whether the NLR at 90 days after LVAD implantation remains associated with mortality.

Methods

Study Cohort

The cohort was retrospectively assembled from all consecutive adults who underwent continuous-flow LVAD implantation (Heartmate II, Heartmate III, or Heartware HVAD), with or without additional right ventricular support, at a single tertiary academic medical center (Tufts Medical Center, Boston) from January 1, 2010, to July 19, 2018. Patients were eligible for cohort inclusion only once, at the time of their first LVAD implantation; for patients who received more than 1 device because of LVAD exchange, the complete period of implantation of all LVADs was counted as the total duration of LVAD support. The Institutional Review Board at Tufts Medical Center approved the study, and requirement for written patient consents was waived owing to its retrospective nature.

Covariates and Outcomes

Patient demographics and clinical data were obtained from the electronic medical record. The period of review extended to the date of death, heart transplantation, transfer of care to another VAD center, or end of follow-up at July 20, 2018. The white blood cell count (WBC), absolute neutrophil and lymphocyte counts, platelets, and hemoglobin were recorded before LVAD implantation (last set of blood tests before surgery, typically hours before implantation) and at 14, 30, 60, 90, 120, 150, 180, and 365 days of LVAD support (±14 days of each time point). Additional laboratory parameters, including creatinine, blood urea nitrogen (BUN) and sodium, were collected for risk adjustment, both at the pre-LVAD time point and at 90 days of LVAD support. Related abnormalities of systemic metabolism have shown recovery at around 90 days after LVAD implantation,[10] and therefore 90 days was pre-specified as the intended time point for pre/post LVAD comparisons.

Statistical Analyses

The cohort was initially divided at the median pre-LVAD NLR; demographics and clinical data were compared between groups for patients with higher versus lower NLR by means of unpaired *t* tests and Fisher exact tests, as appropriate. The change in NLR over time from LVAD implantation to 365 days of LVAD support was displayed as a line graph. The significance of changes in NLR between pre-LVAD and subsequent intervals of LVAD support were assessed by means of paired *t* tests and confirmed with Wilcoxon signed-rank tests owing to the skewed NLR distributions. The cohort was further divided by quartiles of pre-LVAD NLR and a bar chart constructed to illustrate clinical outcomes at the end of follow-up by NLR quartile.

A Kaplan-Meier plot was constructed to display mortality during LVAD support by quartile of pre-LVAD NLR, with log-rank testing for significance, censored on cardiac transplantation or end of follow-up. Unadjusted and adjusted Cox proportional hazards models were constructed to examine the impact of pre-LVAD NLR as a continuous variable on mortality during LVAD support, again censored on cardiac transplantation or end of follow-up. A cubic spline function curve was constructed, with the population mean NLR (2.15) as the reference point, to illustrate the relationship between pre-LVAD NLR and the unadjusted mortality hazard. The impact of pre-LVAD WBC, neutrophils, and lymphocytes on survival during LVAD support were also separately analyzed.

Adjusted Cox models were constructed accounting for potential confounders that were imbalanced in the univariate screen of high versus low NLR groups, including WBC to negate the impact of leukocytosis as well as age, ischemic HF etiology, hemoglobin, sodium and BUN, which was more strongly associated with mortality than creatinine in this cohort and the only candidate covariate to be selected by means of a stepwise selection model. Albumin was lower in the high NLR group but was not available on all subjects and therefore was not included in the final models. We also compared the strength of the pre-LVAD NLR for survival prediction with the established prognostic Heartmate II Risk Score (HMRS) that incorporates patient age, creatinine, albumin, and international normalized ratio (INR).[11] The predictive performance of NLR versus HMRS was compared with the use of 2 methods, a receiver operating characteristic (ROC) curve within a logistic regression model for the binary outcome of mortality during LVAD support and the C-statistic macro within a Cox proportional hazards model as authored by Mithat Gönen for SAS.

A second set of unadjusted and adjusted Cox proportional hazards models was constructed to study the impact of NLR at 90 days on subsequent mortality during LVAD support, with the at-risk period starting on day 90 after LVAD implantation. The covariates selected for adjustment mirrored those used for the pre-LVAD model, but the 90-day values for WBC, hemoglobin, BUN, and sodium were used instead of pre-LVAD values. In addition to adjusting for the 90-day WBC, this model was stratified by the occurrence of infection, either device related or unrelated, per Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) criteria, in the first 105 days of LVAD support. These measures ensured that any relationship between elevated 90-day (±14 days) NLR and subsequent mortality was not attributable to infection.

Movements between quartiles for pre-LVAD and 90-day NLR were tabulated. The relationship between 90-day NLR and lactate dehydrogenase (LDH) was examined with the use of a Pearson correlation coefficient to determine whether inflammatory activation during LVAD support was related to the degree of mechanical hemolysis. Statistical assumptions were assessed for all Cox models, including linearity of the age variable. Additional unadjusted and adjusted Cox model versions were constructed with the use of log-transformed NLR for both the pre-LVAD and 90-day

time points, to ensure consistency of the results given the skewed NLR distribution. The proportional hazards assumption was tested with the use of the Martingale residuals method, and no covariates significantly violated the proportional hazards assumption. Analyses were performed with the use of SAS Enterprise Guide version 7.1 (SAS Institute, Cary, North Carolina), and P values <.05 were considered to be significant. Kaplan-Meier and bar charts were constructed with the use of Prism 7.0 for Mac (Graphpad Software, La Jolla, California).

Results

Three hundred four patients received an LVAD during the study period. Of these, 301 had baseline NLR data, with a median pre-LVAD NLR of 4.7 (quartile 1-quartile 3, 3.0−8.0) and mean (± standard deviation) of 6.7 ± 6.5 (Fig. 1). Patients with higher NLR (≥4.7) had higher-risk pre-LVAD characteristics, including higher WBC, BUN, and HMRS, as well as lower hemoglobin and sodium compared with patients with lower NLR (NLR <4.7; Table 1). There were 145 transplants and 92 deaths during follow-up, with 64 patients surviving on LVAD support until the end of follow-up or transfer to another center. The median duration of LVAD support was of 324 days (interquartile range 131−696 days; n = 301). The crude mortality during LVAD support was 36% of patients with a higher pre-LVAD NLR versus 25% with a lower NLR (P = .046), with the excess mortalities concentrated within quartile 4 of pre-LVAD NLR (NLR ≥8.0; Figs. 2 and 3).

Higher pre-LVAD NLR was significantly associated with increased mortality during LVAD support in the unadjusted analysis (hazard ratio [HR] 1.04, 95% confidence interval [CI] 1.01−1.06, per 1 unit of NLR; P = .001; n = 301 with 92 mortality events; Fig. 4). The model for pre-LVAD NLR expressed as quartiles demonstrated HR 1.22 (95% CI 1.01−1.47; P = .039), although as illustrated in Fig. 3, the favorable survival for patients in quartile 1 of pre-LVAD NLR compared with quartile 4 appears most evident during the first year of LVAD support. Higher pre-LVAD NLR expressed as a continuous variable remained independently associated with mortality after adjustment for pre-LVAD age, ischemic HF etiology, WBC, hemoglobin, BUN, and sodium (HR 1.03, 95% CI 1.01−1.06; P = .012; Table 2). Pre-LVAD WBC and absolute neutrophil count were not significantly associated with mortality during LVAD support. Lower absolute lymphocyte count was associated with mortality in the unadjusted models (HR 0.69, 95% CI 0.49−0.97; P = .032) but lost significance in the adjusted model (HR 0.74, 95% CI 0.53−1.04; P = .078). The pre-LVAD NLR performed favorably compared with the HMRS for predicting mortality during LVAD support within a time-to-event model, as shown by the C-statistic of 0.632 versus 0.588, respectively, for 260 subjects with all available data for pre-LVAD HMRS calculation (Table 3). The pre-LVAD NLR was not significantly associated with future infections (device related or unrelated) during LVAD support. Both unadjusted and adjusted pre-LVAD NLR models yielded the same findings when log NLR was used in place of NLR: unadjusted HR 1.51, 95% CI 1.15−1.99 (P = .003); adjusted HR 1.43, 95% CI 1.03−1.99 (P = .032).

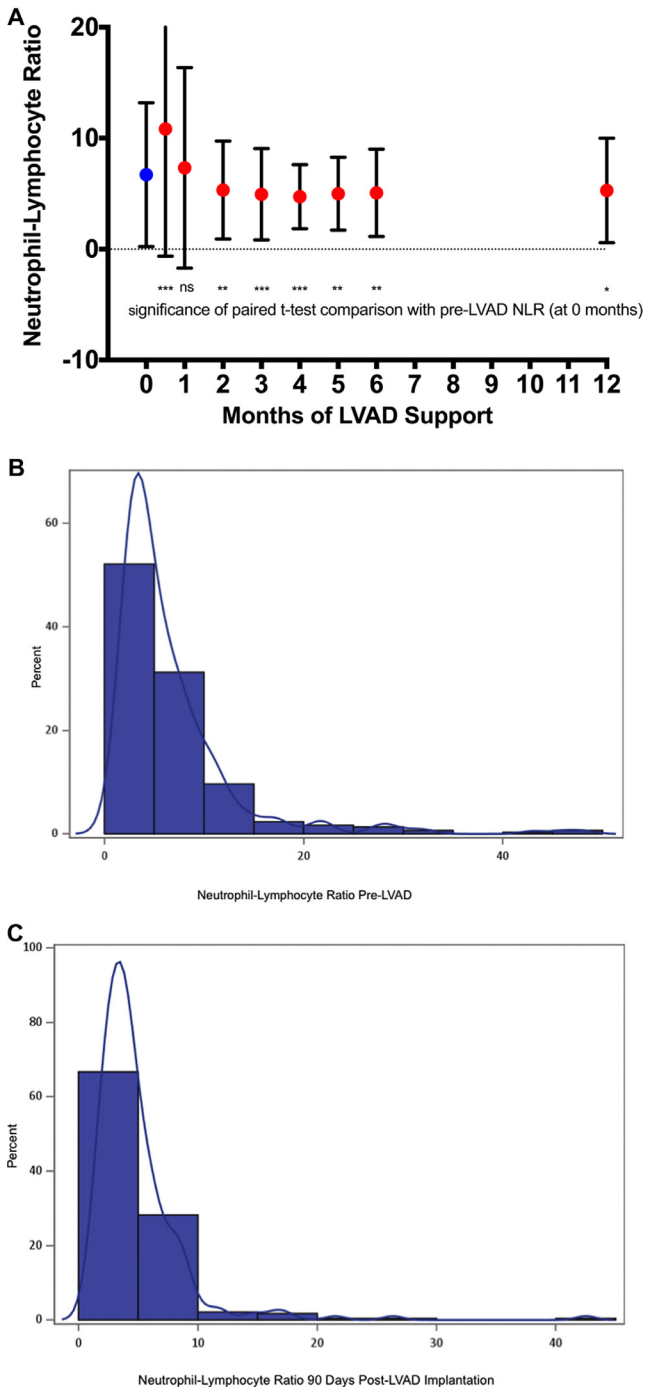

Fig. 1. Neutrophil-lymphocyte ratio (NLR) histograms and trend during left ventricular assist device (LVAD) support. (A) Mean NLRs with error bars displayed from LVAD implantation (day 0) and at intervals through to 365 days of LVAD support. Mean NLR initially rose after LVAD implantation and then reached a significantly lower plateau value by 90 days. NLR distribution (B) before LVAD implantation and (C) 90 days after LVAD implantation.

Table 1. Baseline Characteristics

Pre-LVAD Variable	Full Cohort With Pre-LVAD NLR (n = 301)	Low NLR (n = 151)	High NLR (n = 150)	*P* Value, High vs Low NLR
Age (y)	56 ± 12	55 ± 12	57 ± 12	.181
BMI (kg/m^2)	27.5 ± 5.6	27.5 ± 5.8	27.5 ± 5.3	.950
Female	62 (21%)	34 (23%)	28 (19%)	.477
White race	237 (79%)	117 (77%)	120 (80%)	.673
Diabetes	128 (43%)	64 (42%)	64 (43%)	1.000
Ischemic HF etiology	116 (39%)	54 (36%)	62 (41%)	.345
Heartmate II	123 (41%)	53 (35%)	70 (47%)	.047
Heartmate III	8 (3%)	5 (3%)	3 (2%)	.723
Heartware HVAD	170 (56%)	93 (62%)	77 (51%)	.082
Bridge to transplantation	182 (60%)	94 (62%)	88 (59%)	.557
Lipid-lowering therapy	185 (61%)	92 (61%)	93 (62%)	.906
White blood cell count (10^9/L)	9.4 ± 3.7	7.9 ± 2.9	10.9 ± 3.8	<.001
Hemoglobin (g/dL)	11.1 ± 2.0	11.3 ± 1.8	10.7 ± 2.2	.015
Platelet count (10^9/L)	196 ± 81	202 ± 78	190 ± 84	.213
Absolute neutrophil count (10^9/L)	6.7 ± 3.1	5.0 ± 2.1	8.5 ± 2.9	<.001
Absolute lymphocyte count (10^9/L)	1.4 ± 0.8	1.8 ± 0.9	1.0 ± 0.4	<.001
Neutrophil-lymphocyte ratio	6.7 ± 6.5	3.0 ± 0.9	10.4 ± 7.5	<.001
BUN (mg/dL)	31 ± 18	27 ± 17	35 ± 19	<.001
Creatinine (mg/dL)	1.4 ± 0.7	1.3 ± 0.7	1.5 ± 0.6	.067
Sodium (mEq/L)	134 ± 5	135 ± 4	133 ± 5	<.001
Total cholesterol (n = 198)	129 ± 39	134 ± 40	124 ± 38	.064
Albumin (n = 262)	3.6 ± 0.6	3.7 ± 0.5	3.4 ± 0.6	<.001
INR	1.2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2	.183
Heartmate II risk score (n = 260)	1.3 ± 0.8	1.2 ± 0.7	1.5 ± 0.8	<.001
Left ventricular ejection fraction (%)	12 ± 5	13 ± 5	12 ± 5	.435

Continuous variables presented as mean ± SD; categoric variables presented as n (%). BMI, body mass index; BUN, blood urea nitrogen; HF, heart failure; INR, international normalized ratio; LVAD, left ventricular assist device; NLR, neutrophil-lymphocyte ratio.

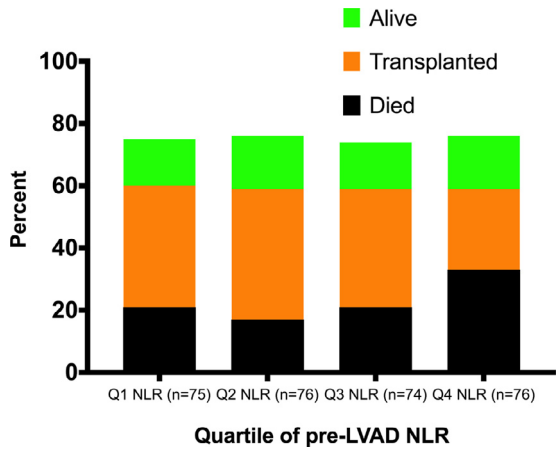

Fig. 2. Crude outcomes during follow-up by quartiles of pre-LVAD NLR. The proportion of patients who died, underwent transplantation, or survived to the end of follow-up are displayed by pre-LVAD NLR quartile. Precise ranges for quartiles of NLR: Q1 0.44−3.02; Q2 3.03−4.69; Q3 4.70−7.99; Q4 8.00−48. Abbreviations as in Fig. 1.

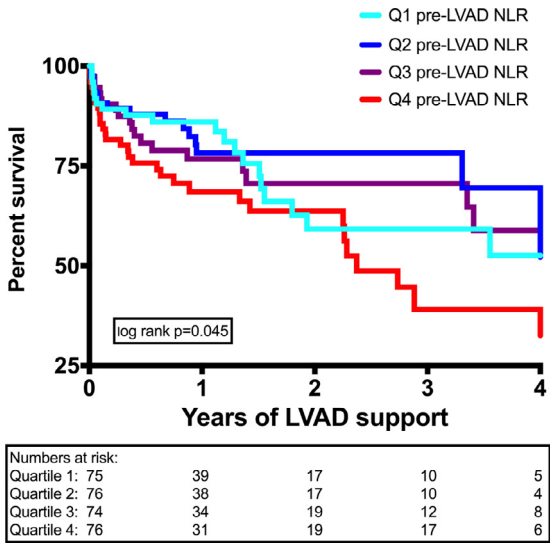

Fig. 3. Kaplan-Meier curves for survival during LVAD support by quartile of pre-LVAD NLR, censored on cardiac transplantation or end of follow-up. Precise ranges for quartiles of NLR: Q1 0.44−3.02; Q2 3.03−4.69; Q3 4.70−7.99; Q4 8.00−48. Abbreviations as in Fig. 1.

After LVAD implantation, the NLR initially rose and then decreased toward a lower plateau at a median of 3.9 and mean of 4.9 by day 90 after LVAD implantation (Fig. 1A; pre-LVAD vs 90-day NLR: $P < .001$ by both *t* test and Wilcoxon signed-rank test; n = 231 pairs). Of 76 patients with pre-LVAD NLRs in quartile 4, 14 died before 90 days of support; those surviving to 90 days had a mean 90-day NLR of 7.3 ± 6.8. Only 45% remained in the highest quartile for 90-day NLR, defined as NLR ≥5.9 (Table 4). There was no correlation between NLR and LDH, a marker of LVAD hemolysis, at 90 days (Pearson correlation coefficient −0.06; $P = .488$). Despite the decrease in NLR over the first 90 days after LVAD implantation, higher 90-day NLR remained associated with increased mortality in both unadjusted (HR 1.11, 95% CI

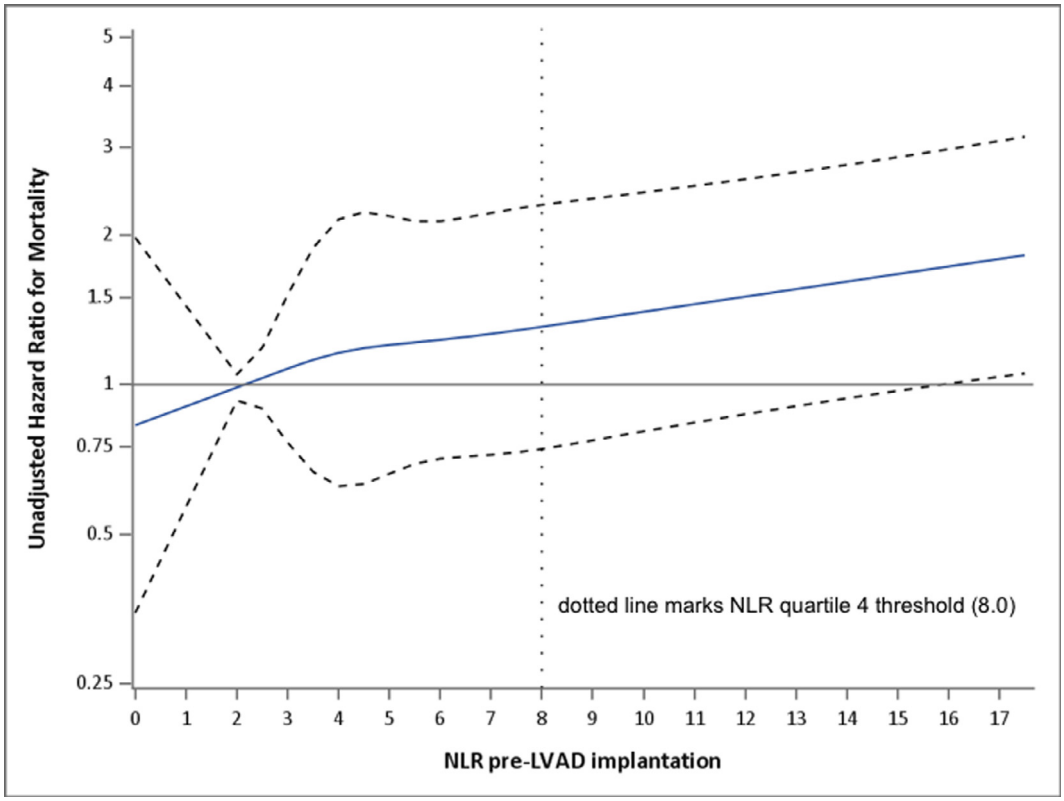

Fig. 4. Spline function curve for the relationship between pre-LVAD NLR and the unadjusted mortality hazard. The mortality hazard is represented for pre-LVAD NLR as a continuous variable. Abbreviations as in Fig. 1.

Table 2. Multivariable Survival Model for Pre-LVAD Neutrophil-Lymphocyte Ratio (n = 301; 92 Events)

Variables	Hazard Ratio	95% CI	*P* value
Pre-LVAD NLR (per 1 unit)	1.03	1.01−1.06	.012
Age (per 1 y)	1.01	0.99−1.03	.399
Ischemic HF etiology	0.92	0.59−1.45	.727
Pre-LVAD WBC (per 10^9/L)	0.99	0.93−1.05	.661
Pre-LVAD hemoglobin (per 1 g/dL)	0.94	0.85−1.04	.229
Pre-LVAD BUN (per 1 mg/dL)	1.01	1.00−1.02	.066
Pre-LVAD sodium (per 1 mEq/L)	1.01	0.97−1.05	.653

WBC, white blood count; other abbreviations as in Table 1.

Table 3. Comparison Statistics for NLR and HMRS

Statistic	Pre-LVAD NLR (n = 260)	Pre-LVAD HMRS (n = 260)
Area under the ROC curve (logistic regression model)	0.569	0.664
C-Statistic (Cox proportional hazards model)	0.632	0.588

HMRS, Heartmate II risk score; ROC, receiver operating characteristic; other abbreviations as in Table 1.

1.07−1.16 per 1 unit of NLR; $P < .001$; n = 231 with 53 events) and adjusted (HR 1.06, 95% CI 1.01−1.13; $P = .033$, adjusted for age, ischemic HF etiology, WBC, hemoglobin, BUN, and sodium at 90 days and stratified by early infections; n = 225 with 52 events; Table 5) analyses. The results were again unchanged when log 90-day NLR was substituted in: unadjusted HR 2.85, 95% CI 1.84−4.42 ($P < .001$); adjusted HR 2.12, 95% CI 1.25−3.61 ($P = .005$).

Discussion

Mean NLR is elevated before LVAD implantation, suggesting systemic inflammatory activation in patients with advanced HF. A higher pre-LVAD NLR is independently associated with increased mortality during LVAD support. NLR rises further in the early post-implantation phase but then deceases to a lower plateau by day 90. Elevated NLR at day 90 after implantation remains independently associated with mortality during subsequent LVAD support, even accounting for infection events. Patients with an elevated NLR before LVAD implantation can experience substantial improvements in NLR and subsequent mortality risk by 90 days of LVAD support, suggesting that NLR elevation is not an inherent fixed patient characteristic, but is modifiable over time with changes in clinical status. This finding underscores the detrimental effect of ongoing systemic inflammatory activity related to the underlying HF process during LVAD support and presents a potentially modifiable target for future novel interventions.

Table 4. Reclassification by Quartile of NLR Between Pre-LVAD and 90-Day Time Points (Patients With NLR Values at Both Time Points, n = 231)

	After 90 Days of LVAD Support			
Before LVAD Implantation	Quartile 1 (n = 58)	Quartile 2 (n = 56)	Quartile 3 (n = 58)	Quartile 4 (n = 59)
Quartile 1 (n = 61)	23	15	16	7
Quartile 2 (n = 63)	20	21	11	11
Quartile 3 (n = 52)	8	12	16	16
Quartile 4 (n = 55)	7	8	15	25

Abbreviations as in Table 1.

Table 5. Multivariable Survival Model for 90-Day Neutrophil-Lymphocyte Ratio (n = 225; 52 Events)

Variable	Hazard Ratio	95% CI	*P* value
NLR at 90 days with LVAD (per 1 unit)	1.06	1.01−1.13	.033
Age (per 1 y)	1.01	0.99−1.04	.347
Ischemic HF etiology	1.09	0.60−1.99	.770
WBC at 90 days (per 10^9/L)	1.05	0.95−1.15	.386
Hemoglobin at 90 days (per 1 g/dL)	0.91	0.77−1.08	.283
BUN at 90 days (per 1 mg/dL)	1.01	0.99−1.03	.357
Sodium at 90 days (per 1 mg/dL)	0.94	0.87−1.02	.142

Stratified by occurrence of any INTERMACS infection event within first 105 days of LVAD support (134 infection events).

Abbreviations: CI, confidence interval; HF, heart failure; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; other abbreviations as in Tables 1 and 2.

The mean pre-LVAD NLR of 6.7 (median 4.7) in this cohort was well above the healthy population mean of 2.15[12] and was similar to a cohort of 1212 US patients hospitalized for acute HF with a median NLR of 5.1.[5] In comparison, other ambulatory chronic HF studies have reported median NLRs of 2.47 and 3.9,[6,13] suggesting that the LVAD candidates in our cohort had a substantially higher burden of systemic inflammation than less advanced HF cohorts.

Our analyses confirm the prognostic strength of NLR as an important biomarker in advanced systolic HF, especially given that it performed favorably when compared within a time-to-event model with the multicomponent HMRS. This suggests that inflammation is more closely related to outcomes during LVAD support than the combination of the patient's age, creatinine, albumin, and INR. Our findings build on the observations of Yost et al who also found a relationship between pre-LVAD NLR and survival in their single-center cohort.[9] When that group analyzed outcomes by NLR tertiles, survival was superior in tertile 1 (lowest NLRs) compared with a combined group of tertiles 2 and 3. Pre-LVAD NLR was also associated with mortality in their logistic regression model, but no time-to-event analyses were used and the relationship between NLR after LVAD implantation and mortality, independently from infectious events, was not explored. Another publication describing 100 LVAD patients from the same center indicated that the NLR reduction in the immediate post-implantation phase is asymptotic, with the greatest reduction occurring in the first 7 days.[14]

The strong performance of the NLR as a risk marker is a confluence of its 2 components: a higher neutrophil count and a lower lymphocyte count both contribute toward the score, with the resulting ratio being more strongly associated with mortality than either individual component, as shown in the present analyses. Activated neutrophils mediate the inflammatory response by means of numerous biochemical mechanisms, which include the release of reactive oxygen species, myeloperoxidase, and proteolytic enzymes that are responsible for tissue injury. In contrast, lymphocytes represent the regulatory pathway of the immune system, with inflammatory activation reportedly promoting lymphocyte apoptosis.[15] Reduced lymphocyte counts have been reported after acute myocardial infarction and have prognostic implications in both coronary artery disease and systolic HF, hence their inclusion in the Seattle Heart Failure Model.[16,17]

The performance of NLR as a prognostic marker raises the possibility that therapies to reduce systemic inflammation may have a role in the management of advanced systolic HF. Despite the substantial improvements in mortality offered by LVAD support for patients with end-stage HF, the burden of adverse events and mortality during LVAD support remains significant: 16% of this cohort died within the first 6 months of LVAD support. Clinical trials of antiinflammatory therapies have been unsuccessful in systolic HF, including infliximab and etanercept.[18−20] However, there may be value in assessing the impact of interventions, such as less invasive surgical device implantation strategies or the reintroduction of neurohumoral HF therapies after LVAD implantation, on the inflammatory state during the early phase of LVAD support, to determine whether modulation of systemic inflammation has any causative role toward adverse outcomes during subsequent support.

Study Limitations

These analyses represent the experiences of a single advanced HF center and may not reflect all LVAD recipients: further prospective multicenter analyses are required to externally validate the prognostic utility of the NLR in LVAD patients. Although the impact of NLR was statistically significant at the preimplantation and 90-day time points, the magnitude of clinical effect of this single

contributor toward LVAD survival was modest, with a 4% increase in mortality hazard per 1-unit pre-LVAD NLR rise in the unadjusted model. However, the magnitude of effect was at least equivalent to other recognized mortality risk factors in LVAD populations. Half of the mortality events occurred within the first 90 days after LVAD implantation and therefore our analysis of the relationship between 90-day NLR and subsequent outcomes was more limited statistically. C-Reactive protein is not routinely collected at our center before LVAD implantation and therefore was not available for comparison with NLR.

Conclusion

Higher NLR before LVAD implantation is a simple and easily obtained inflammatory biomarker that is independently associated with increased mortality during LVAD support. NLR improves during early LVAD support, but a higher NLR at day 90 remains independently associated with subsequent mortality, even when accounting for early infectious events.

Disclosures

Drs Kiernan, DeNofrio, and Couper have served as consultants for Medtronic (formerly Heartware) and Abbott (formerly Thoratec) companies. Drs Sundararajan, Upshaw, and Vest have no relevant conflicts of interest or industry relationships to disclose.

References

1. Mann DL. Innate immunity and the failing heart: the cytokine hypothesis revisited. Circ Res 2015;116:1254–68.
2. Tamhane UU, Aneja S, Montgomery D, Rogers E-K, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol 2008;102:653–7.
3. Gibson PH, Croal BL, Cuthbertson BH, et al. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting. Am Heart J 2007;154:995–1002.
4. Boros AM, Széplaki G, Perge P, et al. The ratio of the neutrophil leucocytes to the lymphocytes predicts the outcome after cardiac resynchronization therapy. Europace 2016;18:747–54.
5. Uthamalingam S, Patvardhan E, Subramanian S, et al. Utility of the neutrophil to lymphocyte ratio in predicting long-term outcomes in acute decompensated heart failure. Am J Cardiol 2011;107. 443−38.
6. Benites-Zapata VA, Hernandez AV, Nagarajan V, Cauthen CA, Starling RC, Tang WHW. Usefulness of neutrophil-to-lymphocyte ratio in risk stratification of patients with advanced heart failure. Am J Cardiol 2015;115:57–61.
7. Shah N, Parikh V, Patel N, Badheka A. Neutrophil lymphocyte ratio significantly improves the Framingham risk score in prediction of coronary heart disease mortality: insights from the National Health and Nutrition Examination Survey—III. Int J Cardiol 2014;171:390–7.
8. Siniorakis EE, Tsarouhas K, Tsitsimpikou C, et al. Neutrophil to lymphocyte (N/L) and platelet to lymphocyte (P/L) ratios in differentiating acute heart failure from respiratory infection. Curr Vasc Pharmacol 2017;15:477–81.
9. Yost GL, Joseph CR, Tatooles AJ, Bhat G. Neutrophil-to-lymphocyte ratio predicts outcomes in patients implanted with left ventricular assist devices. ASAIO J 2015;61:664–9.
10. Vest AR, Kennel PJ, Maldonado D, et al. Recovery of serum cholesterol predicts survival after left ventricular assist device implantation. Circ Heart Fail 2016;9:e002881.
11. Cowger J, Sundareswaran K, Rogers JG, et al. Predicting survival in patients receiving continuous flow left ventricular assist devices. J Am Coll Cardiol 2013;61:313–21.
12. Azab B, Camacho-Rivera M, Taioli E. Average values and racial differences of neutrophil lymphocyte ratio among a nationally representative sample of United States subjects. PLoS One 2014;9:e112361.
13. Osadnik T, Wasilewski J, Pyka Ł, et al. Prognostic value of neutrophil-to-lymphocyte ratio in predicting long-term mortality in patients with ischemic and nonischemic heart failure. Pol Arch Med Wewn 2016;126:166–73.
14. Bhat G, Yost GL, Ibrahim K, Pappas P, Tatooles A. Risk stratification with longitudinal neutrophil to lymphocyte ratio assessment after left ventricular assist device implantation. Int J Artif Organs 2018;41:445–51.
15. Hotchkiss RS, Tinsley KW, Swanson PE, et al. Sepsis-induced apoptosis causes progressive profound depletion of B and CD4 + T lymphocytes in humans. J. Immunol 2001;166:6952–63.
16. Ommen SR, Gibbons RJ, Hodge DO, Thomson SP. Usefulness of the lymphocyte concentration as a prognostic marker in coronary artery disease. Am J Cardiol 1997;79:812–4.
17. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model prediction of survival in heart failure. Circulation 2006;113:1424–33.
18. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Anti-TNF Therapy Against Congestive Heart Failure Investigators. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the Anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 2003;107:3133–40.
19. Mann DL, McMurray JJV, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation 2004;109:1594–602.
20. Gullestad L, Ueland T, Fjeld JG, et al. Effect of thalidomide on cardiac remodeling in chronic heart failure: results of a double-blind, placebo-controlled study. Circulation 2005;112:3408–14.