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ORIGINAL RESEARCH

HEART FAILURE

Elevated Neutrophil-to-Lymphocyte Ratio Predicts Prognosis in Acute Myocarditis

Antonio Cannata, MD, PhD,[a,b] Amitai Segev, MD,[c,d] Cristina Madaudo, MD,[a,e] Emanuele Bobbio, MD, PhD,[f,g] Chiara Baggio, MD,[h] Jonathan Schütze, MD,[i] Piero Gentile, MD,[j] Marta Sanguineti, MD,[k] Luca Monzo, MD, PhD,[l,m] Matteo Schettino, MD,[k] Emma Ferone, MBBS,[a] Ahmed Elsanhoury, MD,[n,o,p] Anan Younis, MD,[c,d] Matteo Palazzini, MD,[j] Adriana Ferroni,[i] Valentina Giani, MD,[j] Matthew Sadler, MD,[b] Daniela Di Lisi, MD, PhD,[c,d] Mohammad Albarjas, MD,[q] Leonardo Calò, MD,[l] Daniel Sado, MD,[b] Christian Lars Polte, MD,[r,s] Andrea Garascia, MD,[j] Paul A. Scott, MD,[b] Ajay M. Shah, MD, PhD,[a] Mauro Giacca, MD, PhD,[a] Gianfranco Sinagra, MD,[h] Entela Bollano, MD, PhD,[f,g] Theresa McDonagh, MD,[b] Carsten Tschöpe, MD,[n,o,t] Giuseppina Novo, MD, PhD,[e] Enrico Ammirati, MD, PhD,[j] Roy Beigel, MD,[c,d] Christoph Gräni, MD,[i] Marco Merlo, MD,[h] Pietro Ameri, MD, PhD,[k,u] Daniel I. Bromage, MD, PhD[a,b]

ABSTRACT

BACKGROUND Neutrophil-to-lymphocyte ratio (NLR) is an easy-to-use inflammatory biomarker. Baseline NLR is independently associated with incident cardiovascular events and all-cause mortality. However, whether this applies to acute myocarditis (AM) has not been evaluated.

OBJECTIVES The present study aimed to investigate the prognostic value of NLR in patients with AM.

METHODS A total of 1,150 consecutive patients with a diagnosis of AM admitted to 10 international tertiary referral cardiac centers were included in the study. The diagnosis was confirmed using cardiac magnetic resonance or endomyocardial biopsy. The primary outcome measure was a composite of all-cause mortality or heart transplantation. Patients were divided into 2 groups according to an NLR cutoff of 4 derived from spline regression analysis and 70:30 train-test split algorithm.

RESULTS Patients with an NLR <4 were younger and more likely to present with chest pain, and those with an NLR ≥ 4 were more likely to present with breathlessness and have other comorbidities. Over a median follow-up of 228 weeks, a NLR ≥ 4 was associated with a worse prognosis ($P < 0.0001$). After adjustment for prognostic variables, NLR emerged as an independent predictor of outcome (HR: 3.03 [95% CI: 1.30-7.04]; $P = 0.010$). Elevated NLR remained associated with worse outcomes among patients with preserved ejection fraction at baseline, who are conventionally considered to be at lower risk of adverse events ($P < 0.0001$).

CONCLUSIONS In patients with AM, elevated NLR is associated with worse prognosis and may be valuable for stratifying patients, even those conventionally considered at low risk. (JACC Heart Fail. 2025;13:770–780)

From the [a]King's College London British Heart Foundation Centre of Excellence, School of Cardiovascular Medicine and Sciences, London, United Kingdom; [b]King's College Hospital NHS Foundation Trust, London, United Kingdom; [c]Cardiovascular Division, Chaim Sheba Medical Center, Tel Hashomer, Ramat-Gan, Israel; [d]The Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; [e]Policlinico P. Giaccone, University of Palermo, Palermo, Italy; [f]Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden; [g]Department of Molecular and Clinical Medicine, Institute of Medicine at Sahlgrenska Academy, University

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Acute myocarditis (AM) is an inflammatory disease of the myocardium commonly caused by viral infections, autoimmune disease, or toxins.[1-5] Its clinical presentation is highly heterogeneous, ranging from subclinical or minimally symptomatic forms to a life-threatening fulminant presentation with cardiogenic shock or cardiac arrest.[1,6,7] The implementation of cardiac magnetic resonance (CMR) has resulted in more frequent diagnosis of AM, especially with milder manifestations and a more benign prognosis, than in the past.[8-10] This translates into challenges in predicting the prognosis of most patients with AM, possibly leading to suboptimal management.[11-13]

Other than left ventricular ejection fraction (LVEF), few easy-to-use biomarkers are available in clinical practice for risk stratification of patients with AM. Classical heart failure (HF) and inflammatory biomarkers, such as brain natriuretic peptide (BNP), troponin, or high-sensitivity C-reactive protein (CRP), are routinely assessed in AM patients, but they lack sensitivity and specificity. Other markers, such as alarmins or circulating microRNA, have increased diagnostic and prognostic accuracy, but are still not validated or widely available.[13,14] Neutrophil-lymphocyte ratio (NLR) is an easily accessible inflammatory biomarker associated with adverse outcomes in various cardiovascular conditions.[7,13-18] NLR appears to have better predictive value than other inflammatory biomarkers, including total white blood cell count, absolute neutrophil count, and absolute lymphocyte count. Elevated NLR is also associated with a higher incidence of cardiac events in patients treated with immune checkpoint inhibitors.[19] However, whether this applies to AM, which is thought to be primarily mediated by cardiac myosin-stimulated $CD4^+$ T cells, is unknown.

This study aimed to address this gap in knowledge by analyzing a multicentric, international cohort of patients with AM, reflecting the contemporary epidemiology of this disease and thus enriched for subjects considered to be at low risk of adverse events using conventional prognostic indices.

METHODS

STUDY DESIGN. We included all consecutive patients aged ≥18 years admitted to 10 hospitals in 6 countries (King's College Hospital, London, United Kingdom; Princess Royal University Hospital, Orpington, United Kingdom; Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste, Italy; ASST Grande Ospedale Metropolitano Niguarda Ca' Granda, Milano, Italy; IRCSS Ospedale Policlinico San Martino, Genova, Italy; Policlinico Casilino, Roma, Italy; Azienda Ospedaliera Universitaria Policlinico Paolo Giaccone, Palermo, Italy; German Heart Center at Charite (DHZC), Berlin, Germany; Chaim Sheba Medical Center, Ramat-Gan, Israel; Sahlgrenska University Hospital, Gothenburg, Sweden; and Inselspital, Bern University Hospital, Bern, Switzerland) with a confirmed diagnosis of AM using either endomyocardial biopsy (EMB) or CMR. The diagnosis of AM was based on CMR findings consistent with AM according to 2018 updated Lake Louise criteria,[20] or EMB compatible with AM according to the Dallas criteria, in the absence of significant coronary artery disease on invasive or noninvasive coronary imaging or low likelihood of coronary artery disease (patients <40 years of age with low clinical suspicion).[13,18,21] EMB was performed according to center-specific criteria, generally in subjects with more severe presentation. Patients with suspected/

ABBREVIATIONS AND ACRONYMS

AM = acute myocarditis

AUC = area under the receiver-operating characteristic curve

BNP = brain natriuretic peptide

CKD = chronic kidney disease

CMR = cardiac magnetic resonance

CRP = C-reactive protein

EMB = endomyocardial biopsy

HF = heart failure

LVEF = left ventricular ejection fraction

NLR = neutrophil-to-lymphocyte ratio

of Gothenburg, Gothenburg, Sweden; [h]CardioThoracoVascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste, Italy; [i]Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [j]Ospedale Niguarda Ca'granda, Milan, Italy; [k]Department of Internal Medicine, University of Genova, Genova, Italy; [l]Policlinico Casilino, Rome, Italy; [m]Université de Lorraine, Centre d'Investigations Cliniques Plurithématique 1433 and Inserm U1116, CHRU Nancy, FCRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France; [n]Berlin Institute of Health (BIH) Center for Regenerative Therapies (BCRT), Berlin, Germany; [o]Department of Cardiology, Angiology, and Intensive Medicine (CVK), German Heart Center at Charite (DHZC), Berlin, Germany; [p]German Centre for Cardiovascular Research (DZHK), partner site Berlin, Berlin, Germany; [q]Princess Royal University Hospital, Orpington, London, United Kingdom; [r]Departments of Clinical Physiology and Radiology, Sahlgrenska University Hospital, Gothenburg, Sweden; [s]Department of Molecular and Clinical Medicine, Institute of Medicine at Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [t]Institute of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland; and the [u]Cardiac, Thoracic and Vascular Department, IRCCS Ospedale Policlinico San Martino, Genova, Italy.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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confirmed COVID-19 or vaccine-related AM, which represent a distinct phenotype of the disease, as well as patients with cardiac sarcoidosis or immune checkpoint inhibitor-related myocarditis were excluded from this analysis.[5,22] Clinical presentation of AM was classified into chest pain, dyspnea, and arrhythmias, based on international consensus.[23] Clinical characteristics, laboratory parameters at admission, echocardiography, and CMR findings were recorded. A likely fulminant presentation was defined as admission due to a life-threatening arrhythmia or aborted sudden cardiac death and/or presence of LVEF <30% at presentation. The study was conducted under London South-East Research Ethics Committee approval (reference 18/LO/2048) granted to the KERRI (King's Electronic Records Research Interface).[24] Participating centers obtained local institutional review board approvals, where necessary, for collecting anonymized data. The study complied with the Declaration of Helsinki.

NLR CUTOFF DERIVATION. To determine NLR, we used the first available full blood count after admission. The use of NLR in clinical practice is so far limited to observational studies, and, therefore, validated cutoff values are not available. To determine a clinically meaningful cutoff for NLR, in the context of AM, the data set was randomly divided using a train-test split with a 70:30 ratio. We then derived the optimal cutoff from the training data set and validated it for the primary endpoint in the test data set. NLR was investigated as a quantitative continuous variable using a penalized spline analysis in both the train and test data sets. From this analysis we selected the optimal cutoff based on the association between baseline NLR and the hazard of the primary outcome. This was then used to divide patients into 2 groups (above and below the cutoff value). We also considered other cutoff values derived from other cohorts in the published reports (ie, 2.5)[14,17] and from the median value in our cohort, which are reported in the sensitivity analyses.

BASELINE CHARACTERISTICS AND OUTCOME MEASURES. The primary outcome was all-cause mortality or heart transplantation. Outcome data were obtained from local or national electronic health records.

SUBGROUP AND SENSITIVITY ANALYSES. Prespecified subgroup analyses were performed to ascertain the usefulness of NLR in patients at low baseline risk, using LVEF as a conventional biomarker,[9] in patients without autoimmune disease (who are less likely to have a history of immunosuppression), without chronic kidney disease (CKD), who did not receive in-hospital steroids (to avoid potential confounding due to immunosuppressive therapy), and with EMB-proven AM. We performed an additional subgroup analysis in patients with available NLR data at discharge and the dynamic change was defined as the difference between the discharge and admission values. Prespecified sensitivity analyses were also performed using different NLR cutoffs.

STATISTICAL ANALYSIS. The results were reported in line with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Supplemental Table 1).[25] Continuous variables were expressed as median (Q1-Q3). Categorical variables were expressed as counts and percentages. Comparisons between groups were made using the Mann-Whitney U test for continuous variables or the Pearson chi-square test or the Fisher exact tests for discrete variables. We divided the total cohort into training and testing data sets using a 70:30 ratio to derive the optimal cutoff. The training data are used to train the algorithm and the testing data were used to evaluate the accuracy and the performance of the trained algorithm. The 2 sub-data sets were representative of the data set.[23] The association of NLR as a continuous variable with adverse outcomes was evaluated using a penalized spline included into a Cox proportional hazard model adjusted for age and sex. Receiver operating characteristic curves were calculated, and the area under the receiver-operating characteristic curve (AUC) with 95% CI was used to compare the ability of the combination of NLR with different variables to predict the endpoint. Survival curves for the primary outcome were estimated and compared between groups using means of the log-rank test. Univariable and multivariable Cox proportional hazard models were fitted to obtain HRs for adverse events in the study population using clinically relevant variables at baseline. We chose variables commonly associated with adverse events such as age, sex, clinical presentation, LVEF at presentation, steroid administration, and presence of late gadolinium enhancement. An event per variable ratio of 1:10 was used. A value of $P < 0.05$ was considered significant. All analyses were performed with R statistical package version 4.2.2 (R Foundation).

RESULTS

STUDY POPULATION. A total of 1,150 patients with AM were included in the study (Table 1). In 949 patients (82%) the diagnosis was confirmed using CMR, in 98 patients (9%) only using EMB, and in 103 (9%) using both a CMR and EMB. Approximately two-thirds of patients were male (n = 827) (72%) with a

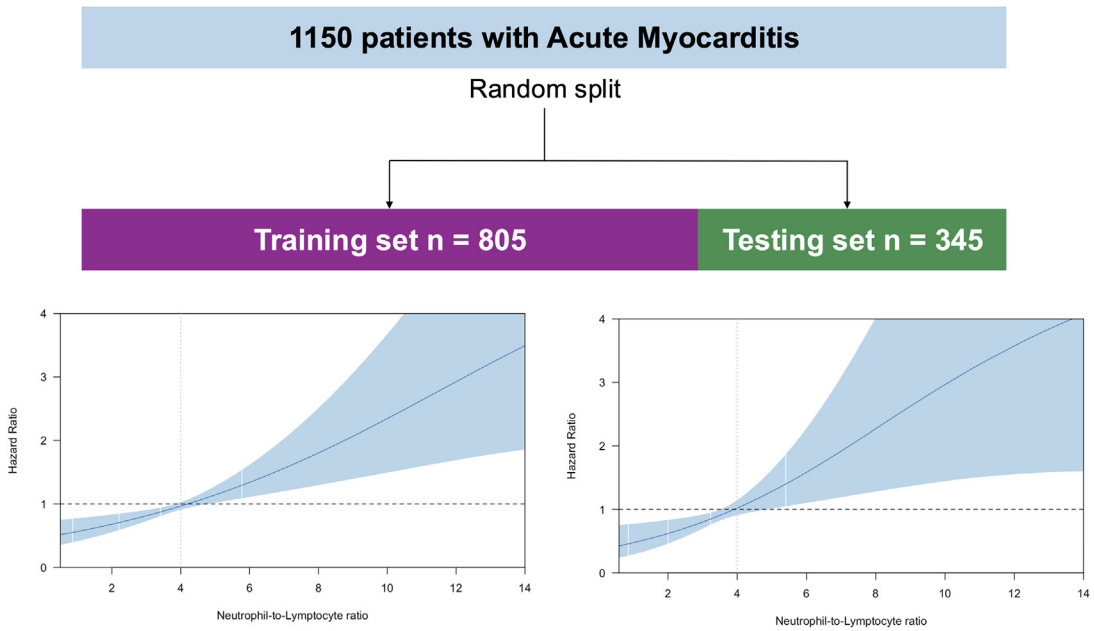
TABLE 1 Characteristics of Study

	Total Cohort (N = 1,150)	NLR <4 (n = 695)	NLR >4 (n = 455)	*P* Value
Male	827 (72)	515 (74)	312 (69)	**0.050**
Age, y	38 (26-50)	37 (25-47)	41 (28-54)	**<0.001**
Prodromal symptoms	700 (64)	411 (62)	289 (67)	0.122
Clinical presentation				**<0.001**
Chest pain	752 (76)	498 (81)	254 (67)	
Dyspnea	168 (17)	78 (13)	90 (24)	
Arrhythmia	69 (7)	35 (6)	34 (9)	
Previous myocarditis	30 (4)	24 (6)	6 (3)	0.082
Likely fulminant	157 (14)	63 (9)	94 (21)	**<0.001**
Comorbidities				
Hypertension	134 (12)	70 (11)	64 (14)	**0.039**
Dyslipidemia	135 (13)	66 (10)	69 (16)	**0.003**
Diabetes	56 (5)	29 (4)	27 (6)	0.228
CKD	23 (3)	8 (2)	15 (6)	**0.005**
Autoimmune disease	63 (9)	30 (6)	33 (13)	**0.005**
SBP, mm Hg	120 (109-130)	120 (110-132)	118 (105-130)	**0.015**
HR, beats/min	84 (71-95)	80 (70-90)	89 (74-101)	**<0.001**
Echo				
LVEF at admission, %	52 (46-60)	54 (50-60)	48 (39-60)	**<0.001**
LVSD at admission, %	302 (28)	131 (20)	171 (38)	**<0.001**
CMR				
LVEF, %	57 (53-63)	58 (54-63)	56 (52-62)	**0.012**
LGE	872 (89)	560 (91)	312 (85)	**0.002**
In-hospital management				
Inotropes	79 (7)	24 (4)	55 (12)	**<0.001**
Steroids	188 (16)	91 (13)	97 (22)	**0.002**
Renal replacement therapy	23 (3)	6 (1)	17 (7)	**<0.001**
Discharge medications				
Aspirin/NSAIDs	453 (41)	295 (45)	158 (37)	**0.011**
RASI	428 (37)	248 (36)	180 (40)	0.252
Beta-blockers	494 (43)	276 (40)	218 (48)	**0.007**
MRAs	106 (9)	59 (8)	47 (10)	0.331
Diuretic agents	131 (12)	71 (10)	60 (13)	0.139
Amiodarone	39 (6)	16 (4)	23 (10)	**0.002**
Immunosuppressants	132 (12)	53 (8)	79 (18)	**<0.001**
Blood values				
CRP, mg/L	62.5 (10-87)	43.7 (7-58)	91.7 (23-138)	**<0.001**
Creatinine, μmol/L	79 (68-92)	77 (67-90)	81 (70-95)	**0.001**
eGFR, mL/min/m^2	91 (79-92)	91 (84-97)	90 (67-91)	**<0.001**
eGFR <60, mL/min/m^2	58 (13)	16 (6)	42 (21)	**<0.001**
NT-proBNP	180 (77-647)	185 (86-559)	132 (70-1,209)	0.387
Troponin × ULN	48 (12-174)	43 (12-153)	54 (12-213)	0.102
Neutrophils, 10^9/L	6.6 (4.1-8.2)	4.8 (3.4-5.8)	9 (6.9-11.0)	**<0.001**
Lymphocytes, 10^9/L	1.86 (1.29-2.20)	2.20 (1.65-2.51)	1.33 (0.96-1.62)	**<0.001**
Monocytes, 10^9/L	0.75 (0.46-0.91)	0.69 (0.43-0.80)	0.85 (0.52-1.05)	**<0.001**
Eosinophils, 10^9/L	0.10 (0.03-0.20)	0.10 (0.05-0.21)	0.06 (0.02-0.12)	**<0.001**
Basophils, 10^9/L	0.05 (0.02-0.06)	0.05 (0.02-0.07)	0.04 (0.01-0.05)	**<0.001**
EMB				
Performed	201 (18)	108 (16)	93 (21)	**0.041**
Inflammatory/aspecific	196 (63)	144 (70)	52 (49)	**<0.001**
Lymphocytic	87 (28)	52 (25)	35 (33)	
Giant cells	28 (9)	9 (4)	19 (18)	
Eosinophilic	1 (0.5)	1 (0.5)	0 (0)	

Values are n (%) or median (25th-75th percentile), unless otherwise indicated. **Bold** indicates statistically significant values.

CKD = chronic kidney disease; CMR = cardiac magnetic resonance; CRP = C-reactive protein; eGFR = estimated glomerular filtration rate; EMB = endomyocardial biopsy; HR = heart rate; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; MRA = mineralocorticoid receptor antagonist; NSAID = nonsteroidal anti-inflammatory drug; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RASI = renin angiotensin system inhibitor; SBP = systolic blood pressure; ULN = times the upper limit of normal.

FIGURE 1 Patient Selection Process and Derivation of the Cutoff Using the Training and Test Split



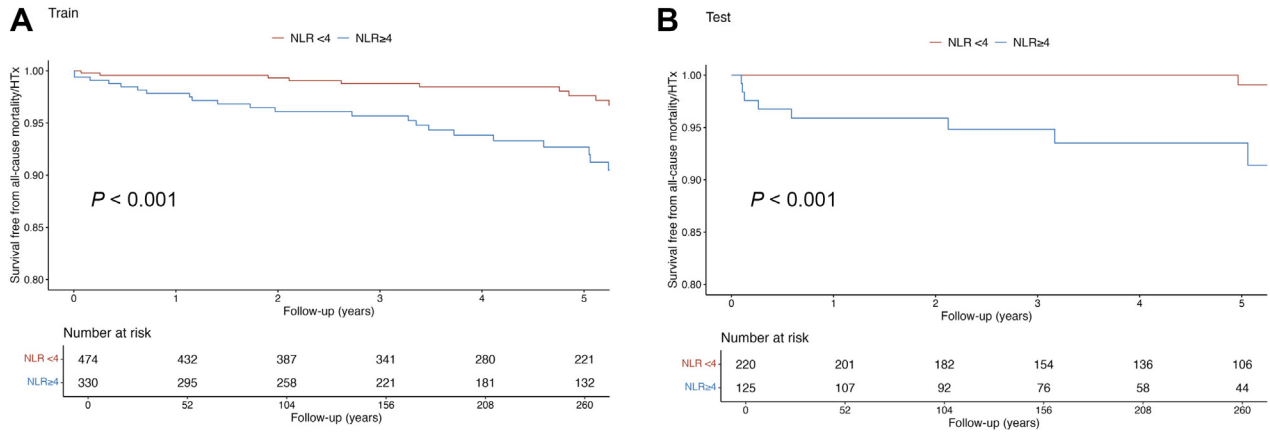
median age of 38 years (Q1-Q3: 26-50 years). The main clinical presentation was chest pain (n = 752) (76%), followed by dyspnea (n = 168) (17%) and arrhythmia (n = 69) (7%).

NLR CUTOFF DERIVATION. NLR values were positively skewed, with a median value of 3.4. From the train-test split, 2 data sets were obtained to derive the optimal cutoff value. Baseline characteristics of the train and test data sets were similar (Supplemental Table 2). In the train model, spline analysis produced a cutoff value of 4.14, above which NLR was associated with increased hazard of the primary outcome (**Figure 1**). The model was then tested in the test data set with comparable results. We therefore selected 4 as a pragmatic and clinically meaningful cutoff.

BASELINE CHARACTERISTICS. Patients with an NLR <4 were more likely to have a chest pain presentation, and those with an NLR ≥4 were more likely to present with dyspnea. The comorbidity profile was similar between the 2 groups. However, patients with a high NLR more often had dyslipidemia (16% vs 10%; $P = 0.003$), CKD (6% vs 2%; $P = 0.005$), and autoimmune disease (13% vs 6%; $P = 0.005$) compared with those with a low NLR. Furthermore, compared with those with low NLR, patients with a high NLR were more likely to have reduced baseline LVEF (<50%) (38% vs 20%; $P < 0.001$), being admitted with a likely fulminant presentation (9 % vs 21%; $P < 0.001$), with lower estimated glomerular filtration rate and more frequently with estimated glomerular filtration rate <60 mL/min (6.0% vs 21%; $P < 0.001$), and were generally more unwell, requiring more inotropic support (12% vs 4%; $P < 0.001$), steroids (22% vs 13%; $P = 0.002$), and renal replacement therapy (7% vs 1%; $P < 0.001$) during their admission. Patients who underwent EMB were generally more unwell at admission compared with those in the CMR only group (Supplemental Table 3).

OUTCOMES. Over a median follow-up of 228 weeks (Q1-Q3: 114-339 weeks) (4.38 years), 63 patients (5.5%) experienced the primary endpoint. Of those 48 patients (4%) died and 15 patients (1%) underwent heart transplantation. NLR ≥4 was significantly associated with worse outcomes in both the training and test set (**Figure 2**) ($P < 0.0001$), which persisted in sensitivity analyses excluding patients with autoimmune disease and restricting the analysis to either only patients diagnosed using EMB or only those in the CMR group (Supplemental Figure 1). In our multivariable analysis, NLR ≥4 remained independently associated with the primary outcome (HR: 3.25 [95% CI: 1.49-7.08]; $P = 0.003$), together with higher age (HR: 1.05 [95% CI: 1.02-1.07]; $P < 0.001$) and LVEF at presentation (HR: 0.96 [95% CI: 0.94-0.99]; $P = 0.011$) (**Figure 3**). As also reported elsewhere, male sex was

FIGURE 2 Kaplan-Meier Curve for All-Cause Mortality or HTx According to NLR Cutoff Value of 4



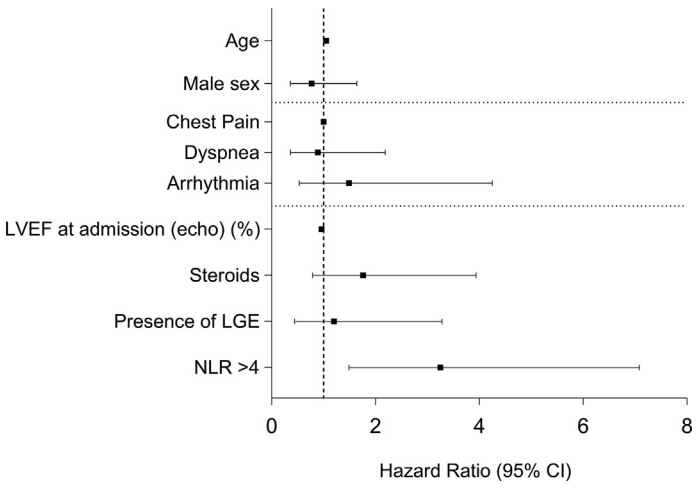
Kaplan-Meier curve for all-cause mortality or HTx according to NLR cutoff value of 4 in the train dataset (A) and in the test dataset (B). HTx = heart transplantation; NLR = neutrophil-to-lymphocyte ratio.

not independently associated with a higher risk of adverse events.[26] CRP above the upper limit of normal was not associated with an increased hazard of mortality (Supplemental Figure 2).

USING NLR TO STRATIFY LOW-RISK PATIENTS. We next investigated a possible role for NLR in risk-stratifying patients with AM and preserved LVEF because they are usually considered at low risk of adverse events.[1,26-28] Using spline analysis, we identified a cutoff LVEF of 51%, below which further reductions were associated with an increased risk of mortality (Supplemental Figure 2). Therefore, we used a pragmatic cutoff of 50%, which is consistent with international HF guidelines.[29-31] Baseline LVEF <50% was associated with worse outcomes compared with LVEF ≥50% (Supplemental Figure 2) ($P < 0.0001$). Among patients with preserved LVEF at baseline, NLR ≥4 remained associated with worse outcomes (**Figure 4**) ($P = 0.0012$).

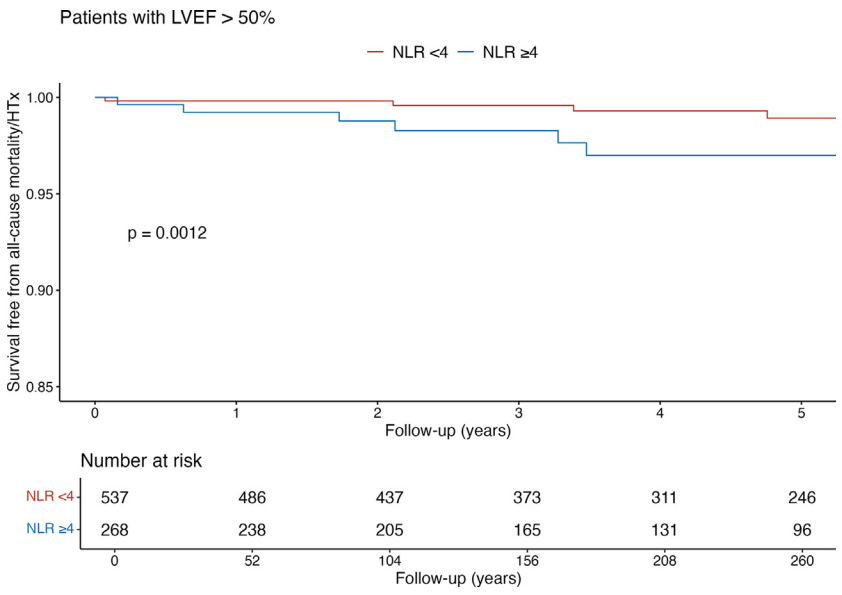
SUBGROUP AND SENSITIVITY ANALYSES. The results obtained from the whole cohort also persisted in the subgroup of patients with LVEF ≥50%, without autoimmune disease, those without CKD, those who did not receive in-hospital steroids, and those with biopsy-proven AM or with only CMR-proven AM (Supplemental Figure 1). Furthermore, among patients with preserved LVEF at baseline, NLR was a better predictor of outcome than baseline LVEF (AUC: 0.726 [95% CI: 0.636-0.815] and AUC: 0.474 [95% CI: 0.341-0.608], respectively) (Supplemental Figure 3). In the subgroup of patients with available data at discharge (n = 568), NLR ≥4 at discharge (HR: 6.33 [95% CI: 2.67-15]; $P < 0.001$; n = 568) (Supplemental Figure 4), as well as the dynamic changes of NLR during admission (HR: 1.14 [95% CI: 1.04-1.24]; $P = 0.003$) remained associated with adverse outcomes. Lastly, in the subgroup of patients with available troponin (n = 728) or N-terminal pro-B-type natriuretic peptide values (n = 258), these biomarkers were not associated with the primary outcome ($P = 0.3$ for troponin and $P = 0.06$ for N-terminal pro-B-type natriuretic peptide) and there was no incremental value of adding these biomarkers to NLR values at admission (Supplemental Figure 5).

FIGURE 3 Forest Plot of Adjusted HR for All-Cause Mortality or HTx



LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; other abbreviations as in **Figure 2**.

FIGURE 4 Kaplan-Meier Curve for All-Cause Mortality or HTx According to NLR Cutoff Value of 4 in the Subgroup of Patients With Baseline LVEF >50%



Abbreviations as in Figures 2 and 3.

The results were also confirmed in sensitivity analyses investigating alternative cutoffs, either proposed elsewhere (ie, 2.5) or the median (3.4) (Supplemental Figure 6).[14,17]

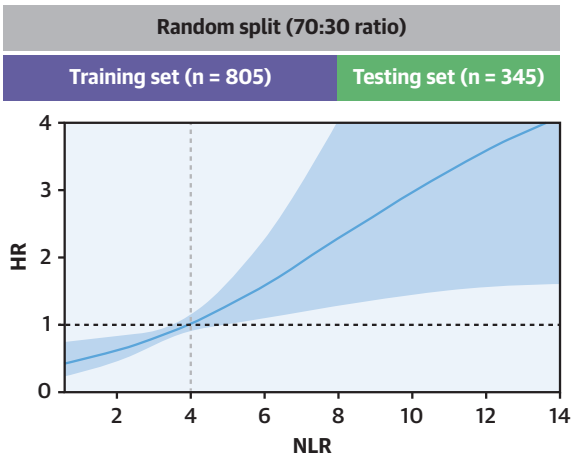
DISCUSSION

By analyzing the largest retrospective cohort of patients with AM, including more than 1,100 patients with CMR-proven AM, and EMB-confirmed in a subset, we found that NLR is an accessible biomarker to predict prognosis. It is independently associated with all-cause mortality and heart transplantation, and it may be helpful in further stratifying patients at low risk of adverse outcomes based on LVEF (**Central Illustration**).

PROGNOSTIC ROLE OF NLR IN MYOCARDITIS. NLR is an inexpensive and universal biomarker that has been studied in several cardiac and noncardiac inflammatory conditions. In cardiovascular disease, elevated NLR has been associated with adverse events in atherosclerosis, acute HF, and valvular heart disease.[1,16] Furthermore, NLR was also used to identify patients at higher risk of cardiac events among those receiving immune checkpoint inhibitors for cancer.[19,32] Neutrophils have a direct role in the pathogenesis of myocardial injury and AM, promoting myeloperoxidase release and neutrophil extracellular trap formation.[4,16,17] Targeting neutrophils in murine models of myocarditis was found to reduce inflammation and improve the pathologic phenotype.[27] Elevated NLR values may reflect an immune response oriented toward inflammation. Neutrophils are necessary for clearing necrotic tissue and initiating fibrotic signaling pathways after acute cardiac injury. This inflammatory phase is characterized by neutrophil release of proinflammatory enzymes, reactive oxygen species, and inflammatory alarmins S100A8 and S100A9, which exacerbate myocardial injury.[11,33] Reduced circulating lymphocytes may also contribute to elevated NLR. The current paradigm is that primed T-helper 17 cells leave the circulation and infiltrate the myocardium in response to injury, causing myocarditis, which may contribute to the association of worse outcomes among patients with elevated NLR.[34]

In a previous study in patients hospitalized with AM, a similar cutoff NLR value of 4 was associated with a surrogate endpoint of longer hospital duration in patients hospitalized with AM,[17] which may reflect

CENTRAL ILLUSTRATION **Prognostic Role of NLR in Patients With Acute Myocarditis (N = 1,150)**

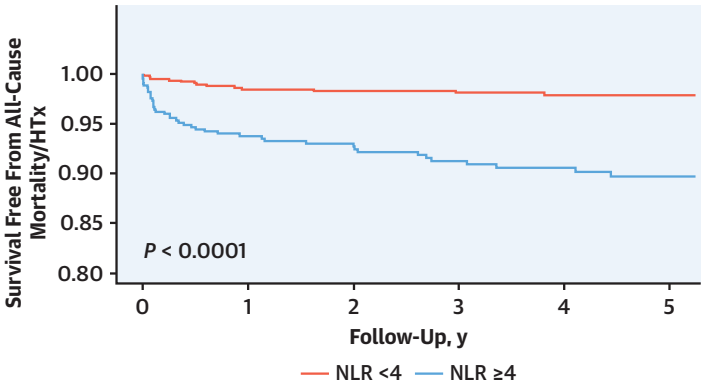


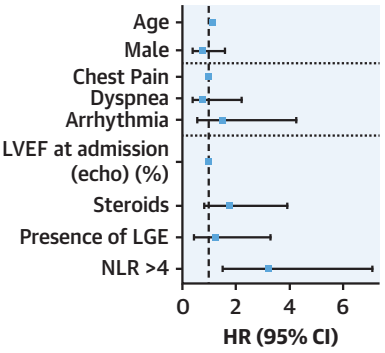
NLR = Neutrophils / Lymphocytes >4

Baseline: ↑ Dyspnea ↓ LVEF ↓ eGFR ↑ Use of inotropic support ↑ Use of steroids

Median follow-up 4.38 years: ↑ All-cause mortality or heart transplant HR: 3.25, 95% CI: 1.49-7.08

Regardless of: Age | Sex | Clinical presentation | LVEF | LGE | In-hospital steroids





- NLR is an inexpensive and easily accessible inflammatory biomarker.
- In patients with AM, elevated NLR (≥4) at admission is associated with worse prognosis.
- NLR could be used for risk stratification in patients with AM, also in those conventionally considered to be at **low-risk** of adverse events.

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AM = acute myocarditis; eGFR = estimated glomerular filtration rate; HTx = heart transplantation; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; NLR = neutrophil-to-lymphocyte ratio.

the role of neutrophils in the pathogenesis of AM.[28,35,36] However, this study used International Classification of Diseases 10th Revision diagnostic codes and was not restricted to CMR- or EMB-confirmed cases. Our study is the first to investigate the prognostic role of NLR in patients with AM.

Because there are no established cutoff values for NLR in the context of AM, we used a train and test

approach to derive and validate the optimal cutoff. Based on this, we selected a pragmatic value of 4, above which there is an increased risk of death or heart transplantation. Nevertheless, NLR was also associated with all-cause mortality or heart transplantation when considering other cutoffs reported elsewhere in the published reports, or the median value.[26] Interestingly, the prognostic value of NLR was still maintained once patients with autoimmune conditions were excluded.

Several parameters and biomarkers have been associated with adverse outcomes in AM. To date, LVEF has emerged as one of the most robust predictors of outcome.[1,21,37-42] Notably, commonly used inflammatory markers, such as CRP, are not strongly associated with disease severity and outcome, which is supported by our analysis.[28] More recently, pathogenic genetic variants, in particular those related to arrhythmogenic and dilated cardiomyopathies, have been identified with increased frequency in patients with AM and have been associated with more severe clinical characteristics or a trend toward adverse outcomes.[1,2,35] Other novel biomarkers, including the circulating human microRNA has-miR-Chr8:96, may help differentiate AM from myocardial infarction.[26] However, microRNA analysis and testing for pathogenic genetic variants are not readily available on admission, require dedicated skills and facilities, and are generally expensive. NLR is more accessible and, as demonstrated in our study, can predict outcomes both alone and in combination with other characteristics.

NLR AS A BIOMARKER FOR RISK STRATIFICATION. Although contemporary analysis indicates that AM has an overall benign prognosis, approximately 6% of AM patients still have adverse outcomes.[27] A worse prognosis may be apparent from the clinical presentation, including patients presenting with fulminant myocarditis, cardiogenic shock, or life-threatening arrhythmias.[1,43,44] However, outcomes are less predictable in patients with less severe clinical presentations. In such patients, a residual risk of long-term adverse events remains.[45] Several markers, including CMR global longitudinal strain, have been investigated in this context. However, despite promise in predicting adverse events,[46] it is expensive and not universally available. Therefore, we investigated the use of NLR to further stratify patients conventionally considered to be at low risk of adverse outcomes (ie, the subgroup of patients with preserved LVEF at baseline). In these patients, elevated NLR remained associated with worse long-term outcomes despite their relatively low risk and consequently low number of events at follow-up. Although the pattern of clinical presentation might be causally related to elevated NLR (eg, by enhanced inflammation leading to worse LV function and higher likelihood of a breathlessness presentation), our study was not equipped to understand these relationships.

The role of immunosuppression in patients with AM is controversial. Immunosuppression is indicated only in patients with the most severe clinical presentations, and, even then, except in Giant Cell Myocarditis, current evidence does not support its routine use.[2,13,47,48] This may be because study inclusion criteria are often based on EMB, which may select for the most unwell patients.[14] Furthermore, most studies excluded patients with evidence of an active viral genome who may not benefit from immunosuppressive therapy or even receive potential harm from empirical immunosuppression.[11,47,48] To date, routine use of corticosteroids in patients with myocarditis is not indicated.

Using NLR may help identify patients who may be at higher risk of adverse events and may be used as an enrichment criterion in randomized clinical trials in myocarditis. Anti-inflammatory therapies targeting interleukin-1b or interleukin-6 in cardiovascular disease have been shown to reduce NLR values.[13-15] Whether these therapies are beneficial in patients with AM, targeting the pathophysiology of myocarditis, is still unknown. To date, there is no evidence supporting the use of NLR to guide treatment. Prospective, randomized validation of NLR is advocated in this setting and may open new avenues for targeted therapies and improved outcomes in AM patients.

STUDY LIMITATIONS. Although we included all consecutive patients enrolled in 10 international centers, a potential selection and referral bias cannot be entirely excluded. All-cause mortality was justified by the lack of granularity available to identify cause-specific mortality. Although validation in other cohorts is not reported, we enrolled patients from different centers, which makes the results more generalizable. We report the largest cohorts of patients with CMR- or EMB-confirmed AM, but it may not be representative of all AM patients. A potential impact of unmeasured confounders cannot be excluded. Furthermore, etiology of AM was not available for all patients. Given the nature of the study, data on the genetic background as well as more detailed CMR data and data on mechanical circulatory

support were not available. Given the available data, it was not possible to investigate dynamic changes of LVEF, both acutely and over follow-up. Although several factors might influence NLR, including administration of steroids and other immune modulators, and viral and bacterial infections, we did not have sufficient power to account for this and the observational nature of our study did not allow us to infer causality. Finally, we could not compare NLR with other novel biomarkers, including pathogenic genetic variants or microRNAs.

CONCLUSIONS

NLR is a promising, inexpensive, and readily available inflammatory biomarker that may be useful for identifying patients with AM at higher risk of adverse outcomes, even when considered at low risk based on LVEF. NLR may be, therefore, valuable for risk stratification of patients with AM. Large prospective studies and clinical trials are required to confirm the independent role of NLR in AM and further investigate its potential for guiding diagnostic work-up and therapeutic strategies.

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ADDRESS FOR CORRESPONDENCE: Dr Antonio Cannata OR Dr Daniel I. Bromage, School of Cardiovascular Medicine and Sciences, James Black Centre, King's College London BHF Centre of Excellence, 125 Coldharbour Lane, London SE5 9NU, United Kingdom. E-mail: antonio.cannata@kcl.ac.uk OR daniel.bromage@kcl.ac.uk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: AM is a highly heterogeneous inflammatory heart disease, ranging from life-threatening conditions to mild and asymptomatic forms.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: There are few biomarkers available in clinical practice for risk stratification of patients with AM.

TRANSLATIONAL OUTLOOK: NLR is an inexpensive and readily available biomarker useful for risk stratification, able to identify patients with AM at higher risk of adverse events, even those traditionally considered at low risk.

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KEY WORDS immunosuppression, lymphocyte, myocarditis, neutrophil, neutrophil-to-lymphocyte ratio, outcomes

APPENDIX For supplemental tables and figures, please see the online version of this paper.