scientific reports

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Prognostic potential of neutrophil-to-lymphocyte ratio for adverse outcomes in dilated cardiomyopathy: a retrospective cohort study

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Neutrophil-to-lymphocyte ratio (NLR), as a novel inflammatory marker, has been shown to be associated with the severity and prognosis of various cardiovascular diseases. The aim of this study was to investigate whether NLR can serve as a biomarker for adverse outcomes and prognostic value in patients with dilated cardiomyopathy (DCM). This was a retrospective analysis of 666 consecutive patients with DCM who were admitted to our center for the first time. We compared the NLR levels among different outcome groups and assessed the survival status of patients in different NLR categories. Additionally, we explored the temporal changes in the predictive performance of NLR over time. Cox regression analysis was used to assess the relationship between NLR and prognosis, and subgroup analysis was performed. Furthermore, we investigated the dose–response relationship between NLR and prognosis. A total of 221 patients experienced all-cause death, and the NLR value in the death group (4.6 ± 5.3) was significantly higher than that in the survival group (3.2 ± 2.9) ($P < 0.05$). In terms of all-cause death, cardiac death, and heart failure death, the cumulative hazard were significantly higher in the NLR ≥ 3 group compared to the NLR < 3 group ($P < 0.001$). NLR showed a high accuracy in predicting these outcomes, but decreased over time. The results of the multivariable Cox regression analysis demonstrated that NLR was independently associated with all-cause death, cardiac death, and heart failure death ($P < 0.05$). Higher NLR values were associated with an increased risk of death, while there was no significant correlation with sudden death. In the fully adjusted model, each increase of 1 or 1 standard deviation (SD) in NLR corresponded to a 5% and 20% increase in the risk of all-cause death, a 4% and 15% increase in the risk of cardiac death, and a 5% and 21% increase in the risk of heart failure death ($P < 0.05$). In the fully adjusted model with all-cause death as the outcome, there was an interaction between NLR and age ($P = 0.023$), and the elderly population at higher risk. For cardiac death and heart failure death, there was an interaction between NLR and LVEF ($P < 0.05$), with the subgroup of LVEF < 35% being at higher risk. The relationship between $\log_2$ (NLR) and the risk of all-cause death exhibited a J-shaped correlation, while it showed a linear correlation with cardiac death and heart failure death. There was a threshold effect between NLR and different outcomes. NLR is independently associated with a higher risk of death in patients with DCM. It can be used to assess high-risk patients and predict adverse outcomes, allowing for early intervention.

Keywords Neutrophil-to-lymphocyte ratio, Dilated cardiomyopathy, Dose–response relationship, Adverse outcomes

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Abbreviations

AUC	Area under the curve
CI	Confidence interval
CRT/ICD	Cardiac Resynchronization Therapy/Implantable Cardioverter Defibrillator
DCM	Dilated cardiomyopathy
eGFR	Estimated glomerular filtration rate
HR	Hazard ratio
NLR	Neutrophil-to-lymphocyte ratio
ROC	Receiver operating characteristic
SD	Standard deviation

Dilated cardiomyopathy (DCM) is a progressive cardiac disorder characterized by left ventricular dilation and systolic dysfunction. It is a major cause of heart failure and can lead to significant mortality[1]. Despite advancements in diagnostic and therapeutic approaches, the prognosis of DCM remains variable, and identifying reliable prognostic markers for adverse outcomes is crucial for risk stratification and guiding clinical management decisions. In recent years, there has been growing interest in the role of systemic inflammation in cardiovascular diseases. Inflammatory processes are known to contribute to the development and progression of various cardiac conditions, including atherosclerosis, acute myocardial infarction, and heart failure[2,3]. In this context, several inflammatory markers have been investigated as potential prognostic indicators in cardiovascular diseases[4].

The neutrophil-to-lymphocyte ratio (NLR), an easily accessible and cost-effective marker of systemic inflammation, has emerged as a promising prognostic marker in various clinical settings. NLR reflects the balance between neutrophils, which are involved in the acute inflammatory response, and lymphocytes, which play a role in regulating the immune response. Elevated NLR has been associated with adverse outcomes in several diseases, including cancer, sepsis, and cardiovascular disorders[5–8]. Despite the growing interest in NLR as a prognostic marker, its potential utility in DCM remains uncertain. There is currently limited research in this area. Therefore, there is a need for well-designed studies to evaluate the prognostic potential of NLR in this specific population.

The aim of this retrospective cohort study was to assess the prognostic value of NLR for adverse outcomes in DCM patients. We hypothesized that elevated NLR would be associated with an increased risk of adverse outcomes. By investigating the relationship between NLR and adverse outcomes in DCM, we aimed to provide valuable insights into the potential clinical utility of NLR as a prognostic marker in this challenging patient population. Understanding the prognostic significance of NLR in DCM could have important implications for risk stratification, treatment optimization, and patient management. If NLR proves to be a reliable prognostic marker, it could be easily incorporated into routine clinical practice, allowing for early identification of high-risk DCM patients who may benefit from more intensive monitoring and targeted interventions. In summary, the prognostic potential of NLR in DCM remains uncertain, and there is a need for further investigation. This retrospective cohort study aimed to fill this knowledge gap by evaluating the association between NLR and adverse outcomes in DCM patients. The findings from this study may contribute to the growing body of evidence regarding the role of systemic inflammation in DCM and have important implications for risk stratification and patient management strategies.

Materials and methods

Study population

The cohort of our study was identified following an evaluation of the medical records system, from October 2012 to May 2020. We diagnosed patients with DCM based on echocardiography, imaging, and clinical symptoms. Secondary cardiomyopathies such as sarcoidosis and chronic myocarditis were excluded based on clinical history, imaging findings (e.g., cardiac MRI), laboratory tests, and, when necessary, endomyocardial biopsy to ensure accurate diagnosis of DCM. The inclusion and exclusion criteria are in line with the Guidelines for the Diagnosis and Treatment of Dilated Cardiomyopathy in China[9], with objective evidence of ventricular enlargement and reduced myocardial contractility: (1) Left ventricular end diastolic dimension (LVDd) > 5.0 cm (female) and LVDd > 5.5 cm (male); (2) Left ventricular ejection fraction (LVEF) < 45% (Simpsons method), left ventricular fractional shortening (LVFS) < 25%. We consecutively enrolled patients with DCM who were admitted to our center for the first time. Although not all patients were admitted due to acute decompensated heart failure, most had severe symptoms at the time of hospitalization, and all patients had varying degrees of cardiac dysfunction. The process of patient recruitment for the study population is shown in Fig. 1. To ensure the reliability of the data, we excluded patients who had incomplete laboratory or imaging data.

Data collection

We collected clinical characteristics of each patient, including medical history and comorbidities, physical examination findings, blood biochemistry, echocardiography, electrocardiography, and the medication treatment regimen. For patients with repeated tests, we only used the results from the first test during hospitalization (Table 1). Clinical characteristic variables were obtained through the electronic medical record system, and prognostic information was obtained through telephone follow-up and review of repeated hospitalization records. The primary endpoint was all-cause death (including heart transplantation), and the secondary endpoints were cardiac death, heart failure death (including heart transplantation), and sudden death. We declare that the organs used for heart transplantation were not from prisoners. All co-authors examined the data separately to ensure accuracy.

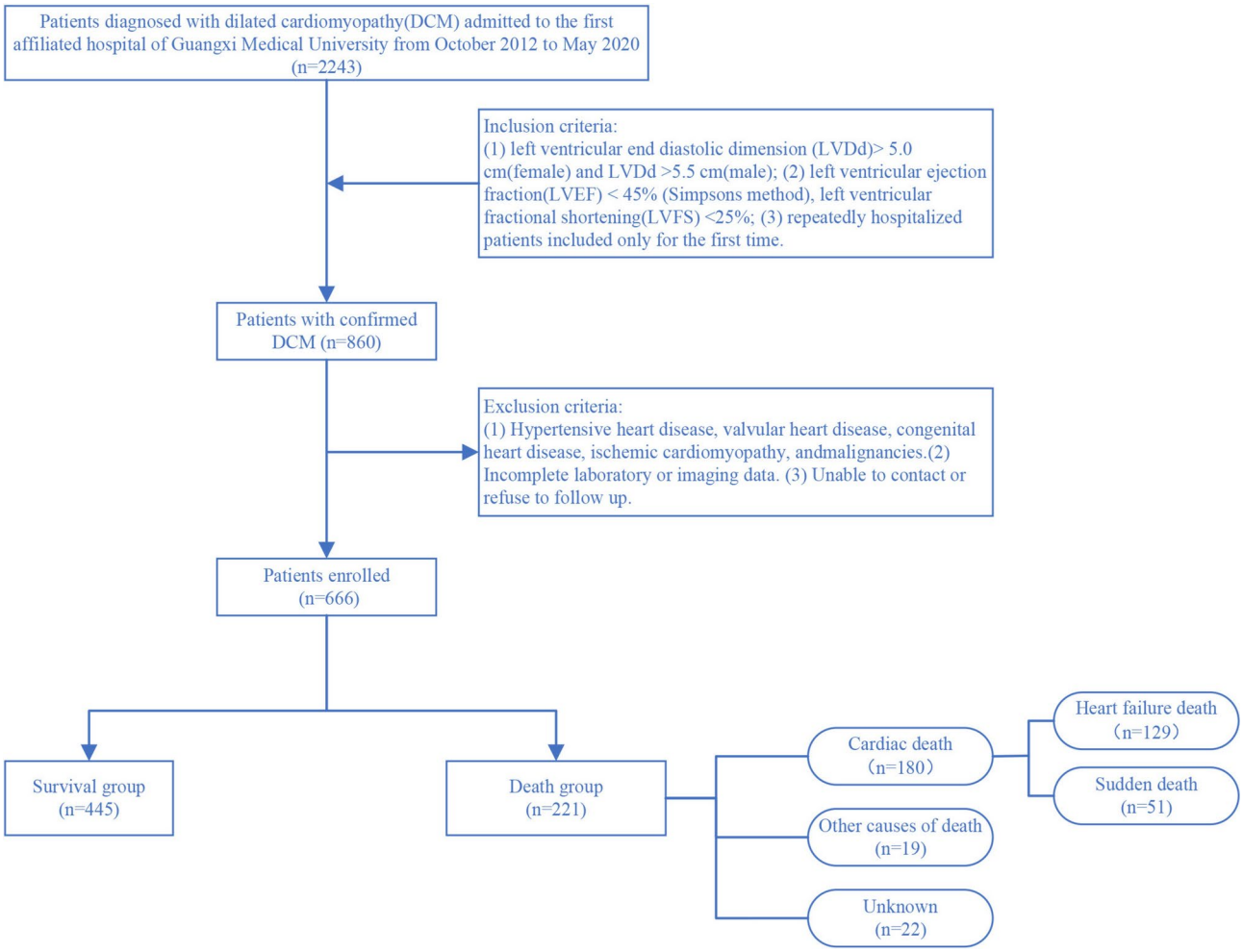

Fig. 1. Flow chart showing the process of patient recruitment for the study.

Relevant definitions

Medical history: symptoms associated with DCM and the time of their appearance. Pulmonary arterial hypertension was defined as the pulmonary artery pressure estimated at ≥ 30 mmHg based on the tricuspid regurgitation pressure difference. The estimated glomerular filtration rate (eGFR) was computed using the CKD-EPI equation[10]. Renal insufficiency was defined as an eGFR of less than 60 ml/min/1.73m^2[11]. Liver function injury was defined as a three-fold increase in AST (≥ 135 U/L) or ALT (≥ 180 U/L) at any time during hospitalization. Sudden death: accidental death within 1 h of cardiac symptoms without progressive cardiac deterioration; death in sleep; or death within 24 h of the last sighting alive[12]. Heart failure death: predictable death due to progressive deterioration of heart function. Cardiac death is defined as a combination of heart failure death and sudden death, as both are related to cardiac causes.

Statistical analysis

Data are presented as mean ± standard deviation (SD) or median (interquartile range, IQR) for continuous variables, and as frequency or percentage for categorical variables. For baseline characteristics analysis, the statistical differences among groups were tested with t-test for continuous variables and chi-square or fisher test for categorical variables. Histograms were drawn to compare NLR levels in patients with different follow-up outcomes. According to the Youden index, the optimal cut-off value of NLR was determined and the patients were divided into groups. Kaplan–Meier curve was drawn, and log rank test was used to compare the cumulative hazard differences between groups. The accuracy of NLR in predicting

Variables	Total (n = 666)	Survival group (n = 445)	Death group (n = 221)	*p*	Statistic
NLR, Mean ± SD	**3.7 ± 3.9**	**3.2 ± 2.9**	**4.6 ± 5.3**	**< 0.001**	**18.89**
Follow-up period, median (IQR)	803.5 (394.0, 1474.0)	964.0 (622.0, 1760.0)	421.0 (48.0, 896.0)	**< 0.001**	111.311
Drinking history, n (%)	305 (45.8)	203 (45.6)	102 (46.2)	0.896	0.017
Smoking history, n (%)	299 (44.9)	196 (44)	103 (46.6)	0.531	0.392
Male, n (%)	508 (76.3)	334 (75.1)	174 (78.7)	0.294	1.103
Age, Mean ± SD	53.7 ± 13.3	53.0 ± 12.7	55.0 ± 14.4	0.068	3.348
Medical history, n (%)				**< 0.001**	24.928
< 1 year	323 (48.7)	242 (54.5)	81 (37)		
1 ~ 5 years	212 (32.0)	137 (30.9)	75 (34.2)		
≥ 5 years	128 (19.3)	65 (14.6)	63 (28.8)		
Grade of heart failure (NYHA)				**0.003**	14.059
I	23 (3.5)	17 (3.8)	6 (2.7)		
II	127 (19.1)	97 (21.8)	30 (13.6)		
III	256 (38.4)	178 (40)	78 (35.3)		
IV	260 (39.0)	153 (34.4)	107 (48.4)		
Pulmonary arterial hypertension, n (%)	413 (62.0)	265 (59.6)	148 (67)	0.063	3.449
Atrial fibrillation, n (%)	139 (20.9)	88 (19.8)	51 (23.1)	0.324	0.975
Diabetes, n (%)	49 (7.4)	24 (5.4)	25 (11.3)	**0.006**	7.59
Admission heart rate, Mean ± SD	89.7 ± 19.4	90.3 ± 19.3	88.5 ± 19.6	0.249	1.333
Mean arterial pressure, Mean ± SD	89.5 ± 14.1	91.4 ± 14.3	85.7 ± 12.9	**< 0.001**	24.82
Fasting blood-glucose, Mean ± SD	5.2 ± 1.6	5.1 ± 1.5	5.2 ± 1.7	0.396	0.721
WBC, Mean ± SD	8.0 ± 2.9	7.9 ± 2.7	8.2 ± 3.3	0.180	1.799
NE, Mean ± SD	5.2 ± 2.6	5.1 ± 2.5	5.5 ± 2.9	**0.027**	4.943
LY, Mean ± SD	1.9 ± 1.1	1.9 ± 0.7	1.8 ± 1.6	0.196	1.679
CK, Mean ± SD	147.6 ± 313.9	132.5 ± 193.5	178.0 ± 469.9	0.078	3.114
CK-MB, Mean ± SD	17.5 ± 13.1	16.6 ± 11.7	19.3 ± 15.3	**0.011**	6.45
LDH, Mean ± SD	290.1 ± 209.5	270.2 ± 187.4	330.3 ± 243.8	**< 0.001**	12.349
α-HBD, Mean ± SD	201.4 ± 93.6	189.0 ± 64.6	226.5 ± 130.9	**< 0.001**	24.639
Hcy, Mean ± SD	15.7 ± 5.5	15.2 ± 5.1	16.8 ± 6.1	**< 0.001**	12.819
AST, Mean ± SD	88.2 ± 831.6	88.5 ± 988.8	87.4 ± 342.5	0.987	0
ALT, Mean ± SD	62.6 ± 195.2	58.1 ± 220.7	71.7 ± 129.2	0.396	0.721
ALB, Mean ± SD	38.4 ± 5.0	38.9 ± 5.0	37.3 ± 4.9	**< 0.001**	14.04
UREA, Mean ± SD	8.0 ± 4.3	7.4 ± 3.6	9.2 ± 5.2	**< 0.001**	26.32
EGFR, Mean ± SD	70.2 ± 30.0	73.7 ± 30.4	63.1 ± 28.0	**< 0.001**	18.841
SCr, Mean ± SD	106.8 ± 70.3	103.3 ± 72.9	113.7 ± 64.3	0.074	3.208
UA, Mean ± SD	507.5 ± 169.8	498.4 ± 163.9	525.9 ± 180.1	**0.049**	3.902
NT-proBNP, Mean ± SD	6667.7 ± 7718.5	5267.1 ± 6321.2	9487.9 ± 9353.0	**< 0.001**	47.226
LAD, Mean ± SD	46.1 ± 7.4	45.5 ± 7.1	47.4 ± 7.7	**0.002**	9.952
LVDd, Mean ± SD	69.7 ± 8.5	68.6 ± 8.0	72.0 ± 9.2	**< 0.00**1	23.494
LVDS, Mean ± SD	58.6 ± 8.2	57.5 ± 7.6	60.8 ± 8.9	**< 0.001**	24.176
LVFS, Mean ± SD	16.0 ± 4.2	16.3 ± 4.2	15.6 ± 4.3	**0.047**	3.965
LVEF, Mean ± SD	32.4 ± 7.7	32.8 ± 7.6	31.5 ± 7.9	**0.031**	4.664
CO, Mean ± SD	7.2 ± 2.8	7.1 ± 2.7	7.5 ± 2.9	0.117	2.464
EDV, Mean ± SD	254.3 ± 75.9	244.3 ± 69.0	274.3 ± 85.0	**< 0.001**	23.925
Types of Arrhythmia					
Sinus, n (%)	105 (15.8)	80 (18)	25 (11.3)	**0.026**	4.94
Atrial, n (%)	186 (27.9)	120 (27)	66 (29.9)	0.432	0.616
Atrial fibrillation, n (%)	15 (2.3)	10 (2.2)	5 (2.3)	1	Fisher
Ventricular, n (%)	179 (26.9)	117 (26.3)	62 (28.1)	0.629	0.233
Conduction block, n (%)	117 (17.6)	72 (16.2)	45 (20.4)	0.182	1.784

Continued

Variables	Total (n = 666)	Survival group (n = 445)	Death group (n = 221)	*p*	Statistic
NLR, Mean ± SD	**3.7 ± 3.9**	**3.2 ± 2.9**	**4.6 ± 5.3**	**< 0.001**	**18.89**
Drug					
Beta blockers, n (%)	584 (87.7)	403 (90.6)	181 (81.9)	**0.001**	10.261
ACEI/ARB, n (%)	556 (83.5)	391 (87.9)	165 (74.7)	**< 0.001**	18.673
Diuretic, n (%)	655 (98.3)	439 (98.7)	216 (97.7)	0.519	Fisher
ICD, n (%)	30 (4.5)	19 (4.3)	11 (5)	0.678	0.172

Table 1. Baseline characteristics of the study population (Grouping by endpoint events). ACEI/ARB, Angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers; α-HBD, Alpha-hydroxybutyrate dehydrogenase; ALB, Albumin; CK, Creatine kinase; CO, cardiac output; EGFR, Estimated glomerular filtration rate; Hcy, Homocysteine; ICD, Implantable cardioverter-defibrillator; LAD, Left atrium anteroposterior dimension; LD1, Lactic dehydrogenase-1; LY, Lymphocyte; LVDd, Left ventricular end diastolic dimension; LVDS, Left ventricular end systolic dimension; LVFS, Left ventricular fractional shortening; LVEF, Left ventricular ejection fraction; NT-proBNP, N terminal pro B type natriuretic peptide; NE, Neutrophils; NLR, Neutrophil to Lymphocyte Ratio; NYHA, New York Heart Association; SCr, Creatinine; UA, Uric acid; WBC, White blood cell count. A P value less than 0.05 indicates a statistical difference and is shown in bold.

all-cause death at different times was assessed by the area under the curve (AUC) of the time receiver operating characteristic (ROC) curve. Univariate Cox regression model was used to analyze the association between baseline variables and all-cause death. Baseline variables with P value less than 0.1 were included as covariates in the multivariate Cox regression model to explore the independent association between NLR and all-cause death. Risk was quantified by hazard ratio (HR) and its 95% confidence interval (CI). In order to enhance the comparability of data, NLR data were normalized (z normalization, log function transformation). Subgroup analysis: we used some relevant effect covariates for stratification and drew forest plots, and P values for interactions were calculated by likelihood ratio tests. Smoothed curve fitting and threshold saturation effect analysis: A generalized additive model was used to assess the dose–response relationship between NLR levels and different adverse outcomes; corresponding adjustments were made in the multivariate-adjusted model. All statistical analyses were performed using R software (http://www.R-project.org); $P < 0.05$ was considered statistically significant.

Results

We conducted follow-up on the enrolled patients and obtained prognostic information at a mean follow-up period of 31.7 ± 24.4 months after discharge. Among the 666 patients, 221 individuals experienced all-cause death. Among them, 129 patients died due to heart failure (including 4 cases of cardiac transplantation), 51 cases experienced sudden death, 19 cases died from other causes (including multiple organ failure, sepsis, severe pneumonia, cerebral hemorrhage, etc.), and the specific cause of death for 22 individuals was unknown.

Participants were grouped based on the outcome, and it was found that the NLR values in the death group (4.6 ± 5.3) were significantly higher than those in the survival group (3.2 ± 2.9). Additionally, compared to the survival group, the death group exhibited longer medical history, larger cardiac chambers, poorer cardiac function, higher proportion of patients with diabetes, lower average arterial pressure, poorer liver and kidney function, and a lower proportion of patients using beta blockers and ACEI/ARB. All of these differences were statistically significant ($P < 0.05$).

As shown in the histograms, the NLR levels in different cause of death groups were generally higher than those in the survival group. Among them, the group with deaths due to other causes had the highest NLR value (8.9 ± 8.5), followed by the heart failure death group (4.4 ± 5.3). After standardizing the NLR data, the results remained consistent (Fig. 2). Using the optimal cutoff value, NLR was divided into two groups: " < 3" and " ≥ 3". The survival curves showed that for the endpoints of all-cause death, cardiac death, and heart failure death, the cumulative hazard of the NLR ≥ 3 group was significantly higher than that of the NLR < 3 group ($P < 0.001$). However, there was no significant difference between the two groups for the endpoint of sudden death (Fig. 3). The time-dependent ROC curves demonstrated that the predictive accuracy of NLR for different outcomes (all-cause death, cardiac death, heart failure death) decreased with longer follow-up time and eventually leveled off. However, NLR did not show predictive value for sudden death as an endpoint (Fig. 4).

As shown in the univariate Cox regression results in Table 2, medical history, grade of heart failure (NYHA), pulmonary arterial hypertension, hyperuricemia, renal insufficiency, liver function injury, and NT-proBNP (≥ 1800 pg/ml) were positively associated with all-cause death. On the other hand, mean arterial pressure, left ventricular ejection fraction (LVEF), beta blockers, and ACEI/ARB were negatively associated with all-cause death ($P < 0.05$). The results of the multivariate Cox regression analysis (Table 3) showed

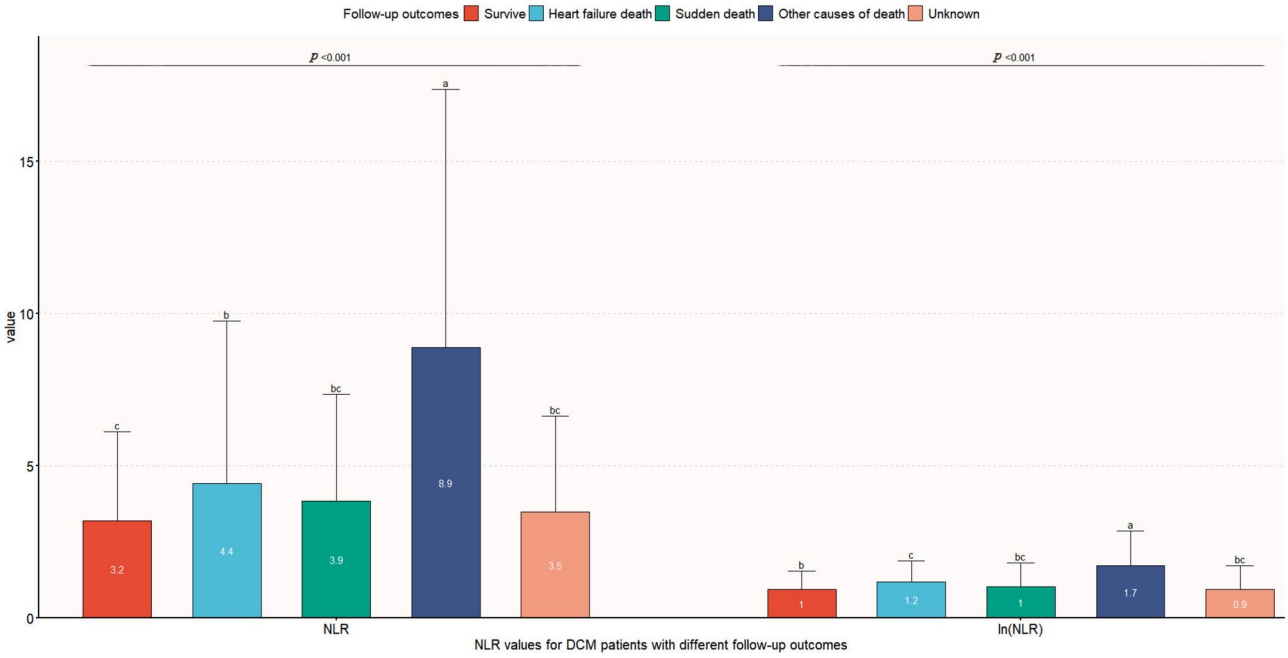

Fig. 2. NLR values for DCM patients with different follow-up outcomes. *Note:* The left half of the graph represents NLR, while the right half of the graph represents Ln (NLR) (Natural Logarithm of NLR). Different colors represent different follow-up outcomes. The numerical values in the boxes represent the group means, and the thin lines above represent the standard deviation. If different groups do not contain the same letters, it indicates statistically significant differences in the comparisons between groups. For example, if Group 1 is marked with "a", Group 2 with "b", and Group 3 with "c", it indicates that the differences between Group 1 and Group 2, Group 1 and Group 3, and Group 2 and Group 3 are statistically significant. If Group 4 is marked with "bc", it indicates that Group 4 does not differ significantly from Groups 2 and 3, but differs significantly from Group 1.

that in both unadjusted and stepwise adjusted expanded models, NLR remained independently associated with all-cause death, cardiac death, and heart failure death ($P < 0.05$). A higher NLR was associated with an increased risk of death. However, there was no significant association between NLR and sudden death ($P > 0.05$). In the unadjusted model, each increment of 1, 1 SD, twofold, or e (natural logarithm) times in NLR corresponded to a 7%, 29%, 44%, or 70% increase in the risk of all-cause death, a 6%, 27%, 41%, or 64% increase in the risk of cardiac death, and a 7%, 28%, 41%, or 82% increase in the risk of heart failure death ($P < 0.001$). In the fully adjusted model, each increment of 1 or 1 SD in NLR corresponded to a 5% or 20% increase in the risk of all-cause death, a 4% or 15% increase in the risk of cardiac death, and a 5% or 21% increase in the risk of heart failure death ($P < 0.05$).

In subgroup analyses, we further investigated the relationship between NLR and different outcomes (all-cause death, cardiac death, heart failure death) in subgroups defined by gender (male, female), age ($< 60, \geq 60$), LVEF ($< 35\%, \geq 35\%$), and eGFR ($< 60, \geq 60$). A forest plot was generated to illustrate the results (Fig. 5). Without adjusting for covariates, NLR was positively correlated with different outcomes in the various subgroups. Additionally, there was an interaction effect between NLR and age (interaction effect $P < 0.05$). Specifically, in the elderly population (age ≥ 60), the impact of NLR on each outcome was more pronounced, indicating a higher risk of adverse outcomes with increasing NLR levels in this age group. In the fully adjusted model, when considering all-cause death as the outcome, the interaction effect between NLR and age persisted ($P = 0.023$), and the elderly population remained at a higher risk (HR = 1.16; 95% CI: 1.09–1.22). Furthermore, when considering cardiac death and heart failure death as the outcomes, an interaction effect between NLR and LVEF was observed (interaction effect $P < 0.05$), with the subgroup with LVEF < 35% identified as the high-risk group, while the subgroup with LVEF ≥ 35% did not show a significant positive association between NLR and the outcomes.

As shown in Fig. 6, the relationship between $\log_2$ (NLR) and the risk of all-cause death exhibits a J-shaped correlation, while it appears to be linearly associated with cardiac death and heart failure death ($P > 0.05$). There is a threshold effect observed between NLR and different outcomes. When $\log_2$ (NLR) equals 1.359, corresponding to NLR = 2.565, the hazard ratio (HR) for all-cause death is 1. When $\log_2$ (NLR) equals 1.327, corresponding to NLR = 2.509, the HR for cardiac death is 1. When $\log_2$ (NLR) equals 1.34, corresponding to NLR = 2.532, the HR for heart failure death is 1. As the NLR value exceeds these thresholds, the HR gradually increases. This result remains consistent before and after adjusting for multiple variables.

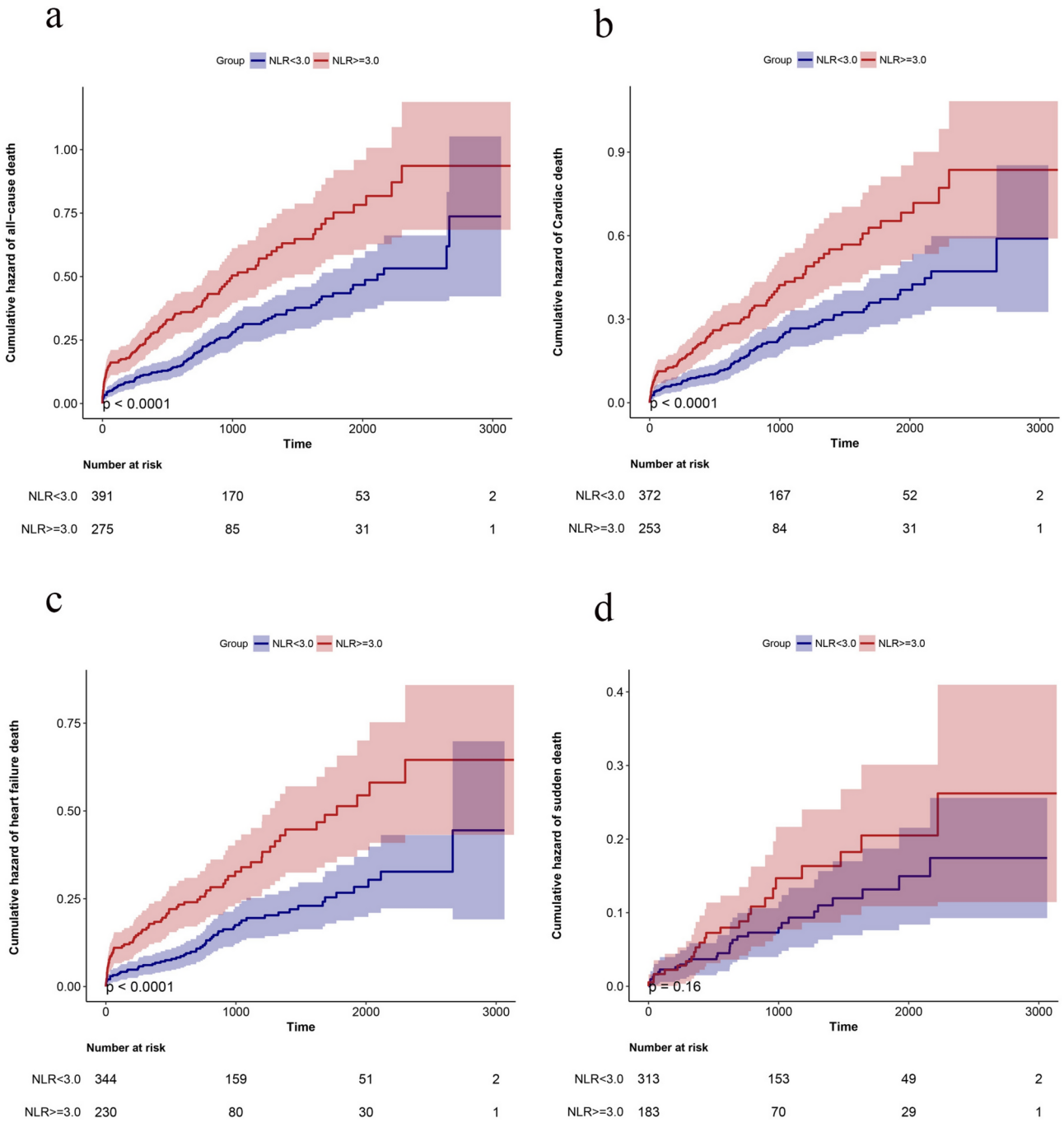

Fig. 3. The Kaplan–Meier curves for different outcomes based on the optimal cutoff values are presented. *Note:* The outcomes for the survival analysis are represented by "**a**", "**b**", "**c**", and "**d**", corresponding to all-cause death, cardiac death, heart failure death, and sudden death, respectively. The x-axis represents time, and the numbers below correspond to the number of patients. The y-axis represents the cumulative hazard for each outcome. Different colored lines represent different groups, and the shaded areas represent the 95% CIs.

Discussion

In this retrospective cohort study, we report, for the first time, the association between NLR and different causes of death in DCM patients. Our results demonstrate that NLR exhibits high accuracy in predicting adverse outcomes (including all-cause death, cardiac death, and heart failure death) in DCM patients. Furthermore, NLR is significantly positively correlated with the risk of these adverse outcomes. This

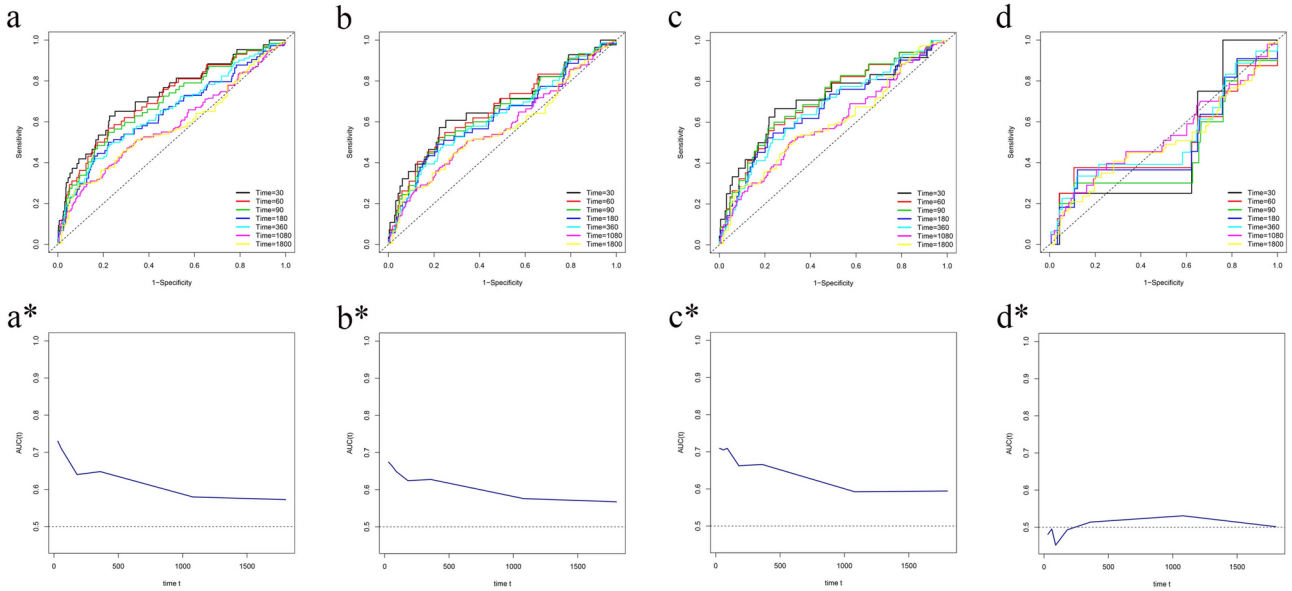

Fig. 4. The ROC curves depict the predictive accuracy of NLR for different outcomes. *Note:* The top row of the graph displays ROC curves at various time points. The labels '**a**', '**b**', '**c**', and '**d**' correspond to the four outcomes: all-cause death, cardiac death, heart failure death, and sudden death, respectively. The bottom row of the graph illustrates the temporal changes in the area under the curves for predicting the corresponding outcomes. The time units in the figures are expressed in days.

relationship remains stable even after adjusting for clinical confounders. These findings support the hypothesis that NLR can serve as a prognostic biomarker in DCM patients.

NLR, as a novel inflammatory biomarker, has been gaining increasing attention due to its affordability and accessibility. Multiple studies in recent years have demonstrated a close association between NLR and the severity as well as prognosis of various cardiovascular diseases[12–18], particularly in relation to heart failure[19–21]. Avci[22] et al. found a significant correlation between NLR and the grade of heart failure (NYHA), NT-proBNP levels, and various echocardiographic parameters, suggesting that higher NLR values are associated with more severe heart failure. Additionally, the study by Benites-Zapata[23] et al. revealed an elevated NLR to be associated with increased risk of death or cardiac transplantation in advanced heart failure patients. Durmus[24] et al. also demonstrated the predictive value of NLR for mortality during the follow-up period of heart failure patients. Dilated cardiomyopathy, being the most common cause of heart failure, also exhibits a positive correlation with NLR in terms of disease severity[22]. Building upon these findings, our study further explores the prognostic potential of NLR for different causes of death in a cohort of DCM patients. In this study, heart failure was the leading cause of death (129/221) among DCM patients, followed by sudden death (51/221). NLR demonstrated higher mean values in the adverse outcome group, particularly in the subgroups associated with inflammation and heart failure-related deaths. Moreover, higher NLR values were associated with worse prognosis. In the multivariable Cox regression analysis, increasing NLR was significantly associated with elevated risks of all-cause death, cardiac death, and heart failure death. This association persisted even after adjusting for covariates. Furthermore, NLR exhibited varying accuracy in predicting different death outcomes, with higher accuracy observed for predicting heart failure death. It is worth noting that NLR showed no association with sudden death and had no predictive value for this outcome, suggesting that the inflammatory mechanisms might not play a significant role in the occurrence of sudden death in DCM, and further exploration of the underlying mechanisms is needed. These results strongly indicate that the association between NLR and different causes of death in DCM patients is likely mediated through the reflection of the severity of heart failure. In other words, higher NLR values indicate poorer cardiac function and more severe disease in DCM patients, consequently increasing the risk of death.

Inflammation plays a crucial role in the occurrence and progression of DCM[25]. The mechanisms underlying the association between elevated NLR and adverse prognosis in DCM may involve the activation of inflammatory pathways, oxidative stress, and endothelial dysfunction, leading to myocardial injury and remodeling[26]. Regardless of genetic or environmental causes, myocardial damage triggers inflammation and recruits immune cells to the heart for myocardial repair[27]. Evidence of inflammatory cell infiltration is frequently found in myocardial biopsy samples of DCM patients[28]. Immune cells release cytokines, promoting remodeling, collagen deposition, and fibrosis[29,30]. Over time, fibrotic scar

	Univariate Cox regression		
Variables	***HR* (95*CI*)**	***P* (Wald's test)**	***P* (LR-test)**
Drinking history	1.05 (0.8, 1.37)	0.729	0.729
Smoking history	1.13 (0.87, 1.48)	0.351	0.352
Male	1.31 (0.94, 1.8)	0.106	**0.098**
Age	1.0091 (0.9988, 1.0196)	0.085	**0.083**
Medical history			**< 0.001**
< 1 year	1 (ref)		
1 ~ 5 years	1.63 (1.19, 2.23)	0.002	
≥ 5 years	2.58 (1.86, 3.59)	< 0.001	
Grade of heart failure (NYHA)			**< 0.001**
I	1 (ref)		
II	0.84 (0.35, 2.01)	0.692	
III	1.07 (0.47, 2.46)	0.867	
IV	1.71 (0.75, 3.89)	0.201	
Pulmonary arterial hypertension	1.39 (1.05, 1.84)	0.021	**0.019**
Atrial fibrillation	1.28 (0.94, 1.75)	0.123	0.131
Diabetes	1.48 (0.97, 2.24)	0.067	**0.081**
Hyperuricemia	1.4 (1.05, 1.87)	0.022	**0.02**
Hyperhomocysteinemia	1.23 (0.94, 1.61)	0.134	0.132
Hypoalbuminemia	1.52 (0.89, 2.62)	0.128	0.152
Renal insufficiency	1.77 (1.36, 2.31)	< 0.001	**< 0.001**
Liver function injury	2.39 (1.56, 3.65)	< 0.001	**< 0.001**
Mean arterial pressure	0.98 (0.97, 0.99)	< 0.001	**< 0.001**
NT-proBNP (≥ 1800 pg/ml)	2.7 (1.82, 4.02)	< 0.001	**< 0.001**
LVEF	0.98 (0.96, 0.99)	0.004	**0.004**
Beta blockers	0.64 (0.45, 0.9)	0.011	**0.015**
ACEI/ARB	0.43 (0.32, 0.59)	< 0.001	**< 0.001**
Diuretic	0.52 (0.21, 1.25)	0.144	0.186
ICD	0.998 (0.5439, 1.8312)	0.995	0.995

Table 2. The unadjusted association between baseline variables and all-cause death. Variables with a P value lessthan 0.1 are included in the adjustment and are shown in bold.

tissue eventually replaces the damaged tissue, further exacerbating dilation and the progression of heart failure. Additionally, as heart failure advances, patients often experience compromised immunity, making them more susceptible to infections, further burdening the heart and worsening the condition, leading to adverse outcomes. Therefore, heart failure and inflammation often intertwine and mutually reinforce each other. They constantly enhance each other, activating different pathological and physiological pathways, resulting in an increased neutrophil count and decreased lymphocyte count. Neutrophils and lymphocytes are crucial components of the immune system, and their imbalance reflects systemic inflammatory status. The calculation of NLR involves dividing the absolute neutrophil count by the absolute lymphocyte count, providing a simple and feasible measure for this imbalance. Thus, NLR becomes a potential indicator for assessing disease severity and prognosis. Increasing evidence supports the use of NLR as a marker of systemic inflammation and its potential prognostic value in cardiovascular diseases[31,32], and our study adds new evidence to this body of knowledge. However, it is important to note that we observed a decline in the predictive performance of NLR over time, suggesting that factors other than NLR may influence the long-term prognosis of DCM patients. Additionally, although the risk threshold of NLR are all close to 2.5 when considering all-cause death, cardiac death, or heart failure death as endpoints, the dose–response curves indicate that the relationship between NLR and different outcomes may vary, requiring further research to elucidate the underlying mechanisms.

The clinical significance of our study results deserves attention. By incorporating NLR into risk stratification models, clinicians may be able to identify DCM patients at higher risk of adverse outcomes and formulate more targeted and personalized management strategies. For example, closer monitoring, early initiation of guideline-directed medical therapy, and more frequent follow-ups to detect and manage complications in a timely manner could benefit patients with elevated NLR, particularly the elderly or high-risk groups with LVEF < 35%. Subgroup analyses revealed that the risk of adverse outcomes was higher in elderly patients and those with LVEF < 35% as NLR values increased. Despite achieving promising

Adverse events	n.total	n.event (%)	Followup time	Variable	*HR*[a] (95%*CI*)	*HR*[b] (95%*CI*)	*HR*[c] (95%*CI*)	*HR*[d] (95%*CI*)
All-cause death	666	221 (33.2)	651,608.0	NLR	1.07 (1.05 ~ 1.09)***	1.06 (1.04 ~ 1.09)***	1.04 (1.01 ~ 1.07)**	1.05 (1.02 ~ 1.08)**
				NLR^Z	1.29 (1.19 ~ 1.4)***	1.26 (1.16 ~ 1.38)***	1.18 (1.06 ~ 1.31)**	1.2 (1.07 ~ 1.35)**
				Log_2(NLR)	1.44 (1.26 ~ 1.65)***	1.35 (1.17 ~ 1.55)***	1.21 (1.04 ~ 1.41)*	1.19 (1.01 ~ 1.39)*
				ln(NLR)	1.7 (1.4 ~ 2.06)***	1.54 (1.26 ~ 1.89)***	1.32 (1.06 ~ 1.65)*	1.28 (1.02 ~ 1.61)*
Cardiac death	625[¶]	180 (28.8)	635,756.0	NLR	1.06 (1.04 ~ 1.09)***	1.05 (1.03 ~ 1.08)***	1.03 (1 ~ 1.07)*	1.04 (1 ~ 1.07)*
				NLR^Z	1.27 (1.15 ~ 1.4)***	1.23 (1.1 ~ 1.37)***	1.14 (1 ~ 1.3)*	1.15 (1.01 ~ 1.33)*
				Log_2(NLR)	1.41 (1.21 ~ 1.64)***	1.31 (1.12 ~ 1.54)**	1.19 (1 ~ 1.42)*	1.17 (0.98 ~ 1.4)
				ln(NLR)	1.64 (1.32 ~ 2.04)***	1.47 (1.17 ~ 1.86)**	1.29 (1 ~ 1.66)*	1.26 (0.98 ~ 1.63)
Heart failure death	574[Ψ]	129 (22.5)	601,415.0	NLR	1.07 (1.04 ~ 1.1)***	1.06 (1.03 ~ 1.09)***	1.04 (1.01 ~ 1.08)*	1.05 (1.01 ~ 1.09)*
				NLR^Z	1.28 (1.15 ~ 1.43)***	1.24 (1.11 ~ 1.4)***	1.18 (1.02 ~ 1.37)*	1.21 (1.04 ~ 1.41)*
				Log_2(NLR)	1.51 (1.27 ~ 1.8)***	1.4 (1.17 ~ 1.69)***	1.3 (1.06 ~ 1.59)*	1.29 (1.05 ~ 1.59)*
				ln(NLR)	1.82 (1.41 ~ 2.34)***	1.63 (1.25 ~ 2.13)***	1.46 (1.09 ~ 1.96)*	1.44 (1.07 ~ 1.95)*
Sudden death	496[£]	51 (10.3)	557,035.0	NLR	1.05 (0.99 ~ 1.11)	1.04 (0.98 ~ 1.11)	1 (0.93 ~ 1.08)	1 (0.92 ~ 1.08)
				NLR^Z	1.21 (0.97 ~ 1.51)	1.18 (0.91 ~ 1.52)	1.02 (0.77 ~ 1.35)	0.99 (0.73 ~ 1.33)
				Log_2(NLR)	1.21 (0.9 ~ 1.63)	1.14 (0.83 ~ 1.55)	0.99 (0.71 ~ 1.39)	0.97 (0.69 ~ 1.35)
				ln(NLR)	1.32 (0.86 ~ 2.03)	1.2 (0.76 ~ 1.89)	0.99 (0.62 ~ 1.6)	0.95 (0.59 ~ 1.55)

Table 3. Unadjusted and adjusted associations between NLR and adverse events. "*", $P < 0.05$; "**", $P < 0.01$; "***", $P < 0.001$; "Z", Z-Score standardization; "HR", Hazard Ratio; "CI", Confidence interval. **¶**: 41 patients were excluded (19 died of other causes and 22 died of unknown causes). **Ψ**: 92 patients were excluded (51 sudden deaths, 19 died of other causes and 22 died of unknown causes). **£**: 170 patients were excluded (129 died of heart failure, 19 died of other causes and 22 died of unknown causes). [a]Unadjusted. [b]Adjusted for age, gender, medical history. [c]Adjusted for b and pulmonary arterial hypertension, diabetes, hyperuricemia, renal insufficiency, liver function injury. [d]Adjusted for c and grade of heart failure (NYHA), mean arterial pressure, nt-probnp (> 1800 pg/ml), LVEF, beta blockers, ACEI/ARB.

results, we must acknowledge the limitations of our study. Firstly, as a retrospective cohort study, it inherently carries biases and unexplained potential confounders, such as missing data on the duration of treatment and the low use of CRT/ICD, which may have impacted the results. Secondly, since our study was conducted at a single center, the generalizability of the results to other ethnicities may be limited, warranting validation through multicenter data. Lastly, the sample size was relatively small, which may restrict the generalizability of our findings. Future prospective studies with larger sample sizes are needed to validate the prognostic value of NLR in DCM and explore its potential integration with other established risk markers. Notably, patients were not stratified by an explicit acute or stable phase in our study. Instead, heart failure severity was assessed using the NYHA classification and incorporated as a covariate in our analyses. Furthermore, to refine our evaluation of cardiac function, we adjusted for LVEF and NT-proBNP levels. This comprehensive approach strengthens the robustness and clinical relevance of our findings. In conclusion, this retrospective cohort study provides supportive evidence for the potential prognostic value of NLR in adverse outcomes of DCM. The association between elevated NLR and increased risk of adverse outcomes highlights its role as a valuable prognostic marker in this patient population. Further research is still required to confirm these findings and assess the clinical utility of NLR in guiding DCM treatment decisions and improving patient outcomes.

Conclusion

NLR is independently associated with adverse outcomes (all-cause death, cardiac death, and heart failure death) in DCM patients and has a high predictive value. Higher NLR values are associated with worse prognosis. When NLR exceeds 2.5, the risk of adverse outcomes increases with increasing NLR values. The use of NLR can aid clinicians in identifying high-risk patients at an early stage. The role of NLR in clinical monitoring warrants further investigation, especially as part of the comprehensive prognostic assessment in elderly patients and those with LVEF < 35%.

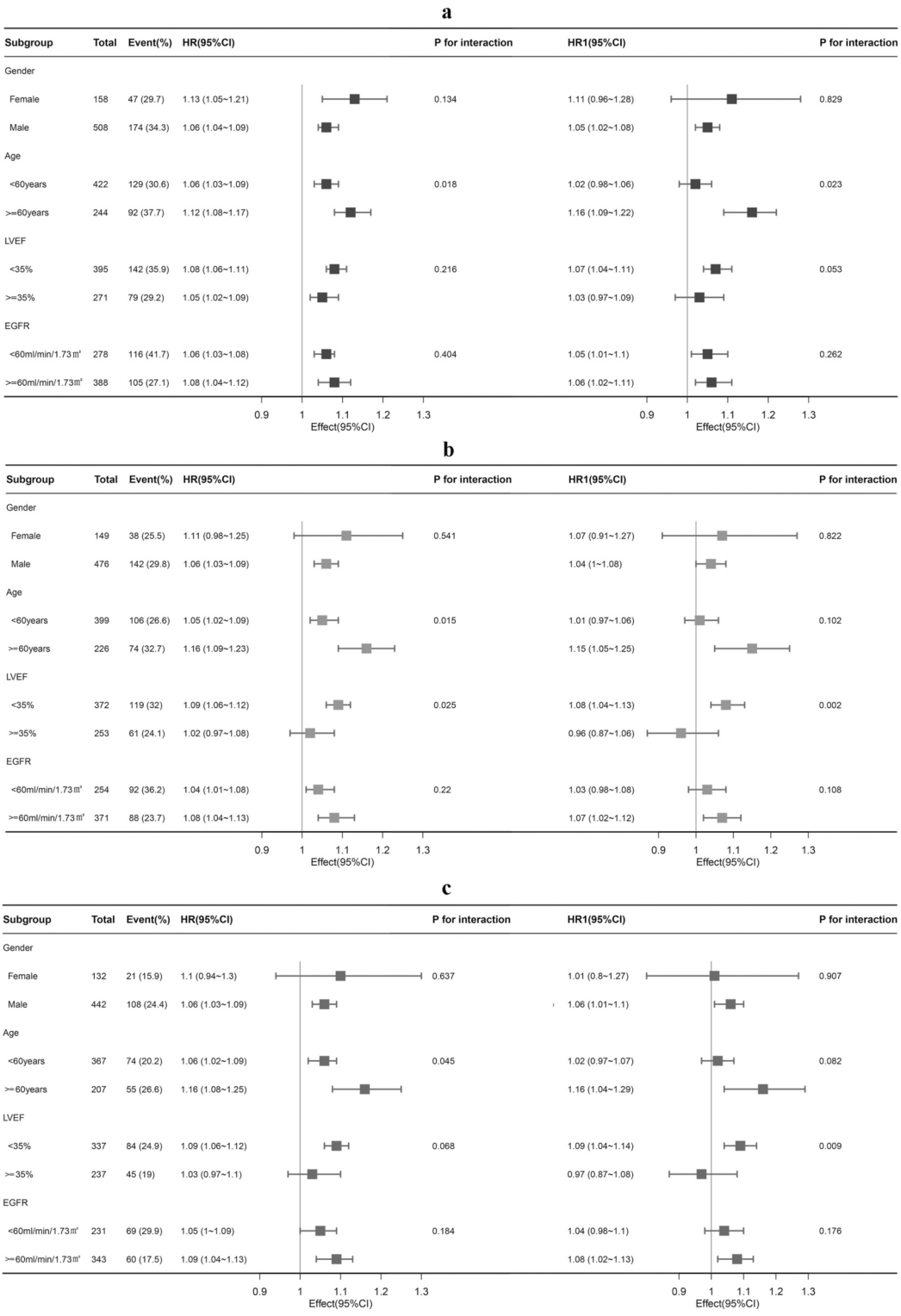

Fig. 5. The correlation between NLR and different outcomes within different subgroups. *Note:* '**a**', '**b**', and '**c**' respectively correspond to all-cause death, cardiac death, and heart failure death. HR represents the hazard ratio in the unadjusted model, while HR1 represents the hazard ratio in the fully adjusted model.

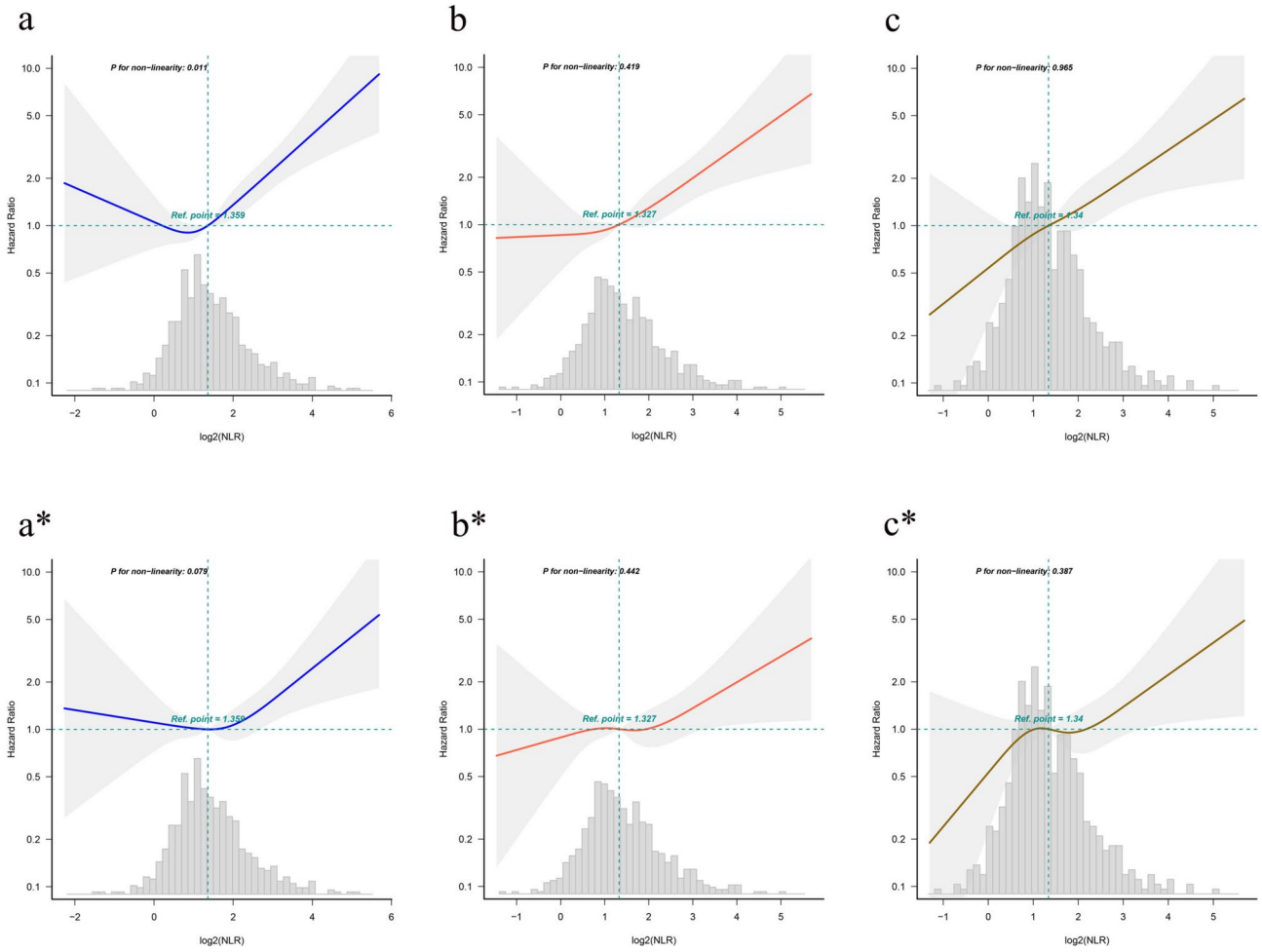

Fig. 6. The dose–response relationship between $\log_2$ (NLR) and different outcomes. *Note:* '**a**', '**b**', and '**c**' respectively correspond to all-cause death, cardiac death, and heart failure death. The symbol '*' represents the full adjustment for covariates.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Received: 4 June 2024; Accepted: 13 March 2025
Published online: 25 March 2025

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Author contributions

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Funding

This work was supported by Innovative Research Team Project of Guangxi Natural Science Foundation (Grant No. 2018GXNSFGA281006) and Guangxi Natural Science Foundation Project (Grant No. 2020GXNSFDA297014).

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The study was conducted following the Declaration of Helsinki (as revised in 2013), and approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University. Written informed consent was waived by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University because of the retrospective nature of this study.

Additional information

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