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ORIGINAL ARTICLE

Prognostic value of neutrophil-to-lymphocyte ratio in predicting long-term mortality in patients with ischemic and nonischemic heart failure

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KEY WORDS

heart failure, long-term mortality, neutrophil-to--lymphocyte ratio

ABSTRACT

INTRODUCTION Previous studies have shown that an elevated neutrophil-to-lymphocyte ratio (NLR) was associated with a poorer long-term prognosis in patients with heart failure (HF).

OBJECTIVES We aimed to study the predictive value of the NLR in patients with left ventricular ejection fraction of 35% or lower. The second objective was to establish whether the NLR has the same prognostic value in patients with ischemic and nonischemic HF.

PATIENTS AND METHODS The study group consisted of a cohort of patients with HF (1387 men, 347 women; median age, 61 years) from the prospective COMMIT-HF registry. The primary endpoint was all-cause mortality. Patients were divided into tertiles based on the NLR values on admission. The first (low), second (medium), and third (high) tertiles were defined as NLR ≤2.04 (n = 578), NLR 2.05–3.1 (n = 578) and NLR >3.1 (n = 578), respectively.

RESULTS During long-term follow-up, 443 deaths were reported. The 12-month mortality in patients in the third NLR tertile was almost 3-fold higher compared with those in the first tertile (7.61% vs 20.07%; P <0.001). In a multivariate analysis, the NLR was an independent factor of mortality (hazard ratio [HR], 2.31; 95% confidence interval [CI], 1.82–2.92; P <0.0001). In addition, the multivariate analysis revealed that the third NLR tertile in the ischemic HF group was an independent factor related to long-term mortality (HR, 1.51; 95% CI, 1.11–2.04; P = 0.008). In the nonischemic HF group, the influence of the NLR on long-term survival was not confirmed.

CONCLUSIONS The association between the NLR and the risk of death in long-term follow-up was confirmed only in the subgroup of patients with ischemic HF.

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INTRODUCTION The use of laboratory biomarkers is becoming increasingly popular as a new approach to risk stratification in patients with various cardiovascular diseases.[1,2] The neutrophil-to--lymphocyte ratio (NLR) is a new addition to the list of these systemic inflammatory markers and has been proposed as a risk stratification index, beyond those provided by conventional risk scores for predicting long-term mortality in patients with cardiovascular diseases.[3-14] In patients with advanced heart failure (HF), an elevated NLR is a negative prognostic marker of short- and long--term mortality.[15,16] However, data regarding the prognostic value of the NLR among patients with ischemic or nonischemic HF are lacking.

The present study was undertaken to investigate the relation between the NLR on admission and long-term all-cause mortality in a large cohort of patients with a left ventricular ejection fraction (LVEF) of 35% or lower. The second objective was to establish whether the NLR has the same prognostic value in patients with ischemic and nonischemic HF.

PATIENTS AND METHODS The cohort analyzed in this study was a subset of the population from the prospective Contemporary Modalities in Treatment of Heart Failure registry (COMMIT-HF, ClinicalTrials.gov Identifier: NCT02536443), which is currently ongoing at the 3rd Department of Cardiology of the Silesian Center for Heart Diseases in Zabrze, Poland. The COMMIT-HF is a registry of a broad, unselected patient population admitted to our institution, with a LVEF of 35% or lower, with the exclusion of patients with acute coronary syndromes. The baseline characteristics of patients and in-hospital data were recorded on case report forms. In this database, information on demographic data, concomitant diseases, and laboratory parameters, such as neutrophil and leukocyte counts, are stored. All patients underwent LVEF assessment in the first 24 hours of admission. Patients with medical conditions or treatments known to affect the white blood cell count, such as disorders of the hematopoietic system, cancer, chronic or acute infection, and glucocorticoid therapy, were excluded from the study. We analyzed a total of 1734 consecutive patients who had been treated at our institution between January 2009 and December 2013.

There is still no consensus on the cut-off points to define the levels of the NLR[17]; therefore, patients were divided into tertiles based on admission NLR values. The first (low), second (medium), and third (high) tertiles were defined as NLR ≤2.04 (n = 578), NLR 2.05–3.1 (n = 578), and NLR >3.1 (n = 578), respectively. A survival analysis, stratified by the NLR tertile, was used to evaluate the predictive value of the NLR in the whole cohort and separately for patients with ischemic and nonischemic HF. The ischemic etiology of HF was established in patients with a history of myocardial infarction, percutaneous coronary interventions, coronary artery bypass grafting, or with multi-vessel coronary artery disease diagnosed by means of coronary angiography in the absence of concomitant underlying causes of HF. The study was approved by an institutional review board at the Regional Medical Chamber.

Leukocyte and neutrophil counts were determined using an automated Sysmex XS1000i hematology analyser (Sysmex Corporation, Kobe, Japan). The NLR was calculated as the ratio of neutrophil cell count to lymphocyte cell count, obtained from blood samples drawn in fasting state.

Information on survival was based on the National Health Fund insurance status, which can be electronically verified as the National Health Fund insurance policy that is obligatory for all Polish citizens. Insured patients were marked as alive. Complete follow-up data were available for the whole study cohort.

Statistical analysis Continuous variables were described as mean and standard deviation or median with interquartile range. Categorical variables were expressed as frequencies and percentages. The assumption of normality for continuous variables was verified by the Shapiro–Wilk test. Continuous variables were compared across the NLR tertiles with the analysis of variance or the Kruskal–Wallis test, which are appropriate for categorical variables, and were compared with the χ^2 test.

The Kaplan–Meier method with log-rank testing was used to compare survival probability between the NLR tertiles. Univariate and multivariate Cox regression models were used to evaluate the association between the NLR tertiles and mortality. The stepwise selection method of model building was used, with a P value set to 0.2 to allow a confounder into the model, and a P value set to 0.1 for a confounder to stay in the model. Crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were presented. The interpretation of statistical significance was based on an α value of 0.05. Statistical analyses were performed using the SAS statistical software package, version 9.4 (SAS Institute Inc., Cary, North Carolina, United States) and the STATISTICA 10 software (StarSoft Inc., Tulsa, Oklahoma, United States).

RESULTS The study sample consisted of a cohort of 1734 patients with systolic HF (1387 men), with a median age of 61 years (interquartile range, 53–71 years). The baseline characteristics of patients across the NLR tertiles are listed in **TABLE 1**.

The ischemic etiology of HF was diagnosed in about 65% of patients across the NLR tertiles. There was a stepwise relationship between NLR intervals and comorbidities in the whole group. Patients in the highest NLR tertile were significantly older and more often had diabetes, anemia, atrial fibrillation, and at least stage III of chronic kidney disease. They also had a higher New York Heart Association functional class on admission, lower LVEF and left ventricular end-diastolic volume, and more often had significant valvular disease compared with patients in the low NLR tertile.

Laboratory findings revealed a stepwise relationship between hemoglobin concentrations, white blood cell count, bilirubin, blood urea nitrogen, creatinine, uric acid, and N-terminal pro-B-type natriuretic peptide. According to admission laboratory status, patients in the third NLR tertile had significantly lower hemoglobin levels, higher white blood cell count, bilirubin, blood urea nitrogen, creatinine, and uric acid values when compared with patients in the first tertile.

There were some significant differences between the NLR tertile subgroups in the prescribed treatment at hospital discharge. Patients in the

TABLE 1 Baseline characteristics of patients classified according to neutrophil-to-lymphocyte ratio (NLR)

Clinical characteristics		Low tertile (n = 578)	Medium tertile (n = 578)	High tertile (n = 578)	*P* value
age, y		59.7 ±12.5	61.2 ±12.7	61.6 ±12.9	0.02
women		115 (19.9)	104 (18.0)	128 (22.2)	0.2
diabetes mellitus		235 (40.6)	218 (37.7)	262 (45.3)	0.03
hypertension		306 (53.0)	294 (50.9)	291 (50.3)	0.6
hyperlipidemia		253 (43.7)	212 (36.6)	224 (38.7)	0.04
anemia		173 (30.0)	202 (34.9)	251 (43.4)	<0.001
previous myocardial infarction		276 (47.7)	261 (45.1)	286 (49.4)	0.3
previous percutaneous coronary intervention		267 (46.3)	261 (45.1)	264 (45.6)	0.7
previous coronary artery bypass grafting		136 (23.5)	133 (23.0)	125 (21.6)	0.8
previous stroke		36 (6.3)	41 (7.1)	38 (6.2)	0.8
chronic kidney disease stage III–V		122 (21.1)	169 (29.2)	211 (36.5)	<0.001
atrial fibrillation		189 (32.7)	172 (29.7)	216 (37.3)	0.02
NYHA class on admission	I	123 (21.3)	85 (14.7)	102 (17.6)	0.016
	II	246 (42.6)	253 (43.8)	195 (33.7)	<0.001
	III	183 (31.7)	187 (32.4)	194 (33.6)	0.78
	IV	26 (4.4)	53 (9.1)	87 (15.1)	<0.001
systolic blood pressure, mmHg		123.2 ±19.9	124.1 ±74.1	126.8 ±74.1	0.4
diastolic blood pressure, mmHg		76.2 ±12.1	75.9 ±13.6	76.7 ±14.3	0.6
heart rate, bpm		76.8 ±17.8	77.9 ±16.7	83.8 ±44.9	<0.001
laboratory tests	NLR	1.54 (1.28–1.79)	2.47 (2.27–2.78)	4.42 (3.58–6.31)	<0.001
	hemoglobin, g/dl	8.7 ±1.1	8.6 ±1.1	8.3 ±1.2	<0.001
	WBC count, ×1000/µl	7.0 ±1.9	7.7 ±4.5	8.8 ±3.1	<0.001
	bilirubin, µmol/l	14.3 ±8.9	15.2 ±15.1	18.7 ±15.8	<0.001
	blood urea nitrogen, mmol/l	3.14 ±2.04	3.21 ±1.75	4.21 ±2.61	<0.001
	creatinine, µmol/l	93.9 ±37.6	101.1 ±61.7	111.4 ±72.6	<0.001
	NT-proBNP, pg/ml	1004.0 (575.1–2889.0)	1792.0 (770.2–4632.5)	2796.0 (1382.0–6251.0)	<0.01
	cholesterol, mmol/l	4.6 ±1.4	4.5 ±1.3	4.5 ±3.0	0.7
	uric acid, mmol/l	425.9 ±124.0	436.4 ±121.6	450.4 ±149.6	0.02
treatment	antiplatelet drugs	413 (71.4)	407 (70.4)	395 (68.3)	0.5
	oral anticoagulants	180 (31.2)	197 (34.0)	19 (37.8)	0.06
	digoxin	131 (22.6)	121 (20.9)	154 (26.7)	0.06
	diuretics (loop and thiazide)	480 (83.1)	485 (83.9)	497 (86.0)	0.4
	spironolactone/eplerenone	492 (85.1)	493 (85.3)	463 (80.1)	0.05
	statins	452 (78.2)	431 (74.6)	412 (71.2)	0.02
	ACEI/ARB	479 (82.8)	487 (84.2)	420 (72.6)	<0.001
	β-blockers	559 (96.7)	551 (95.3)	533 (92.3)	0.02
	calcium-channel blockers	44 (7.5)	45 (7.8)	51 (8.9)	0.6
	insulin	71 (12.2)	79 (13.6)	112 (19.3)	0.002
etiology of heart failure	ischemic	385 (66.4)	362 (62.6)	379 (65.5)	0.4
	valvular	37 (6.4)	59 (10.2)	60 (10.4)	0.01
	other	157 (27.2)	157 (27.2)	139 (24.1)	0.4
LVEF, %		26.8 ±5.8	26.0 ±5.8	25.1 ±6.5	<0.001
LV end-systolic diameter, mm		52.6 ±10.0	52.9 ±11.2	52.9 ±10.9	0.4
LV end-diastolic diameter, mm		64.8 ±8.7	65.5 ±9.6	64.7 ±9.6	0.9
LV end-systolic volume, ml		153 ±68	158 ±81	147 ±68	0.1
LV end-diastolic volume, ml		204 ±79	211 ±98	195 ±78	0.04
severe mitral insufficiency		64 (11.1)	72 (12.5)	96 (16.6)	0.01
severe aortic valve insufficiency/stenosis		17 (2.9)	36 (6.2)	44 (7.6)	0.001
all-cause 12-month mortality		44 (7.6)	56 (9.7)	116 (20.0)	<0.001

Continuous variables are presented as median (interquartile range) or mean ± standard deviation. Dichotomic variables are presented as number (percentage) of patients.
Abbreviations: ACEI, angiotensin-converting-enzyme inhibitors; ARB, angiotensin II receptor blockers; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; WBC, white blood cell

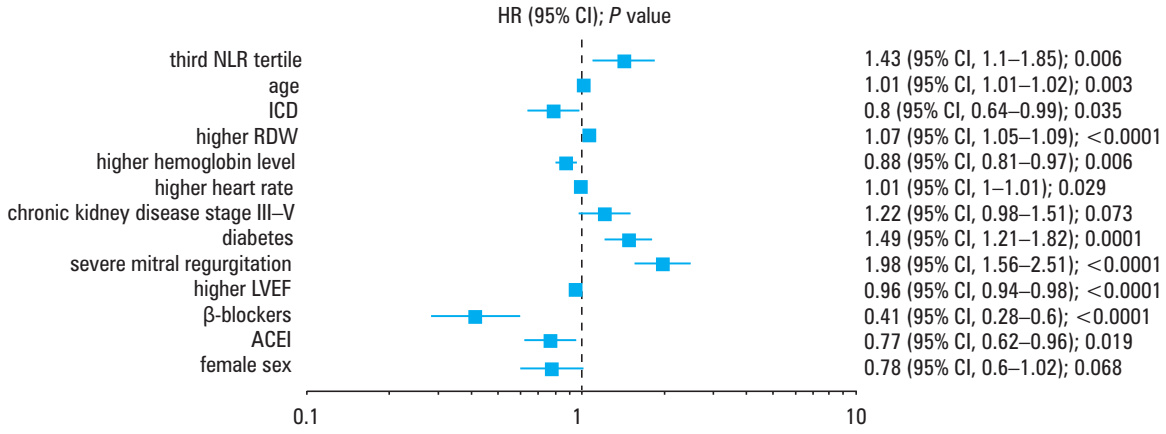

FIGURE 1 Predictors of mortality in the whole study group

Abbreviations: CI, confidence interval; HR, hazard ratio; ICD, implantable-cardioverter defibrillator; RDW, red cell distribution width; others, see **TABLE 1**

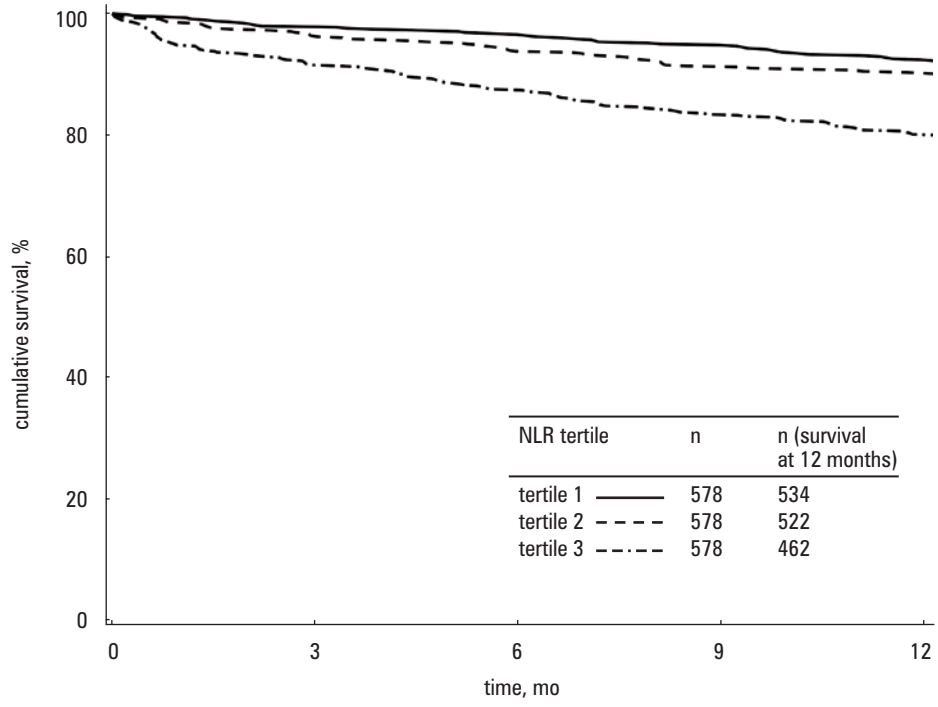

FIGURE 2 Kaplan–Meier curves comparing 12-month survival across neutrophil-to-lymphocyte ratio (NLR) tertiles in the whole study group

third tertile, compared with those in the first tertile, were less frequently treated with statins, β-blockers, aldosterone blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor antagonists. Patients in the highest tertile were more often on insulin therapy.

Follow-up data were available for the whole cohort. A median follow-up duration was 660 days (interquartile range, 331–1074 days). The primary endpoint was all-cause mortality. During the follow-up period, 443 deaths were reported. There was an almost 3-fold increase in all-cause 12-month mortality in the group of patients with NLR values within the third tertile compared with those in the first tertile (7.61% vs 20.07%; P <0.001).

The HR of the long-term all-cause mortality was significant both in the second (HR, 1.37; 95% CI, 1.06–1.77; P = 0.014) and the third NLR tertile (HR, 2.31; 95% CI, 1.82–2.92; P <0.0001). The Cox regression analysis revealed that in the whole study population, the third NLR tertile was an independent factor related to higher long-term mortality (HR, 1.43; 95% CI, 1.10–1.85; P = 0.006), along with older age, higher heart rate on admission, diabetes, chronic kidney disease, severe mitral insufficiency, and higher red cell distribution width (RDW) value. Higher LVEF, as well as administration of angiotensin-converting enzyme inhibitors and β-blockers were shown to improve survival (**FIGURE 1**). **FIGURE 2** shows the Kaplan–Meier curves for the overall survival in months across the NLR tertiles in the whole study group.

The Kaplan–Meier analysis of the subpopulation with ischemic HF revealed significant differences in survival between the NLR tertiles, as shown in **FIGURE 3**. This was also reflected in the multivariate analysis, where the third NLR tertile was an independent factor related to higher

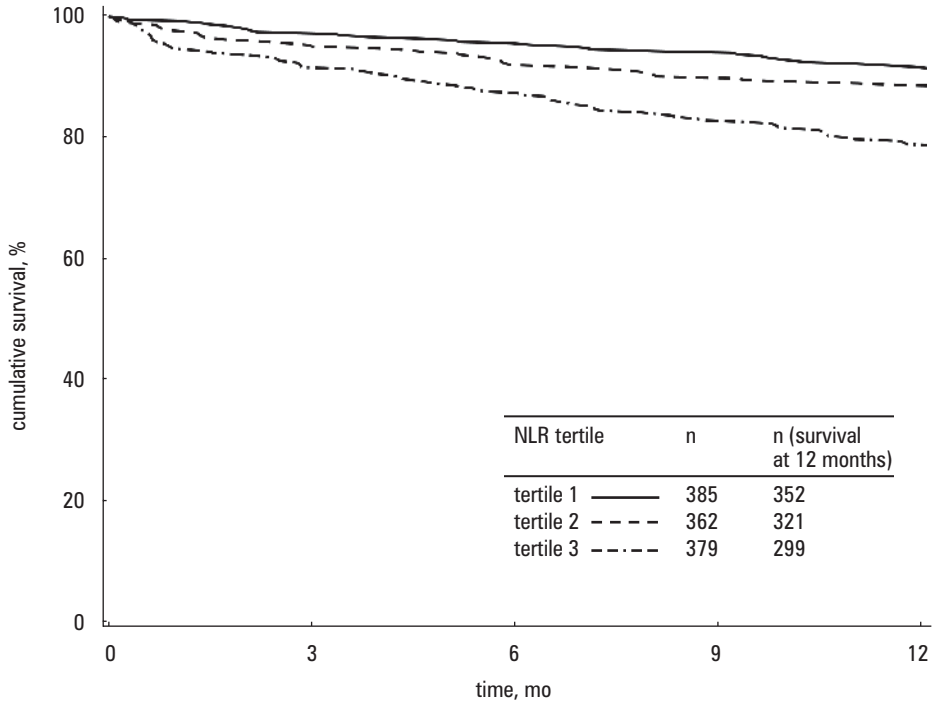

FIGURE 3 Kaplan–Meier curves comparing 12-month survival across neutrophil-to-lymphocyte ratio (NLR) tertiles in the subpopulation of patients with ischemic heart failure

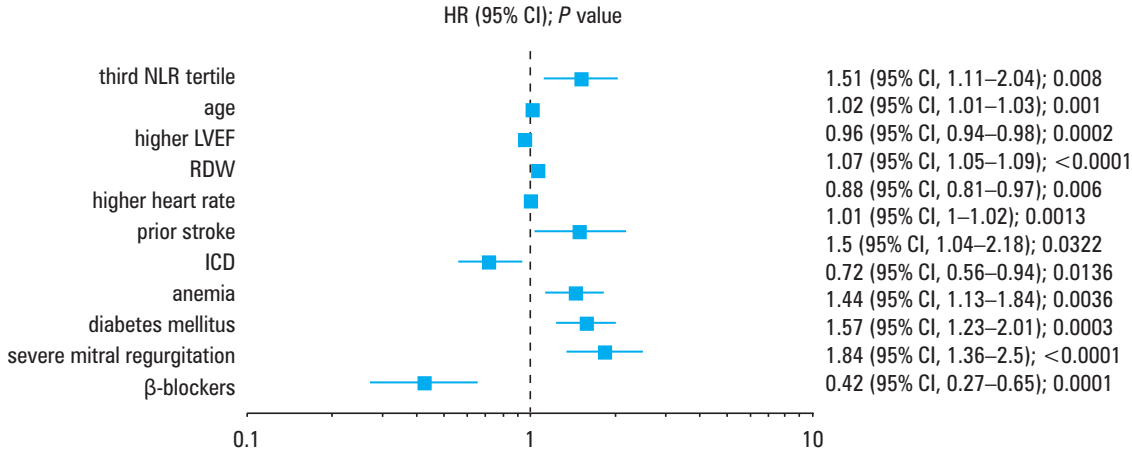

FIGURE 4 Predictors of mortality in the subpopulation of patients with ischemic heart failure. Abbreviations: see **TABLE 1** and **FIGURE 1**.

long-term mortality (HR, 1.51; 95% CI, 1.11–2.04; $P = 0.008$; **FIGURE 4**).

In the nonischemic HF group, the Kaplan–Meier analysis also revealed significant differences in survival between the NLR tertiles (**FIGURE 5**); however, the influence of the NLR on long-term survival was not confirmed after adjusting for prognostic covariates with multivariable Cox proportional models (**FIGURE 6**). In this population, the factors that independently impaired long-term survival were the presence of severe mitral insufficiency, severe aortic valve disease, diabetes mellitus, and higher RDW value. Higher LVEF and β-blocker administration were identified to have protective effect.

DISCUSSION There were 2 major findings of this study regarding patients with LVEF of 35% or lower. First, in the whole study population there was an almost 3-fold increase in mortality during 12-month follow-up among patients with NLR values within the third tertile compared with the first tertile (7.61% vs 20.07%, $P < 0.001$). Second, the high NLR tertile was associated independently with an increased risk of long-term all--cause mortality only in the subpopulation of patients with LVEF of 35% or lower with ischemic etiology, whereas in participants with nonischemic HF, after adjusting for potential confounding factors, there was no independent relation between the NLR tertile and mortality. In this subpopulation, the only factors independently impairing 12-month survival were severe mitral insufficiency, severe aortic valve disease, diabetes mellitus, and higher RDW value.

The NLR calculated on the basis of a complete blood count with differential test results is an inexpensive and easily obtainable marker of inflammation. Numerous studies have demonstrated that an increased neutrophil count might reflect inflammation and that lymphopenia is an indicator of physiologic stress. Both parameters

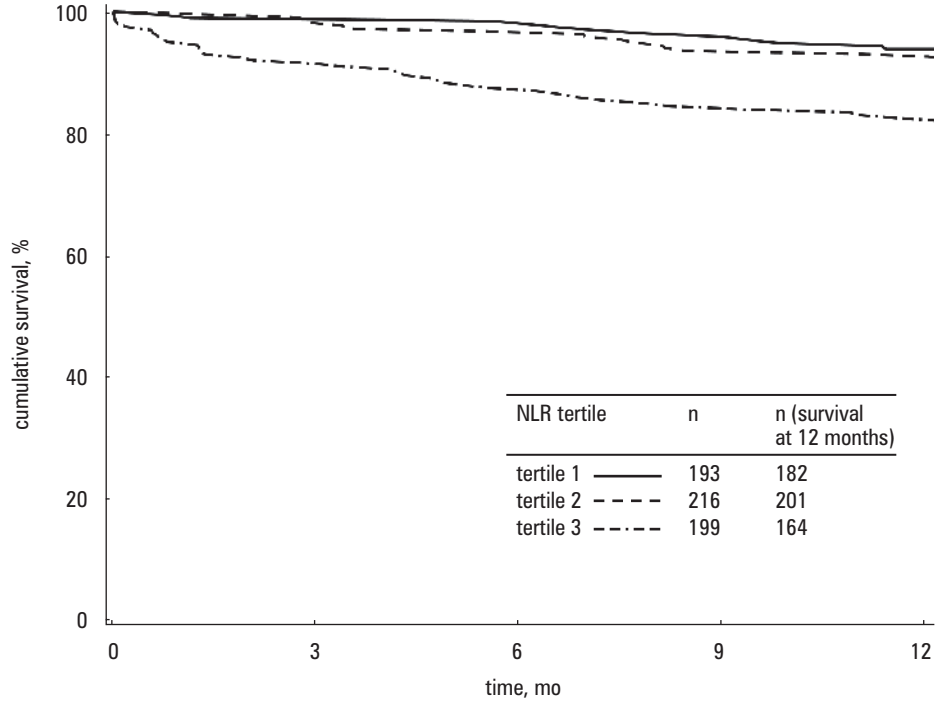

FIGURE 5 Kaplan–Meier curves comparing 12-month survival across neutrophil-to-lymphocyte ratio (NLR) tertiles in the subpopulation of subjects with nonischemic heart failure

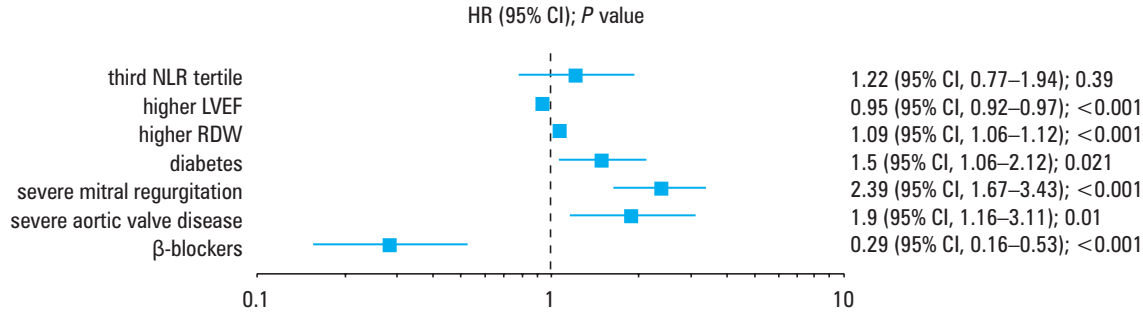

FIGURE 6 Predictors of mortality in the group of patients with non-ischemic heart failure. Abbreviations: see **TABLE 1** and **FIGURE 1**.

have been associated with poor outcomes in patients with cardiovascular disease. However, the NLR has been shown to predict mortality more accurately than other absolute neutrophil or lymphocyte counts.[18-22]

The post hoc analysis of the National Health and Nutrition Examination Survey-III (1988–1994), including subjects without coronary heart disease, revealed that the NLR can independently predict cardiovascular mortality in an asymptomatic general population.[23] The NLR has been analyzed in numerous studies. It has been associated with poor clinical outcome in various cardiac diseases, including stable coronary artery disease as well as acute coronary syndromes.[24,25] A meta-analysis of 10 cohort studies provided evidence that the NLR is a negative predictor of all-cause mortality in patients undergoing coronary angiography or invasive revascularization, including coronary artery bypass grafting.[26,27] These unfavorable outcomes in patients with coronary artery disease can be attributed to observations indicating that the ratio is an independent predictor of both the extent and the complexity of coronary artery disease graded by the SYNTAX and Gensini scores.[28-33] Additionally, the presence of arterial stiffness and coronary calcium score affect long-term prognosis.[34] Therefore, we hypothesize that low-grade systemic inflammation may affect the outcome of patients with HF through acceleration of coronary artery disease, but not through direct progressive myocardial injury from inflammatory mediators.[5-7] However, this particular issue was out of scope of the study, and further research is required in this field.

Earlier studies have shown that in patients with advanced decompensated HF, an elevated NLR is associated with increased long-term risk of mortality; however, those studies did not analyze HF etiology.[16,17] In a retrospective analysis of the Studies Of Left Ventricular Dysfunction (SOLVD), an increased risk of death was associated with elevated white blood cell count, but the relationship was limited only to participants with cardiomyopathy of ischemic origin.[35]

Our study extends the results of the previous reports. To the best of our knowledge, this is the first study to comprehensively assess the relation between the NLR and long-term prognosis in patients with ischemic and nonischemic HF. In

conclusion, we found that the NLR measured on admission may provide valuable information on risk stratification in patients with a LVEF of 35% or lower in a subgroup of patients with ischemic HF. In our large cohort of patients, the NLR was an independent long-term prognostic risk factor.

Study limitations This study has several limitations. It was a single-center observational study derived from a real-world practice. We used a single blood sample to calculate the NLR and included all-cause mortality as our endpoint. Nonetheless, potential disadvantages of the retrospective analysis are diminished by the fact that patients' data were input into a computer database by the attending physician upon the patient's admission to our center. Strengths of this study include a large patient cohort, detailed data on clinical, echocardiographic, and laboratory parameters, as well as a long follow-up period. Considering the retrospective character of our analysis, the results should be regarded as hypothesis-generating and need to be confirmed in prospective trials.

Contribution statement JW, ŁP, and MG conceived the concept of the study. JW and ŁP contributed to the design of the research. MH, TO, AK, MS, JN, and PD analyzed the data. ZK, MB, and MK were involved in data collection. All authors edited and approved the final version of the manuscript.

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ARTYKUŁ ORYGINALNY

Rola prognostyczna wskaźnika stosunku ilości neutrofilów do limfocytów w rokowaniu długoterminowym u pacjentów z niewydolnością serca o etiologii niedokrwiennej i nie-niedokrwiennej

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SŁOWA KLUCZOWE

niewydolność serca, stosunek ilości neutrofilów do ilości limfocytów, śmiertelność długoterminowa

STRESZCZENIE

WPROWADZENIE Wcześniejsze badania wykazały, że podwyższone wartości wskaźnika stosunku ilości neutrofilów do limfocytów (*neutrophil-to-lymphocyte ratio* – NLR) wiązały się z gorszym rokowaniem długoterminowym u pacjentów z niewydolnością serca (*heart failure* – HF).

CELE Celem badania była ocena wartości prognostycznej NLR u pacjentów z frakcją wyrzutową lewej komory ≤35%. Drugim celem było zbadanie, czy NLR ma taką samą wartość predykcyjną w podgrupach pacjentów z HF o etiologii niedokrwiennej i nie-niedokrwiennej.

PACJENCI I METODY Grupa badana składała się z pacjentów z HF (1387 mężczyzn i 347 kobiet, średni wiek 61 lat) włączonych do prospektywnego rejestru COMMIT-HF. Jako pierwszorzędowy punkt końcowy przyjęto zgon ze wszystkich przyczyn. Pacjentów podzielono na tertyle w zależności od wartości NLR przy przyjęciu. Pierwszy (niski), drugi (średni) i trzeci (wysoki) tertyl zdefiniowano odpowiednio jako NLR ≤2,04 (n = 578), NLR 2,05–3,1 (n = 578) i NLR >3,1 (n = 578).

WYNIKI W obserwacji odległej zanotowano 443 zgony. Śmiertelność 12-miesięczna pacjentów w trzecim tertylu wartości NLR była prawie 3-krotnie większa niż w pierwszym tertylu (7,61% *vs* 20,07%, p <0,001). W analizie wieloczynnikowej NLR był niezależnym czynnikiem ryzyka zgonu (HR = 2,31; 95% CI 1,82–2,92; p <0,0001). Ponadto analiza wieloczynnikowa wykazała, że w podgrupie pacjentów z HF o etiologii nie-dokrwiennej trzeci tertyl wartości NLR był niezależnym czynnikiem ryzyka zgonu w obserwacji odległej (HR = 1,51; 95% CI 1,11–2,04; p = 0.008). W podgrupie pacjentów z HF o etiologii nie-niedokrwiennej związek pomiędzy NLR a śmiertelnością nie został potwierdzony.

WNIOSKI Związek pomiędzy NLR a ryzykiem zgonu w obserwacji odległej został potwierdzony tylko w podgrupie pacjentów z HF o etiologii niedokrwiennej.

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