

The neutrophil to lymphocyte ratio in heart failure: a comprehensive review

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Introduction. Heart failure (HF) and systemic inflammation are interdependent processes that continuously potentiate each other. Distinct pathophysiological pathways are activated, resulting in increased neutrophil count and reduced lymphocyte numbers, making the neutrophil to lymphocyte ratio (NLR) a potential indirect marker of severity. We conducted this comprehensive review to characterize the role of NLR in HF.

Methods. We searched the PubMed (MEDLINE) database using the key words “neutrophil”, “lymphocyte”, “heart failure”, “cardiomyopathy”, “implantable cardioverter defibrillator”, “cardiac resynchronization therapy” and “heart transplant”.

Results. We identified 241 publications. 31 were selected for this review, including 12,107 patients. NLR was correlated to HF severity expressed by clinical, biological, and imaging parameters, as well as to short and long-term prognosis. Most studies reported its survival predictive value. Elevated NLR (>2.1–7.6) was an independent predictor of in-hospital mortality [adjusted HR 1.13 (95% CI 1.01–1.27) – 2.8 (95% CI 1.43–5.53)] as well as long-term all-cause mortality [adjusted HR 1.43 (95% CI 1.1–1.85) – 2.403 (95% CI 1.076–5.704)].

Higher NLR levels also predicted poor functional capacity [NLR > 2.26/2.74, HR 3.93 (95% CI 1.02–15.12) / 3.085 (95% CI 1.52–6.26)], hospital readmissions [NLR > 2.9/7.6, HR 1.46 (95% CI 1.10–1.93) / 3.46 (95% CI 2.11–5.68)] cardiac resynchronization therapy efficacy [NLR > 3.45/unit increase, HR 12.22 (95% CI 2.16–69.05) / 1.51 (95% CI 1.01–2.24)] and appropriate implantable cardioverter defibrillator shocks (NLR > 2.93), as well as mortality after left ventricular assist device implantation [NLR > 4.4 / quartiles, HR 1.67 (95% CI 1.03–2.70) / 1.22 (95% CI 1.01–1.47)] or heart transplant (NLR > 2.41, HR 3.403 (95% CI 1.04–11.14)].

Conclusion. Increased NLR in HF patients can be a valuable auxiliary biomarker of severity, and most of all, of poor prognosis.

Key words: neutrophil to lymphocyte ratio, NLR, heart failure, cardiomyopathy, survival prognosis.

INTRODUCTION

Heart failure (HF) and systemic inflammation are two interlinked, continuously evolving, and coexisting processes that constantly emphasize each other [1,2]. The initial cytokine hypothesis postulated that endogenous cytokines induce HF progression [3]. However, more and more data support the reverse theory as well, proving that HF induces inflammation in both the myocardium itself as well as other tissues and organs [4]. Regardless of the HF substrate, its multiple possible etiologies or its coinciding risk factors, inflammation parameters are related to HF prognosis, with worst outcomes in patients with more prevalent and higher expression of inflammatory biomarkers [5].

HF and inflammation influence the leukocyte homeostasis. Neutrophils are highly susceptible to inflammation not only in infection, but also in heart failure, where an increased lifespan was observed due to delayed apoptosis [6]. Modulating signaling pathways by myeloperoxidase release, for example, they lead to tissue and endothelial damage, contributing to myocardial remodeling [7]. Neutrophilia was therefore independently associated to heart failure severity and prognosis [8, 9].

Systemic release of cytokines induced either by the severity of congestion or by episodes of acute decompensation may lead to lymphocyte apoptosis, while higher levels of cortisol and catecholamines secondary to physiological stress may also play an important part in the lymphocytes' number and

function [10, 11]. Considered another marker of inflammation and severity in HF, lymphopenia was also independently correlated to poor NYHA class [12] and mortality [13, 14].

Consequently, integrating different yet interdependent immune pathways, the neutrophil to lymphocyte ratio (NLR) was independently correlated to prognosis in various cardiovascular diseases [15], predominantly ischemic heart disease [16], but also arrhythmias [17], valvular disease [18] and heart failure [18].

The purpose of this review was to assess the utility of NLR in HF patients.

MATERIAL AND METHODS

Search strategy

We initially searched the PubMed database from its launch to February 1st 2019 using the key words “neutrophil”, “lymphocyte”, “heart failure”, “cardiomyopathy”, “implantable cardioverter defibrillator”, “cardiac resynchronization therapy” and “heart transplant”. A second search was conducted on May 1st 2019 using the same strategy and these results were considered final. The strategy is detailed in Table 2 Supplemental material.

Only articles written in English were evaluated.

References of all included studies as well as excluded reviews or letters to the editor were screened for inclusion.

Two authors independently reviewed the articles obtained from the literature search and selected the ones to be included in the analysis. In case of disagreement, a third author decided the inclusion or exclusion of articles.

Inclusion criteria

Types of studies

Prospective as well as retrospective observational or descriptive studies that analyzed the neutrophil lymphocyte ratio in adult heart failure patients were evaluated.

Types of participants

In order to be considered for the review, the studies had to have a clear description of the

selected study sample and to mention that the patients had heart failure.

We applied no restriction regarding sample size, study duration, or interventions administered to the patients.

Exclusion criteria

Case reports, reviews, and letters to the editor were excluded. Studies including children or adolescents were excluded. Studies that had no mention of heart failure as a baseline characteristic of patients were excluded. Studies that analyzed populations with other baseline cardiovascular diseases, such as ischemic heart disease or arterial hypertension, with only part of the participants having heart failure were excluded. Studies with no separate analysis for heart failure patients were excluded. Studies about valvular replacement procedures with no mention of heart failure were excluded. Since the baseline characteristics of patients did not include HF, studies where NLR was used as a predictor for developing HF were excluded.

Outcomes

We applied no restrictions in regard to reported outcomes, therefore we included studies describing associations of NLR with parameters of heart failure severity, comorbidities, or biomarkers, as well as studies demonstrating the predictive value of NLR for short or long-term mortality, hospital readmissions, major cardiovascular adverse events, poor functional capacity, response to cardiac resynchronization therapy, adequate implantable cardioverter defibrillator shocks, mortality after left ventricular assist device implantation or after heart transplantation.

RESULTS

We identified 241 publications. 31 publications fulfilled the inclusion and exclusion criteria and were selected for the review with a total of 12107 patients. The selection process is detailed in Figure 1.

Details and characteristics of all included studies are listed in Table 1.

Table 1

Summary of studies included in the review

Author, year	Type of study No of pts.	Duration of follow-up	Baseline pathology	Outcome	NLR cut-off	Risk associated to increased NLR	Parameters in multivariable analysis	Parameters associated with increased NLR
Uthamalingam, 2011 [19]	Retrospective 1212 patients	Median 26 IQR 15–36 months	ADHF	All-cause mortality	Third tertile median 9.6 IQR 7.6–13.1	Adjusted HR 2.23, 95% CI 1.63–3.02 p < 0.001	age, gender, cardiac risk factors, LVEF, medications, hemoglobin, BUN, creatinine, BNP, AF	older age, female gender, HTN, DM, CAD history, AF, ↑ heart rate, ↑ frequency of pulmonary congestion, peripheral edema, distended jugular veins, NYHA class III or IV, ↑ incidence of radiological signs of heart failure: cardiomegaly, pleural effusions, and interstitial edema, ↓ LVEF ↑NT-proBNP, ↑ BUN, ↑ serum creatinine
				In-hospital mortality	Third tertile median 9.6 IQR 7.6–13.1	Adjusted OR 2.8 95% CI 1.43–5.53 p = 0.03	age, gender, cardiac risk factors, LVEF, medications, hemoglobin, BUN, creatinine, BNP, AF	
				30-day HF readmission	Third tertile median 9.6 IQR 7.6–13.1	Univariate OR 3.46 95% CI 2.11–5.68 p < 0.001		
Benites-Zapata, 2015 [20]	Retrospective 527 patients	Median 11.3 IQR 3.4–21.1 months	Advanced HF	All-cause mortality	Third tertile NLR > 5.4	Univariate HR 2.57 95% CI 1.72–3.85 p < 0.01		older age, male gender, HTN, need for LVAD support, ↑ BNP, ↑ serum creatinine, ↑ BUN, ↑ total bilirubin, ↓ serum sodium, ↓ albumin, ↓ total proteins
					Third tertile NLR > 5.4	Adjusted HR 2.16 95% CI 1.21–3.83 p < 0.01	age, sex, black race, diabetes, HTN, no ischemic failure, COPD, CAD, stroke, AF, LVAD, creatinine, eGFR, albumin, BUN, BNP, platelets, beta-blocker	
				Heart transplant	Third tertile NLR > 5.4	Univariate HR 1.0 95% CI 0.66–1.66 p = 0.84		
					Third tertile NLR > 5.4	Adjusted HR 0.80 95% CI 0.47–1.43 p = 0.043	age, sex, black race, cigarette smoker, HTN, dyslipidemia, no ischemic failure, COPD, stroke, LVAD, albumin, sodium, mean platelet volume, aspirin, beta-blocker, ACE-I, hydralazine	

Table 1 (continued)

Author, year	Type of study No of pts.	Duration of follow-up	Baseline pathology	Outcome	NLR cut-off	Risk associated to increased NLR	Parameters in multivariable analysis	Parameters associated with increased NLR
Wasilewski, 2016 [21]	Retrospective 1734 patients	Median 660 IQR 331–1074 days	HF LVEF \leq 35%	All-cause mortality	Third tertile NLR > 3.1	Univariate HR 2.31 95% CI 1.82–2.92 p < 0.0001	age, sex, ICD, RDW, hemoglobin, heart rate, CKD stage III–V, diabetes, severe MR, LVEF, beta-blockers, ACEI	older age, DM, anemia, AF, CKD stage III and up, \uparrow NYHA class, \downarrow LVEF, \uparrow valvular disease, \downarrow hemoglobin levels, \uparrow white blood cell count, \uparrow NT-proBNP, \uparrow bilirubin, \uparrow BUN, \uparrow creatinine, \uparrow uric acid
Wan, 2018 [22]	Retrospective 197 patients	Median 660 IQR 331–1074 days	Ischemic HF subgroup 1126 patients	All-cause mortality	Third tertile NLR > 3.1	Multivariate HR 1.51 95% CI 1.11–2.04 p = 0.008	age, LVEF, RDW, heart rate, prior stroke, ICD, anemia, DM, severe MR, beta-blockers	
Cakici, 2014 [23]	Prospective 94 patients		Chronic HF	Poor functional capacity < 5 MET	Second half NLR > 3.96 (mean) NLR > 2.74 Se 79.4% Sp 80% p < 0.001	HR 3.085 95% CI 1.520–6.260 p = 0.002		interleukin-1 receptor 2, solute carrier family 22 member 4, vanin 3, Annexin A3, BMX non-receptor tyrosine kinase, and interleukin-1 receptor type 1
Turfan, 2014 [24]	Prospective 167 patients		ADHF, LVEF < 50%	In-hospital mortality	NLR > 4.78 Se 66.7% Sp 60.5%	Univariate HR 1.181 95% CI 1.035–1.347 p = 0.013 Multivariate OR 1.156 95% 1.001–1.334 p = 0.048		

Table 1 (continued)

Author, year	Type of study No of pts.	Duration of follow-up	Baseline pathology	Outcome	NLR cut-off	Risk associated to increased NLR	Parameters in multivariable analysis	Parameters associated with increased NLR
Ostrowska, 2017 [25]	Retrospective 638 patients		ADHF	In-hospital mortality	3.5 (2.3–5.4) vs 7.7 (4.0–15.3), p < 0.001 discharged home vs in-hospital mortality	Multivariate analysis – independent predictor p < 0.001		
Liu, 2016 [26]	Retrospective 179 patients	Hospitalization	Chronic HF	In-hospital mortality	NLR > 3.317 Se 100% Sp 68.1% p < 0.001	AUC 0.885, 95% CI 0.799–0.971 p < 0.01		
Tasal, 2013 [27]	Retrospective 219 patients	Hospitalization	Advanced ADHF	In-hospital mortality	NLR ≥ 5.542 Se 67% Sp 66% p < 0.001	Univariate baseline NLR HR 1.092 95% CI 1.038–1.149 p = 0.001 Univariate NLR after levosimendan HR 1.198 95% CI 1.114–1.288 p < 0.001 Multivariate NLR after levosimendan HR 1.310 95% CI 1.158–1.483 p < 0.001		
Durmus, 2015 [28]	Prospective 56 patients	12.8 ± 7.6 months	ADHF with LVEF < 50%	All-cause mortality	NLR > 5.1 Se 75% Sp 62% p = 0.045	AUC 0.730 p = 0.045 Multivariate HR 1.680 95% CI 1.013–2.786 p = 0.045		

Table 1 (continued)

Author, year	Type of study No of pts.	Duration of follow-up	Baseline pathology	Outcome	NLR cut-off	Risk associated to increased NLR	Parameters in multivariable analysis	Parameters associated with increased NLR
Fu, 2015 [29]	Prospective 306 patients	Mean 471 days Median 342 days	Chronic HF, age \geq 60 years	All-cause mortality		Univariate HR 1.066		
						Multivariate HR 1.039 95% CI 1.007–1.073 p = 0.016		
Huang, 2017 [30]	Retrospective 1923 patients	28.6 \pm 20.7 months	ADHF	All-cause mortality		Univariate HR 1.160 95% CI 1.112–1.210 p < 0.01		
						Multivariate HR 1.137 95% CI 1.015–1.274 p = 0.03		
Avcı, 2014 [31]	Prospective 87 patients	Outpatient visit	IDC – outpatients	Severe chronic HF	NLR > 2.25 Se 82% Sp 65% p < 0.001			
				BNP levels		Multivariate analysis – independent predictor, p = 0.025		
Yıldız, 2015 [32]	Prospective 37 patients	Outpatient visit	IDC LVEF < 40%	Functional capacity < 5 MET	NLR > 2.26 Se 83% Sp 69% p = 0.002	Multivariate HR 3.93 95% CI 1.024–15.123 p = 0.046		

Table 1 (continued)

Author, year	Type of study No of pts.	Duration of follow-up	Baseline pathology	Outcome	NLR cut-off	Risk associated to increased NLR	Parameters in multivariable analysis	Parameters associated with increased NLR
Sobrinho-Marquez, 2018 [33]	Prospective 87 patients	5 years	HF due to familial or IDC evaluated for non-urgent transplant	All-cause mortality or heart transplant	2.25 (0.65–18.4) vs 2.77 (1–35.75), p = 0.56	Univariate HR 1.894 95% CI, 1.493–2.402 p < 0.001		
						Multivariate HR 1.425, 95% CI, 1.109–1.832 p = 0.006		
Yan, 2016 [34]	Retrospective 1355 patients	Median 18 IQR 12 to 29 months	Chronic HF in elderly	MCE		Univariate HR 2.774 95% CI, 1.650–4.563 p < 0.001		
				Cardiac death	highest tertile NLR > 2.9	Multivariate HR 1.747 95% CI, 1.032–2.958 p = 0.038		
				Rehospitalization for HF		Univariate HR 1.717 95% CI, 1.311–2.249 p < 0.001		
				CKD		Multivariate HR 1.461, 95% CI 1.108–1.927 p = 0.007		
Yan, 2017 [35]	Retrospective 1355 patients	Median 18 IQR 12 to 29 months	CHF	AF	NLR continuous variable in Multivariate analysis	Multivariate HR 1.170, 95% CI 1.054–1.298 p = 0.003		
				Composite of death and CHF rehospitalization	Highest tertile median NLR 4.1 IQR 3.39–6.01	Univariate HR 1.586 95% CI, 1.243–2.025 p < 0.001		

Table 1 (continued)

Author, year	Type of study No of pts.	Duration of follow-up	Baseline pathology	Outcome	NLR cut-off	Risk associated to increased NLR	Parameters in multivariable analysis	Parameters associated with increased NLR
Gurkan, 2017 [38]	Retrospective 40 patients	Mean 34.8 ± 23 months	Peripartum cardiomyopathy	Persistent left ventricular systolic dysfunction	Median, range 3.96 (1.55–18) vs 3 (1.5–5.25), p = 0.025	Univariate HR 6.375 95% CI 1.163–34.934 p = 0.033		
						Multivariate HR 12.773 95% CI 1.487–109.758 p = 0.02		
Agacikien, 2013 [39]	Prospective 70 patients	6 months	Chronic HF, NYHA III or IV, QRS ≥ 120 msec, LVEF ≤ 35%, CRT implantation	Response to CRT		Multivariate HR 1.506 95% CI 1.011 – 2.243 p = 0.035		
Balci, 2016 [40]	Retrospective 157 patients	6 months	Severe symptomatic HF (NYHA class III or ambulatory IV), LVEF ≤ 35%, LBBB, QRS ≥ 120 msec, CRT implantation	Response to CRT	NLR > 3.45 Se 64.0% Sp 74.8% p < 0.001	Multivariate HR 12.216 95% CI 2.161–69.052 p = 0.005		
Boros, 2016 [41]	Prospective 122 patients	2 years, median 787 days	Chronic HF, NYHA class II–IV, QRS > 120 msec, LVEF < 35%, CRT implantation	All-cause 2-year mortality	NLR > 2.95	Univariate HR 1.48, 95% CI 1.13–1.94 p = 0.004		
		Multivariate HR 2.44, 95% CI 1.04–5.71 p = 0.03						
		6 months		No 6-month reverse remodelling	NLR > 2.95 Se 61% Sp 63% p = 0.01	Univariate HR 0.67, 95% CI 0.46–0.99 p = 0.04		
						Multivariate HR 0.38, 95% CI 0.17–0.85 p = 0.01		

Table 1 (continued)

Author, year	Type of study No of pts.	Duration of follow-up	Baseline pathology	Outcome	NLR cut-off	Risk associated to increased NLR	Parameters in multivariable analysis	Parameters associated with increased NLR
Hashimoto, 2016 [42]	Prospective 120 patients	Median 61.2 IQR 39.8–87.6 months	Cardiomyopathy, NYHA class II and III, ICD implantation	All-cause mortality	NLR \geq 2.1 (median NLR of the study group)	Univariate HR 3.252, 95% CI 1.600–7.135 p < 0.01		
				Appropriate ICD shocks		Multivariate HR 2.403, 95% CI 1.076–5.704 p = 0.03		
Ucar, 2017 [43]	Retrospective 205 patients	Median 43 Range 7–125 months	IDC, LVEF \leq 35%, NYHA II–III class with optimal medical therapy, ICD implantation	Appropriate ICD shocks	NLR > 2.93 Se 71% Sp 62%	Multivariate analysis β = 0.212 p < 0.008		
Yost, 2015 [44]	Retrospective 273 patients	365 days	Patients implanted with LVAD	All-cause post-operative mortality	NLR tertiles 2 (mean 4.0 \pm 0.6) and 3 (mean 9.15 \pm 6)	Multivariate HR 1.159 95% CI 1.022–1.314 p = 0.021		
				Postoperative RV failure		Multivariate HR 1.117 95% CI 1.039–1.201 p = 0.003		
Bhat, 2018 [45]	Retrospective 100 patients	30 days and two post-operative outpatient visits	Patients implanted with LVAD	Longer length of stay	< 66% NLR improvement			
				RV failure	< 66% NLR improvement			

Table 1 (continued)

Author, year	Type of study No of pts.	Duration of follow-up	Baseline pathology	Outcome	NLR cut-off	Risk associated to increased NLR	Parameters in multivariable analysis	Parameters associated with increased NLR
Ferra, 2019 [46]	Retrospective 188 patients	6 months	Patients implanted with LVAD	Mortality	NLR at 4–6 months > median 4.4	Multivariate HR 1.67 95% CI 1.03–2.70 P = 0.037		
						Univariate HR 1.04 95% CI, 1.01–1.06 p = 0.001		
						Univariate HR 1.22 95% CI 1.01–1.47 p = 0.039		
Sundararajan, 2019 [47]	Retrospective 301 patients	365 days	Patients implanted with LVAD	All-cause mortality	Pre-LVAD log NLR	Multivariate HR 1.03 95% CI 1.01–1.06 p = 0.012		
						Univariate HR 1.5 95% CI 1.15–1.99 p = 0.003		
						Multivariate HR 1.43 95% CI 1.03–1.99 p = 0.032		
						Univariate HR 1.11, 95% CI, 1.07–1.16, p < 0.001		
						Multivariate HR 1.06 95% CI 1.01–1.13 p = 0.033		
					Log 90-day NLR	Univariate HR 2.85, 95% CI 1.84–4.42 p < 0.001 Multivariate HR 2.12, 95% CI 1.25–3.61 p = 0.005		

Table 1 (continued)

Author, year	Type of study No of pts.	Duration of follow-up	Baseline pathology	Outcome	NLR cut-off	Risk associated to increased NLR	Parameters in multivariable analysis	Parameters associated with increased NLR
Karacaglar, 2015 [48]	Retrospective 43 patients	Mean 33 months	Adult patients who underwent orthotopic heart transplant	Asymptomatic graft rejection		No correlation		
Choi, 2018 [49]	Retrospective 74 patients	Median 49.4, IQR 37.4–61.1 months	Cardiac transplant recipients without acute rejection in the first 3 months, aged 18 years or older, creatinine < 2 mg/dL	Clinically significant acute rejection	Δ LNR at 3 months \leq 0.046	Kaplan Meier survival analysis, $p = 0.035$		
						Time to acute rejection 233 ± 130 vs 740 ± 313 days		
Seropian, 2018 [50]	Retrospective 111 patients	1 year	Cardiac transplant recipients	In-hospital mortality	NLR > 2.41, Se 86%, Sp 67%	Univariate HR 2.53 95% CI 1.03–6.2 $p = 0.043$		
						Multivariate HR 2.77 95% CI, 1.12–6.87 $p = 0.028$		
Argan, 2016 [51]	Prospective 130 patients	Mean 16, range 1–39 months	Chronic HF, LVEF \leq 45%, NYHA II–IV	Composite all-cause death and re-hospitalization Progression of renal dysfunction	no correlation NLR > 3 Se 68% Sp 75% $p = 0.001$	Univariate HR 3.068 95% CI 0.970–9.705		
						Multivariate HR 3.403 95% CI 1.039–11.144 $p = 0.04$	age > 50 years, male sex, DM, ischemic HF, pulmonary vascular resistance, creatinine, eGFR, by-pass time, PLR > 92.5	

ACEI, angiotensin converting enzyme inhibitor; ADHF, acute decompensated heart failure; AF, atrial fibrillation; AUC, area under curve; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; HTN, arterial hypertension; ICD, implantable cardioverter defibrillator; IDC, idiopathic dilated cardiomyopathy; IQR, interquartile range; LBBB, left bundle branch block; LNR, lymphocyte to neutrophil ratio; LVAD, left ventricle assist device; LVEF, left ventricular ejection fraction; MCE, major cardiac events; MET, metabolic equivalent of task; MR, mitral regurgitation; NLR neutrophil-to-lymphocyte ratio; NT-proBNP, N terminal pro brain natriuretic peptide; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width; RV, right ventricle.

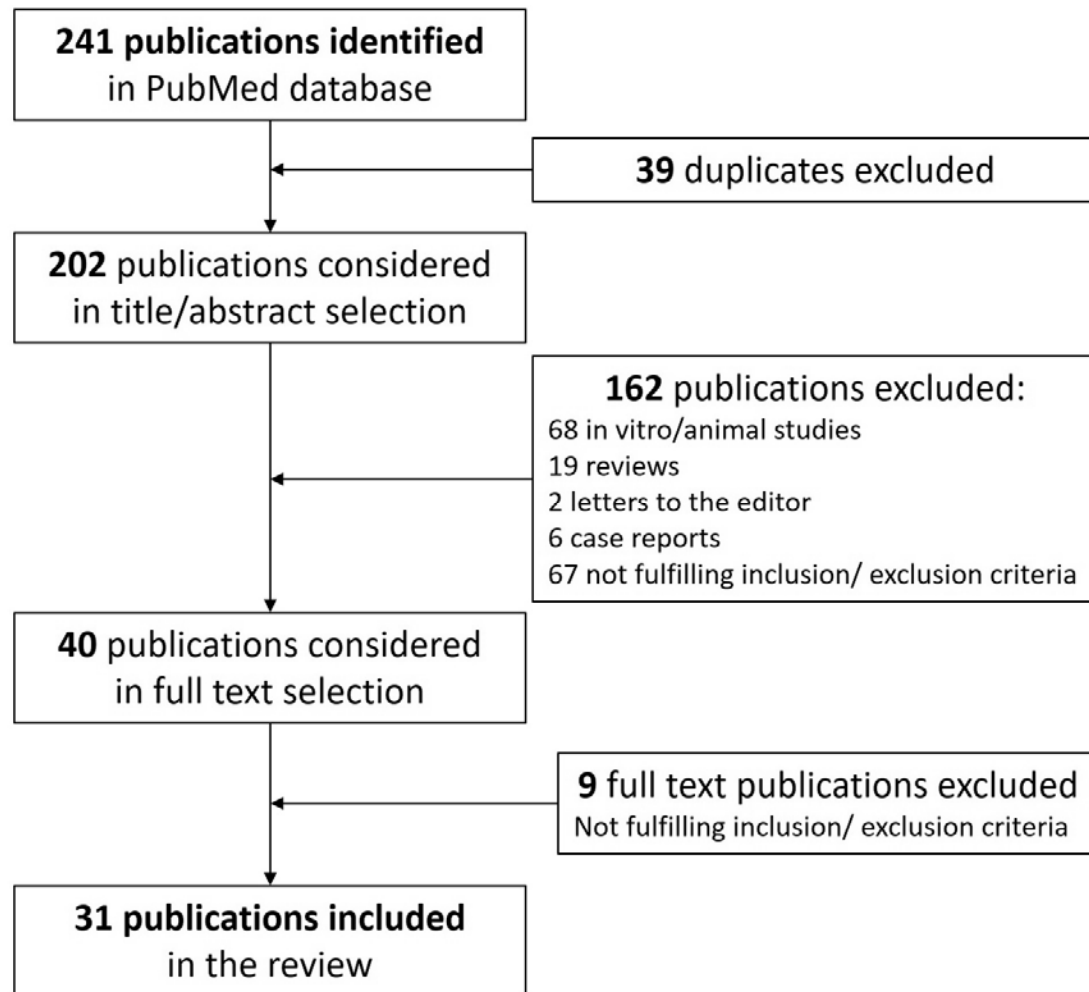


Figure 1. Selection process of articles.

Table 2

Supplemental material. Search strategy

Search strategy	Retrieved Articles
((neutrophil [Title/Abstract] OR "neutrophils" [MeSH Terms]) AND (lymphocyte [Title/Abstract] OR "lymphocytes" [MeSH Terms])) OR neutrophil lymphocyte [Title/Abstract] OR (("neutrophils" [MeSH Terms] OR "neutrophils" [All Fields] OR "neutrophil" [All Fields]) AND "lymphocytes" [MeSH Terms]) AND ((heart [Title/Abstract] AND failure [Title/Abstract]) OR "heart failure" [MeSH Terms])	112
((neutrophil [Title/Abstract] OR "neutrophils" [MeSH Terms]) AND (lymphocyte [Title/Abstract] OR "lymphocytes" [MeSH Terms])) OR neutrophil lymphocyte [Title/Abstract] OR (("neutrophils" [MeSH Terms] OR "neutrophils" [All Fields] OR "neutrophil" [All Fields]) AND "lymphocytes" [MeSH Terms]) AND ("cardiomyopathies" [MeSH Terms] OR cardiomyopathy [Title/Abstract])	65
((neutrophil [Title/Abstract] OR "neutrophils" [MeSH Terms]) AND (lymphocyte [Title/Abstract] OR "lymphocytes" [MeSH Terms])) OR neutrophil lymphocyte [Title/Abstract] OR (("neutrophils" [MeSH Terms] OR "neutrophils" [All Fields] OR "neutrophil" [All Fields]) AND "lymphocytes" [MeSH Terms]) AND ((transplant [Title/Abstract] OR transplantation [Title/Abstract]) AND (heart [Title/Abstract] OR "heart failure" [MeSH Terms]))	53
((neutrophil [Title/Abstract] OR "neutrophils" [MeSH Terms]) AND (lymphocyte [Title/Abstract] OR "lymphocytes" [MeSH Terms])) AND (resynchronization [Title/Abstract] OR (resynchronization [All Fields] AND "therapeutics" [MeSH Terms]))	3
((neutrophil [Title/Abstract] OR "neutrophils" [MeSH Terms]) AND (lymphocyte [Title/Abstract] OR "lymphocytes" [MeSH Terms])) AND ((implantable [Title/Abstract] AND defibrillator [Title/Abstract] AND (cardiac [Title/Abstract] OR cardioverter [Title/Abstract])) OR ICD [Title/Abstract] OR (implantable [All Fields] AND ("heart" [MeSH Terms] OR "heart" [All Fields] OR "cardiac" [All Fields]) AND "defibrillators" [MeSH Terms]) OR "defibrillators, implantable" [MeSH Terms])	8

Congestive heart failure

General characteristics and heart failure severity

NLR was correlated to parameters of HF severity, such as New York Heart Association (NYHA) class, left ventricular ejection fraction (LVEF), and natriuretic peptide levels in different groups of HF patients [19, 20, 21]. It was also associated with comorbidities such as atrial fibrillation (AF), arterial hypertension (HTN), diabetes mellitus (DM) and chronic kidney disease (CKD) [19, 20, 21]. Regarding laboratory parameters, higher NLR was correlated to higher creatinine and BUN, lower estimated glomerular filtration rate (eRFG), sodium, albumin, total proteins, and lower hemoglobin levels [19, 20, 21].

In patients with acute decompensated heart failure (ADHF) the highest NLR tertile was associated to older age, female gender, HTN, DM, history of coronary artery disease (CAD), and history of AF [19]. On clinical examination, patients with NLR values in highest tertile had higher heart rates, and higher frequency of pulmonary congestion, peripheral edema, distended jugular veins, as well as higher NYHA class (III or IV) [19]. These patients also had increased incidence of radiological signs of heart failure: cardiomegaly, pleural effusions, and interstitial edema [19]. The highest tertile NLR was also associated with lower LVEF, higher levels of NT-proBNP, BUN, and serum creatinine [19].

In patients with advanced heart failure, higher NLR values were associated with older age, male gender, history of HTN, and the necessity for left ventricular assist device (LVAD) support [20]. These patients also had increased levels of BNP, serum creatinine, BUN and total bilirubin, and decreased levels of serum sodium, albumin, and total proteins [20].

In patients with HF with an LVEF of 35% or lower, higher NLR levels were correlated to older age, increased prevalence of DM, anemia, AF and CKD stage III and up [21]. Patients from this group with NLR in the highest tertile also had higher NYHA functional class, lower LVEF and more frequently significant valvular disease [21]. From the laboratory parameters, higher NLR was correlated to lower hemoglobin levels, higher white blood cell count, NT-proBNP, bilirubin, BUN, creatinine and uric acid [21].

Genes associated with elevated NLR in chronic heart failure

Studying genetic correlations of elevated NLR levels in 197 patients with chronic HF, Wan *et al.* found

associations with interleukin-1 receptor 2 (IL1R2), solute carrier family 22 member 4 (SLC22A4), vanin 3 (VNN3), Annexin A3 (ANXA3), BMX non-receptor tyrosine kinase (BMX), and interleukin-1 receptor type 1 (IL1R1) [22]. These differentially expressed genes were mostly enhanced in neutrophil activation and neutrophil mediated immunity, fluid shear stress and atherosclerosis, as well as transcriptional misregulation in malignancy, suggesting a possible interconnection of these pathways with those activated in heart failure [22]. In multivariate regression analysis including age and gender, a higher expression of SLC22A4 (OR 5.219, $p = 0.003$), IL1R2 (OR 5.228, $p = 0.007$), VNN3 (OR 3.478, $p = 0.012$) and male sex were independently associated with elevated NLR in HF patients [22].

Functional capacity in congestive heart failure

In a small sample of 94 patients with congestive heart failure undergoing symptom-limited treadmill testing to assess functional capacity (FC), NLR was correlated with exercise performance, a marker not only for patients' quality of life, but also a predictor of morbidity and mortality [23]. A cut-off point of 2.74 was established for predicting poor FC [23]. Moreover, patients with $NLR > 3$ had more frequent AF, higher NT-proBNP values, increased left atrial (LA) dimensions and systolic pulmonary artery pressure (sPAP), lower LVEF and more severe left ventricular (LV) diastolic dysfunction [23].

In-hospital mortality after acute decompensated heart failure

Patients with HF admitted for acute decompensation with higher NLR levels had higher in-hospital mortality, as first reported by Uthamalingam *et al.* Those with NLR values in the highest tertile had an increased rate of in-hospital death, compared to those in the first tertile (OR 2.8, 95% CI 1.43–5.53, $p = 0.03$) as well as compared to those in the second tertile (OR 1.68, 95% CI 1.00–3.03, $p = 0.05$) [19].

Another report of the utility of NLR in HF short-term prognosis is the study authored by Turfan *et al.*, investigating a cohort of 167 patients with acute HF with reduced LVEF $< 50\%$ [24]. NLR predicted in-hospital mortality with an AUC of 0.687 and a cut-off level > 4.78 with 66.7% sensitivity and 60.5% specificity [24]. In multivariate logistic regression, age, LVEF and $NLR > 4.78$ (OR 1.156, 95% CI 1.011–1.334, $p = 0.048$) were independent predictors of in-hospital mortality [24].

In a large cohort of 638 consecutive patients with acute decompensated heart failure, patients with in-hospital death had significantly higher NLR values compared to those discharged home (3.5 (2.3–5.4) compared to 7.7 (4.0–15.3), $p < 0.001$). Higher NLR values were correlated to in-hospital mortality in both univariate and multivariate analysis [25].

Liu et al. also proved that higher NLR values were associated with in-hospital mortality in a sample of 179 patients with chronic failure [26]. Individuals surviving the admission for HF had significantly lower mean NLR levels compared to those that did not (3.9 versus 10.2, $p < 0.05$) [26]. NLR was correlated to in-hospital mortality with an AUC of 0.885 (95% CI 0.799–0.971, $p < 0.05$) and a cut-off value > 3.317 with 68.1% specificity and 100% sensitivity [26].

Furthermore, NLR proved useful in patients with acute decompensation of advanced heart failure receiving levosimendan treatment, as reported by Tasal et al. [27]. Significant decrease of NLR levels was observed in patients with favorable outcomes after levosimendan infusion [27]. The NLR values after levosimendan treatment were independent predictors of in-hospital mortality with an OR of 1.310, 95% CI 1.158–1.483, $p < 0.001$, in multivariate analysis including all hemodynamic, hematological, and biochemical variables associated with mortality [27]. In ROC curve analysis a cut-off level of $\text{NLR} \geq 5.542$ after levosimendan infusion was established for predicting in-hospital mortality with a 67% sensitivity and 66% specificity [27].

Readmissions for acute decompensated heart failure

Patients evaluated after one admission for acute decompensated heart failure with a high NLR level, respectively in the highest tertile, had a significantly higher 30-day risk of readmission compared to those with NLR values in the second tertile (OR 3.46, 95% CI 2.11–5.68, $p < 0.001$) [19].

Post-discharge mortality after acute decompensated heart failure

In a large cohort of patients discharged after hospitalization for ADHF, Uthamalingam et al. reported an increased risk of long-term mortality for patients with higher NLR on admission [19]. During a median follow-up period of 26 months (interquartile range 15 to 36), patients with NLR values in the highest tertile had an adjusted HR of 2.1, 95% CI 1.53–2.88, $p < 0.001$ for mortality

compared to those in the first tertile [19]. Compared to those in the second tertile, the adjusted HR was 1.48, 95% CI 1.02–2.14, $p = 0.03$ [19].

NLR levels were also associated with increased post-discharge mortality in patients with heart failure evaluated for advanced heart failure therapies and consideration for heart transplant or mechanical circulatory assist devices [20]. After a median follow-up of 11.3 (interquartile range 3.4 to 21.1) months, those with NLR values in the second (adjusted HR 2.16, 95% CI 1.21–3.83, $p < 0.001$) and third tertiles (adjusted HR 1.83, 95% CI 1.07–3.14, $p = 0.03$) had significantly higher risk of all-cause mortality, compared to the first tertile [20].

After a mean follow-up period of 12.8 ± 7.6 months in small cohort of 56 HF patients with both reduced as well as preserved EF, NLR predicted all-cause mortality with an AUC of 0.730 and a cut-off level of $\text{NLR} > 5.1$, with 75% sensitivity and 62% specificity ($p = 0.045$) [28]. In multivariate logistical regression alongside age, sex, LVEF and platelet to lymphocyte ratio, NLR was an independent predictor of mortality with an OR of 1.680 (95% CI 1.013–2.786, $p = 0.045$) [28].

NLR was also an independent predictor of all-cause mortality (adjusted HR 1.039, 95% CI 1.007–1.073, $p = 0.016$) in a cohort of 306 HF patients aged over 60 years, followed-up for a mean period of 471 (median 342) days, alongside age, sex, plasma albumin, and NT-proBNP levels [29].

Patients with HF with a $\text{LVEF} \leq 35\%$ with NLR values in the highest tertile had a HR of 1.43 (95% CI 1.1–1.85, $p = 0.006$) of all-cause mortality during a median follow-up period of 660 days (interquartile range, 331–1074 days) [21]. During the first 12 months after inclusion, in the entire study group, an increase in mortality of almost 3-fold was observed for patients with the highest tertile NLR values compared to those in the lowest tertile [21]. After adjusting for other predictors of survival, in multivariate analysis, NLR levels in the highest tertile were predictors of long-term mortality only for patients with ischemic HF (HR 1.51, 95% CI 1.11–2.04, $p = 0.008$), and not for those with non-ischemic HF (HR of 1.22, 95% CI 0.77–1.94, $p = 0.39$) [21].

Huang et al. also reported the role of NLR for post-discharge mortality prediction in 1923 patients hospitalized for ADHF followed-up for a mean duration of 28.6 ± 20.7 months [30]. NLR was a significant predictor of mortality in univariate analysis (HR 1.160, 95% CI 1.112–1.210, $p < 0.01$) as well as multivariate analysis adjusting for NT-proBNP levels

(HR 1.137, 95% CI 1.015–1.274, $p = 0.03$) or in multivariate analysis adjusting for age, sex, mean blood pressure, LVEF, serum sodium levels, hemoglobin, eGFR, treatment with renin-angiotensin system blockers, beta-blockers and spironolactone (HR 1.162, 95% CI 1.094–1.235, $p < 0.01$) [30].

Special populations of heart failure

Dilated cardiomyopathy

In patients with idiopathic dilated cardiomyopathy (IDC), higher NLR values were associated to higher NYHA class and higher BNP levels [31]. NLR was correlated to the severity of chronic HF, a cut-off value of $NLR \geq 2.25$ associating 82% sensitivity and 65% specificity to predict severity of the cardiac condition [31]. Parameters of cardiac remodeling, such as LV and LA volumes and dimensions, LV systolic and diastolic function, sPAP and right ventricular systolic motion were significantly impaired in patients with a $NLR \geq 2.25$ [31].

FC is an important prognostic predictor in heart failure. In patients with IDC, NLR was significantly correlated to FC assessed by treadmill testing, correlating therefore with their outcomes [32]. In the same cohort, NLR was also correlated to both systolic and diastolic LV dysfunction, independently of the FC [32].

However, regarding prognosis, during a five-year follow-up of a small HF group with advanced idiopathic or familial dilated cardiomyopathy evaluated for non-urgent heart transplant, Sobrino-Marquez *et al.* found no correlation of median NLR on initial work-up with survival or necessity for surgical intervention [33].

Heart failure in elderly patients

In elderly patients with CHF, NLR was independently correlated with the occurrence of major cardiovascular events (MCE), as well as with CKD [34]. During a median follow-up period of 18 months, those with the highest tertile of the NLR (median 4.1, interquartile range 3.39 to 6.01) had a significantly higher incidence of cardiac death and rehospitalization for heart failure [34].

Studying the same cohort of 1355 older patients, Yan W *et al.* also found an independent correlation between NLR and the presence of AF [35]. Moreover, when computing the multivariate analysis including the NT-proBNP values, NLR was an independent predictor of MCE [35]. Patients with the NLR levels in the highest tertile had a 1.407-fold higher risk of MCE [35].

Peripartum cardiomyopathy

Given the hypothesis of systemic inflammation contributing to the pathophysiology of peripartum cardiomyopathy, biomarkers such as C-reactive protein, TNF- α , and interleukin-6 were correlated to severity and prognosis of this disease [36, 37]. Gurkan U. and his collaborators also proved the utility of NLR, as an inflammatory biomarker, in 40 patients with peripartum cardiomyopathy [38]. In multivariate logistic regression, NLR was identified as an independent predictor of persistent LV systolic dysfunction after a mean follow-up period of 34.8 ± 23 months [38].

Response to device therapy in heart failure

Resynchronization therapy

Studying a cohort of 70 patients undergoing cardiac resynchronization therapy (CRT) implantation, Agacik *et al.* proved the role of baseline NLR in predicting clinical and functional response to the device therapy [39]. In multivariable analysis including age, etiology of cardiomyopathy, baseline LVEF, NYHA functional class, CRP, and NLR, NLR was the only independent predictor of CRT responsiveness at 6 months (OR 1.506, 95% CI 1.011–2.243, $p = 0.035$) [39]. Moreover, a significant decrease in mean NLR values from 2.4 ± 1 at baseline to 2.1 ± 0.7 after 6 months was associated with echocardiographic response to CRT [39].

Balci *et al.* also analyzed a group of 157 patients with severe symptomatic HF despite optimal medical therapy, with reduced LVEF and left bundle branch block that received resynchronization therapy in combination with a cardioverter defibrillator [40]. NLR levels > 3.45 before CRT implantation predicted non-responsiveness to the therapy with a 64% sensitivity and 74.8% specificity and an AUC in ROC analysis of 0.718 (95% CI 0.633–0.803, $p < 0.001$) [40]. In multivariate analysis alongside ischemic etiology, prior percutaneous coronary intervention (PCI) reperfusion therapy, history of HTN, and statin treatment, $NLR > 3.45$ was an independent predictor of CRT non-responsiveness (OR 12.216, 95% CI 2.161–69.052, $p = 0.005$) [40].

The utility of NLR in predicting response to CRT was also confirmed in a prospective study by Boros and collaborators [41]. Patients with lower baseline NLR achieved reverse remodeling of the left ventricle after 6 months post CRT implantation (OR 0.38, 95% CI 0.17–0.85, $p = 0.01$ for $NLR \leq 2.95$) [41]. Patients with higher baseline NLR (> 2.95) had a higher risk for all-cause mortality during the

follow-up period of two years (HR 2.44, 95% CI 1.04–5.71, $p = 0.03$) [41]. Both statistical analysis for the prediction of reverse remodeling and all-cause long-term mortality were computed using multiple prediction parameters, including NT-proBNP values, making NLR an independent predictor of outcomes [41].

Implantable cardioverter defibrillator

In 120 patients with heart failure NYHA classes II and III, with implantable cardioverter defibrillators (ICD) for either primary or secondary prevention, higher NLR was correlated to all-cause mortality but not to appropriate ICD shocks [42]. In multivariate survival analysis, NLR, BNP levels and eGFR were independent predictors of mortality during a median follow-up period of 61.2 months [42]. Patients with lower NLR levels (<2.1) had decreased mortality, but not different numbers of appropriate ICD shocks [42].

In patients with IDC receiving an ICD for primary prevention of sudden cardiac death, NLR did predict arrhythmic events and appropriate ICD therapy with an AUC of 0.707 (95% CI 0.629–0.785, $p < 0.001$), higher NLR being correlated to these outcomes [43]. Consequently, Ucar et al. suggested the use of NLR as an additional biomarker for stratifying the ventricular arrhythmic risk in patients with IDC [43].

Left ventricular assist device

In a cohort of 273 patients with advanced HF who received left ventricular assist devices (LVAD), NLR was an independent predictor of postoperative mortality (OR 1.159, 95% CI 1.022–1.314, $p = 0.021$) as well as postoperative right ventricular failure (OR 1.117, 95% CI 1.039–1.201, $p = 0.003$) [44]. Associated with older age, ischemic etiology of HF, CKD and increased incidence of ventricular tachycardia, NLR was also directly correlated to length of hospital stay [44].

Bhat et al. further proved that the NLR variability in time was correlated to outcomes in HF patients receiving LVAD therapy [45]. Highest NLR levels were recorded immediately after surgery with a tendency to decrease after approximately 30 days to levels similar to the preoperative ones [45]. However, patients whose NLR failed to improve 10 days postoperative had higher probability of a longer length of stay, of developing right HF and a trend toward reduced survival rates [45].

Another longitudinal analysis of NLR in patients with advanced HF receiving LVAD therapy

as bridge to transplant, carried out by Ferrera et al., confirmed the rise and fall in NLR levels immediately after and several months after surgery [46]. Patients with NLR higher than median during the 4–6 months follow-up had higher rates of stroke and mortality [46]. NLR during follow-up higher than 4.4 was an independent predictor of mortality, associating significantly shorter survival time [46].

Retrospectively examining a cohort of 301 patients with LVAD support monitored for 365 days, Sundararajan et al. highlighted the importance of determining NLR levels both pre-LVAD and during follow-up [47]. Higher NLR prior to LVAD implantation as well as higher NLR after 90 days post-operatively were independent predictors of mortality [47].

Heart transplantation

In patients with advanced HF during a median follow-up period of 11.3 months (IQR 3.4 to 21.1), higher NLR values did not correlate to more frequent heart transplantation (adjusted HR 0.80, 95% CI 0.47–1.43, $p = 0.43$) [20].

In a retrospective analysis of 47 patients who received orthotopic heart transplant, periodically followed-up with routine endomyocardial biopsies, Karacaglar et al. found no correlation between NLR and to asymptomatic graft rejection [48]. This study measured NLR on each visit and correlations were made to the results of EMB collected on the same evaluation.

However, when evaluating lymphocyte to neutrophil ratio (LNR) variability in time, at baseline, 3, 6 and 12 months after heart transplantation in a cohort of 74 patients, decreasing LNR was correlated with acute rejection [49]. Lower LNR during the first three months of follow-up was an independent predictor of clinically overt acute graft rejection [49]. In other words, higher NLR would be associated with acute rejection after heart transplantation.

Another study published by Seropian et al. proved that higher NLR before heart transplantation was an independent predictor of one-year mortality (HR 3.403, $p < 0.05$) [50]. Higher NLR on admission was correlated to higher necessity of renal replacement therapy ($p < 0.05$) and trending towards an association with higher in-hospital mortality (AUC 0.644, 95% CI 0.492–0.797) [50].

Heart failure and renal dysfunction

Monitoring the renal function of patients with HF with reduced LVEF during a 16-month follow-up

period, Argan et al. observed that NLR levels were correlated to kidney disease progression [51]. In ROC analysis, $NLR > 3$ had a sensitivity of 68% and specificity of 75% to predict worsening renal function with an AUC of 0.72, 95% CI 0.58–0.85, $p = 0.001$ [51]. Furthermore, patients with a $NLR < 3$ had significantly higher rates of survival without progression of kidney dysfunction [51].

CONCLUSIONS

In HF patients, NLR was correlated to severity of the cardiac condition quantified by higher NYHA class and NT-proBNP levels, and lower LVEF. NLR was increased in patients with higher comorbidity burden, including valvular heart disease, ischemic coronary disease, AF, DM, HTN, and CKD.

Factors generally associated with poor prognosis in HF, such as older age, increased levels of creatinine, BUN, uric acid, bilirubin, liver enzymes and decreased levels of hemoglobin, albumin, and sodium were associated with higher NLR levels. These patients also presented with echocardiographic parameters of advancing HF, including LV systolic and/or diastolic dysfunction and increased pulmonary artery systolic pressure.

NLR was an independent predictor of all-cause mortality in numerous studies, in various subcategories of HF patients ranging from stable to end-stage, and from indications of device implantation to cardiac transplant, with a cut-off level ranging from >2.1 to >7.6 .

Therefore, in HF patients, increased NLR could be a valuable auxiliary biomarker of severity, but most of all, of poor prognosis.

Introducere. *Insuficiența cardiacă (IC) și inflamația sistemică sunt procese interdependente ce se potențează reciproc, continuu. Diverse căi fiziopatologice sunt activate, rezultând în creșterea numărului de neutrofile și scăderea numărului de limfocite, ceea ce face din raportul neutrofile-limfocite (NLR) un potențial marker indirect de severitate. Am realizat această lucrare pentru a caracteriza rolul NLR în IC.*

Metode. *Folosind cuvintele cheie “neutrophil”, “lymphocyte”, “heart failure”, “cardiomyopathy”, “implantable cardioverter defibrillator”, “cardiac resynchronization therapy” și “heart transplant” am căutat articole în baza de date PubMed (MEDLINE).*

Rezultate. *Am indentificat 241 publicații. 31 au fost selectate pentru această sinteză, incluzând 12107 pacienți. NLR a fost corelat cu severitatea IC exprimată prin parametri clinici, biologici și imagistici, precum și cu prognosticul pe termen scurt și lung. Majoritatea studiilor au raportat valoarea lui prognostică pentru supraviețuire. NLR crescut ($>2.1-7.6$) a fost predictor independent pentru mortalitatea intra-spital [HR ajustat 1.13(95% CI 1.01–1.27)–2.8(95% CI 1.43–5.53)] precum și pentru mortalitatea de orice cauză pe termen lung [HR ajustat 1.43(95% CI 1.1–1.85)–2.403(95% CI 1.076–5.704)].*

Valorile mari ale NLR au fost de asemenea predictor pentru capacitatea funcțională scăzută [NLR $> 2.26/2.74$, HR 3.93 (95% CI 1.02–15.12)/3.085 (95% CI 1.52–6.26)], reinternări [NLR $> 2.9/7.6$, HR 1.46 (95% CI 1.10–1.93)/3.46 (95% CI 2.11–5.68)], terapia de resincronizare eficientă (NLR > 3.45 /creșterea cu o unitate, HR 12.22 (95% CI 2.16–69.05)/1.51 (95% CI 1.01–2.24)] și administrarea de șocuri adecvate prin defibrilatorul implantabil (NLR > 2.93), precum și mortalitatea după implantarea dispozitivului de asistare ventriculară [NLR > 4.4 /cuartile, HR 1.67 (95% CI 1.03–2.70)/1.22 (95% CI 1.01–1.47)] sau după transplantul cardiac (NLR > 2.41 , HR 3.403 (95% CI 1.04–11.14)].

Concluzie. *NLR crescut la pacienții cu IC poate fi un biomarker auxiliar valoros pentru cuantificarea severității și, mai ales, pentru prognostic.*

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