

Review

Evaluation of the Neutrophil-to-Lymphocyte Ratio in Mortality of Individuals with Acute Heart Failure: An Integrative Literature Review

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Abstract: Acute heart failure (AHF) is a syndrome resulting from structural or functional abnormalities of the heart, possibly associated with systemic inflammation. In this context, the neutrophil-to-lymphocyte ratio (NLR) has been studied as a potential inflammatory marker easily accessible in clinical practice. This study aims to verify whether there is a relationship between NLR and mortality from AHF, as well as its contribution to the management and prognosis of the disease. An integrative literature review was conducted using the PubMed, Lilacs, and Scielo databases, covering publications from 2011 to 2021. The descriptors used were "heart failure," "mortality," and "neutrophil-to-lymphocyte ratio," combined to refine the search. Four articles were selected at the end of the search stages, 60% of which were published after 2018, and only 20% were more than 10 years old. The countries of origin of these studies include South Korea, Spain, the United States, Romania, and Turkey. Positive evidence was found for the hypothesis that NLR is related to mortality in AHF. The following considerations should be made elevated NLR values were predictors of AHF decompensation and in-hospital mortality; the higher the marker, the worse the survival rates. Additionally, the low cost and wide availability of complete blood counts support its high applicability. In this sense, the development of further studies will allow for more precise cut-off values and greater accuracy. It is concluded that NLR is related to mortality in AHF. Therefore, the biomarker is effective in risk stratification and prognosis of these patients.

Keywords: Heart failure, Mortality, Neutrophil-to-Lymphocyte Ratio.

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1. Introduction

Acute heart failure is a clinical syndrome that occurs due to the heart's inability to meet metabolic demands, resulting from structural or functional abnormalities of the heart. These signs and symptoms may be new or arise from the decompensation of pre-existing chronic heart failure, leading to acute symptoms that require immediate medical intervention [1]. The epidemiology of AHF is influenced by an intricate interaction of risk factors, genetic predisposition, and socio-environmental conditions. Epidemiological studies indicate an increasing incidence of AHF in various populations, with higher rates in the elderly and individuals with comorbidities. The most frequent risk factors associated were systemic arterial hypertension, anemia, coronary artery disease, dyslipidemia, and diabetes mellitus, respectively. Demographic analysis reveals an uneven distribution of AHF, affecting men more often than women [2].

The increase in systemic inflammation levels related to the aging process is a factor in the development of chronic diseases, particularly cardiovascular diseases [3]. In this context, markers have been studied for their prognostic aspects [4], and the neutrophil-to-lymphocyte ratio (NLR) has gained special attention due to its ability to reflect both specific immune response effects (lymphocytes) and non-specific immune responses (neutrophils), making it potentially useful for risk stratification in chronic diseases with predictable and comparable value [5].

Heart failure is one of the leading causes of mortality and morbidity worldwide and in Brazil. Currently, the disease affects about 2 million Brazilians, with an incidence of 240,000 new cases per year, and between 1998 and 2019, 567,789 deaths due to HF were recorded in adults over 50 years old. Systemic inflammation is considered an important pathophysiological factor in the development and progression of heart failure, both in acute and chronic forms. Although it seems to influence each type differently, there is a growing body of evidence linking pro-inflammatory cytokines and chemokines to the entire disease spectrum [6].

In acute heart failure, the pathophysiological mechanisms connecting its cause to inflammation are not yet fully understood. However, significant evidence suggests that inflammation may contribute to changes in vascular resistance, fluid redistribution from systemic circulation, pulmonary congestion, diastolic dysfunction, and systemic hypoperfusion in patients with this condition [7]. It is also known that a large number of cytokines and pro-inflammatory mediators are involved in the pathophysiology of acute heart failure, including C-reactive protein (CRP), tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), interleukin-6 (IL-6), and galectin-3 (Gal-3). These have been associated with the development and progression of the disease, representing predictors of poor prognosis in the medium and long term [7].

Recently, in the field of oncology, inflammatory cells (platelets, leukocytes, neutrophils) have gained prominence as reliable prognostic markers in several malignant tumors [8]. Other studies on chronic diseases have observed an association between inflammatory status and clinical outcomes through the use of complete blood count, with NLR, LMR (lymphocyte-to-monocyte ratio), PLR (platelet-to-lymphocyte ratio), and MPV (mean platelet volume) being the most studied indices. NLR has proven effective in predicting the prognosis of cancer treatments, coronary interventions, myocardial revascularization surgery, and Alzheimer's disease [9]. In heart failure, these inflammatory changes are already present and have recently been evaluated as potential markers for early diagnosis, as well as indicators of risk and prognosis.

Thus, this study aims to assess how the neutrophil-to-lymphocyte ratio can assist in the management of heart failure throughout its course, how it applies in relation to disease mortality, and at what stages it can provide valuable information to the medical team.

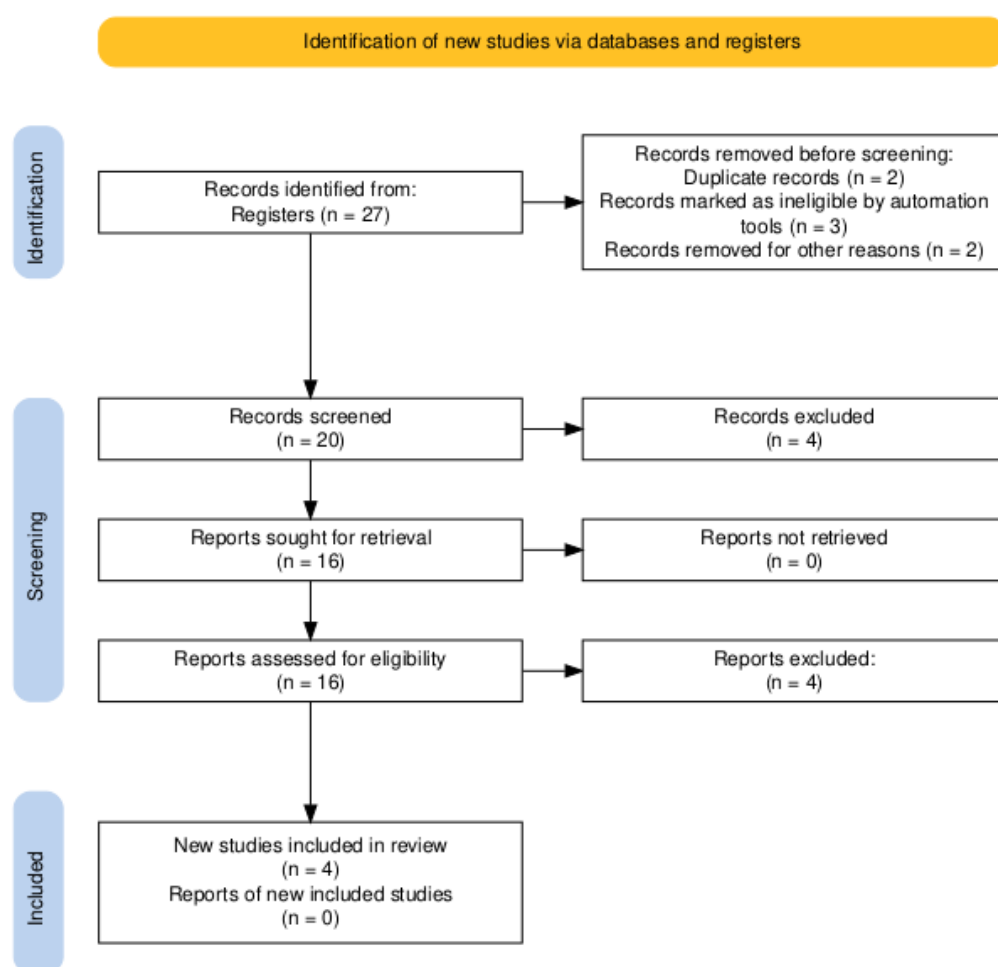
2. Methods

The present study analyzed literature data using an integrative review structure, which, based on evidence, allows for the evaluation, synthesis, and understanding of a phenomenon, aiming to provide an overview of complex concepts, theories, or relevant health problems from pre-existing studies, enabling the proposition of interventions [10]. Six methodological steps were conducted for the selection of articles: 1. formulation of the guiding question or research hypothesis, identifying the problem, presenting the search mechanism, and specifying the descriptors or keywords; 2. establishing inclusion and exclusion criteria for selecting the articles to compose the sample; 3. exploratory reading of article titles and abstracts for pre-selection; 4. analytical reading of the articles to compile, analyze, and categorize the information; 5. interpretation of the results; and 6. synthesis followed by the presentation of the identified results, which address the guiding question [11].

Therefore, in this study, the concepts explored were Neutrophil-to-Lymphocyte Ratio, heart failure, and mortality. Based on these concepts, the guiding question was defined: Is there an association between elevated NLR and mortality in acute heart failure? After formulating the research question, a bibliographic search was conducted on the PubMed, Lilacs, and Scielo platforms. The study was conducted between January and March 2024. Texts were selected through platform searches, applying filters for articles published between 2014 and 2024, covering the last ten years of publications on the subject. The inclusion criteria for the publications were: scientific articles published in English, Portuguese, or Spanish, between 2014 and 2024, available online, and fully accessible for free. Articles without abstracts in the database, incomplete articles, editorials, letters to the editor, reflective studies, and systematic or integrative literature reviews were excluded.

After defining the guiding question, locating, and selecting the articles, 27 publications were initially identified as potentially eligible for inclusion in this review. After applying the inclusion and exclusion criteria, the sample was reduced to 20 publications. Abstracts from 16 records were analyzed to verify if they met the eligibility criteria and answered the question guiding this review, resulting in the exclusion of 12 records. Only 4 articles were fully analyzed to confirm eligibility for quantitative synthesis and data analysis, as outlined in the selection flowchart (Figure 1).

Figure 1. Flowchart of the Publication Selection.



3. Results

Within the timeframe defined for this study (2014-2024), 4 articles were found and analyzed, published in the years 2014, 2016, 2020, and 2021. These articles are summarized in Table 1. The publications were from different journals, namely: Clinics, Scandinavian Cardiovascular Journal, Expert Review of Cardiovascular Therapy, and Journal of Clinical Medicine. The studies were conducted in the United States, Turkey, Romania, and South Korea.

Tabela 1. Sumarização dos artigos revisados.

Reference	Sample Studied	Variables Studied	Main Results	Conclusions/Limitations
12	26-month follow-up of >1000 patients with HF	Neutrophil-to-lymphocyte ratio (NLR)	Decompensated HF with elevated NLR had higher 30-day readmission rates compared to those with lower NLR	NLR was shown to be an efficient marker in cardiovascular diseases, with high values associated with HF decompensation and long-term mortality
13	5625 patients hospitalized with acute heart failure syndrome in 10 referral hospitals nationwide, from March 2011 to February 2014	Neutrophil-to-lymphocyte ratio (NLR)	Patients in the fourth quartile showed higher overall in-hospital mortality and three-year post-discharge mortality	Regardless of the number of HF exacerbations and LVEF severity, the higher the NLR, the worse the overall in-hospital survival and three-year post-discharge survival. For non-infection/non-ischemia cases, the appropriate NLR cutoff for overall in-hospital mortality and three-year post-discharge mortality was 5; for infection/ischemia cases, the appropriate cutoff was 7
14	167 patients hospitalized due to acute HF from January 2010 to October 2012	Neutrophil-to-lymphocyte ratio (NLR)	The NLR value required to detect in-hospital mortality with a sensitivity of 66.7% and a specificity of 60.5% was 4.78	Elevated NLR values were strong predictors of in-hospital mortality in HF patients, independent of other cardiovascular risk factors. NLR can be used as a prognostic marker. Age and LVEF were related to mortality. Elevated NLR appears to be a short-term mortality predictor in patients with reduced EF

15	HF patients admitted to the Cardiology Department of Colentina Clinical Hospital from January 2011 to December 2014	NLR; LMR; PLR	Patients with NLR values in the highest tertiles were older, with longer hospital stays and higher in-hospital mortality rates compared to those in the lowest tertiles	NLR, LMR, and PLR are readily available, easy-to-use, cost-effective biomarkers that could be used for in-hospital prognosis of heart failure as auxiliary parameters alongside validated biomarkers. The strongest predictive value was found for NLR and LMR
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Reduced lymphocyte count was reported by Turfan et al. [14] as an independent predictor of death risk in patients with Acute Coronary Syndrome (ACS), with an NLR > 4.78 showing a sensitivity of 66.7% and specificity of 60.5% for detecting in-hospital mortality, alongside known predictors such as age and ejection fraction ($p < 0.05$). The study analyzed 167 patients hospitalized due to acute HF from January 2010 to October 2012. Patients with known evidence of acute myocardial ischemia, cardiogenic shock, hematologic diseases, metastatic bone marrow neoplasms, sepsis, pregnancy, severe arthritis, inflammatory bowel diseases, infections, chronic inflammatory conditions, glucocorticoid therapy, history of glucocorticoid use in the previous 3 months before admission, and/or other diseases that increase extracellular fluid (e.g., hypothyroidism and liver cirrhosis) were excluded from the study.

Similarly, Afari et al. [12], who conducted a 26-month follow-up of a sample of over 1000 HF patients, found that a higher NLR was associated with frequent decompensation and long-term mortality. Patients with decompensated acute heart failure and elevated NLR had significantly higher 30-day readmission rates compared to those with lower NLR ($p < 0.001$) [PL3]. Besides elevated NLR, a decrease in left ventricular ejection fraction was also linked to increased mortality. A likely explanation is an inflammatory surge of cytokines and proteolytic enzymes that play a role in negative myocardial remodeling. The authors found that patients with HF and NLR > 3 had worse functional status than those with NLR < 3 ($p < 0.001$). An NLR cutoff of 2.74 demonstrated a sensitivity of 79.4% and a specificity of 80% in predicting poor functional status in heart failure patients.

In a study conducted by Cho et al. [13], which analyzed 5625 patients hospitalized with acute heart failure syndrome in 10 referral hospitals nationwide from March 2011 to February 2014, it was found that regardless of the number of HF exacerbations and the severity of left ventricular ejection fraction, the higher the NLR, the worse the overall in-hospital survival and three-year post-discharge survival. When the aggravating factor was unrelated to infection and ischemia, an NLR cutoff of 5 was associated with overall in-hospital mortality and three-year post-discharge mortality. However, when the aggravating factor was infection and/or ischemia, the appropriate NLR cutoff for overall in-hospital mortality and three-year post-discharge mortality was 7. In summary, patients presenting signs or symptoms of acute heart failure, such as pulmonary edema, objective findings of left ventricular systolic dysfunction, or structural heart disease, were enrolled in the study, with no other specific exclusion criteria ($p < 0.05$) [PL4].

Corroborating these findings, the study by Delcea et al. [15], which analyzed HF patients admitted to the Cardiology Department of Colentina Clinical Hospital from January 2011 to December 2014, showed that patients with higher NLR values were significantly older, had longer hospitalizations, and higher in-hospital mortality rates

compared to those with lower NLR levels. In this study, the authors found that patients with an NLR of 3.68 had a 2.22 times higher risk of requiring prolonged hospitalization and a 7.21 times higher risk of in-hospital mortality ($p < 0.001$) [15].

These studies have significant limitations, and overall, the sample size and retrospective nature reduce the accuracy and reliability of the results. The study by Turfan et al. [14] emphasized that other inflammatory markers were not analyzed or compared with NLR, and readmissions were not included in the study outcomes. Afari et al. [12] noted that variability in follow-up and the population sample, as well as the lack of standardization in heart failure decompensation criteria, compromised the generalizability of the results. In Cho et al.'s study [12], the NLR value was only analyzed at the time of hospital admissions, preventing the assessment of the effects of changes in this marker during hospitalization. Furthermore, they pointed out potential confounding factors such as nutritional status and the interference of comorbidities. Delcea et al. [15] highlighted the inability to assess variables such as diuretic dosage and hospital complications, lack of information on pre-admission treatment, and strict exclusion criteria that resulted in lower mortality in the cohort. Additionally, the predictive models for in-hospital mortality or prolonged hospitalization were not validated.

3. Conclusion

Given the objective of analyzing whether there is an association between neutrophil-to-lymphocyte ratio and mortality in acute heart failure, as well as its contribution to the management and prognosis of the disease in a hospital setting, this review highlights and increases the pre-test value and the likelihood of the association of NLR with fatal and non-fatal cardiovascular outcomes, which need to be confirmed in large prospective studies.

In this context, research aimed at evaluating the degree of improvement in risk prediction by adding NLR to established scores is necessary and welcome. In summary, while the potential prognostic value of NLR needs to be better studied in its clinical applications, it is very easy to use. However, it is extremely important to conduct more longitudinal studies and clinical trials with larger population samples, along with standardized measurement and more precise cutoff values, to increase the evidence for using this marker in clinical practice.

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References

1. Beltowski J. Microalbuminúria e o risco de mortalidade em pacientes com insuficiência cardíaca aguda. *Arq Bras Cardiol*. 2022;118(4):710-1.
2. Nogueira PR, Rassi S, Corrêa K de S. Perfil epidemiológico, clínico e terapêutico da insuficiência cardíaca em hospital terciário. *Arq Bras Cardiol* [Internet]. 2010 Sep;95. Available from: [URL]. Accessed: [date].
3. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol*. 2018;14:576-90.
4. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet*. 2010;375:132-40.
5. Bhat T, Tel S, Rija J, Bhat H, Raza M. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. *Expert Rev Cardiovasc Ther*. 2013;11:55-9.
6. Reina-Couto M, et al. Inflammation in human heart failure: major mediators and therapeutic targets. *Front Physiol*. 2021 Oct;12.
7. Garofalo M, et al. Inflammation in acute heart failure. *Front Cardiovasc Med*. 2023 Nov;10.

8. Zhong JH, Huang DH, Chen ZY. Prognostic role of systemic immune-inflammation index in solid tumors: a systematic review and meta-analysis. *Oncotarget*. 2017 Jun 29;8(43):75381-8. doi: 10.18632/oncotarget.18856.
9. Soares IHS, et al. Valor preditor de morbimortalidade da relação neutrófilo-linfócito em pacientes com doença renal crônica: revisão integrativa da literatura. *Res Soc Dev*. 2021;10(15).
10. Botelho LLR, Cunha CCA, Macedo M. O método da revisão integrativa nos estudos organizacionais. *Gestão Soc*. 2011;5(11):121-36. doi: 10.21171/ges.v5i11.1220.
11. De Sousa LD, Lunardi Filho WD, Lunardi VL, Santos SS, dos Santos CP. The nursing scientific production about the clinic: an integrative review. *Rev Esc Enferm USP*. 2011;45(2):494-500.
12. Afari ME, Bhat T. Neutrophil to lymphocyte ratio (NLR) and cardiovascular diseases: an update. *Expert Rev Cardiovasc Ther*. 2016. doi: 10.1586/14779072.2016.1154788.
13. Cho JH, Cho HJ, Lee HY, Ki YJ, Jeon ES, Hwang KK, Chae SC, Baek SH, Kang SM, Choi DJ, Yoo BS, Kim KH, Kim JJ, Oh BH. Neutrophil-Lymphocyte Ratio in Patients with Acute Heart Failure Predicts In-Hospital and Long-Term Mortality. *J Clin Med*. 2020 Feb 18;9(2):557. doi: 10.3390/jcm9020557. PMID: 32085596; PMCID: PMC7073552.
14. Turfan M, Erdogan E, Tasal A, Vatankulu MA, Jafarov P, Sonmez O, et al. Neutrophil-to-lymphocyte ratio and in-hospital mortality in patients with acute heart failure. *Clinics*. 2014;69(3):190-3.
15. Delcea C, Buzea CA, Vijan A, Draghici A, Stoichitoiu LE, Dan G-A. Comparative role of hematological indices for the assessment of in-hospital outcome of heart failure patients. *Scand Cardiovasc J*. 2021;55(4):227-36. doi: 10.1080/14017431.2021.1900595.