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SYSTEMATIC REVIEW

The Neutrophil-to-Lymphocyte Ratio's Predictive Utility in Acute Pulmonary Embolism: Systematic Review

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ABSTRACT

Acute pulmonary embolism is a cardiovascular emergency with a significant morbidity and mortality. In the last decade, attempts have been made to find prognostic markers for pulmonary embolism. We conducted a systematic review of the literature for studies that assess the relationship between the neutrophil-to-lymphocyte ratio (NLR) and disease progression in patients with pulmonary embolism. We included a total of seven studies published between 2016 and 2021, reporting on a total of 4,272 patients. The mean NLR observed in these studies was 5.93, with values ranging from 5.12 to 7.3. Elevated NLR was significantly associated with an increased rate of mortality in all studies. Furthermore, the collected data revealed a 2-to-15 times higher mortality rate in the group with NLR values higher than the mean. Due to its accessibility and the simplicity with which it can be calculated, as well as the outcomes revealed in this review, we strongly emphasize that NLR should be used more in medical practice.

Keywords: neutrophil-to-lymphocyte ratio, acute pulmonary embolism, mortality rate, inflammatory markers, NLR cut-off value

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INTRODUCTION

Acute pulmonary embolism (APE) is a cardiovascular emergency with a significant morbidity and mortality, ranking third worldwide in terms of mortality.[1] Despite being intensively studied, APE is associated with a high in-hospital mortality rate of 60–70 per 100,000 individuals.[2] In the USA, the yearly incidence of patients diagnosed with pulmonary embolism is 23–69 per 100,000 individuals.[3] Inflammation certainly plays an important role in thrombosis, causing endothelial damage, activating procoagulant factors, and inhibiting anticoagulation.[4] In the last de-

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cade, attempts have been made to find prognostic markers for the severity of pulmonary embolism and improve its mortality rate. These markers include troponin, brain natriuretic peptide (BNP), N-terminal pro b-type natriuretic peptide (NT-proBNP), and heart-type fatty acid-binding protein (H-FABP), but each marker has its limitations, most of them being difficult to use and expensive.

As a result, researchers started to investigate inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), which has been corelated with a high risk of morbidity and mortality in clinical care. This marker has been discovered to have significant associations in the following areas: cardiovascular surgery, cardiology, gastric cancer, pancreatic cancer, colorectal cancer, and ovarian cancer.[5–21] Numerous studies have been published in the last decade regarding the relationship between the NLR and the progress of patients diagnosed with APE.[22–24]

In this study, we systematically evaluated the relationship between NLR use and the prognosis of patients with pulmonary embolism. The reported optimal cut-off values of NLR differ from one published work to another, not having a fixed value, with direct applicability in medical practice. Our aim is to provide a foundation for further research towards the accurate identification of the association between the NLR and the severity of the disease in patients with pulmonary embolism.

MATERIALS AND METHODS

SEARCH STRATEGY

We conducted a systematic review of the literature for studies that assess the relationship between the NLR and disease progression in patients with pulmonary embolism. The study was carried out in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement,[25] using MEDLINE, Science Direct, Scopus, and Web of Science databases. These databases were searched for relevant studies published over a period of six years, from January 2016 to December 2021.

To prevent the possibility of selection bias, the search was undertaken individually by two different reviewers. Following the main screening, additional studies were included from the reference lists of reviews as well as other collected publications. The included publications had to be compatible with the following search terms: neutrophil-to-lymphocyte ratio, acute pulmonary embolism, pulmonary embolism, mortality rate, NLR cut-off value, systematic review, and meta-analysis, combined with the Boolean logical operators "AND" and "OR".

STUDY SELECTION

Following the main screening, the studies were evaluated according to a set of predetermined inclusion and exclusion criteria (secondary screening) that were based on existing comparable systematic reviews and meta-analyses focused on the topic of this investigation. We included studies conducted on patients diagnosed with APE with reported mean values for NLR and patients in whom there was a correlation between the NLR cut-off values and patient prognosis. We excluded studies that were not published in English, case reports, case studies, special articles, letters to the editor, or other non-clinical literature that was not considered either systematic review or meta-analysis, studies not reporting mean or median values and standard deviation of NLR, studies not employing a clear definition regarding the diagnosis of APE, or studies that did not offer enough data on the correlation between NLR and patient outcome.

DATA EXTRACTION AND RECORDING

The data was extracted in a top-down manner, with the selected full-text studies being individually inspected for relevant patient and study data by three reviewers in order to provide redundancy while minimizing individual mistakes. The reviewers extracted the data using a standardized data extraction form in Microsoft Excel that contained all of the relevant data items. Duplicate information/studies were eliminated after all reviewers had extracted individual data. The resulting collection of research data was compiled into a single database for subsequent analysis.

The data items extracted from the full-text versions of individual studies included the name of the first author, year of publication, study design, sample size, mean age, gender ratio, the studied marker (NLR), outcomes, and follow-ups.

STATISTICAL ANALYSIS

Continuous data were expressed as means, categorical data were expressed as percentages, and a probability (p) value of 0.05 was accepted as statistically significant.

RESULTS

STUDY SELECTION

The electronic database search identified a total of 1,328 publications. Due to a lack of relevance for our study, the

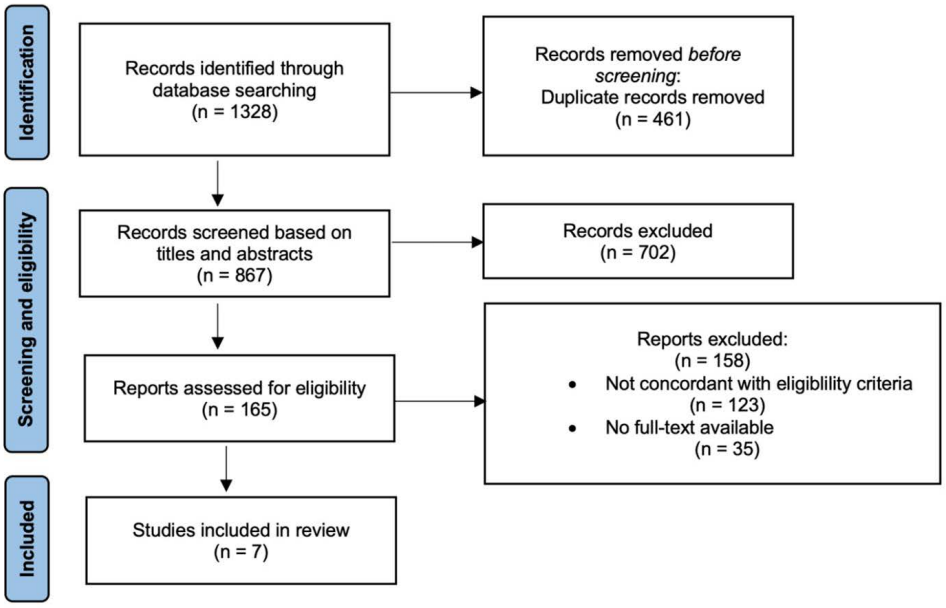

FIGURE 1. PRISMA flow diagram[25] showing the selection of the publications included in the review

majority of these publications were filtered out by the two reviewers. After the main screening, duplicates were eliminated, and adherence to the inclusion and exclusion criteria was assessed. This process yielded a total of 16 publications, from which we excluded five more due to the inadequacy of the revealed data and another four due to the insignificant number of individuals included in the reports. At the end, we were able to include seven studies in our systematic review, reporting on a total of 4,272 patients. All seven studies were published between 2016 and 2021. The selection procedure is presented in Figure 1.

GENERAL CHARACTERISTICS

Table 1 presents the general characteristics of the included publications. The mean NLR value was 5.93, ranging from 5.12 to 7.3. Regarding mortality rates, three publications reported 30-day mortality, two studies reported in-hospital mortality, one study reported 30-day and 12-month mortality, and one study reported 30-day and 20-month mortality.

From each publication included in this systematic review, we gathered information on the comorbidities identified in patients with APE, which included hypertension, heart failure, type 2 diabetes (T2D), chronic obstructive pulmonary disease (COPD), and malignancy (Table 2). We should note that one of the studies (Duman *et al.*) addressed only non-massive APE, therefore their percentages were lower overall.

In-hospital mortality varied from 8.88 to 14.65%, and 30-day mortality ranged between 7% and 13.8%. One of the studies revealed a significantly higher mortality rate during the 12-month follow-up (39.2%), which can be probably attributed to the higher mean age of the study

TABLE 1. The main characteristics of the included studies

Study	Year	Study design	Sample size	Age (years)	Male sex (%)	NLR cut-off	Outcomes	Follow-up
Karataş *et al.*[26]	2016	Retrospective	203	65.8	43	5.93	30-day mortality	20-month mortality
Soylu *et al.*[27]	2016	Retrospective	142	58.9	59.8	5.7	In-hospital mortality	In-hospital mortality
Ma *et al.*[28]	2016	Retrospective	248	66.7	56	5.99	30-day mortality	30-day mortality
Kasapoğlu *et al.*[29]	2019	Retrospective	550	68	50.3	7.3	30-day mortality	30-day mortality
Phan *et al.*[30]	2020	Retrospective	191	59.5	50.9	5.46	In-hospital mortality	In-hospital mortality
Efros *et al.*[31]	2021	Retrospective	2,072	73.3	42.5	5.12	30-day mortality	12-month mortality
Duman *et al.*[32]	2021	Retrospective	828	62	47	6.1	30-day mortality	30-day mortality

TABLE 2. Comorbidities and mortality rates in the included studies

	Karataş *et al.*[26]	Soylu *et al.*[27]	Ma *et al.*[28]	Kasapoğlu *et al.*[29]	Phan *et al.*[30]	Efros *et al.*[31]	Duman *et al.*[32]
Hypertension	45%	32.4%	32.66%	–	54.45%	44.83%	4.7%
Heart failure	18%	11.3%	18.5%	11%	12.56%	5.83%	1.6%
T2D	19%	21.8%	10.4%	15%	19.9%	18.87%	2.1%
COPD	10%	13.4%	20.16%	25.6%	10.99%	9.1%	1.9%
Malignancy	–	20%	7.2%	4%	–	26.97%	–
In-hospital mortality	–	10.5%	–	–	14.65%	8.88%	–
30-day mortality	7%	–	8.06%	13.8%	–	–	13.8%
12–24-month mortality	10%	–	–	–	–	39.2%	–

T2D – type 2 diabetes; COPD – chronic obstructive pulmonary disease

population of 73.7 years, compared to other studies that reported mean ages between 58.9 and 68 years (Table 2)

In five of the seven studies included in our analysis, the mean value of the NLR was determined separately for patients who died (NLR-d) and those who survived (NLR-s). In four of the five studies, the NLR was around double in those who died. In a study conducted by Karataş *et al.*, the mean NLR was 2.16 times higher in the patients who died (NLR-d: 9.02; NLR-s: 4.17; p = 0.01). In the study of Ma *et al.*, the mean NLR was 2.25 times higher (NLR-d: 10; NLR-s: 4.43; p <0.001). Phan *et al.* reported a 2.07 times higher NLR (NLR-d: 8; NLR-s: 3.91; p <0.001), and Duman *et al.* a 1.73-times higher NLR in patients who died (NLR-d: 4.85; NLR-s: 2.79; p = 0.001). In this last study, both values were low probably due to the fact that the study did not include patients with massive APE. The study of Kasapoğlu *et al.* reported significant differences between the two groups (NLR-d: 8.4; NLR-s: 7.6; p = 0.003) (Table 3).

In the other two studies, patients were divided into two groups based on whether their NLR values were lower or higher than the mean. Mortality rates were calculated separately for each group. The acquired data showed that in one of the studies, conducted by Soylu *et al.*, the mortality rate was more than four times higher in the group with higher NLR values (14.4% vs. 3.4%; p <0.001). Another study, by Efros *et al.*, reported a 15 times higher mortality rate in the higher NLR group (21.1% vs. 1.4%; p <0.001) (Table 4).

TABLE 3. Mean value of NLR in surviving and deceased patients

Study	Survivors (NLR-s)	Deceased (NLR-d)	p value
Karataş *et al.*[26]	4.17	9.02	0.01
Ma *et al.*[28]	4.43	10	<0.001
Kasapoğlu *et al.*[29]	7.6	8.4	0.003
Phan *et al.*[30]	3.91	8.1	<0.001
Duman *et al.*[32]	2.79	4.85	<0.001

NLR-s – neutrophil-to-lymphocyte ratio in patients who survived; NLR-d – neutrophil-to-lymphocyte ratio in patients who died

DISCUSSION

This systematic review encompassed the latest studies that suggest a correlation between a high NLR and the prognosis of patients with APE. One of the included studies found that a high NLR was related to an increased mortality rate of up to 15 times, referring to both short- and long-term survival.

The predictive markers studied for prognosis assessment in patients with APE include D-dimers, NT-proBNP, and cardiac troponin I (cTnI). D-dimers are produced due to fibrinolytic degradation and high levels have been associated with a high morbidity and mortality. NT-proBNP levels have also been correlated with the severity of right ventricular dysfunction, and cTnI reflects myocardial damage. However, the results regarding these biomarkers have been inconsistent, and their routine use in medical practice requires further studies.[33–35]

In a 2014 study that included 266 patients with APE, Cavus *et al.* comparatively analyzed the mean value of NLR in patients who died and patients who survived. They found NLR levels to be almost three times higher in those who died (9.0 versus 3.7; p <0.001), demonstrating a connection between NLR and mortality.[36] Another predictive marker of mortality in patients with APE is the platelet-to-lymphocyte ratio (PLR), the usefulness of which has

TABLE 4. Mortality rate (%) based on the cut-off value of NLR

Study	Mean NLR	NLR < mean	NLR > mean	p value
Soylu *et al.*[27]	5.12	3.4%	14.4%	<0.001
Efros *et al.*[31]	4.44	1.4%	21.1%	<0.001

NLR – neutrophil-to-lymphocyte ratio

been demonstrated by numerous recently published studies. However, although its specificity was statistically significant in association with NLR, the PLR was inconsistent and had no individual predictive value, as it was also found by two of the studies (Karataş *et al.* and Ma *et al.*) included in our systematic review.

APE has a high fatality rate and an unpredictable course. Identifying prognostic markers of unfavorable prognosis would have a massive benefit in clinical management and therapy. The NLR is easily calculated and easily accessible in medical practice.

The Pulmonary Embolism Severity Index (PESI) is currently used to divide patients into five risk classes associated with progressive rates of morbidity and mortality, as follows: class I – very low risk; class II – low risk; class III – intermediate risk; class IV – high risk; class V – very high risk. The last two classes are associated with the highest mortality rate. PESI is based on 11 predictive indicators derived from patient history and clinical examination. Given the ease with which NLR may be used in clinical practice, the correlation of NLR with each PESI risk class would be more accurate in predicting the morbidity and mortality of APE patients. We noticed from the included studies that the mean value of NLR for both the surviving and the deceased group was lower in a study conducted by Duman *et al.*, which included patients with non-massive APE. This suggests that there may be a connection between NLR and the severity of the embolic event. Further studies are needed to evaluate the association of NLR values with each PESI risk class for a more accurate assessment.

CONCLUSIONS

According to our findings, a high NLR is related to an elevated risk for both short- and long-term mortaliy in patients with acute pulmonary embolism. Because the ratio is easy to calculate in daily medical practice, we believe that, combined with other risk variables and predictors, it may be considered a major tool in assessing the prognosis of patients with acute pulmonary embolism.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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