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Journal of Interdisciplinary Medicine

REVIEW

VASCULAR SURGERY // CARDIOLOGY

The Role of Systemic Inflammatory Markers in the Progression and Risk of Abdominal Aortic Aneurysm Rupture – a Systematic Review

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ARTICLE HISTORY

Received: November 15, 2023
Accepted: February 2, 2024

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ABSTRACT

Abdominal aortic aneurysm (AAA) is a serious condition where the aorta becomes abnormally dilated, which can lead to serious health risks. Inflammation plays a crucial role in AAA. The neutrophil-to-lymphocyte ratio (NLR) is a known prognostic marker for various medical conditions, including AAA. This review aims to assess the role of NLR in predicting adverse outcomes in patients with AAA. A systematic review of articles from PubMed covering the years 2013 to 2023 was conducted using the PRISMA guidelines. Out of 1,701 articles identified, 24 full-text publications were screened, and only 8 were included. The studies used receiver operating characteristic analysis to determine the best NLR cut-offs, which ranged from 4 to 9.7. The studies provide evidence that links NLR to mortality and rupture in patients with AAA. The utility of NLR utility extends beyond AAA, demonstrating significance in conditions like acute limb ischemia, chronic kidney disease, and coronary artery disease. This review underscores the potential of NLR as a valuable prognostic tool in AAA, offering insights for risk stratification and patient management.

Keywords: abdominal aortic aneurysm, inflammatory biomarkers, mortality, outcome

INTRODUCTION

Abdominal aortic aneurysm (AAA) represents a potentially lethal medical condition characterized by the abnormal dilation of the aorta, the largest blood vessel in the abdomen. In AAA the maximum diameter of the abdominal aorta exceeds 30 mm, or there is an enlargement of >50% compared to the healthy aorta. The most frequent risk factors of AAA include smoking, aging, and male sex,[1,2] but the latest studies suggest a more significant role of inflammation responses,

mediated by matrix metalloproteinase activation, oxidative stress, intraluminal thrombus, smooth muscle apoptosis, and extracellular matrix degeneration.[3–5]

The neutrophil-to-lymphocyte ratio (NLR) was recently suggested as a prognostic marker for various diseases, such as end-stage kidney disease,[6] acute limb ischemia,[7] or in the assessment of outcome and patency after lower limb revascularization[8] and arteriovenous fistulae maturation.[9]

Despite numerous attempts at the medical management of AAA, the surgical approach remains the most suitable, especially for those at risk of rupture.[10,11]

The primary aim of this systematic review was to assess the prognostic significance of NLR in predicting adverse outcomes in patients with AAA. Our secondary aim was to establish a threshold biomarker value associated with the risks of rupture, mortality, and complications following surgical or endovascular interventions.

METHODS

We performed a systematic review of the literature, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, using papers from the PubMed database and the search terms 'abdominal aortic aneurysm' and 'NLR'.

Two independent reviewers (C.P. and A.V.M.) conducted the literature search. We included all papers with relevant titles that were published in English between January 1, 2013, and January 1, 2023. Studies in languages other than English, studies unrelated to this topic, inadequate data presented, non-confirmatory instances, and duplicate publications were excluded.

A total of 1,701 articles fit the search parameters, and an additional 5 articles were added from the reference lists of these articles. After removing duplicates and applying the inclusion and exclusion criteria, only 24 full-text publications were eligible. We eliminated 16 papers due to unclear methodology and bias, and included a total of 8 articles in our systematic review. The PRISMA flow chart is shown in Figure 1.

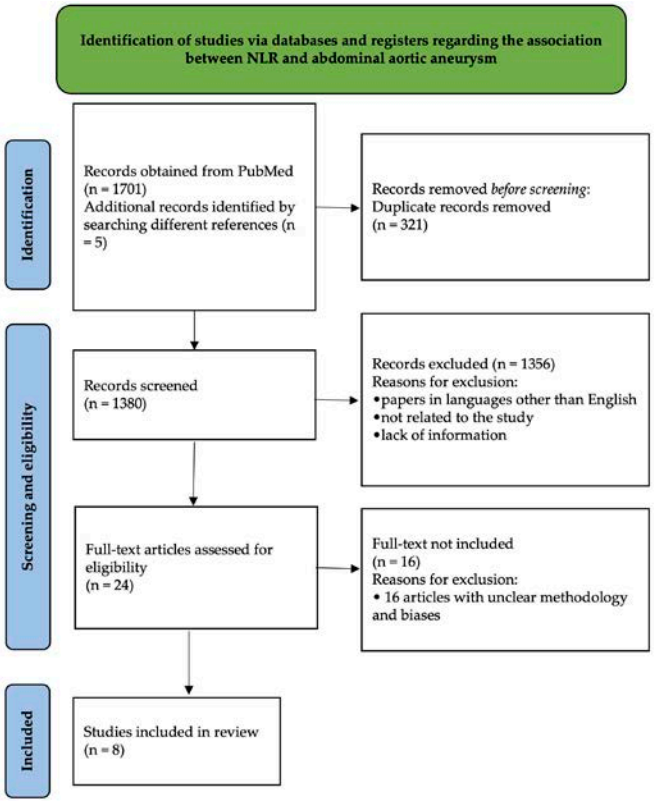

FIGURE 1. PRISMA flow chart

RESULTS

In this comprehensive systematic review, we included eight studies published in the past decade, involving a total of 3,549 patients diagnosed with AAA. The average age of the patients was 75.8 years, with an average maximum diam-

TABLE 1. The demographic and clinical data of the participants

Study	Year	Country	No. of patients	Mean age (years)	Male sex, n (%)	Hypertension, n (%)	Ischemic heart disease, n (%)	Diabetes, n (%)	Peripheral arterial disease, n (%)	Active smoking, n (%)
Appleton *et al.*[12]	2014	UK	350	72.9	275 (78.57%)	291 (83%)	154 (44%)	–	46 (13%)	123 (35%)
Kordzadeh *et al.*[13]	2015	UK	80	75	66 (82.5%)	43 (64.2%)	–	–	–	19 (25%)
Aurelian *et al.*[14]	2019	Romania	255	68.3	230 (90.4%)	189 (74.11%)	–	36 (14.11%)	–	66 (25.88%)
Bath *et al.*[15]	2019	USA	1,908	72.2	1,457 (76.4%)	–	885 (46.4%)	386 (20.2%	–	–
King *et al.*[16]	2020	USA	108	75.5	78 (72.2%)	88 (81.5%)	52 (48.1%)	27 (25%)	25 (23.1%)	32 (19.6%)
Tuncay *et al.*[17]	2021	Turkey	42	–	–	35 (83.3%)	11 (26.19%)	10 (23.8%)	–	17 (40.47%)
Octeau *et al.*[18]	2021	USA	777	75.8	652 (84%)	686 (88%)	523 (67%)	332 (43%)	–	111 (14%)
Garagoli *et al.*[19]	2022	Argentina	29	-	20 (68.96%)	20 (68.96%)	-	4 (13.79%)	-	18 (62.06%)

TABLE 2. AAA characteristics and outcomes, and cut-off values of NLR

Study	AAA diameter (cm)	Study group value	Control group value	Cut-off value	AUC/ROC analysis	Sensitivity (%)	Specificity (%)	Outcome	Follow-up period
Appleton *et al.*[12]	–	4.2	2.8	5	–	–	–	Mortality	30 days
Kordzadeh *et al.*[13]	7.55	–	–	5	–	–	–	Mortality	30 days
Aurelian *et al.*[14]	6.84	9.3	3.39	5	–	–	–	Rupture	–
Bath *et al.*[15]	–	13.8	5.93	9.7	0.662	–	–	Composite outcome: in-hospital mortality, cardiac problem, or myocardial infarction	–
King *et al.*[16]	5.55	–	–	4	0.780	62.2%	87.3%	Mortality	5 years
Tuncay *et al.*[17]	–	8.9	4.4	6.6	–	80%	89%	Rupture	2.5 years
Octeau *et al.*[18]	5.6	–	–	3.6	–	–	–	Mortality	5 years
Garagoli *et al.*[19]	–	–	–	6.4	0.88	100%	77%	Mortality	In-hospital

TABLE 3. The association of OR and HR values with outcomes in AAA

Study	OR/HR	95% CI		p value	Outcome	Kaplan–Meier	logrank p value
		Lower	Upper				
Kordzadeh et al.13	4.28	1.27	14.42	0.02	Mortality	–	–
Aurelian et al.14	5.085	3.002	8.61	<0.0001	Rupture	–	–
Bath et al.15	2.19	1.45	3.31	0.002	Renal failure	–	–
	2.41	1.21	4.77	0.01	Cardiac complication		
	1.73	1.22	2.45	0.003	Respiratory problems		
	2.59	1.65	4.07	<0.001	Infection		
King et al.16	1.19	1.12	1.27	<0.001	Mortality	Mortality based on NLR optimal cut-off value	<0.001
Octeau et al.18	1.046	1.016	1.078	0.003	Mortality	–	–

eter of the abdominal aorta of 6.385 cm. The study population consisted predominantly of male patients (79.21%). Hypertension emerged as the most prevalent comorbidity, affecting 82.38% of patients, followed by ischemic heart disease (51.02%) and diabetes (25.48%). In addition, 23.52% of the patients were active smokers. Other details regarding various variables are presented in Table 1.

From the eight studies reviewed, only three conducted receiver operating characteristic (ROC) analyses, revealing optimal NLR cut-off values. Specifically, Bath *et al.*[15] identified a value of 9.7, while Garagoli *et al.*[19] determined a cut-off value of 6.4, with a sensitivity of 100% and specificity of 77%. In the study by King *et al.*,[16] the optimal NLR cut-off was found to be 4, with a sensitivity of 62.2% and specificity of 87.3%. Notably, three studies opted for a threshold value of 5, as detailed in Table 2.

Kordzadeh *et al.*,[13] King *et al.*,[16] and Octeau *et al.*[18] provided evidence supporting the association between NLR and the risk of mortality within 30 days and over a 5-year period following surgical or endovascular interventions for AAA. In the investigation conducted by Aurelain *et al.*,[14] outlined in Table 3, elevated baseline NLR values were identified as being positively correlated with the risk of AAA rupture (odds ratio (OR) 5.085, p <0.0001). Additionally, Bath *et al.*[15] showcased that heightened levels of this biomarker are linked to increased risks of renal failure, cardiac complications, respiratory problems, and infection.

DISCUSSION

This type of analysis has been shown to be useful not only in assessing the impact of AAAs, but also in other conditions, such as acute limb ischemia. In this regard, Fajardo *et al.* showed that mortality was lower in the NLR <5 group (33%) than in the NLR >5 group (49%) (p ≤0.001), and amputation-free survival (AFS) was significantly higher in the NLR <5 group (50%) than in the NLR >5 group (26%) (p ≤ 0.001). In a multivariate analysis, preoperative NLR >5 was independently associated with 5-year AFS (hazard ratio (HR) 2.325, 95% confidence interval (CI) 1.732–

3.121).[20] Furthermore, a more recent study by Pasqui *et al.*,[21] which also included the platelet-to-lymphocyte ratio (PLR), showed that freedom from all amputations was significantly higher when the NLR and PLR were below the identified cut-off values ($p < 0.0001$). In the same study, the NLR and PLR were found to be independent risk factors.[21]

Another field in which the NLR has shown its usefulness is nephrology, more specifically chronic kidney disease (CKD), a global public health problem with a high mortality rate and a rapid progression to end-stage kidney disease (ESKD). Recently, the role of inflammation and the correlation between inflammatory markers and the progression of CKD have been studied. Malhotra *et al.*[22] have shown that NLR could be a potential substitute marker for hs-CPR in patients undergoing hemodialysis, as it is a useful systemic inflammation test, especially in places with limited resources. Its superiority has also been proven in other studies in which the NLR reached higher levels than other markers, such as hs-CPR and interleukins, or served as an indicator of acute kidney injury in patients with sepsis or of cardiovascular events in patients with ESKD.[23,24] Patients with ESKD have to undergo hemodialysis, some of them using the arteriovenous fistula performed by the vascular surgeon. Some studies found a link between high inflammatory status and the failure of the arteriovenous fistula,[25,26] making them a useful tool for preoperative risk group stratification, better patient management, and developing predictive patterns.

The association between inflammation and atherosclerosis is well known. This process affects all arteries, particularly the cerebral, the peripheral, and the coronary arteries. Regarding the latter, several studies demonstrated that these hematological parameters are associated with the severity and prognosis of coronary artery disease. Nunez *et al.* showed that the highest values of NLR measured within the first 96 h after the onset of ST-elevation myocardial infarction symptoms carried a significant prognostic value for subsequent mortality. Moreover, this association remained significant after adjusting for key predictors such as age, reperfusion criteria, renal function, and indicators of myocardial extensions (left ventricular dysfunction, systolic blood pressure, and Killip's classification).[27]

Similar results were obtained in China, where a cohort study involving 2,618 patients with acute myocardial infarction presented high NLR values (>5.509) and a high risk of mortality during hospitalization. The predictive role of high NLR values regarding negative outcomes, especially major adverse cardiovascular events (MACE), was confirmed by another study, which compared the neutrophil-to-monocyte ratio (NMR), PLR, the lymphocyte-to-monocyte ratio (LMR), and NLR and found that these markers had the best ability to predict in-hospital death after non-ST-elevation myocardial infarction.[28,29]

Study limitations

The main limitation of this study is the absence of ROC analysis in five of the eight enrolled studies. Hence, the threshold values of the NLR were not proposed and calculated according to the Youden index but were implemented from other studies in which the role of the NLR in other cardiovascular pathologies was analyzed. Therefore, it is necessary to carry out prospective multicenter studies to identify a threshold value of the NLR that can be implemented in current practice for a better stratification of risk groups. Furthermore, the heterogeneity of the groups and of the surgical or endovascular treatment between the studies, as well as the presence of AAA rupture influence the evolution of the patients and the laboratory data.

CONCLUSIONS

AAA is a potentially fatal disorder characterized by abnormal aortic dilation, with inflammation having a critical role in its pathogenesis. The NLR has emerged as a possible predictive marker, with implications in a variety of medical settings. This systematic review showed that the NLR is useful in predicting the development, progression, and rupture of AAA, and the mortality risk of patients with this condition.

ACKNOWLEDGEMENT

This work was supported by the George Emil Palade University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, Research Grant number 165/6/10.01.2023.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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