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RESEARCH

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Prognostic Significance of Preoperative Neutrophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio in Patients with Ruptured Abdominal Aortic Aneurysm Undergoing Endovascular Aneurysm Repair

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Abstract

Background Ruptured abdominal aortic aneurysm (RAAA) is a fatal disease. This study aimed to assess the prognostic value of the preoperative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in patients with RAAA undergoing endovascular aneurysm repair (EVAR).

Materials and methods This retrospective study included patients with RAAA who underwent EVAR from 2012 to 2022. NLR and PLR were measured when patients were first admitted to the hospital before receiving any treatment. Risk factors associated with overall survival in this patient group were identified through univariate and multivariate analyses. Nomograms and artificial neural networks were developed to evaluate the prognosis of these patients.

Results A total of 50 patients were included in this study. The optimal cut-off points for predicting overall survival were an NLR of 19.6 and a PLR of 190.5. Univariate and multivariate analyses revealed that NLR (hazard ratio 0.271, $p=0.024$) and PLR (hazard ratio 0.272, $p=0.041$). Were independent risk factors for overall survival. Nomograms and artificial neural networks also showed the prognostic value of preoperative NLR and PLR in this patient group.

Conclusion Preoperative NLR and PLR are independent and valid predictors of prognosis in patients with RAAA undergoing EVAR. The higher the preoperative NLR and PLR of the patients, the worse their prognosis.

Keywords Ruptured abdominal aortic aneurysm, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Endovascular aneurysm repair, Prognosis

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Introduction

Abdominal aortic aneurysm (AAA) is a multifactorial degenerative disease that leads to persistent dilatation of the aortic wall as it progresses [1]. Ruptured AAA (RAAA) is the most common and dangerous complication, with a mortality rate of over 90% in patients who do not receive surgical intervention [2]. Although the treatment options for RAAA include open surgery and endovascular aneurysm repair (EVAR), even emergency surgery carries a high mortality rate of nearly 50%, posing a serious threat to the lives of the patients [3]. The choice of treatment remain uncertain. Thus, finding simple and easily accessible indicators to guide frontline clinicians in developing appropriate and timely treatment plans is important to improving the prognosis of patients. Therefore, identifying preoperative indicators that can predict the prognosis of this patient group is urgent.

The neutrophil-to-lymphocyte ratio (NLR) is commonly used as a marker of the systemic inflammatory response, while the platelet-to-lymphocyte ratio (PLR) indicates thrombosis and inflammation [4, 5]. Emerging evidence suggests that inflammatory markers, such as NLR and PLR, are associated with poor prognosis following the repair of vascular diseases like AAA and aortic dissection [6]. These markers have also been studied in some cancers, such as liver and gastric cancers [7, 8]. However, the role of NLR and PLR in assessing long-term survival in RAAA patients receiving EVAR is still not very clear.

Thus, this study aimed to assess the prognostic value of NLR and PLR in predicting long-term survival in patients with RAAA who undergo EVAR.

Materials and methods

Patient criteria

The study was approved by the Ethics Committee of the First Affiliated Hospital of the Naval Medical University, and all participants provided informed consent. We conducted a retrospective analysis of clinical data collected from patients who underwent EVAR for RAAA at the First Affiliated Hospital of the Naval Military Medical University from June 2012 to December 2022. Patients were eligible for inclusion if they had a confirmed diagnosis of RAAA by computer tomography angiography and signed an EVAR informed consent form approved by the institutional review board. Patients with any of the following criteria were excluded from the study: (1) active malignancy; (2) acute infection; (3) anti-inflammatory medication within the last three months; (4) hematopoietic or autoimmune disorders; and (5) lost to follow-up after surgery. Baseline clinical characteristics, imaging findings, surgical records, and clinical outcomes of the patients were obtained from their medical records.

Blood test

Blood tests are performed on patients during their emergency visit, with venous blood collected preoperatively using a tourniquet. The absolute values of neutrophils, lymphocytes, and platelets are measured using a fully automated hematology analyzer. NLR is defined as being calculated by dividing the number of neutrophils by the number of lymphocytes, while PLR is calculated by dividing the number of platelets by the number of lymphocytes.

Clinical risk factors

Clinical risk factors were assessed prior to or at cohort entry and included demographic characteristics, co-morbidities (such as hypertension, diabetes, chronic kidney disease, cerebrovascular disease, and ischemic heart disease), and AAA-related variables. The study also included RAAA-related variables such as maximum AAA diameter, aneurysm neck morphology, angle and length, aneurysm neck calcification, and appendage thrombosis of aneurysm neck.

Treatment and follow-up

All patients received EVAR as treatment. Postoperative outcomes included any cause of death, which was determined through follow-up visits or telephone consultations if patients were unable to visit our hospital outpatient office. Long-term survival was calculated from the date of surgery until the date of death or the end of the follow-up period on December 31, 2022, whichever occurred first. The primary endpoint is death from any cause during the perioperative period or long-term follow-up period. The secondary endpoint was death from any cause within 30 days after surgery.

Nomograms and artificial neural networks (ANN)

Nomograms and ANNs were developed based on the risk factors obtained from univariate and multifactorial analyses. Using the nomogram, patients were able to predict their one-, three-, and five-year survival based on risk factors such as NLR and PLR. The predictive power of the nomogram was evaluated using the C-index. Calibration plots were able to validate the predictive performance of the column line plots. A detailed description of the ANN building has been reported in our previous study [9].

Statistical analysis

Statistical analyses were performed using Prism software (GraphPad Prism software, La Jolla, CA, USA) and IBM SPSS Statistics for Windows, version 26.0 (IBM

Corp., Armonk, NY, USA). The predictive value of NLR and PLR for the primary endpoint was estimated using receiver operating characteristic (ROC) curves, and the area under the ROC curve (AUC) was calculated to compare the discriminatory performance of NLR and PLR with 95% confidence intervals (CI). The Youden index was determined by the ROC curve relationship. Cutoff values of NLR, PLR were determined based on the value corresponding to the maximum value. Categorical variables were compared using the chi-square test or Fisher's exact test. A P value of <0.05 was considered statistically significant. Univariate analyses were conducted to identify significant differences in population characteristics affecting mortality, and logistic regression analysis was used for multi-factor analysis to identify significant variables. Nomograms were developed using the Regression Modeling Strategies package in R (version 3.0.2; R Package for Statistical Computing; www.r-project.org). ANN was built using SPSS Clementine version 12.0 software for Windows (IBM Corp., Chicago, IL, USA).

Results

Inclusion criteria, NLR, and PLR

A flowchart depicting the inclusion and exclusion criteria for patients is shown in Fig. 1. Out of 67 patients with RAAA who underwent EVAR in our department during the study period, 50 patients were included in the analysis after excluding those who did not meet the criteria. The ROC curve analysis revealed that the optimal cut-off values for NLR and PLR were 19.6 and 190.5, respectively. The area under the curve for NLR and PLR was 0.80 (95% CI, 0.66–0.94) and 0.82 (95% CI, 0.68–0.96), respectively (Fig. 2). The cut-off values corresponded to sensitivity and specificity values of 71% and 91% for NLR, and for PLR, they were 82% and 79%, respectively. Above cutoff value is high NLR/PLR group, below cutoff value is low NLR/PLR group.

Baseline characteristics

The baseline characteristics of patients with RAAA undergoing EVAR are shown in Table 1. Among them, 15 (30%) were aged > 80 years, and eight (16%) were female. Fourteen patients (28%) had a body mass index (BMI) of > 25 kg/m^2, and seven (14%) were smokers. Hypertension was the most prevalent comorbidity (68%), followed by ischemic heart disease (14%). Cerebrovascular disease, diabetes, and chronic kidney disease were present in 12%, 8%, and 2% of the patients, respectively.

Characteristics of AAA

As shown in Table 2, the morphology of AAAs in these patients was irregular, straight, ortho trapezoidal, and inverted trapezoidal in 22, 20, 5, and 3 patients, respectively. The maximum AAA diameter was > 60 mm in

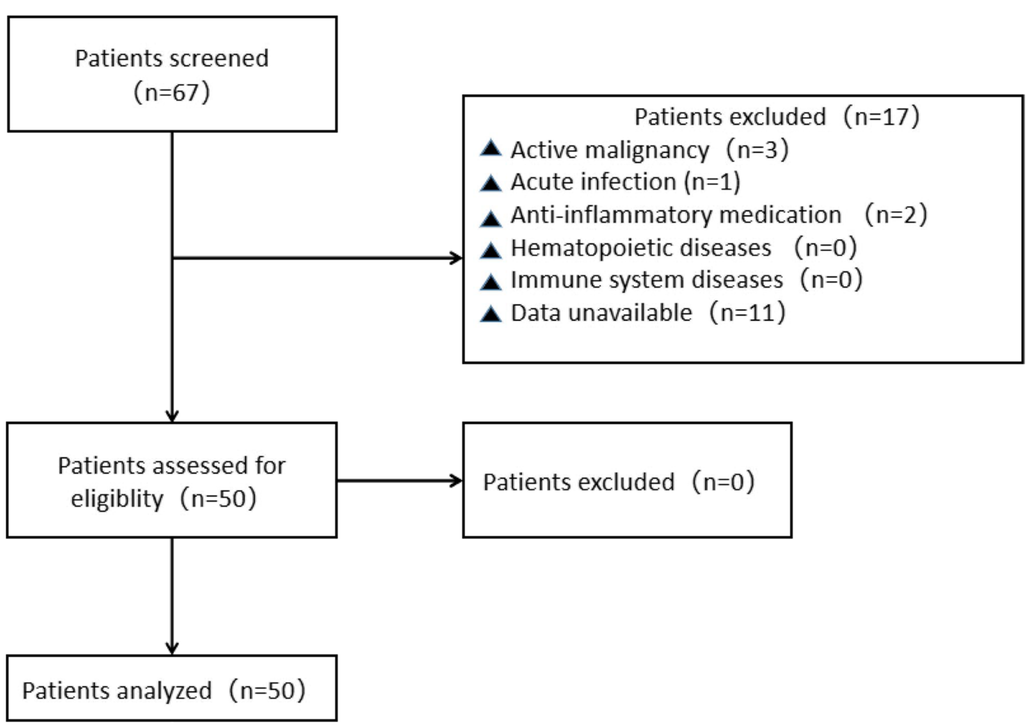

Fig. 1 Patient selection process

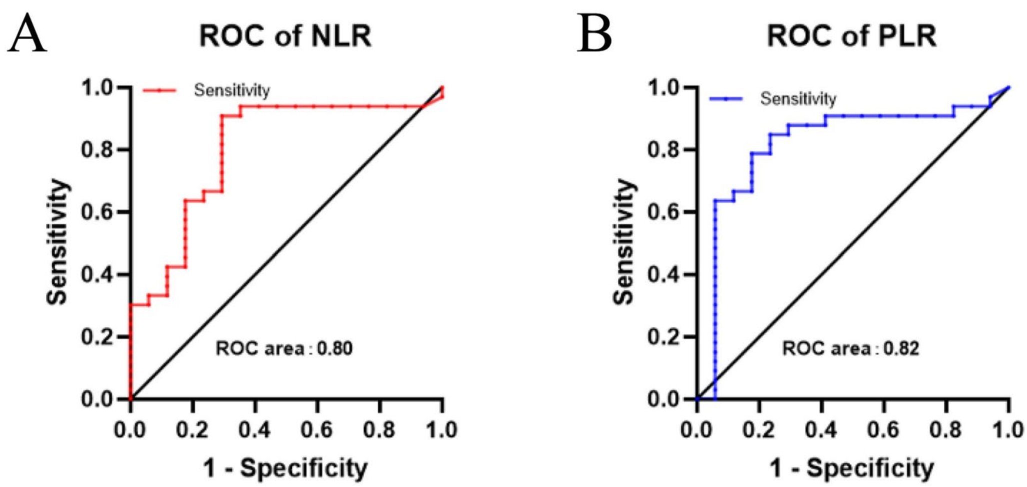

Fig. 2 NLR and PLR ROC curves of patients with RAAA. **A** The AUC of NLR was 0.80. **B** The AUC of PLR was 0.82. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic curve; RAAA, ruptured abdominal aortic aneurysm; AUC, area under the receiver operating characteristic curve

Table 1 Patients' demographic characteristics and comorbidities

Patients	
Parameters	N. of patients(%)
Octogenarian	15 (30%)
Female	8 (16%)
BMI > 25	14 (28%)
Smoking	7 (14%)
Comorbidities	
Hypertension	34 (68%)
Diabetes	4 (8%)
Chronic kidney disease	1 (2%)
Cerebrovascular disease	6 (12%)
Ischemic heart disease	7 (14%)

Table 2 Characteristics of the aneurysm

Aneurysm	
Parameters	N. of patients(%)
Maximal aneurysm diameter > 60 mm	23 (46%)
Proximal neck length < 15 mm	9(18%)
Proximal neck angle > 60 degrees	11(22%)
Calcification of aneurysm neck	28(56%)
Appendage thrombosis of aneurysm neck	20(40%)
Aneurysm neck morphology	
Inverted trapezoid	3 (6%)
Positive trapezoid	5 (10%)
Irregular shape	22 (44%)
Straight	20 (40%)

23 patients. Nine patients had short aneurysm necks (< 15 mm), and 11 had angular necks (> 60 degrees). Calcification and appendage thrombosis in the neck of the aneurysm were observed in 28 and 20 patients, respectively.

Relationship between preoperative NLR, PLR and clinical characteristics of patients

We analyzed the relationship between preoperative NLR, PLR, and clinical characteristics of patients with RAAA who underwent EVAR (Table 3). The high NLR group included 15 (30%) patients, while the low NLR group included 35 (70%) patients. Preoperative NLR showed a significant correlation with patient age, comorbid cerebrovascular disease, maximum AAA diameter, and aneurysmal neck appendage thrombus ($P < 0.05$), while it was not significantly correlated with gender, BMI, smoking, other co-morbidities, or other characteristics of AAA ($P > 0.05$) (Table 4). The high PLR group included 18 (36%) patients, while the low PLR group included 32 (64%) patients. Preoperative PLR showed a significant correlation with patient age, aneurysm neck angulation, and appendage thrombosis of aneurysm neck ($P < 0.05$), but not with gender, BMI, smoking, co-morbidities, or other characteristics of AAA ($P > 0.05$).

Correlation between preoperative NLR, PLR and postoperative overall survival

A total of 17 patients died in this study, of which 8 patients died in the perioperative period. The mean follow-up for this group was 25 months, with a 30-day survival rate of 78%. There were many causes of death,

Table 3 Correlation of NLR, PLR with patient's clinical features

Clinical characteristics	NLR			PLR		
	Low	High	P	Low	High	P
Age (years)			< 0.001			0.021
≥ 80	5	10		6	9	
< 80	30	5		26	9	
Gender			0.614			0.088
Female	5	30		3	5	
Male	3	12		29	13	
BMI			0.582			0.495
> 25	9	5		10	4	
≤ 25	26	10		22	14	
Smoking			0.328			0.197
Absent	6	1		6	1	
Present	29	14		26	17	
Hypertension			0.597			0.266
Absent	12	4		12	4	
Present	23	11		20	14	
Diabetes			0.172			0.543
Absent	31	15		30	16	
Present	4	0		2	2	
Chronic kidney disease			0.508			0.449
Absent	34	15		31	18	
Present	1	0		1	0	
Cerebrovascular disease			0.037			0.095
Absent	33	11		30	14	
Present	2	4		2	4	
Ischemic heart disease			0.091			0.209
Absent	32	11		29	14	
Present	3	4		3	4	

mainly including circulatory instability, respiratory failure, cardiac failure, multi-organ failure. The Kaplan–Meier survival curves showed that patients in the NLR and PLR low-expression groups had longer overall survival (Fig. 3). Univariate analysis demonstrated that preoperative NLR, PLR, maximum AAA diameter, and aneurysmal neck appendage thrombus were significantly associated with long-term survival in patients with RAAA undergoing EVAR ($P < 0.05$), while age, gender, and co-morbidities were not significantly associated with long-term survival ($P > 0.05$) (Table 5). Further, multivariate analysis showed that preoperative NLR and PLR were independent risk factors for long-term survival in patients ($P < 0.05$).

Nomogram and ANN models established based on NLR, PLR

Important clinical characteristics of each patient with RAAA undergoing EVAR were assigned scores according to the nomogram, including preoperative NLR, PLR, maximum AAA diameter, and aneurysmal neck appendage thrombosis. The resulting total score was used to predict the one-, three-, and five-year survival rates of the patients (Fig. 4). The higher the total score, the worse the prognosis for the patient. The C-index of this nomogram is 0.859, indicating good predictive performance. The calibration chart also demonstrated the good predictive performance of the nomogram for one-, three-, and five-year overall survival rates in this patient group.

An ANN model was developed based on several major risk factors related to preoperative NLR and PLR scores (Fig. 5). The proportion of overall survival importance accounted for in the ANN model is as follows: preoperative PLR (0.432), NLR (0.276), maximum AAA diameter (0.172), and aneurysmal neck appendage thrombosis (0.120).

Table 4 Correlation of NLR, PLR with aneurysm characteristics

Aneurysm characteristics	NLR			PLR		
	Low	High	P	Low	High	P
Maximal aneurysm diameter			0.003			0.423
< 60 mm	23	3		18	8	
≥ 60 mm	12	12		14	10	
Proximal neck length			0.172			0.086
< 15 mm	27	14		24	17	
≥ 15 mm	8	1		8	1	
Proximal neck angle			0.602			0.004
≤ 60 degrees	28	11		29	10	
> 60 degrees	7	4		3	8	
Calcification of aneurysm neck			0.106			0.585
Absent	18	4		15	7	
Present	17	11		17	11	
Appendage thrombosis of aneurysm neck			0.012			0.022
Absent	25	5		23	7	
Present	10	10		9	11	
Aneurysm neck morphology			0.46			0.298
Inverted trapezoid	2	1		2	1	
Positive trapezoid	5	0		5	0	
Irregular shape	14	8		12	10	
Straight	14	6		13	7	

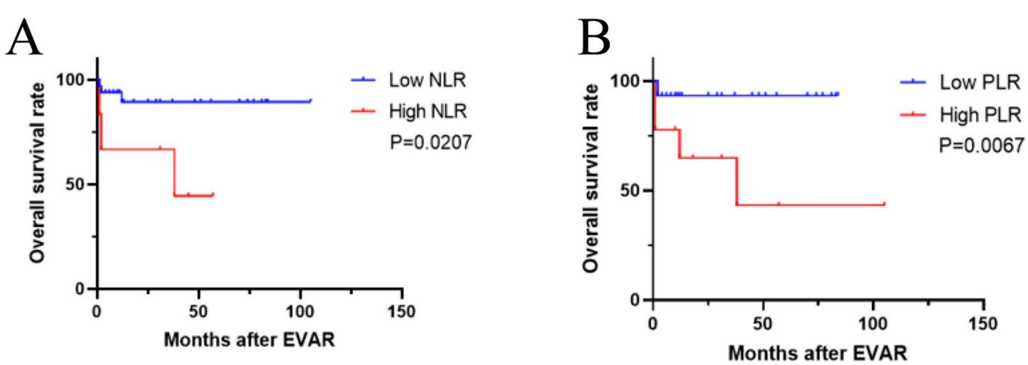

Fig. 3 Kaplan–Meier survival analysis between the preoperative NLR, PLR, and overall survival of patients with RAAA undergoing EVAR. Patients with higher NLR and PLR have shorter overall survival (**A**, **B**). NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; RAAA, ruptured abdominal aortic aneurysm; EVAR, endovascular aneurysm repair

Discussion

The incidence of RAAA is increasing annually, and once ruptured, it can be extremely hazardous [10]. Despite significant improvements in the diagnosis and treatment of RAAA in recent years, the prognosis for patients remains unfavorable [11]. The main treatment modalities for RAAA include traditional open surgical treatment and EVAR [12]. Although open surgery provides complete hemostasis, abdominal cavity decompression, and reconstruction of all branch arteries [13], the operation is prolonged, leading to high levels of trauma and numerous serious complications. Studies have demonstrated that for patients with RAAA, EVAR is not inferior to open surgery [14]. EVAR has become the preferred treatment option, especially for elderly patients with combined respiratory and cardiovascular disease, with the added advantages of less trauma, reduced blood transfusions, and faster recovery times. However, there is a mortality rate of up to 30–80% for patients who arrive at the hospital in time and undergo emergency surgery [15].

Table 5 Univariate and multivariate analyses of characteristics with overall survival

Variable	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Age (< 80 years vs ≥ 80 years)	2.155(0.829–5.596)	0.115		
Gender (male vs female)	0.959(0.275–3.343)	0.947		
BMI(> 25 vs ≤ 25)	1.033(0.363–2.935)	0.952		
Smoking(absent vs present)	0.756(0.173–3.313)	0.711		
Hypertension(absent vs present)	1.138(0.400–3.239)	0.808		
Diabetes(absent vs present)	0.737(0.097–5.581)	0.768		
Chronic kidney disease(absent vs present)	0.048(0.000–9.944)	0.684		
Cerebrovascular disease(absent vs present)	0.921(0.210–4.031)	0.913		
Ischemic heart disease(absent vs present)	2.321(0.750–7.181)	0.144		
Maximal aneurysm diameter (< 60 mm vs ≥ 60 mm)	2.952(1.033–8.436)	0.043		
Proximal neck length(< 15 mm vs ≥ 15 mm)	0.035(0.000–7.495)	0.221		
Proximal neck angle (≤ 60 degrees vs > 60 degrees)	1.470(0.517–4.175)	0.470		
Severe calcification of aneurysm neck (Absent vs Present)	2.159(0.758–6.152)	0.150		
Appendage thrombosis of aneurysm neck (Absent vs Present)	3.173(1.168–8.617)	0.024		
Aneurysm neck morphology (Inverted trapezoid vs Positive trapezoid vs Irregular shape vs Straight)	0.803(0.448–1.439)	0.460		
NLR (low vs high)	7.762(2.679–22.44)	< 0.001	0.271(0.076–0.968)	0.024
PLR (low vs high)	7.691(2.473–23.92)	< 0.001	0.272(0.070–1.063)	0.041

The search for biomarkers that can predict the prognosis of this patient group is therefore urgent.

In recent years, there has been an increasing focus on hematological markers that reflect the systemic inflammatory response, such as NLR, PLR, and the systemic inflammatory response index [16, 17]. These markers are readily available and can be used as relevant indicators to assess the prognosis of patients [18, 19]. Gomez et al. evaluated the prognostic value of preoperative NLR in patients undergoing radical resection for hepatocellular carcinoma [20]. PLR has also been used as a prognostic marker in the clinical outcome of patients with advanced lung cancer receiving immunotherapy [21]. Lymphocyte-to-monocyte ratio combined with cancer antigen 125 can predict the prognosis of patients with ovarian cancer [22]. The prognostic value of these markers in cardiovascular diseases such as coronary artery disease, aortic dissection, and AAA has also been demonstrated [23–25]. Elevated systemic inflammatory response index is an independent risk factor for aortic-related adverse events after aortic repair in patients with type B aortic dissection [26]. Preoperative NLR predicts overall mortality and reintervention rates in patients with AAA treated with EVAR [27, 28], and it also predicts 30-day mortality in patients with RAAA treated with open surgery [29]. However, there is no literature on the relationship between preoperative NLR and PLR and prognosis in patients with RAAA treated with EVAR as the preferred treatment. Therefore, we aimed to demonstrate that preoperative NLR and PLR are potential prognostic indicators in patients with RAAA treated with EVAR and to develop a predictive model based on NLR, PLR, and related indicators to predict the prognosis of this patient group.

In this study, we retrospectively analyzed the clinical data on patients with RAAA who underwent EVAR at the First Affiliated Hospital of the Naval Military Medical University. Firstly, we determined the optimal threshold values of preoperative NLR and PLR based on the ROC curve, which were 19.6 and 190.5, respectively, with the greatest joint sensitivity and specificity. We then analyzed the correlation between preoperative NLR and PLR and the clinical characteristics of the patients. The results showed that an increase in NLR was positively correlated with patient age, combined cerebrovascular disease, maximum AAA diameter, and aneurysmal neck appendage thrombus. Additionally, an increase in PLR was significantly correlated with patient age, aneurysmal neck angle, and aneurysmal neck appendage thrombus. This suggests that preoperative NLR and PLR are not only related to the clinical characteristics of the patient but also to the underlying characteristics of the aneurysm, possibly due to the inflammatory response caused by aneurysm rupture. Certainly, more than half of the abdominal aortic aneurysms in this study were not very large, with diameters of less than 60 mm, and it is possible that spontaneous rupture of the aneurysm occurred due to the patient's own prominent inflammatory state.

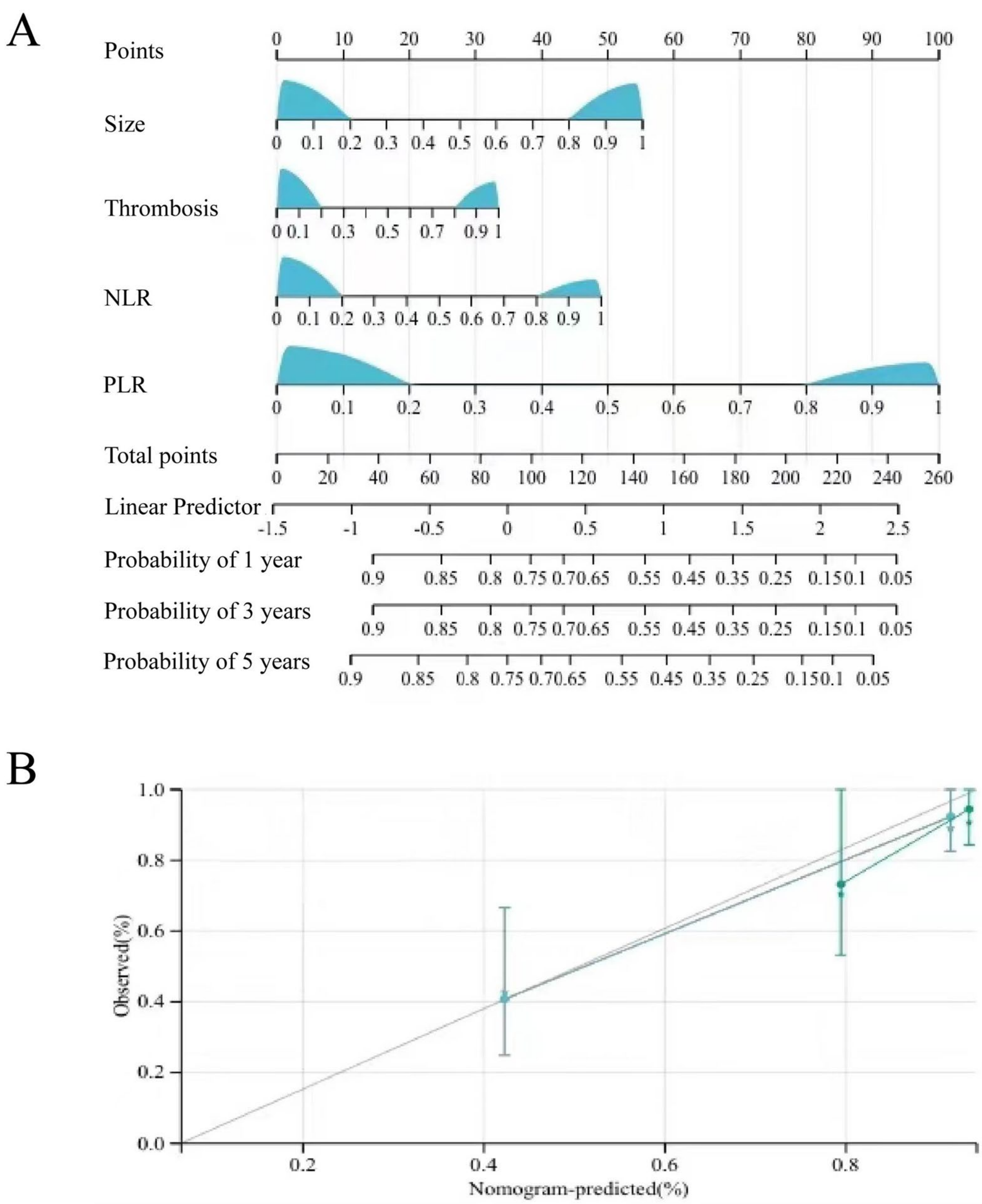

Fig. 4 Nomogram predicting the probability of one-, three-, and five-year survival rates after treatment with EVAR. **A** A nomogram based on preoperative NLR and PLR. **B** Good calibration for predicting survival. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; EVAR, endovascular aneurysm repair

To investigate whether preoperative NLR and PLR are associated with the prognosis of patients with RAAA, we performed univariate and multivariate analyses. Univariate analysis revealed that maximum AAA diameter, appendage thrombosis of aneurysm neck, and preoperative NLR and PLR were all significant prognostic factors for overall survival in this patient group. However, further multivariate analysis revealed that only preoperative NLR and PLR were independent risk factors. The Kaplan–Meier survival analysis showed that patients with higher preoperative NLR and PLR had shorter long-term survival. Some attached thrombus often exists in the aneurysm cavity, and the thrombus contains a large number of neutrophils. Neutrophils in the aneurysm cavity with attached thrombus will preferentially accumulate and release a large number of chemokines, which will lead to the aggravation of inflammatory reaction, increase the content of pro-MMP-9 and pro-MMP-8, and

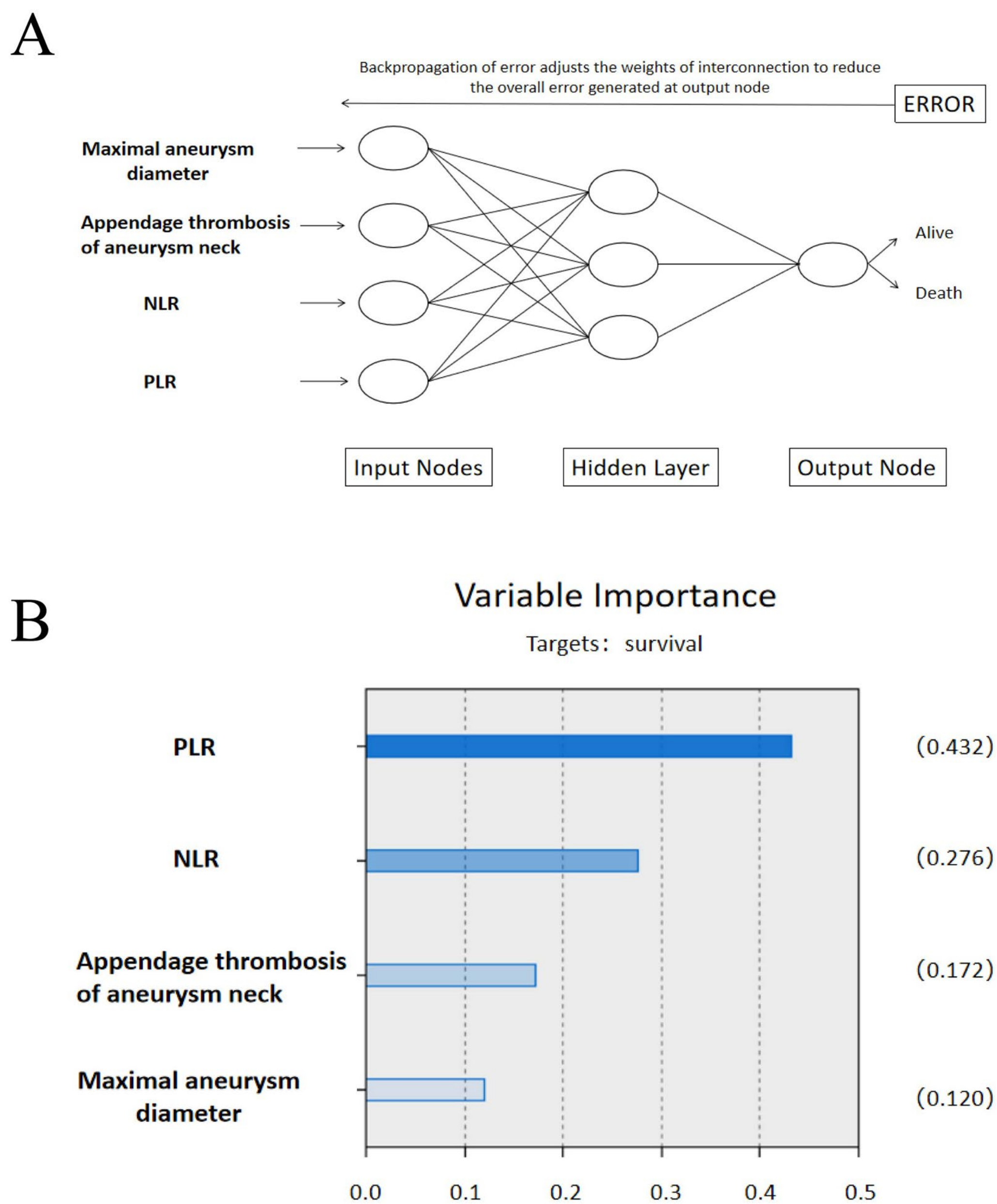

Fig. 5 **A** ANN schematic for predicting overall survival in patients with RAAA treated with EVAR. **B** Significance of the risk factors in the ANN model. RAAA, ruptured abdominal aortic aneurysm; EVAR, endovascular aneurysm repair; ANN, artificial neural networks

promote the progression of the disease. At the same time, the aortic wall covered by thrombus is thinner, which is more likely to lead to the rupture of aneurysm. This may be the reason why elevated NLR and PLR lead to poorer prognosis.

Further development of artificial intelligence has led to the emergence of a new computer technique, ANN, which can be used to compare the proportion of relevant prognostic factors in predicting long-term survival in clinical patients [30]. According to our results, the higher proportion of NLR and PLR and the lower proportion of maximum AAA diameter and appendage thrombosis of aneurysm neck are consistent with the results obtained from univariate and multivariate analyses, which underscores the accuracy and credibility of our findings. Nomograms are frequently used to predict the survival of patients with tumors, such as overall and recurrence-free survival [31], and they are now being used in cardiovascular disease as well. Predicting 30-day postoperative mortality in patients with acute type A aortic coarctation who underwent total aortic arch replacement with the frozen elephant trunk technique [32] and also predicting in-hospital mortality in patients with type B aortic dissection [33]. Our nomogram combines preoperative NLR, PLR, maximum AAA diameter, and appendage thrombosis of aneurysm neck to predict long-term survival in patients with RAAA undergoing EVAR, which is not available in other conventional prediction models. The strength of this study is that we primarily examined the prognostic value of preoperative NLR and PLR in patients with RAAA receiving EVAR. Furthermore, we included a long follow-up period, which has rarely been studied before.

However, our study has some limitations. Firstly, it was a retrospective study based on a single-center database, and its external validity may be limited. Secondly, the sample size was small, and further multicenter and large data studies are needed to validate this in a more convincing manner. Finally, due to the preoperative preparation, the condition of the patient may have changed between the blood test and the surgery, and the blood indicators may not reflect the immediate status of the patient.

Conclusion

NLR and PLR are more readily available and inexpensive serum indicators and are routinely assessed in all emergency patients. Our study shows that elevated preoperative NLR and PLR are independent risk factors for long-term survival in patients with RAAA who have received EVAR. Based on nomograms and ANN models, the long-term prognosis of this patient group can be assessed.

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Author contribution
Biao Wu and Shibo Xia wrote the main manuscript text. Li Chen,Jiefu Fan and Wenying Guo prepared Figs. 1, 2, 3, 4 and 5. Zhishi Wu and Hao Zhang prepared Figs. 1, 2, 3, 4 and 5. Lei Zhang reviewed the manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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