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ORIGINAL RESEARCH

Factors Influencing Early Diagnosis of Ruptured Abdominal Aortic Aneurysms: The Role of Neutrophils

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Background: Currently, there is no effective and convenient indicator for the early differential diagnosis of ruptured abdominal aortic aneurysms (rAAAs) from unruptured abdominal aortic aneurysms (AAAs).

Objective: The aim of this study was to explore indicators for the early differential diagnosis of rAAAs in a clinical setting.

Methods: This case–control study included 276 subjects within the last 5 years (220 patients with unruptured AAAs; 56 patients with rAAAs) in the initial analysis and 229 subjects (186 patients with unruptured AAA's; 43 patients with rAAA's) after subgroup analysis. The meaningful indicators were screened via univariate analysis and logistic regression analysis. The diagnostic performance and clinical usefulness of the indicators were assessed and compared using receiver operating characteristic (ROC) curve analysis, decision curve analysis (DCA) and clinical impact curve (CIC).

Results: A high venous blood neutrophil counts (OR = 1.316, $P = 0.007$) was found to be a risk factor for rAAAs in the initial model. After subgroup analysis, the levels of neutrophils (OR = 1.394, $P = 0.017$) and D-dimer (OR = 1.023, $P = 0.043$) were both significantly greater in patients with a rAAA. Abdominal pain (OR = 32.613, $P = 0.044$) and back pain (OR=91.946, $P = 0.036$) were strongly associated with the rupture of AAA. The results of the receiver operating characteristic (ROC) analysis revealed that neutrophils (AUC: 0.847, 95% CI: 0.774–0.921) and NLR (AUC: 0.795, 95% CI: 0.717–0.873) had good diagnostic performance for rAAA. DCA demonstrated that the net benefit of neutrophils was greater than that of other indicators. The CIC confirmed that the model has good clinical usefulness.

Conclusion: The use of neutrophils may enhance the early diagnostic accuracy for identifying rAAAs and holds potential for clinical and scientific applications.

Keywords: rupture abdominal aortic aneurysm, abdominal aortic aneurysm, neutrophils, NLR, D-dimer, diagnostic performance

Introduction

An abdominal aortic aneurysm (AAA) is a life-threatening cardiovascular disease, characterized by the expansion of the abdominal aorta by more than 50% of its normal diameter. This is caused by immune cell-mediated inflammation and degradation of the medial layer that ultimately leads to aortic rupture and bleeding. The incidence of AAA ranges from 1.2% to 2%, with approximately 8% of males over the age of 65 affected.[1] The mortality rate attributable to AAA is about 15,000 per year in the United States.[2] AAAs are more common in elderly individuals, with an increased risk in male smokers.[3–5] Other variables, such as oxygen-dependent COPD, coronary artery disease, hypertension, cerebrovascular and peripheral arterial disease, and mixed connective tissue disease, are related to the natural history of AAAs.[6]

AAAs have no obvious symptoms in the early stages; however as the disease progresses, the aneurysm gradually increases in size, leading to an increased risk of rupture, with a mortality rate of up to 90% once rupture occurs.[7] Sixty percent of patients with ruptured abdominal aortic aneurysms die instantly or before they reach the hospital.

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Although ruptured abdominal aortic aneurysms (rAAAs) are relatively rare compared with AAAs, the incidence and prevalence rates are higher in certain populations and geographic regions, which may be influenced by genetic factors and lifestyle choices (eg, smoking).[8]

Imaging remains the primary method of diagnosis and differential diagnosis. Currently, the primary predictor of rAAAs is the maximum diameter of the AAA, with other risk factors, including the aneurysm expansion rate, recent surgeries, uncontrolled hypertension, and smoking.[9,10] However, the logistic regression prediction model, which is based on the maximum diameter and patient sex, has only 60% sensitivity and 77% specificity in predicting the risk of rupture.[10] Furthermore, as the gold standard for diagnosing AAAs,[11] computed tomography angiography (CTA) also poses risks of radiation exposure, contrast agent allergies, and potential kidney damage. Transthoracic or transesophageal ultrasound, MRI and other imaging methods are time-consuming and laborious, and carry various risks during the examination process.[12] Therefore, clinicians urgently require identification of an effective and convenient blood biomarker for the early diagnosis of rAAAs.

Blood biomarker detection is simpler, rapid, economical and safe. In recent years, systemic inflammation-based biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR), have shown potential value in the diagnosis and prognosis of various diseases.[13] Previous studies have demonstrated that NLR is significantly elevated in patients with rAAA and is associated with poor outcomes.[14] Perhaps of interest, similar finding were done for cerebral aneurysm patients where neutrophils and D-dimer associated with the severe outcome of patients.[15] And in aortic dissection patients it predicted mortality.[16] However, the independent diagnostic value of routine blood parameters in rAAA and their comparison with NLR have not been systematically investigated.

Patients

Ethics Statement

This study was performed in accordance with the 1964 helsinki declaration and its later amendments and was approved by the Ethics Committee of the First Hospital of Hebei Medical University (IRB: V120240920). This retrospective study was approved by the Ethics Committee of the First Hospital of Hebei Medical University with exemption of informed consent.

Patient Enrollment

Consecutive individuals suspected of having an AAA and seeking medical attention at a large tertiary care center between January 2019 and December 2024 were included in this study. Patients were considered for inclusion in the analysis on the basis of the following criteria: (1) a maximum diameter of anteroposterior abdominal aneurysm > 30 mm on abdominal ultrasound, computed tomography angiography (CTA) or digital subtraction angiography and (2) complete baseline clinical data. The exclusion criteria were as follows: (1) had inflammatory aneurysms; (2) had aneurysms resulting from connective tissue disorders; (3) had familial aneurysms; (4) had comorbid severe coagulopathies (e.g., hemophilia); and (5) had incomplete patient baseline clinical data.

Methods

Clinical Parameter Collection

Venous blood samples were collected in EDTA anticoagulant tubes immediately upon admission without any intervention and processed within 2 hours to ensure sample integrity. Blood test indicators, including neutrophils, lymphocyte, red blood cell count, hemoglobin, and platelet count, were collected, with the testing process based on the standards set by the International Committee for Standardization in Hematology. Fibrinogen, D-dimer and other indicators were tested in strict accordance with the instrument operation manual and relevant clinical test standards. The calibration and quality control of biochemical indicators, such as calcium, phosphorus, creatinine, and urea, followed the relevant guidelines of the American Clinical Laboratory Standardization Institute. All test indicators were tested using the standardized testing procedures and instruments at the Laboratory Department of the hospital to ensure accuracy and reliability of the data.

The baseline demographics, clinical data, and imaging test results of all patients were acquired from medical records for analysis.

Quality Control

To ensure the quality of the data, information collection and data entry were carried out by professionally trained researchers in strict adherence with standard operating procedures. Two-person verification of each dataset was performed to ensure the accuracy and completeness of the data. For doubtful data, timely communication and verification with the doctor in charge were conducted to ensure the authenticity and reliability of the data.

Statistical Analysis

For continuous variables, the normality test was performed first. If the data were normally distributed, they were expressed as the mean ± standard deviation, and comparisons between groups were made using the independent samples *t* test; if the data were not normally distributed, they were expressed as the median (interquartile range) [M (P25, P75)], and comparisons between groups were made using the Mann–Whitney *U*-test. For categorical variables, the number of cases (percentage) [n (%)] was used, and comparisons between groups were made using the χ^2 test or Fisher's exact test (when the theoretical frequency was less than 5). Factors that may be associated with ruptured abdominal aortic aneurysms were initially screened by univariate analysis, and variables with $P < 0.05$ in the univariate analysis were included in the multifactorial logistic regression model to determine the independent risk factors. The results of the multifactorial analysis are expressed in terms of odds ratios (ORs) and 95% confidence intervals (CIs). To assess the risk of bias, multiple testing corrections were applied to ensure the robustness of the results, and dual independent entry with cross-verification was implemented during data collection to minimize data entry errors.

Clinical indicators identified as significant in the multifactorial analysis, along with NLR, were included to evaluate their diagnostic efficacy and clinical utility. The diagnostic efficacy of these methods for ruptured abdominal aortic aneurysms was assessed by calculating the area under the curve (AUC), and the optimal cutoff value was determined by using the Youden's Index. Finally, decision curve analysis (DCA) and a clinical impact curve (CIC) were performed to determine and compare the clinical usefulness of those indicators. Statistical analyses were performed using the SPSS 27.0.1 software and R software 4.4.0. GraphPad Prism 9.5 and R software 4.4.0 were used to generate the ROC curve and other graphs. The test level was $\alpha = 0.05$. ($P < 0.05$)

Subgroup Analysis Screening

Based on the results of the preliminary analysis, neutrophils were significantly elevated in patients with a rAAA. A variety of factors can cause elevated neutrophil counts. These severe confounders were taken into account during screening: (1) fever ($T \geq 38$ °C); (2) severe infections or inflammation, such as severe pneumonia, sepsis, and soft tissue infections; (3) autoimmune diseases, such as SLE and rheumatoid arthritis; (4) trauma and Burns; (5) malignant tumors; (6) renal failure; and (7) antibiotic or anti-inflammatory drug use.

Results

Participants Enrollment

Notably, the data for this study were obtained from a clinical center with extensive experience in treating patients with ruptured abdominal aortic aneurysms. There were 315 patients with suspected AAAs during the study period. After initial screening, 276 eligible patients with AAAs were enrolled in the current analysis. Next, they were divided into two groups according to the final diagnosis: the unruptured AAA group (n=220) and the rAAA group (n=56) (Figure 1. Initial part). The above criteria for further screening were developed after the initial analysis, and 229 patients with AAAs who met the criteria were included in the further analysis, including 186 in the unruptured AAA' group and 43 in the rAAA' group (Figure 1. Subgroup analysis part). CTA and digital subtraction angiography images of unruptured and ruptured AAA are shown in Figure 2.

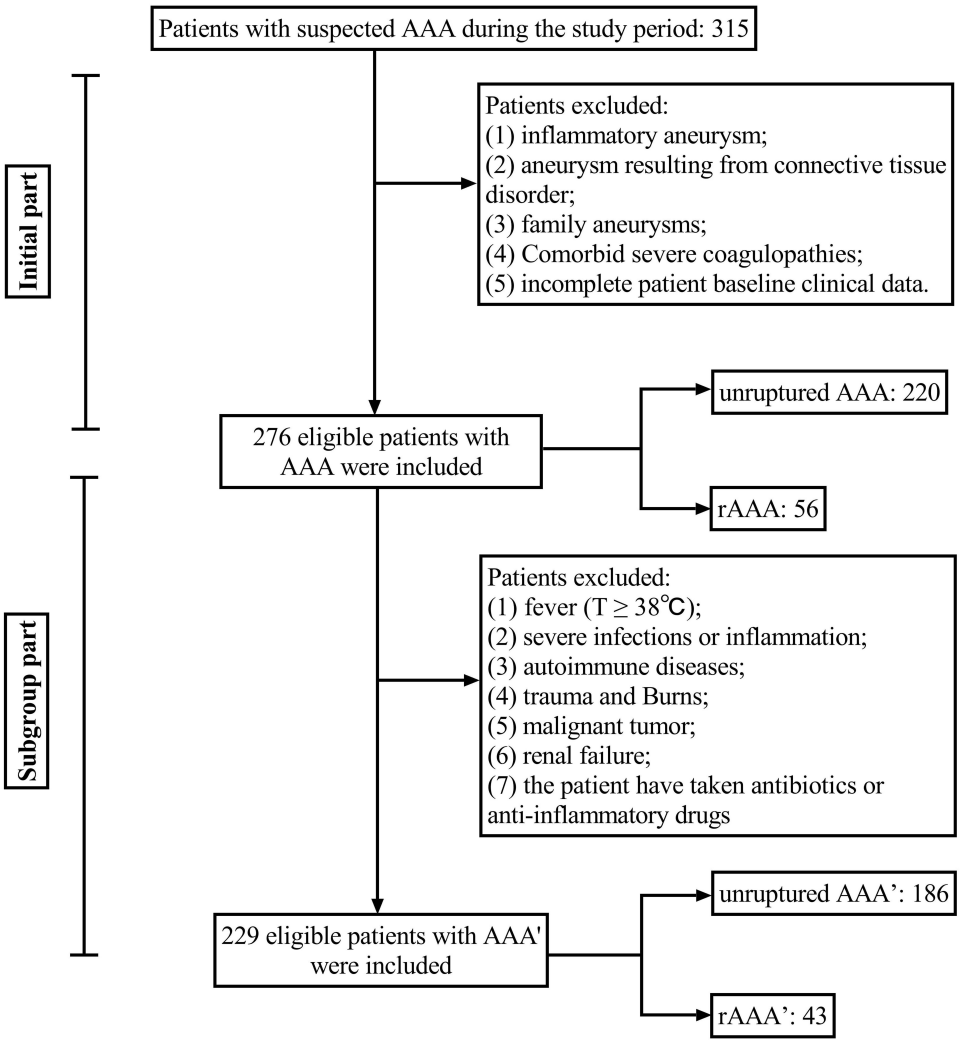

Figure 1 Study flowchart.

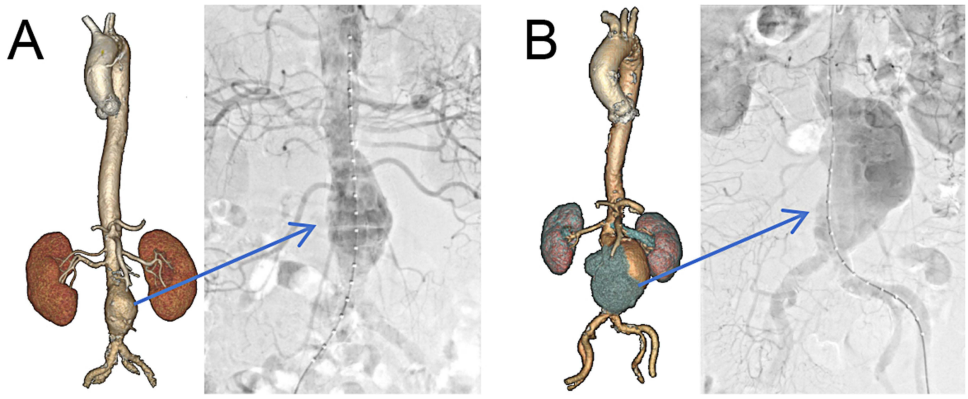

Figure 2 CTA and digital subtraction angiography images (**A**) unruptured AAA, (**B**) rAAA.

Initial Analysis Results

The detailed demographic and clinical characteristics are summarized in Table 1. The unruptured AAA group consisted of 220 patients, with asymptomatic predominating. Among these patients, the average age ranged from 68 to 78 years (median age, 73 years), and 91.4% were men. The rAAA group included 56 patients, 71.4% of whom had acute abdominal pain as the main manifestation. The average age of the patients in this group ranged from 65 to 78 years (median age, 71.5 years), and 87.5% were male. The results of the univariate analysis are shown in Table 2. Compared with the unruptured AAA group, the

Table 1 Baseline Characteristics (Unruptured AAA': Unruptured AAA Subgroup Analysis, rAAA': rAAA Subgroup Analysis)

Characteristics	Initial Analysis (n=276)		*P* value	Subgroup Analysis (n-229)		*P* value
	Unruptured AAA (n=220)	rAAA (n=56)		Unruptured AAA' (n=186)	rAAA' (n=43)	
Age (years)	73 (68~78)	71.5 (65~77.75)	0.375	73 (67.25~78)	72 (66~78)	0.736
BMI	24.04 (20.19~27.89)	24.10 (20.96~27.24)	0.923	24.09 (20.45~27.73)	24.25 (20.89~27.61)	0.805
Gender[men, n(%)]	201 (91.4)	49 (87.5)	0.377	171 (91.9)	39 (90.7)	0.791
Symptoms, n(%)						
Abdominal pain	63 (28.6)	40 (71.4)	<0.001	53 (28.5)	33 (76.7)	<0.001
Back pain	13 (5.9)	12 (21.4)	<0.001	12 (6.5)	9 (20.9)	0.003
Lumbago	12 (41.4)	17 (30.4)	<0.001	10 (5.4)	12 (27.9)	<0.001
Leg pain	12 (5.5)	1 (7.7)	0.247	9 (4.8)	1 (2.3)	0.467
Abdominal pulsatile masses	20 (9.1)	3 (5.4)	0.367	16 (8.6)	3 (7)	0.728
Vomiting	6 (2.7)	6 (10.7)	0.009	4 (2.2)	4 (9.3)	0.021
Loss of consciousness	1 (0.5)	1 (1.8)	0.294	1 (0.5)	1 (2.3)	0.256
Asymptomatic	112 (50.9)	1 (1.8)	<0.001	96 (51.6)	1 (2.3)	<0.001
SBP (mmHg)	142 (133~158)	149 (131~155.5)	0.020	133 (124~141)	123 (106~140)	0.001
DBP (mmHg)	88 (80~94)	81.75 (76.5~95.5)	<0.001	80.81 (69.9~91.72)	72.26 (58.33~86.19)	<0.001
Hypertension history [yes, n(%)]	145 (65.9)	40 (71.4)	0.433	128 (68.8)	31 (72.1)	0.674
Diabetes history [yes, n(%)]	19 (8.6)	4 (7.1)	0.718	19 (10.2)	3 (7)	0.516
CHD history [yes, n(%)]	52 (23.6)	7 (12.5)	0.070	44 (23.7)	5 (11.6)	0.083
History of cerebrovascular disease [yes, n(%)]	56 (25.5)	15 (26.8)	0.839	48 (25.8)	13 (30.2)	0.554
Smoking history [yes, n(%)]	123 (55.9)	30 (53.6)	0.753	100 (53.8)	22 (51.2)	0.758
In-hospital mortality [yes, n(%)]	0 (0.0)	9 (16.1)	<0.001	0 (0.0)	7 (16.3)	<0.001
Hospital stay (days)	8 (5~11)	7.5 (2~12)	0.176	8 (5~11)	5 (1~12)	0.054

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease.

Table 2 Univariate Analysis of Laboratory Test Results (Unruptured AAA': Unruptured AAA Subgroup Analysis, rAAA': rAAA Subgroup Analysis)

Parameters	Initial Analysis		*P* value	Subgroup Analysis		*P* value
	Unruptured AAA (n=220)	rAAA (n=56)		Unruptured AAA' (n=186)	rAAA' (n=43)	
Neutrophils (10^9/L)	4.1 (3.3~6.1)	8.65 (4.95~12.47)	<0.001	3.99 (3.26~5.9)	9.28 (5.47~12.94)	<0.001
Lymphocyte (10^9/L)	1.3 (1~1.73)	1.02 (0.72~1.51)	0.005	1.3 (1.02~1.74)	1.11 (0.72~1.64)	0.079

(*Continued*)

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Table 2 (Continued).

Parameters	Initial Analysis		*P* value	Subgroup Analysis		*P* value
	Unruptured AAA (n=220)	rAAA (n=56)		Unruptured AAA' (n=186)	rAAA' (n=43)	
RBC (10^{12}/L)	4.26 (3.87~4.58)	3.55 (2.88~4.24)	<0.001	4.31 (3.89~4.59)	3.63 (2.99~4.26)	<0.001
Mean red blood cell volume (fl)	93.4 (89.8~96.2)	92.9 (88.53~95.7)	0.496	93.5 (89.9~96.4)	93.1 (88.6~95.8)	0.339
RDW-CV (%)	13.4 (12.9~14)	13.3 (13~14.175)	0.644	13.4 (13~13.9)	13.3 (13~14.1)	0.792
Hematocrit (%)	39.5 (36.2~43)	32.8 (27.1~38.95)	<0.001	39.75 (36.6~43.1)	33.5 (27.6~39.6)	<0.001
Platelet (10^9/L)	190 (154~232)	183.5 (150~217)	0.216	189 (153~228.25)	180 (136~209)	0.064
Mean platelet volume (fl)	9 (8.1~9.7)	8.7 (8.15~9.5)	0.347	9 (8.1~9.7)	8.9 (8.25~9.78)	0.661
PDW (%)	16.5 (16.2~17)	16.5 (16.2~17)	0.909	16.5 (16.2~17)	16.5 (16.2~16.9)	0.815
Thrombocytocrit (%)	0.17 (0.14~0.21)	0.16 (0.13~0.20)	0.216	0.17 (0.14~0.20)	0.15 (0.11~0.19)	0.231
Hemoglobin (g/L)	131 (121~143)	108 (90~130.5)	<0.001	132 (122.75~144)	110 (90~134)	<0.001
Fibrinogen (g/L)	3.34 (2.83~3.91)	3.41 (2.29~4.62)	0.749	3.28 (2.74~3.86)	3.23 (1.96~4.55)	0.612
D-dimer (mg/L)	1.92 (0.98~4.57)	5.63 (2.12~19.6)	<0.001	2 (0.95~4.65)	8.84 (2.32~21.11)	<0.001
Antithrombin III activity (%)	92.19 (78.61~105.76)	81.76 (57.57~105.92)	0.005	92.81 (79.25~106.38)	76.95 (52.10~101.79)	<0.001
Anti-Xa activity (U/mL)	0 (0~0.03)	0 (0~0.05)	0.912	0.01 (0~0.04)	0 (0~0.05)	0.995
Calcium (mmol/L)	2.25 (2.13~2.37)	2.14 (1.97~2.31)	<0.001	2.25 (2.14~2.37)	2.11 (1.96~2.26)	<0.001
Phosphorus (mmol/L)	1.09 (0.95~1.21)	1.15 (1.0~1.49)	0.012	1.1 (0.97~1.22)	1.16 (1.05~1.55)	0.004
Urea (mmol/L)	5.61 (4.67~7.25)	7.55 (5.61~11.85)	<0.001	5.67 (4.73~7.30)	8.11 (5.62~11.91)	<0.001
Creatinine (μmol/L)	77.9 (65.93~89.08)	93.8 (72.98~159.58)	<0.001	78.4 (67.93~91.05)	99 (75.1~160)	<0.001
Triglyceride (mmol/L)	1.17 (0.86~1.57)	1.06 (0.77~1.48)	0.287	1.16 (0.87~1.57)	1.01 (0.74~1.43)	0.127
Total cholesterol (mmol/L)	4.33 (3.64~5.17)	4.16 (3.13~4.81)	0.074	4.41 (3.41~5.41)	3.81 (2.48~5.13)	0.017
HDL (mmol/L)	1.02 (0.86~1.21)	0.95 (0.76~1.15)	0.021	1.06 (0.82~1.30)	0.91 (0.62~1.20)	0.009
LDL (mmol/L)	2.77 (2.28~3.31)	2.55 (1.8~3.08)	0.043	2.77 (2.28~3.29)	2.33 (1.65~2.84)	0.004
Lipoprotein (mg/L)	281.5 (121.4~557.3)	190.2 (94.15~383.2)	0.108	277.7 (125.7~529.3)	180.7 (88.55~328.85)	0.038
ALT (U/L)	14.4 (10.3~22.5)	15.05 (10.43~24.55)	0.543	14.2 (10.25~22)	15.2 (10.3~23.8)	0.423
AST (U/L)	18.55 (15.7~23.98)	19 (15.45~27.78)	0.633	18.45 (15.8~23.45)	19.5 (14.5~29.4)	0.375
Total bilirubin (μmol/L)	13.15 (10.43~16.88)	12.15 (9.2~18.3)	0.914	13.1 (10.25~16.83)	14.8 (9.8~19.1)	0.388
Albumin (g/L)	38.75 (36.1~41.7)	32.75 (29.05~37.3)	<0.001	39.05 (36.48~41.83)	32.8 (28.6~37.3)	<0.001

Abbreviations: RBC, red blood cell; RDW, red blood cell distribution width; PDW, platelet distribution width; FDP, fibrin degradation product; HDL, high density lipoprotein; LDL, low density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; hs-CRP, hypersensitive C-reactive protein.

rAAA group was characterized by higher levels of neutrophils, D-dimer, phosphorus, urea, and creatinine, along with lower levels of RBC, hematocrit, hemoglobin, calcium, HDL, LDL and albumin. No significant differences were found in the other laboratory test indicators between the groups. Baseline variables that showed significant variations were included in the logistic regression analyses (Table 3). High levels of neutrophils (OR=1.34, 95% CI: 1.081~1.66, $P = 0.008$) were found to be a risk factor in the initial model. Symptoms including abdominal pain (OR=25.209, 95% CI: 1.959~324.403, $P = 0.013$), back pain (OR=41.03, 95% CI: 2.084~807.848, $P = 0.015$), and lumbago (OR=22.948, 95% CI: 1.637~321.778, $P = 0.02$) were also identified as significant risk factors.

Table 3 Multivariate Analysis of Laboratory Test Results (Initial Analysis)

Parameters	Initial Analysis	*P* value
	OR (95% CI)	
Abdominal pain	29.897(2.25~397.23)	0.010
Back pain	47.264(2.336~956.264)	0.012
Lumbago	19.648(1.531~252.139)	0.02
Vomiting	11.733(0.304~453.598)	0.187
Asymptomatic	0(0~0)	0.996
SBP (mmHg)	0.977(0.939~1.015)	0.232
DBP (mmHg)	0.98(0.917~1.047)	0.542
Neutrophils (10^9/L)	1.316(1.079~1.605)	0.007
Lymphocyte (10^9/L)	0.69(0.273~1.74)	0.432
RBC (10^{12}/L)	0.463(0.173~1.24)	0.126
D-dimer (mg/L)	1.018(0.995~1.041)	0.088
Antithrombin III activity (%)	0.99(0.949~1.032)	0.630
Calcium (mmol/L)	55.519(0.049~62,948.164)	0.263
Phosphorus (mmol/L)	8.333(0.532~130.452)	0.131
Urea (mmol/L)	1.038(0.838~1.287)	0.730
Creatinine (μmol/L)	0.997(0.972~1.022)	0.805
HDL (mmol/L)	1.14(0.075~17.455)	0.925
LDL (mmol/L)	0.995(0.644~1.538)	0.983
Albumin (g/L)	0.899(0.759~1.064)	0.215

Subgroup Analysis Results

Baseline clinical parameters are comparable between initial analysis and subgroup analysis. After subgroup analysis, a total of 229 patients were included for further analysis. There were 186 patients in the unruptured AAA' group, most of whom were asymptomatic (51.6%). The remaining 43 subjects constituted the rAAA' group, 33 (76.7%) of whom experienced acute abdominal pain. All four groups were more likely to have a higher history of hypertension (> 60%) and a lower history of diabetes (< 11%). There were no in-hospital deaths in either the unruptured AAA group or the unruptured AAA' group, whereas the rAAA and rAAA' groups had a high risk of in-hospital death (16%, $P < 0.001$). Factors with $P < 0.05$ in the univariate analysis were then included in the multivariate analysis. The admission neutrophil count (OR=1.579, 95% CI: 1.238~2.012, $P < 0.001$) remained significant after subgroup analysis, as shown in Figure 3. D-dimer (OR=1.023, 95% CI: 1.001~1.046, P=0.042) was found to be a risk factor after adjusting for other confounders. The distributions of neutrophil and D-dimer levels in each group are shown in Figure 4. Furthermore, back pain was strongly associated with the rupture of AAA.

Assessment of Diagnostic Performance

ROC analysis was conducted to determine the ability of the biomarkers to distinguish rAAAs from unruptured AAAs (Figure 5). Neutrophils (AUC: 0.847, 95% CI: 0.774~0.921), NLR (AUC: 0.795, 95% CI: 0.717–0.873), and D-dimer

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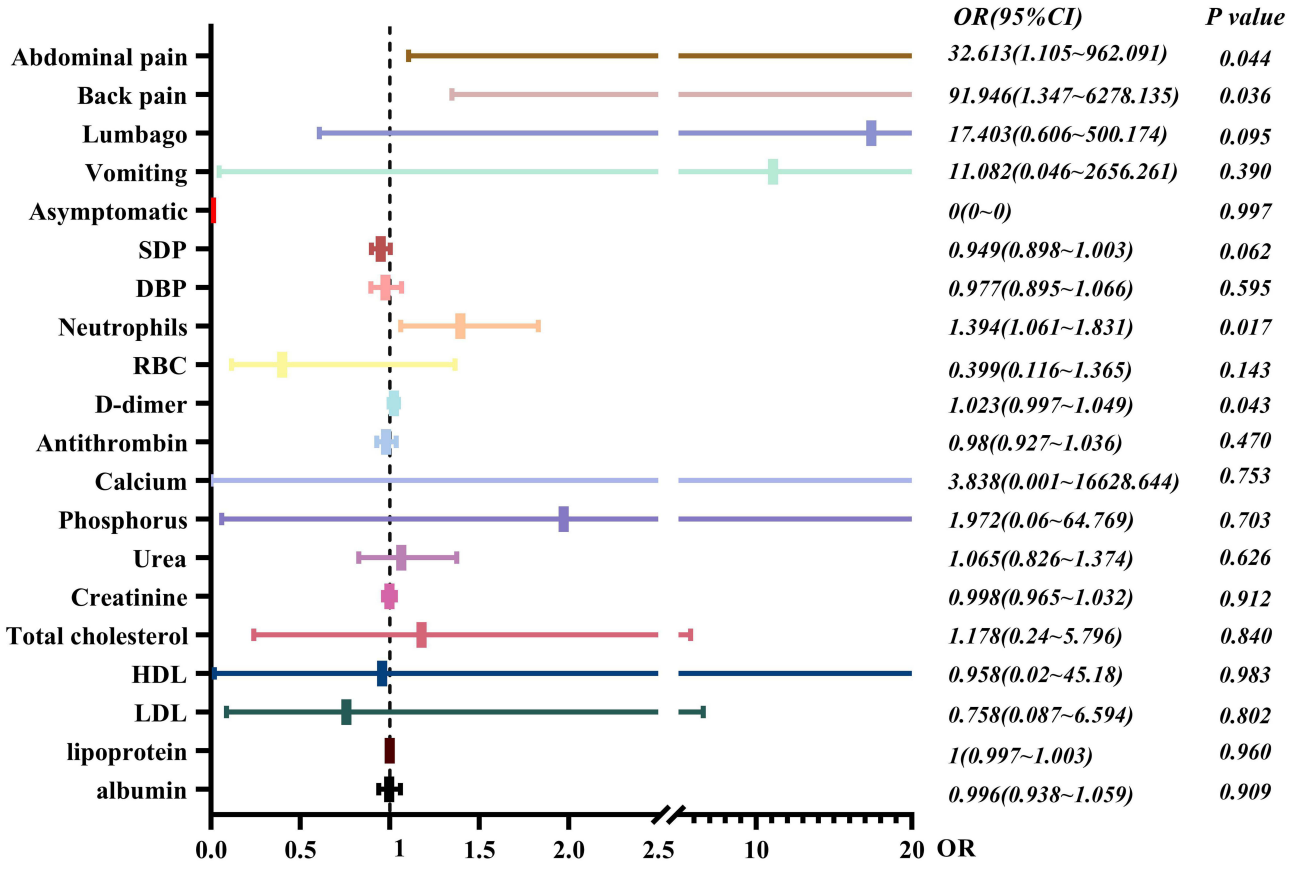

Figure 3 Multivariate analysis of laboratory test results (Subgroup Analysis).

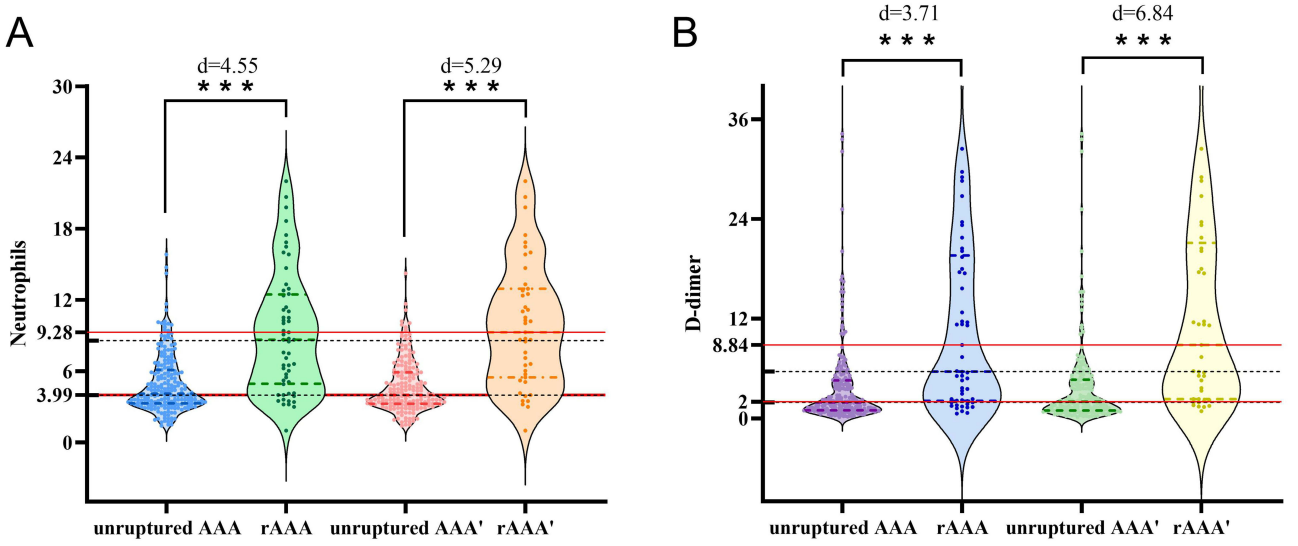

Figure 4 Distribution of neutrophils (**A**) and D-dimer (**B**) levels in each group (unruptured AAA': unruptured AAA subgroup analysis, rAAA': rAAA subgroup analysis, ***$P < 0.001$, d: difference between the two groups). The lines represent the median values of each group (Black dashed lines: initial analysis; Red solid lines: subgroup analysis).

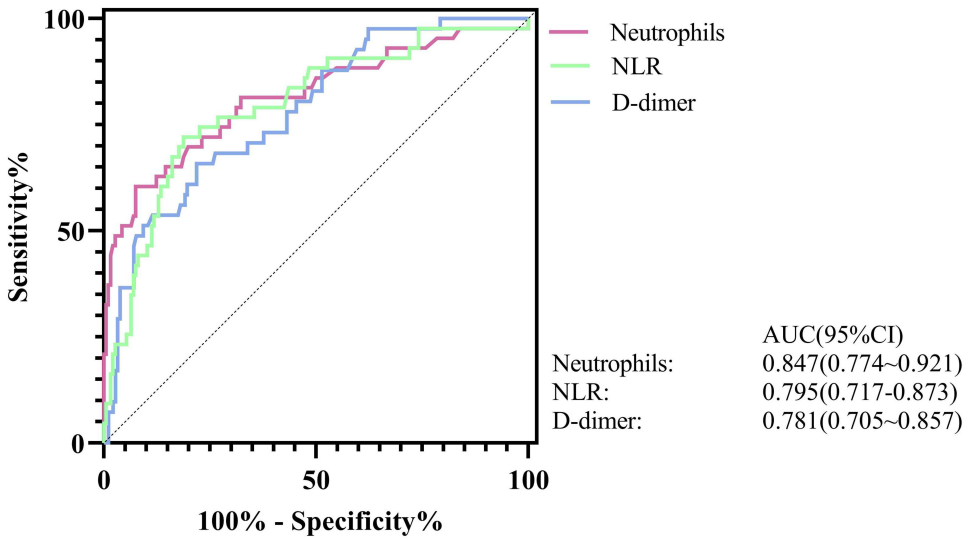

Figure 5 ROC curves of neutrophils, NLR, and D-dimer for the early diagnosis of rAAA.

(AUC: 0.781, 95% CI: 0.705~0.857) all showed high diagnostic performance. Neutrophils had the highest diagnostic performance, with the optimal cut-off value of 8.4×10^9/L (Youden's Index: 0.563). The optimal cut-off values, sensitivity, specificity, Youden's index, and AUC for each biomarker are detailed in Table 4.

Assessment of the Clinical Usefulness

Figure 6A shows a decision curve analysis (DCA) for neutrophils, NLR, D-dimer, abdominal pain and back pain (the net benefits (y-axis) at various threshold probabilities (x-axis) for the differential diagnosis of rAAAs). The net benefits at different risk thresholds for each biomarker are presented in Table 5. The net benefit of neutrophils was greater than that of the other two indicators and was positive at different risk thresholds. For example, at a threshold probability of 20%, compared with the strategy of'treat-none' (assuming that no patients have an rAAA), the uses of those indicators would lead to the equivalents of a net 88, 84, 71, 86 and 41 true positives per 1000 patients, respectively, with no increase in the number of false-positives. Finally, a clinical impact curve (CIC) was plotted to evaluate the clinical usefulness and applicability net benefits of the model. The CIC analysis is shown in Figure 6B–F. When the risk threshold was >20%, the positive estimates for those indicators (except for abdominal pain) were close to the actual prevalence.

Discussion

In the present study, we investigated the relationships among clinical data, blood biomarkers, and abdominal aortic aneurysm rupture in a cohort of patients with AAAs. The principal findings were as follows: 1) Neutrophil counts and D-dimer levels were significantly higher in rAAAs compared to unruptured AAAs, even after subgroup analysis; back pain was strongly associated with the rupture of AAA. 2) Neutrophil counts demonstrated superior diagnostic

Table 4 Diagnostic Performance of Biomarkers for Ruptured AAA

Parameters	Optimal Cut-Off Value	Sensitivity	Specificity	Youden' s Index	AUC (95% CI)
Neutrophils	8.4×10^9/L	0.634	0.929	0.563	0.847(0.774~0.921)
NLR	5.4	0.721	0.812	0.533	0.795(0.717–0.873)
D-dimer	4.99 mg/L	0.659	0.781	0.44	0.781(0.705~0.857)

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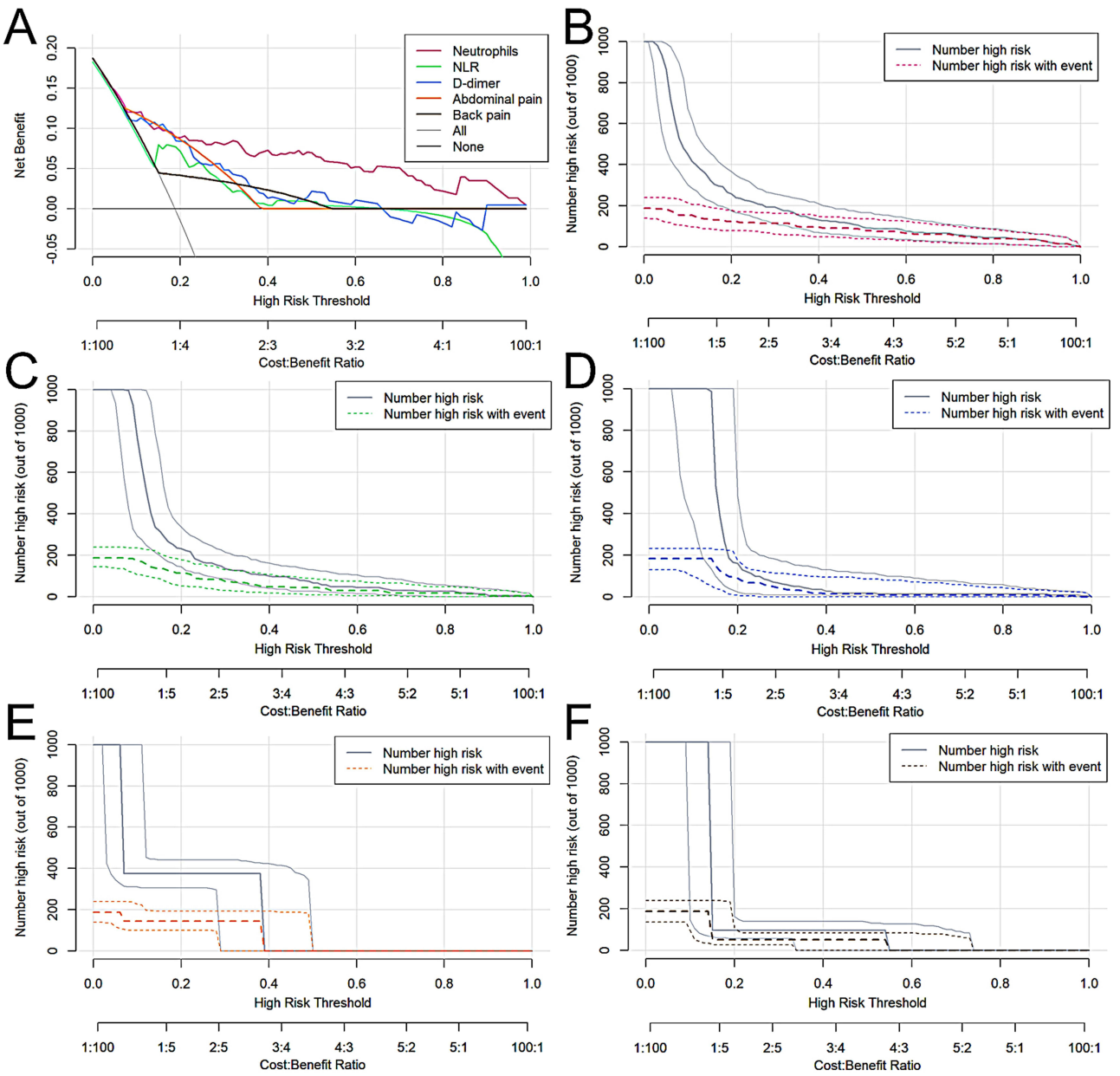

Figure 6 (**A**) Decision curve analysis (DCA) depicting the clinical usefulness of neutrophils, NLR, D-dimer, and symptoms (abdominal pain and back pain) at various threshold probabilities. The Y-axis shows the net benefit. The X-axis shows the corresponding risk threshold. The gray line represented the assumption that all patients have rAAA. The thin black line represented the assumption that no patients have rAAA. (**B**–**F**) Clinical impact curve (CIC) of neutrophils (**B**), NLR (**C**), D-dimer (**D**), Abdominal pain (**E**) and Back pain (**F**). The Y-axis shows the number of people at high risk per thousand. The X-axis shows the corresponding risk threshold. Of 1000 patients, the gray curve showed the total number who would be deemed at high risk for each risk threshold. The colorful curve (number of high-risk individuals with event) shows how many of those would be true positives (cases).

performance for rAAAs, outperforming both D-dimer and NLR, as evidenced by higher AUC values in ROC analysis. 3) At low risk thresholds, decision curve analysis demonstrated that all indicators yielded a positive net benefit for rAAA. Among them, the neutrophil count provided the highest net benefit, while abdominal pain had the lowest diagnostic net benefit for rAAA. These results suggest that blood neutrophil counts are a feasible and practical early diagnostic tool for rAAA, with potential advantages over other indicators.

Although aneurysm diameter currently remains the most important susceptibility factor for assessing growth and perioperative rupture risk,[17] it should be emphasized that historical estimates of rupture risk related to diameter are now considered to be overestimates, as they are primarily based on retrospective observations and autopsy studies.[8] The

Table 5 Net Benefit at Different Risk Thresholds for Each Biomarker

Risk Threshold	Net Benefit (95% CI)					
	Treat All	Neutrophils	NLR	D-Dimer	Abdominal Pain	Back Pain
0	0.188 (0.140, 0.240)	0.188 (0.140, 0.240)	0.188 (0.144, 0.240)	0.183 (0.129, 0.232)	0.183(0.14, 0.24)	0.188(0.135, 0.240)
0.1	0.098 (0.044, 0.156)	0.120 (0.071, 0.177)	0.109 (0.067, 0.163)	0.092 (0.043, 0.147)	0.118(0.074, 0.167)	0.098(0.044, 0.156)
0.2	−0.015 (−0.075, 0.050)	0.088 (0.005, 0.143)	0.084(0.035, 0.146)	0.071 (0.002, 0.112)	0.086(0.039, 0.142)	0.041(0.013, 0.073)
0.3	−0.160 (−0.229, −0.085)	0.081 (0.039, 0.128)	0.048 (0.004, 0.099)	0.031 (−0.004, 0.093)	0.045(0, 0.105)	0.034(0.005, 0.067)
0.4	−0.354 (−0.410, −0.246)	0.073 (0.031 0.116)	0.013 (−0.007, 0.076)	0.004 (−0.009, 0.078)	0(0, 0.064)	0.023(0, 0.057)
0.5	−0.624 (−0.721, −0.520)	0.070 (0.026, 0.105)	0.022 (−0.017, 0.052)	0.009 (−0.013, 0.067)	0(0, 0)	0.009(0, 0.048)
0.6	−1.031 (−1.151, −0.900)	0.052 (0.015, 0.100)	0.011 (−0.024, 0.041)	0.002 (−0.020, 0.049)	0(0, 0)	0(0, 0.033)
0.7	−1.707 (−1.868, −1.533)	0.051 (0.001, 0.095)	−0.013 (−0.036, 0.036)	−0.001 (−0.031, 0.036)	0(0, 0)	0(0, 0.012)
0.8	−3.061 (−3.301, −2.999)	0.021 (−0.008, 0.079)	−0.017 (−0.052, 0.031)	−0.009 (−0.054, 0.022)	0(0, 0)	0(0, 0)
0.9	−7.122 (−7.603, −6.598)	0.035 (−0.004, 0.061)	0.004 (−0.070, 0.026)	−0.031 (−0.080, 0.022)	0(0, 0)	0(0, 0)

expansion of abdominal aortic aneurysms (AAAs) is driven by several potential pathogenic mechanisms related to inflammation and tissue degradation.[18] The inflammatory process that occurs in the AAA wall is a critical factor in aneurysm formation.[19] Inflammation involves many cells of the immune system. The most important cells include neutrophils, macrophages, and mast cells.[20] These cells penetrate the layers of the aorta (intima, media, and adventitia), leading to the production of secretory molecules such as inflammatory factors and extracellular proteases.[21] Studies have shown that inflammation of the aortic wall may be a more accurate predictor of the risk of aneurysm expansion and rupture than the aortic diameter is.[22]

Among inflammatory biomarkers, the neutrophil-to-lymphocyte ratio (NLR) has gained increasing attention as a systemic inflammation-based biomarker in various diseases, including cardiovascular disorders and malignancies. NLR reflects the dynamic balance between innate immunity (represented by neutrophils) and adaptive immunity (represented by lymphocytes), making it a potential indicator of systemic inflammatory status and stress response.[23,24] In the context of abdominal aortic aneurysm (AAA), elevated NLR has been consistently associated with ruptured AAA (rAAA) and adverse clinical outcomes, including higher 30-day mortality rates.[14,25] These findings underscore the potential utility of NLR as both a diagnostic and prognostic marker in rAAA.

Building on previous research, the diagnostic performance of absolute neutrophil counts, D-dimer, and NLR in predicting rAAA was directly compared in this study. Our results demonstrated that neutrophil counts exhibited the highest diagnostic accuracy. Decision curve analysis (DCA) further supported the clinical utility of neutrophil counts, revealing the greatest net benefit for rAAA diagnosis compared to NLR and D-dimer. While NLR showed significant diagnostic value, its lower performance may be attributed to its dependence on both neutrophil and lymphocyte counts, which can be influenced by various physiological and pathological factors. In contrast, absolute neutrophil counts provide a more direct measure of systemic inflammation, which is a key driver of AAA rupture.

Neutrophils are the primary defense against a wide range of pathogens, whose main functions include phagocytosis, degranulation, and the formation of neutrophil extracellular traps.[26] A cohort study revealed strong associations between elevated neutrophil counts and AAAs.[27] Neutrophils have significant potential for enhancing the early differential diagnosis of rAAAs in patients with a known AAA in clinical settings.[28] The superior performance of neutrophil counts in our study aligns with the pathophysiological role of neutrophils in rAAA.

Neutrophils are central to the inflammatory cascade that contributes to vascular wall degradation and rupture. Increasing evidence suggests that neutrophils can influence multiple pathways through neutrophil extracellular traps, which in turn induce the formation and progression of abdominal aortic aneurysms.[29,30] Their activation leads to the release of proteolytic enzymes and reactive oxygen species, which exacerbate extracellular matrix degradation and

weaken the aortic wall. This mechanistic insight aligns with our findings, supporting the clinical relevance of neutrophil counts as a biomarker for rAAA. Elevated neutrophil counts at admission improved the early identification of rAAAs. Thus, AAA patients with high neutrophil counts should have blood flow access established and rapid ultrasound screening early to gain valuable time for surgery. This would avoid delays in diagnosis and treatment, as well as deterioration of the disease.

DCA and CIC are tools used in clinical medical research and public health to assess the impact of diagnostic tests, treatment options or predictive models in actual clinical practice.[31,32] Decision curve analysis applies this strategy to account for clinical consequences, thereby quantifying benefits and harms.[33] The threshold probability is used in a simple formula to calculate the net benefit of the prediction model. Net benefit aids in determining the most valuable and optimal choice for clinical application by identifying the model yielding the highest net benefit across all probability thresholds.[34–36] The CIC is another type of plot produced by the decision curve. For a single-risk model, the CIC shows the estimated number of individuals who would be declared high risk for each risk threshold and visually shows the proportion of those who are true positives.[37] According to the results of DCA and CIC, a greater net benefit and reduction in the number of false-positives could be achieved by the combined use of neutrophils. In actual clinical practice, measuring neutrophil counts can provide early and effective screening results for rAAAs, offering clinicians a crucial reference for further imaging tests. This helps identify patients who require urgent aortic imaging, thereby saving diagnostic time and limited emergency resources.

There are several limitations in this study. First, we recorded indices only within 12 hours after admission; however, the inflammatory response may have evolved within a few days of aneurysm rupture. Thus, future studies are needed to explore the changes in and predictive value of inflammatory factors at different time points after onset. Second, the clinical setting is far more complicated than a statistical model. Logistic regression analyses that included only initial analysis results at admission and clinical characteristics did not consider more complex parameters, which may have improved discrimination. In addition to the statistical calculations, a combination of both angio-CT at admission and biomarker neutrophils may be more promising for predicting an impending rAAA. In addition, this was a single-center retrospective study. The small sample size of this study may introduce confounding bias. The insights from this study could be expanded by including more patients through multicenter studies.

Conclusion

In summary, the prevalence of elevated neutrophil counts increased in patients with a rAAA. Neutrophil counts may aid in differentiating between ruptured and unruptured AAAs in patients with a known AAA, potentially enhancing early diagnosis and clinical decision-making. This study may provide novel insight into diagnostic strategies for rAAAs.

Data Sharing Statement

All data in this study may be available from the corresponding author upon reasonable requests.

Ethics and Consent Statements

The requirement for patient consent was waived by the Ethics Committee of the First Hospital of Hebei Medical University due to the retrospective nature of the study, which involved analyzing de-identified medical records of discharged patients. The waiver was granted under the following conditions: (1) the risks to participants were no more than minimal; (2) the waiver would not adversely affect participants' rights or welfare; and (3) the data used could not identify individuals and did not involve personal privacy or commercial interests. All patients were informed about the study via telephone, and their consent was obtained. Strict measures were implemented to ensure patient data confidentiality, with all data used solely for research purposes and protected in compliance with ethical standards.

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Disclosure

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