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ORIGINAL RESEARCH

Analysis of Risk Factors and the Establishment of a Predictive Model for Thrombosis in Patients with Antineutrophil Cytoplasmic Antibody-Associated Vasculitis

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Purpose: To explore the risk factors for thrombi occurring in patients with antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) and establish a risk prediction model to better predict the risk of thrombosis in patients with AAV.

Patients and Methods: We retrospectively analyzed 117 AAV patients who had been hospitalized in The Second Affiliated Hospital of Chongqing Medical University between October 2010 and December 2021. For all patients, we recorded demographic characteristics and clinical data, analyzed the risk factors for thrombosis in AAV patients and then developed a risk prediction model.

Results: Stepwise logistic regression analysis indicated that a high complement C3 level, a high BVAS score and a high Padua score were independent risk factors for thrombosis in AAV patients. According to multivariate analysis, a predictive model for thrombus risk was successfully established; the area under the ROC curve(AUC) was 0.803 (95% CI: 0.716–0.890) and the maximum Youden index, sensitivity and specificity were 0.487, 59.0% and 89.7%, respectively.

Conclusion: A high complement C3 level, high BVAS score, and a high Padua score were shown to be independent risk factors for thrombosis in AAV patients. We developed a risk prediction model based on these three risk factors that could predict the risk of thrombosis in AAV patients to some extent.

Keywords: antineutrophil cytoplasmic antibody, thromboembolism, risk factors, risk prediction model

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) mainly includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) and is a group of autoimmune diseases involving multiple systems throughout the body. The survival rate of AAV patients has been significantly improved due to the use of glucocorticoids, immunosuppressors and CD20 monoclonal antibody over the last few decades. As awareness of this disease has increased, there has been increasing concern over the thromboembolic events that can occur with AAV. These thromboembolic events increase the difficulty of treating the disease and can affect the prognosis.

A number of studies have shown that the risk of arteriovenous thrombosis occurring in patients with AAV is clearly increased,[1–3] although the pathogenic mechanisms involved are not clear. Such mechanisms may involve neutrophil extracellular traps (NETs), injury incurred by endothelial cells, the initiation of a coagulation cascade, the defect of fibrinolytic activity and the use of glucocorticoids.[4–6] Moreover, existing research conclusions relating to the risk factors for the thromboembolic events that occur in patients with AAV are inconsistent, the predictive values for whether

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thromboembolism will occur in patients during the course of disease are limited, and there is no clinical guideline relating to autoimmune disease and thrombi at present.

In this study, we retrospectively analyzed potential risk factors for thromboembolism in AAV patients and developed a new risk prediction model to identify high-risk patients in the early stages of disease so that we could take targeted preventive measures.

Methods

Between October 2010 and December 2021, 39 patients were hospitalized and diagnosed with AAV thromboembolism in our hospital. All of these patients had a complete set of clinical data and thromboembolic events had been verified by computed tomography, magnetic resonance imaging, digital subtraction angiography or color Doppler ultrasound. As a control group, we randomly recruited 78 patients with AAV but without thromboembolism who had been hospitalized during the same period of time. The patients included conformed to the diagnostic criteria for systemic vasculitis formulated by the 2012 Chapel Hill Meeting.[7] The exclusion criteria were as follows: (1) systemic vasculitis concomitant with other connective tissue diseases; (2) drug-induced secondary vasculitis; or (3) an incomplete data.

The demographics, clinical manifestation, and laboratory results of each patient at first diagnosis were collected, including inflammatory markers, routine blood results, renal function, blood fat, complement C3, complement C4, and ANCA. ANCA was detected by indirect immunofluorescence and enzyme linked immunosorbent assay (ELISA); the disease activity per patient was calculated according to the Birmingham Vasculitis Activity Score Version 3[8] and the Padua rating scale[9] to evaluate the risk of thrombi. According to the Declaration of Helsinki, all patients agreed to participate and publish their data. The Ethics Committee at the Second Affiliated Hospital of Chongqing Medical University approved this study.

Statistical Analysis

Data were processed by SPSS software (version 25.0; IBM, Armonk, NY, USA) and R software (version 3.5.2; R Foundation, Vienna, Austria). To improve the reliability of data from a small sample size, all data were deemed to be non-parametric. Measurement data were expressed as medians (quartiles) and compared by the rank sum test. Numerical data were expressed as percentage ratios or rates, and compared by the Chi-squared test or Fisher's exact test. Variables with a $P < 0.1$ in the single factor analysis were included in multi-factor logistic regression analysis (the step-back method) so that we could screen the specific risk factors for thrombosis in AAV patients. The risk prediction model was subsequently established pursuant to the risk factors determined by multi-factor logistic regression analysis. Receiver operator characteristic curve (ROC) analysis and DeLong inspection were used to evaluate the predictive value of the risk prediction model. $P < 0.05$ was deemed to be of statistical significance.

Results

Basic Information

Of the 39 patients with AAV, 20 were male and 19 were female; the median age was 70 years. Arterial thrombosis occurred in 23 of the 39 patients (58.97%); venous thrombi formed in 18 of the patients (46.15%), while both arterial and venous thrombi occurred in two patients (5.13%). Thrombosis occurred in 34 of the 39 patients (87.18%) three months before and after the diagnosis of AAV. Thrombosis occurred in four of these patients (10.26%) three months to one year after the diagnosis of AAV. Thrombus developed in one patient (2.56%) more than one year after the diagnosis of AAV (Table 1). Of the 78 AAV patients without thromboembolism, there were 39 males and 39 females; the median age was 63 years. All patients were treated with prednisolone and immunosuppressants.

Comparison of General Information and Clinical Manifestations

Compared to AAV patients without thrombi, we found that age and hypertension ratio of patients in the AAV thrombus group were significantly higher ($P = 0.019$ and $P = 0.019$, respectively). There was no significant difference between the

Table 1 General Information on 39 AAV Patients

No.	Sex/Age	TE Events	Treatment	The Time of Thrombus Occurrence
1	M/67	Ischemic stroke	GC, CYC	3 months before and after AAV diagnosis
2	M/66	Ischemic stroke	GC, CYC	3 months before and after AAV diagnosis
3	M/65	Deep venous thrombosis	GC, IVIG	3 months before and after AAV diagnosis
4	M/77	Deep venous thrombosis	GC, CYC	3 months before and after AAV diagnosis
5	F/75	Pulmonary embolism	GC, CYC	3 months before and after AAV diagnosis
6	M/28	Splenic infarction	GC, CYC, IVIG, PE	3 months before and after AAV diagnosis
7	M/60	Myocardial infarction	GC, CYC	3 months before and after AAV diagnosis
8	F/67	Ischemic stroke	GC, CYC, PE	3 months before and after AAV diagnosis
9	F/82	Ischemic stroke	GC, CYC, IVIG	3 months before and after AAV diagnosis
10	F/67	Ischemic stroke	GC, CYC, IVIG	3 months before and after AAV diagnosis
11	F/63	Deep venous thrombosis	GC, CYC	3 months before and after AAV diagnosis
12	M/20	Deep venous thrombosis	GC, CYC, IVIG	3 months before and after AAV diagnosis
13	M/59	Ischemic stroke	GC, CYC	3 months before and after AAV diagnosis
14	M/65	Ischemic stroke	GC, CYC, IVIG	3 months before and after AAV diagnosis
15	F/64	Deep venous thrombosis	GC, CYC, IVIG	3 months before and after AAV diagnosis
16	M/67	Deep venous thrombosis	GC, CYC, PE	3 months before and after AAV diagnosis
17	F/37	Deep venous thrombosis, pulmonary embolism	GC, CYC	3 months before and after AAV diagnosis
18	M/81	Pulmonary embolism	GC, CYC, IVIG	3 months before and after AAV diagnosis
19	F/81	Ischemic stroke	GC, CRRT	3 months before and after AAV diagnosis
20	M/70	Myocardial infarction	GC, CYC	3 months before and after AAV diagnosis
21	M/72	Ischemic stroke	GC, CYC	3 months before and after AAV diagnosis
22	F/75	Ischemic stroke	GC, CYC	3 months before and after AAV diagnosis
23	M/52	Deep venous thrombosis	GC, PE, CRRT, RTX	3 months before and after AAV diagnosis
24	F/68	Deep venous thrombosis	GC, CYC, IVIG	3 months before and after AAV diagnosis
25	M/69	Ischemic stroke	GC, CYC	3 months before and after AAV diagnosis
26	F/49	Ischemic stroke	GC, PE, CRRT	3 months before and after AAV diagnosis
27	F/67	Deep venous thrombosis	GC, CYC	3 months before and after AAV diagnosis
28	M/66	Deep venous thrombosis	GC, CYC, PE	3 months before and after AAV diagnosis
29	M/70	Ischemic stroke	GC, CYC	3 months before and after AAV diagnosis
30	F/74	Ischemic stroke	GC, CYC, IVIG	3 months before and after AAV diagnosis
31	F/83	Ischemic stroke	GC, CYC, IVIG	3 months before and after AAV diagnosis
32	M/70	Ischemic stroke	GC, CYC	3 months before and after AAV diagnosis
33	F/56	Deep venous thrombosis	GC, IVIG, CRRT	3 months before and after AAV diagnosis
34	M/60	Deep venous thrombosis, pulmonary embolism	GC, CRRT	3 months before and after AAV diagnosis
35	F/62	Deep venous thrombosis	GC, CYC, CRRT	3 months to 1 year after AAV diagnosis
36	F/85	Ischemic stroke, deep venous thrombosis	GC, CYC, IVIG	3 months to 1 year after AAV diagnosis
37	F/67	Ischemic stroke, pulmonary embolism	GC, IVIG	3 months to 1 year after AAV diagnosis
38	M/80	Ischemic stroke	GC, CYC	3 months to 1 year after AAV diagnosis
39	F/59	Ischemic stroke	GC, CYC, IVIG	More than 1 year after AAV diagnosis

Abbreviations: F, female; M, male; GC, glucocorticoids; CYC, cyclophosphamide; IVIG, intravenous immunoglobulin; CRRT, continuous renal replacement therapy; PE, plasma exchange; RTX, rituximab.

AAV thrombus group and the AAV group without thrombi in terms of gender, BMI, course of disease, smoking history, diabetes, coronary heart disease, or fever and organ involvement ($P > 0.05$; Table 2).

Comparison of Laboratory Results, BVAS Scores and Padua Scores

In terms of laboratory results, white blood cell count, neutrophil count and D-dimer were significantly higher in the AAV thrombus group than those in the AAV group without thrombi ($P = 0.013$, $P = 0.049$ and $P = 0.009$, respectively). The levels of albumin and high-density lipoprotein were significantly lower than those in the AAV group without thrombi ($P = 0.017$ and $P = 0.005$, respectively).

Table 2 Comparison of General Information and Clinical Manifestation

Characteristics	TE (n=39)	No TE (n=78)	z/X^2	P
Sex, male, n(%)	20(51.3)	39(50.0)	0.017	0.896
Age(y), median (IQR)	70(60–75)	63(54–69)	−2.338	0.019
BMI(kg/m^2), median (IQR)	20.4(18.7–22.8)	21.3(18.7–23.9)	−1.021	0.379
Course of a disease(m), median (IQR)	2(0.7–12)	2(1–7.5)	−0.75	0.453
Smoking status, n(%)	16(41.0)	34(43.6)	0.070	0.792
Hypertension, n(%)	19(48.7)	21(26.9)	5.489	0.019
Diabetes, n(%)	7(17.9)	7(9.0)	1.227	0.268
Coronary artery disease, n(%)	4(10.3)	2(2.6)	1.779	0.182
Fever, n(%)	15(38.5)	24(30.8)	0.692	0.405
Organs involved, n(%)				
Skin	3(7.7)	4(5.1)	0.019	0.890
ENT	17(43.6)	26(33.3)	1.777	0.278
Lung	28(73.7)	50(64.1)	1.065	0.302
Heart	5(12.8)	5(6.4)	0.670	0.413
Digestive system	3(7.7)	6(7.7)	0.000	1.000
Kidney	28(71.8)	42(53.8)	4.495	0.062
Peripheral nervous system	7(17.9)	7(9.0)	1.227	0.268
Arthralgia	9(23.1)	17(21.8)	2.267	0.322

Abbreviations: AAV, antineutrophil cytoplasmic antibody–associated vasculitis; TE, thromboembolism; IQR, interquartile range; BMI, body mass index.

In terms of disease activity and thrombus assessment, compared to the AAV group without thrombi, both the BVAS score and the Padua score were significantly higher in the AAV with thrombi ($P < 0.001$ and $P = 0.001$, respectively) (Table 3).

Multivariate Logistic Regression Analysis

Thromboembolism in AAV was used as the dependent variable for multivariate logistic regression analysis; variables that were significant ($P < 0.1$) in single factor analysis were used as concomitant variables. Multivariate logistic regression (the step-back method) showed that a high complement C3 level (odds ratio [OR]: 7.653; 95% confidence interval [CI]: 1.666–35.164), a high BVAS score (OR: 1.161; 95% CI: 1.068–1.263) and a high Padua score (OR 1.422: 95% CI: 1.091–1.854) were identified as independent risk factors for thrombosis in AAV patients (Table 4).

Establishment and Evaluation of a Predictive Model

A predictive model for the risk of thromboembolism (Table 4) was established in line with the results arising from multivariate logistic regression analysis. The regression equation is as shown in Equation (1).Equation (1): Logit(P)= −6.594 + 2.035 × complement C3 + 0.150 × BVAS score + 0.352 × Padua score. A ROC curve was generated from the model along with a separate Padua rating scale for predicting thrombus in AAV patients. DeLong inspection was used to compare the AUC of the model and the Padua rating scale(Figure 1). The AUC of the new risk prediction model was 0.803 (95% CI: 0.716–0.890), thus, showing that the predictive performance of the model was good. The maximum Youden index, sensitivity and specificity were 0.487, 59.0% and 89.7%, respectively. The AUC of the Padua rating scale was 0.671 (95% CI: 0.560–0.782); DeLong inspection showed that the new risk prediction model was significantly superior to the separate Padua rating scale ($P = 0.001$).

Discussion

Although the survival rate for AAV patients has improved over the last few decades, the mortality rate for this condition is still 2.7-fold higher than that of the common population.[10] As a key complication of AAV, arteriovenous thromboembolism increases the difficulty of treating AAV patients and can also influence the death rate.[11,12] Therefore, identifying

Table 3 Comparison of Laboratory Results, BVAS Scores and Padua Scores

	TE (n=39)	No TE (n=78)	z/X^2	P
ESR(mm/h), median (IQR)	71.00(43.00–90.00)	69.50(39.00–93.00)	−0.272	0.786
CRP(mg/L), median (IQR)	86.30(22.73–134.77)	38.21(5.00–121.79)	−1.647	0.099
PCT(ng/L), median (IQR)	0.33(0.12–2.08)	0.27(0.09–0.51)	−1.553	0.120
HB(g/L), median (IQR)	93.00(77.00–111.00)	98.00(79.75–115.00)	−0.613	0.540
WBC (×10^9/L), median (IQR)	10.56(7.82–15.70)	9.23(6.06–12.43)	−2.495	0.013
Neutrophil count (×10^9/L), median (IQR)	8.23(5.66–12.87)	6.92(4.41–9.86)	−1.969	0.049
Lymphocyte count (×10^9/L), median (IQR)	1.19 (0.88–1.65)	1.08 (0.79–1.47)	−1.234	0.217
PLT(×10^9/L), median (IQR)	310.00(214.00–406.00)	273.00(203.50–360.50)	−1.292	0.196
ALB(g/L), median (IQR)	29.50(25.50–33.00)	32.55(28.08–36.00)	−2.385	0.017
Blood creatinine (μmol/L), median (IQR)	116.70(64.90–394.70)	110.40(57.95–411.85)	−0.020	0.984
GFR (mL/min), median (IQR)	41.90(11.50–90.80)	49.15(12.30–95.25)	−0.020	0.984
Triglyceride(mmol/L), median (IQR)	1.20(0.87–1.26)	1.30(0.95–1.33)	−1.428	0.153
Cholesterol(mmol/L), median (IQR)	3.86(3.20–4.22)	3.99(3.50–4.45)	−1.580	0.114
HDL(mmol/L), median (IQR)	1.02(0.91–1.06)	1.14(1.02–1.22)	−2.790	0.005
LDL(mmol/L), median (IQR)	1.99(1.69–2.20)	2.00(1.58–2.25)	−0.657	0.511
D- dimer (n g/m l), median (IQR)	2176.20(374.50–2862.20)	888.35(268.03–1223.40)	−2.611	0.009
AECA, n(%)	5(12.8)	10(12.8)	0.000	1.000
p-ANCA, n(%)	34(87.2)	66(84.6)	0.138	0.711
c-ANCA, n(%)	2(5.1)	12(15.4)	1.714	0.190
PR3, n(%)	2(5.1)	12(15.4)	1.714	0.190
MPO, n(%)	34(87.2)	66(84.6)	0.138	0.711
C3(g/L), median (IQR)	1.13(0.95–1.34)	1.04(0.85–1.22)	−1.717	0.086
C4(g/L), median (IQR)	0.27(0.19–0.35)	0.25(0.19–0.30)	−1.340	0.180
BVAS score, median (IQR)	19.00(15.00–24.00)	14.50(8.00–18.00)	−4.198	0.000
Padua score, median (IQR)	3(2–6)	2(2–3)	−3.245	0.001

Abbreviations: TE, thromboembolism; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; PCT, procalcitonin; HB, hemoglobin; WBC, white blood cells; PLT, Platelet; ALB, albumin; GFR, Glomerular filtration rate; HDL, high density lipoprotein; LDL, Low density lipoprotein; AECA, anti-endothelial cell antibody; C3, complement C3; C4, complement C4.

Table 4 Multivariate Logistic Regression Analysis

Variable	B	Sb	Wald χ^2	P	OR	95% CI	
						Low	High
C3	2.035	0.778	6.842	0.009	7.653	1.666	35.164
BVAS score	0.150	0.043	12.220	0.000	1.161	1.068	1.263
Padua score	0.352	0.135	6.789	0.009	1.422	1.091	1.854
Constant	−6.594	1.366	23.311	0.000	0.001		

Abbreviations: BVAS, Birmingham Vasculitis Activity Score; C3, complement C3.

potential risk factors for thrombosis will help us to develop a predictive model for the risk of thrombi so that we can identify high-risk patients in the early phases of disease and thus perform targeted interventions and prevent thrombosis.

Our results suggested that age, proportion of hypertension, white blood cell count, neutrophil count and D-dimer levels of patients in the AAV group with thrombi were significantly higher than those in the AAV group without thrombi. The levels of albumin and high-density lipoprotein were significantly lower than those in the group without thrombi, indicating that these indicators might be potential risk factors for thromboembolic events. The influences of advanced age and high blood pressure on thrombi have been proven previously.[13,14] An increased level of D-dimer indicates that hypercoagulability and hyperfibrinolysis have occurred and that the risk of thromboembolism has increased. Serum albumin is associated with anti-inflammatory, antioxidant, anticoagulant and anti-platelet aggregation activity as well as colloid osmosis.[15] High-density lipoprotein plays a role in the reverse transport of cholesterol and also has anti-thrombosis

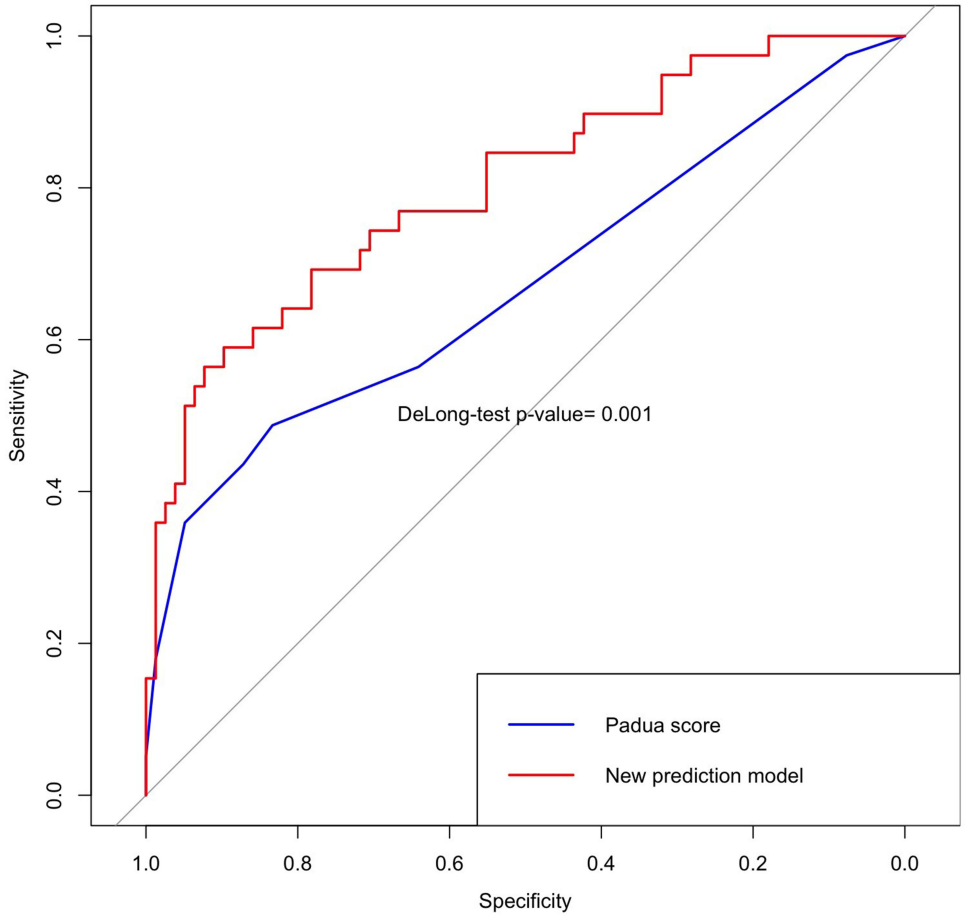

Figure 1 ROC curve for the new risk prediction model and Padua rating scale.

characteristics.[16] Therefore, it has been suggested that if we wish to prevent thrombosis in aged patients, then it is important to control blood pressure and correct hypoalbuminemia and lipid metabolism disorders.

The multivariate analysis carried out in this study proved that patients with AAV and high levels of complement C3 were more likely to develop thrombi. Complement C3 is the core component of the complement system and is activated by classical, lectin and alternative pathways. A substantial body of evidence now indicates that complement C3 is closely associated with the coagulation system.[17,18] During the coagulation process, the coagulation/fibrinolytic cascade can activate complement C3. In contrast, the components of the complement system are also involved in thrombin activation and the regulation of platelet aggregation. The interaction between complement C3 and the coagulation system is helpful in promoting coagulation and reduce fibrinolysis and can ultimately result in a prethrombotic state.[19,20] Research has shown that complement activation may contribute to thromboembolism and high concentrations of complement C3 were associated with high risk of venous thromboembolism.[17] It is worth noting that new discoveries over recent years have shown that activation of the complement system is involved in the pathogenesis of AAV, especially the alternative complement pathway.[21,22] This may be a common link between AAV and thrombosis, and the specific underlying mechanism needs further fundamental research. Therefore, it is important that we consider complement C3 as an important factor. However, in our single factor analysis, the difference in complement C3 between patients in the two groups was not statistically significant; it is likely that this is because the sample size of our study was too small and that the complement system activation resulted in the partial depletion of complement C3 during the onset of AAV.

The multivariate analysis performed in this study indicated that AAV patients with a high BVAS score were more likely to undergo thromboembolic events. The BVAS score is a good indicator for evaluating systemic vasculitis disease activity and higher scores indicate a higher levels of disease activity. Previous studies showed that high levels of

inflammatory activity might trigger hypercoagulability in patients with inflammatory disease.[23,24] Compared with patients with inactive AAV, the levels of neutrophil extracellular traps (NETs) was previously found to be significantly increased in patients with active AAV.[25] NETs were activated by neutrophils and further formed, which played a key role in activating the coagulation cascade reaction, collecting platelets, and acting as a scaffold for thrombus assembly. These are all processes that facilitate the development of thrombosis, thus, suggesting that the risk of thrombosis was higher in patients with active AAV. Furthermore, our results showed that AAV patients had a high incidence of early thrombosis after diagnosis; this was consistent with previous studies;[3,26] consequently, it is important that we consider the relationship between inflammatory activity and thrombosis. Therefore, AAV patients in the active stage of the disease require active treatment and the control of inflammation to prevent thrombosis; furthermore, close attention should be paid to the occurrence of thromboembolic events.

The multivariate analysis in this study showed that AAV patients with a high Padua score were more likely to suffer from thromboembolism. The Padua prediction score scale is a venous thromboembolism (VTE) risk evaluation model that was first proposed by Professor Barbar in 2010.[9] The Padua thrombus scale items are succinct and clear; this scale is based on scientific items and is used widely in the clinic. The predictive value of the Padua scale for predicting thrombotic risk has been confirmed by many studies. In the present study, we found that a high Padua score was also of predictive value for arteriovenous thrombosis in AAV patients to some extent, but more research is needed. Thus, it is necessary to perform dynamic Padua score determination in AAV patients and take the appropriate preventive measures in a timely manner in patients with a high score.

At present, most studies on thromboembolism in AAV patients are still focused on the analysis of occurrence risk and risk factors. In this study, we established a risk prediction model for thrombus in AAV patients. The new model features three risk factors (complement C3 level, BVAS score, Padua score) that were identified by multivariate analysis. Receiver operator characteristic curve (ROC) analysis and DeLong inspection results showed that the new risk model could be used to predict the risk of thrombosis in AAV patients to some extent. The new model was superior to the separate Padua rating scale and was capable of rapidly evaluating the risk of thromboembolism in AAV patients clinically. The new model also supported the early identification of patients at high risk of thromboembolism and provided efficient indication to administer relevant preventive measures in high-risk groups to reduce the risk of thromboembolic events. Therefore, when patients are newly diagnosed with AAV, it is important that clinicians consider the dynamic BVAS activity score and Padua score and pay more attention to the risk of thrombosis in patients with a high level of complement C3, a high BVAS activity score and a high Padua score.

It is worth noting that this is a retrospective study and inherent limitations should not be ignored, including recall bias and limited data. Also, the Padua score is primarily used to predict the risk of VTE. Although this study shows that this score has some value in the assessment of arteriovenous thrombosis, more research is needed to explore the appropriate scale for arterial thrombosis in AAV patients. Finally, in terms of treatment, this study did not cover the effect of different doses of glucocorticoids or different immunosuppressants on thrombosis in patients with AAV, so it cannot provide effective guidance for clinical medication.

In summary, this study analyzed the risk factors of thromboembolism in ANCA-associated vasculitis patients, constructed a thrombus risk prediction model and provided a method for the early identification of thrombosis in AAV patients to help clinicians to actively prevent thrombosis in patients with AAV.[27]

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Disclosure

The authors report no conflicts of interest in this work.

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