Analysis of risk factors associated with diffuse alveolar haemorrhage in patients with ANCA-associated vasculitis and construction of a risk prediction model using line graph

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Abstract

Objective

This study aims to analyse the risk factors associated with diffuse alveolar haemorrhage (DAH) in patients with ANCA-associated vasculitis (AAV) and construct a risk prediction model using line graph.

Methods

A retrospective study was conducted from January 2012 to May 2023 at the First Clinical College of Three Gorges University, focusing on patients diagnosed with AAV. Clinical and laboratory data were collected from these patients. The potential predictors subsets of high-risk AAV combined with DAH were screened by LASSO regression and 10-fold cross-validation method, and determined by using multivariate Logistic regression analysis, then were used for developing a prediction nomogram for high-risk AAV combined with DAH using the R software. ROC curve analysis was used to validate the model's stability. Internal validation was performed using a bootstrap method. The discrimination of the nomogram was determined by calculating the average consistency index (C-index). The calibration curve was used to assess the calibration of the nomogram.

Results

A total of 234 patients with AAV were included, among whom 85 developed DAH, with an incidence rate of 36%, and the average age was 63±12. Multivariable logistic regression analysis showed that Age [OR=1.037 (95%CI: 1.006, 1.071), p=0.019], platelet count (PLT) [OR=0.996 (95%CI: 0.992, 0.999), p=0.029], ESR [OR=1.028 (95%CI: 1.015, 1.042), p<0.01], HB [OR=0.978 (95%CI: 0.959, 0.996), p=0.024], and haematuria [OR=3.77 (95%CI: 1.677, 8.976), p=0.001] were found to be independent predictors of AAV combined with DAH and were used to construct a nomogram. The AUC-ROC values of the nomogram for DAH in AAV patients was 0.852 (95%CI: 0.801, 0.903), and the C-index could reach 0.824 after internal verification, showing good differentiationand consistency.

Conclusion

The new nomogram, which included age, Hb, ESR, PLT and haematuria as variables, had the potential to predict the risk of AAV patients complicated with DAH.

Key words

ANCA-associated small vessel vasculitis, diffuse alveolar haemorrhage, risk factor risk prediction model

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Introduction

Anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) is a group of autoimmune diseases characterised by small-vessel necrosis and inflammation (1) with the target of ANCA autoantigen is myeloperoxidase (MPO-ANCA) and protease 3 (PR3-ANCA) (2). AAV includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) (3). In Europe, the overall incidence rate of AAV is approximately (46–184) per million people (4). In Asian countries, such as Japan, MPA tends to be the dominant subtype, but the incidence rate of GPA is lower compared to European countries (5).

Diffuse alveolar haemorrhage (DAH) is a serious complication of AAV, and its characteristics may include respiratory symptoms, impaired oxygenation, and activated immune response. DAH can lead to respiratory symptoms such as dyspnoea and coughing up blood, while the filling of the alveoli with blood can impair the exchange of oxygen and carbon dioxide, leading to hypoxemia as well as respiratory acidosis. In addition, the entry of blood and inflammatory metabolites into the alveoli caused by DAH may activate the immune system, leading to inflammatory reactions and damage to the lungs (6, 7). In the past decade, despite advances in therapy methods for patients with severe active AAV, the mortality rate of AAV combined with DAH can be as high as 50–65% (8). In addition, there is currently no consensus on the risk factors for AAV combined with DAH, it is important to identify the risk factors that may contribute to DAH. In the following analysis of AAV-related DAH, we aim to summarise its characteristics as much as possible, providing theoretical support for subsequent risk factor analysis and nomogram development.

Materials and methods

Research objects

This retrospective study was conducted in the First Clinical College of Three Gorges University from January 2012 to May 2023. Patients selected were older than 18 years of age, had complete data, and met the 2012 Chapel Hill revised criteria (3). Patients who met at least 3 of the following 4 criteria were diagnosed with DAH (9): (i) pulmonary symptoms including haemoptysis, dyspnoea, hypoxaemia; (ii) imaging showed new infiltrates, and bronchoscopy did not reveal gross bronchial injury; (iii) clinical manifestations included haemoptysis, dyspnoea, hypoxemia, cough, etc. Haemoglobin levels were found to be decreased disproportionate to the amount of haemoptysis (4). Bronchoalveolar lavage (BAL) fluid appeared grossly bloody and/or contained numerous haemosiderin-laden macrophages after Prussian blue staining. In addition, patients were excluded if the DAH could be explained by another medical condition, such as Severe coagulation disorders, acute pulmonary oedema, pulmonary embolism, or definite pulmonary infections were excluded. or other diseases.This study has been reviewed and approved by the Ethics Committee of our hospital (approval no.: 2022-123-01).

Collection of clinical data

The age of first onset, sex, smoking, combined hypertension, diabetes and basic lung diseases were collected.

Alcohol abuse, dependence and harmful alcohol use are now generally referred to as alcohol use disorders (AUDs) (10, 11).

Data collection of involved organs: AAV-related kidney, ear, nose and throat, gastrointestinal tract and nervous system, etc.

The involvement of the ear, nose, and throat organs in ANCA-associated vasculitis (AAV) is defined (12, 13) as the manifestation of AAV affecting the ears, nose, and throat, leading to symptoms such as nasal congestion, epistaxis, otitis media, hearing loss, and throat ulcers. Renal disease was defined (12) as the presence of haematuria >10RBCs/hpf, proteinuria >1g, hypertension, creatinine >125μmol or rise in creatinine >30%, or creatinine clearance fall >25%, attributable only to vasculitis, as per the BVAS form. Acute renal failure was defined by the presence of progressively raised serum creatinine or 15% declined clearance rate of serum cre-

atinine on the baseline within days or weeks. Chronic kidney disease was defined as an eGFR <60mL/min/1.73m^2. The nervous system involvement (12) was subdivided into central nervous system (stroke, meningitis, cord lesion, and cranial nerve palsy) and peripheral nervous system (sensory peripheral neuropathy and motor mononeuritis multiplex).

When the gastrointestinal tract is affected by AAV (14), it can lead to various symptoms, including gastrointestinal bleeding, abdominal pain, diarrhoea, decreased appetite, nausea, as well as complications such as gastrointestinal ulcers, inflammation, and narrowing.

Laboratory data collection

Laboratory data included in this study were the ANCA subtype associated with the initial occurrence of DAH, haemoglobin (Hb) level, platelet count (PLT), white blood cell count (WBC), albumin (ALB), erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (CRP), complement levels (C3, C4), serum creatinine (Scr), blood urea nitrogen (BUN), serum uric acid (UA), 24-hour urine protein quantification, endogenous creatinine clearance rate (CCr), activated partial thromboplastin time (APTT), prothrombin activity (PTA), and haematuria, and the modified British Thoracic Society pneumonia severity score (CURB-65 score).

ANCA classification criteria of patients (MPA, GPA or EGPA): The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) jointly released new classification criteria for GPA, MPA, and EGPA in 2022 to clarify ANCA diagnosis (15-17).

Statistical analysis

Analysis of the collected data was performed using R language (R4.3.1)/ SPSS 23 software. Count data was expressed as the number of cases and rates [n(%)] and intergroup comparisons were conducted using chi-square test (χ^2). When continuous data followed a normal distribution, it was presented as mean ± standard deviation (x±s), and intergroup comparisons were performed using t-test. For non-normally distributed continuous data, median (interquartile range) [M(Q1, Q3)] was used to represent the data, and nonparametric rank sum test was employed for intergroup comparisons. The optimal risk factors selected by the Lasso model were further subjected to univariate analysis (p<0.05 indicating statistical significance), and independent risk factors with p<0.05 were included in the logistic regression for multivariate analysis. Calculation and plotting of C-index, calibration curve, ROC curve, clinical decision curve, and nomogram were conducted.

The creation and validation of column line graph models

The "glmnet" package in R language (R4.2.1) software is used for Lasso re-

Table I. Comparison of baseline data of two groups of AAV patients with or without DAH.

Variable	Non-DAH group (n=149)	DAH group (n=85)	t/χ^2value	p-value
Sex, n (%)			0.067	0.795
Female	78 (52)	43 (51)		
Male	71 (48)	42 (49)		
Age, years	58 ± 10	63 ± 12	-3.245	0.001
Smoking, n (%)			0.115	0.734
No	102 (68)	60 (71)		
Yes	47 (32)	25 (29)		
AUDs, n (%)			0.541	0.462
No	120 (81)	65 (76)		
Yes	29 (19)	20 (24)		
Haemoptysis, n (%)			54.026	< 0.001
No	118 (79)	26 (31)		
Yes	31 (21)	59 (69)		
Dyspnoea, n (%)			21.543	< 0.001
No	96 (64)	28 (33)		
Yes	53 (36)	57 (67)		
COPD, n (%)			0.913	0.339
No	140 (94)	77 (91)		
Yes	9 (6)	8 (9)		
Hypertension, n (%)			7.469	0.006
No	82 (55)	31 (36)		
Yes	67 (45)	54 (64)		
Diabetes, n (%)			0.007	0.935
No	132 (89)	75 (88)		
Yes	17 (11)	10 (12)		
CHD, n (%)			0.01	0.919
No	139 (93)	79 (93)		
Yes	10 (7)	6 (7)		
ENT, n (%)			1.21	0.299
No	148 (99)	83 (98)		
Yes	1 (1)	2 (2)		
GI, n (%)			0.001	0.971
No	68 (46)	39 (46)		
Yes	81 (54)	46 (54)		
NS, n (%)			1.429	0.232
No	138 (93)	82 (96)		
Yes	11 (7)	3 (4)		
AKI, n (%)			0.086	0.77
No	142 (95)	81 (95)		
Yes	6 (5)	5 (5)		
CKD, n (%)			-4.36	< 0.001
0	64 (43)	17 (20)		
1	5 (3)	1 (1)		
2	2 (1)	1 (1)		
3	11 (7)	8 (9)		
4	20 (13)	6 (7)		
5	47 (32)	52 (61)		

Data are shown as mean (SD) for continuous variables and as percentages for categorical variables. COPD: chronic obstructive pulmonary disease; CHD: coronary heart disease; ENT: ear, nose and throat organs were damaged; GI: gastrointestinal organ damage; NS: nervous system damage.

gression to select independent risk factors. The 10-fold cross-validation method is used to determine the optimal risk prediction factor subset. The optimal parameter (lambda) in the Lasso model is determined by selecting the minimum standard through cross-validation. Multiple logistic regression analysis is then performed to establish a risk prediction model. The risk predictive ability of the model is evaluated using the receiver operating characteristic (ROC) curve and area under the curve (AUC). The validation of the column line graph risk prediction model is conducted using the Bootstrap method, which involves repeated sampling (1000 times) to calculate the relative calibration C-index. The C-index indicates the discriminative ability of the model; 0.5–0.7 suggests low discriminative ability, 0.7–0.9 indicates moderate discriminative ability, and >0.9 indicates high diagnostic value (18). Clinical decision curves and nomogram graphs are calculated and plotted.

Results

General data and regression analysis of AAV combined with DAH patients

A total of 234 patients meeting the study criteria were included in this study, including 212 patients with MPA, 8 patients with EGPA, and 14 patients with GPA. There were 85 cases of AAV with DAH and 149 cases of AAV without DAH. The time (days) from AAV diagnosis to DAH complications was (median, 10, quartiles 7, 14). Univariate statistical analysis was performed on the collected data. The AAV without DAH group had a mean age of 58 ± 10, with 71 males (48%), while the AAV combined with DAH group had a median age of 63±12, with 42 males (49%). There was no statistical significance in ANCA classification between two groups (p>0.05). Age, haemoptysis, dyspnoea, hypertension, red blood cells, haemoglobin, ESR, PLT, creatinine, blood urea nitrogen, and complement C3 showed statistically significant differences between the two groups (p<0.05), as shown in Table I and Table II. Lasso regression was performed using patient data, and ten-fold cross-validation analysis was conducted (Fig. 1), resulting in the identification of the minimum penalty λ+1 (0.032). Ultimately, age, hypertension, HB, ESR, PLT, C3, CKD, haematuria, and 24-h UTP were selected as independent variables associated with AAV combined with DAH.

Table II. Comparison of clinical data of two groups of AAV patients with or without DAH.

Variables	Non-DAH group (n=149)	DAH group (n=85)	T/c2/Z value	p-value
RBC (10^12/L)	3.25 (2.65, 3.71)	2.6 (2.17, 3.12)	-4.692	< 0.001
HB (g/L)	94 (77, 108)	75 (66, 85)	-5.863	< 0.001
ESR (mm/h)	29 (11, 51)	42 (23, 77.5)	-3.666	< 0.001
WBC (10^9/L)	8.26 (6.17, 10.73)	7.51 (5.51, 9.81)	-1.642	0.101
PLY (g/L)	218 (158, 295)	159 (110, 243)	-3.668	< 0.001
LY (10^9/L)	1.1 (0.79, 1.48)	0.71 (0.41, 1.07)	-5.107	< 0.001
NEUT (10^9/L)	6.25 (4.18, 8.79)	6.35 (4.34, 8.72)	-0.208	0.835
CRP (mg/dl)	37.18 (8.84, 87.91)	43.22 (16.7, 104)	-1.565	0.118
Scr (umol/L)	164 (73, 473.9)	503 (201.5, 724.5)	-4.630	< 0.001
BUN	10.02 (6.32, 21.49)	20.7 (12.2, 28.4)	-4.245	< 0.001
ANCA, n (%)			2.717	0.099
PR3	5 (3)	8 (9)		
MPO	144 (97)	77 (91)		
C3	0.95 (0.81, 1.15)	0.87 (0.71, 0.95)	-4.041	< 0.001
C4	0.25 (0.2, 0.3)	0.25 (0.18, 0.31)	-0.524	0.601
24-h UTP	0.56 (0.22, 1.24)	1.52 (0.5, 2.27)	-4.414	< 0.001
CCr	26.5 (8.32, 111.18)	10.71 (7.14, 21.21)	-3.276	0.001
Haematuria			31.38	< 0.001
No	76 (51)	12 (14)		
Yes	73 (49)	73 (86)		
ALT (IU/L)	15 (9, 24)	14 (9, 20)	-0.989	0.323
AST(IU/L)	18 (14, 24)	18 (13, 23)	-0.704	0.459
Alb	30.12 ± 5.19	29.42 ± 4.76	1.024	0.307
CK	38 (24, 71)	58 (35, 91)	-3.01	0.003
APTT(S)	38.8 (35.6, 42.7)	38.7 (34, 42.1)	-0.49	0.624
PTA(S)	97 (85, 109)	92 (81, 105)	-1.469	0.142
CURB-65 score, n (%)			-7.86	0.432
0	49 (33)	36 (42)		
1	31 (21)	12 (14)		
2	39 (26)	22 (26)		
3	27 (18)	7 (8)		
4	2 (1)	3 (4)		
5	1 (1)	5 (6)		
ANCA diagnosis, n (%)			-1.484	0.138
MPA	138 (93)	74 (87)		
EGPA	6 (4)	2 (2)		
GPA	5 (3)	9 (11)		

RBC: red blood cells; HB: haemoglobin; ALT: alanine aminotransferase; AST: glutamic oxalacetic transaminase; LDH: lactate dehydrogenase; APTT: activated partial thromboplastin time; PTA: prothrombin activity; CK: creatine kinase; LY: lymphocyte count; NEUT: neutrophil count; Scr: serum creatinine; AKI: acute kidney injury; UTP: 24-h urine protein; CCr: endogenous creatinine clearance rate.

Multivariate logistic regression analysis and nomogram establishment

The 9 selected independent variables were included in multivariate logistic regression analysis, and the results showed that age, HB, lower levels of PLT, ESR, and haematuria (p<0.05) could be regarded as independent risk factors for DAH of AAV. The results were shown in Table III, and R language software was used to construct a risk prediction model for DAH of AAV for the above 5 independent risk factors (Fig. 2).

Evaluation of risk prediction model

The ROC curve analysis of the constructed nomogram graph risk prediction model associated with DAH in AAV patients yielded an area under the curve (AUC) value of 0.852 (95%CI: 0.801–0.903), as shown in Figure 3. The validation of the nomogram graph risk prediction model was conducted using the Bootstrap method with 1000 repeated samples. The calculated C-index was 0.824, indicating good discrimina-

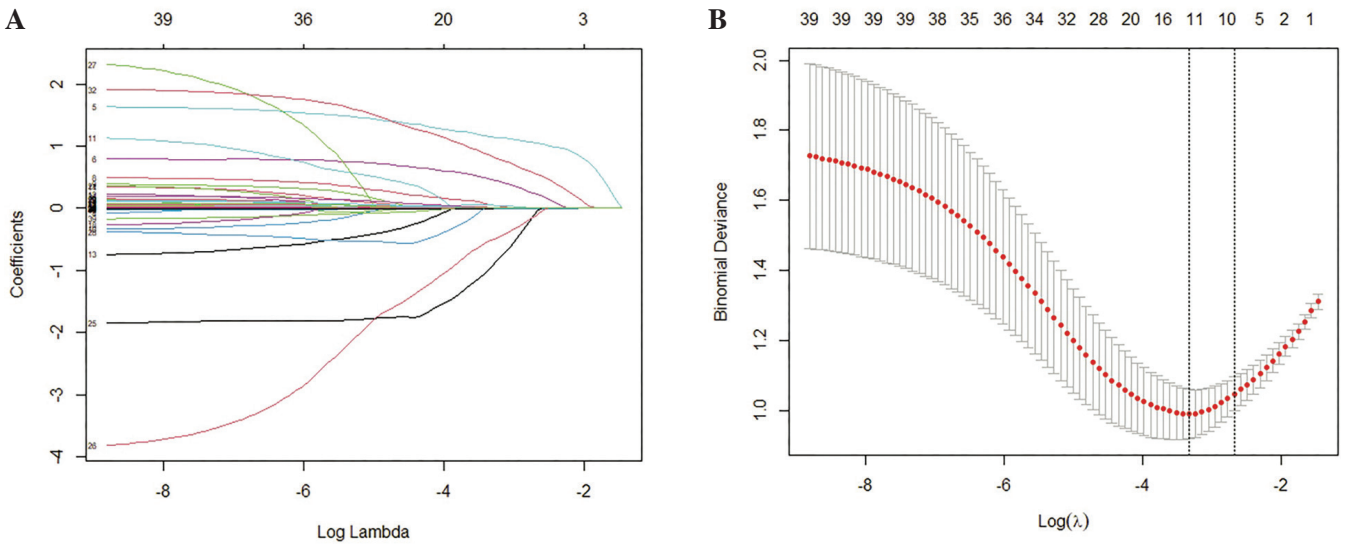

Fig. 1. LASSO regression was used for risk factor screening. (A) LASSO coefficient profiles of the 39 variables. The coefficient profile plot was produced against the log (λ) sequence. (B) The optimal parameter selection (lambda) in the LASSO model employed ten-fold cross-validation criteria. The left dashed line represents Lambda at the minimum error point (lambda. min), while the right dashed line represents Lambda at the standard error point (lambda.1-SE).

Table III. Logistic multivariate regression analysis of AAV combined with DAH patients.

Variables	β	Odds ratio (95% CI)	*p*-value
Age	0.036	1.037 (1.006—1.071)	0.019
Hypertension	0.418	1.520 (0.751—3.092)	0.243
HB	-0.021	0.978 (0.959—0.996)	0.024
PLT	-0.003	0.996 (0.992—0.999)	0.029
ESR	0.027	1.028 (1.015—1.042)	<0.01
C3	-0.846	0.429 (0.072—2.434)	0.343
CKD	0.032	1.033 (0.857—1.242)	0.728
Haematuria	1.327	3.770 (1.677—8.976)	0.001
24-h UTP	0.173	1.189 (0.919—1.551)	0.188

β is the regression coefficient. CI: confidence interval.

tion and consistency of the constructed risk prediction model. The calibration curve demonstrated good agreement between the observed values and the risk prediction model predicted values (Fig. 4). The decision curve analysis showed that taking measures in AAV patients when the threshold probability was between 1% and 81% resulted in the greatest benefit (Fig. 5).

Discussion

ANCA targets specific antigens including MPO and PR3. MPO-ANCA is frequently observed in patients with MPA and EGPA, whereas PR3-ANCA is found in approximately 80% of individuals with GPA (19). GPA is characterized by granulomatous lesions and commonly affects the upper and lower respiratory tract as well as the kidneys, making it the most common form of pulmonary vasculitis (20). EGPA has a lower incidence compared to other ANCA-associated vasculitides and typically presents with a prodromal phase of rhinosinusitis and asthma, followed by eosinophilia and vasculitis (21). MPA, on the other hand, is distinguished by DAH caused by pulmonary capillarities, which can manifest as the primary lung manifestation in some cases (22). Severe ANCA is primarily characterised by DAH. In this study, a significant proportion of MPA patients had DAH, accounting for 87%, which aligns with the aforementioned characteristics. ANCA serves not only as a diagnostic indicator but also plays a role in the pathogenesis of AAV. In this study, there were no significant differences in MPA, GPA and EGPA between the two groups, which may be related to the sample size of patients. In addition, the use of ANCA levels to assess disease activity or recurrence in AAV remains controversial (23, 24). Symptoms commonly associated with DAH include cough, dyspnoea, and haemoptysis. In our study, more than 69% of patients presented with haemoptysis, while less than half exhibited concealed alveolar haemorrhage, which manifested as dyspnoea and decreased haemoglobin levels. Therefore, prompt thoracic HRCT or bronchoalveolar lavage should be conducted in cases of unexplained dyspnoea or decreased haemoglobin levels.

In this article, age, HB, PLT, ESR, and haematuria are identified as risk factors for DAH in AAV. DAH is an important clinical manifestation of AAV and can lead to pulmonary dysfunction and even life-threatening conditions. Therefore, understanding the relationship between AAV with DAH and age is crucial for diagnosis and treatment. In this study, 85 patients were included, with an average onset age of 63±12 years. The majority of patients were middle-aged and elderly, which is consistent with previous literature reports (25). Although older patients are more likely to develop AAV with DAH there have been reports suggesting that younger patients can also be affected, according to existing studies, younger patients may also exhibit more severe symptoms of alveolar haemorrhage (26-28).

The relationship between decreased haemoglobin and ANCA-associated

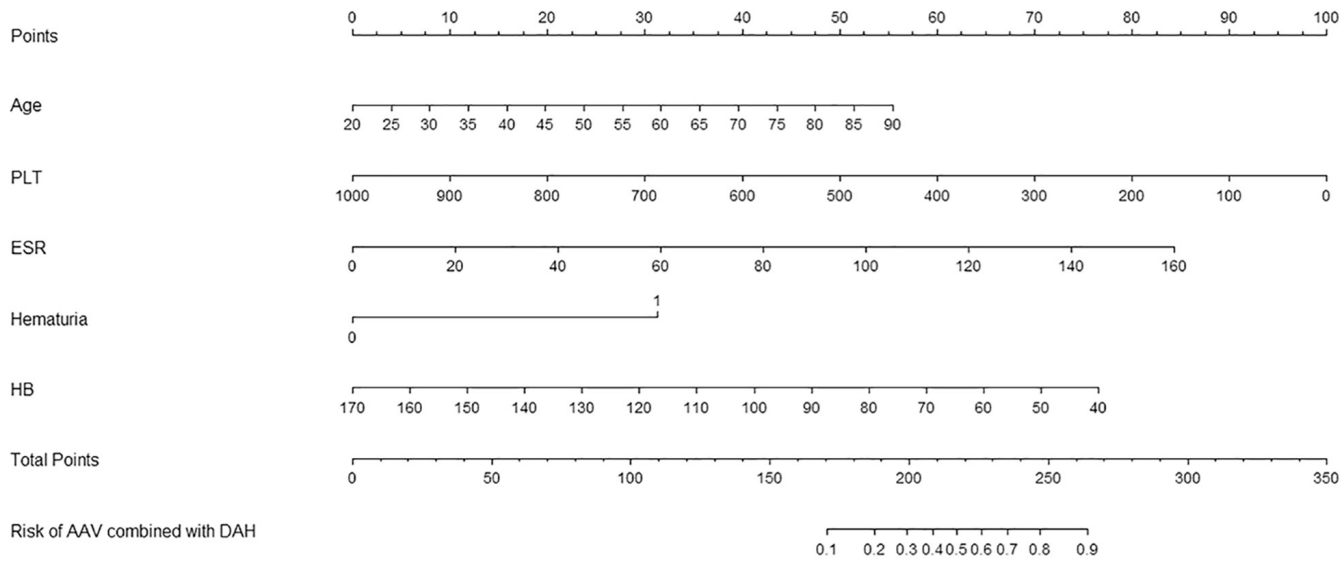

Fig. 2. Nomogram of AAV combined with DAH risk prediction model.
For all patients, adding up the points identified on the points scale for all five indicators. Then, the sum is located on the "Total Points" axis. Finally, the risk of AAV combined with DAH according to the nomogram is the probability of "AAV combined with DAH" corresponding to "Total Points".

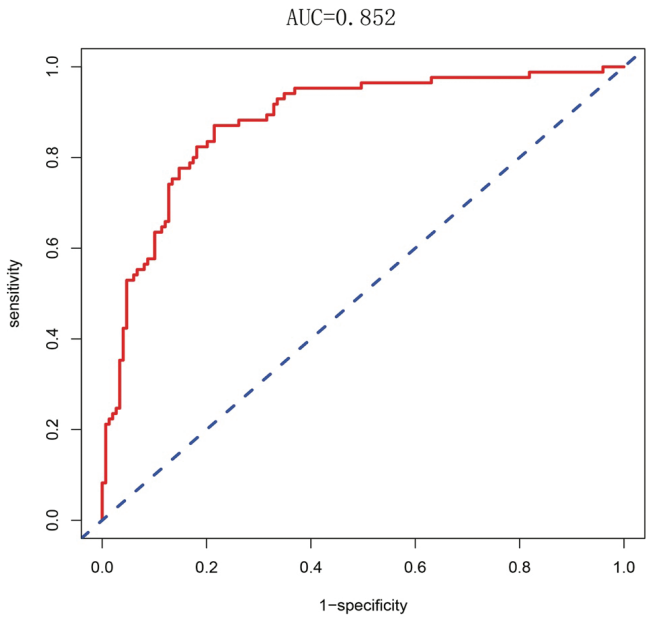

Fig. 3. ROC curve of AAV combined with DAH risk prediction model.
x-axis: the false positive rate for risk prediction (1-specificity),
y-axis: the true positive rate for risk prediction (sensitivity).

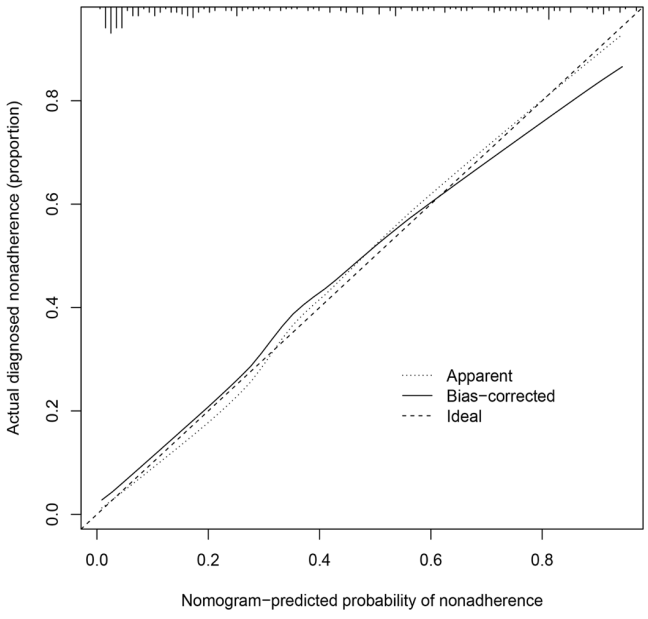

Fig. 4. Calibration curve of the fitted nomogram prediction model.
The diagonal dotted line represents a perfect prediction by an ideal model. The solid line represents the performance of the nomogram, of which a closer fit to the diagonal dotted line represents a better prediction.

diffuse alveolar haemorrhage in vasculitis is mainly reflected in the following aspects: (1) loss of red blood cells due to alveolar haemorrhage: damage to the lung endothelial or epithelial cells and the entry of red blood cells into the alveolar cavity results from a breakdown in the integrity of the alveolar-capillary interface, resulting in decreased haemoglobin (29); (2) kidney damage: ANCA-associated vasculitis can cause glomerulonephritis, resulting in impaired kidney function. Damage to the kidneys leads to loss of red blood cells and decreased erythropoietin production, which ultimately reduces haemoglobin (30). Decreased haemoglobin in ANCA-associated vasculitis with diffuse alveolar haemorrhage may be due to these factors.

PLT are an important part of the clotting process, they promote the formation of blood clots and thus prevent bleeding (31). ESR is a common inflammatory marker to assess the degree of inflammatory response (32). During ANCA-associated vasculitis episodes, there is increased activity of underlying disease, inflammation, and immune responses, leading to elevated ESR and inflammatory damage to blood vessel walls (33, 34). In a retrospective analysis of 1000 cases of bronchoalveolar lavage fluid

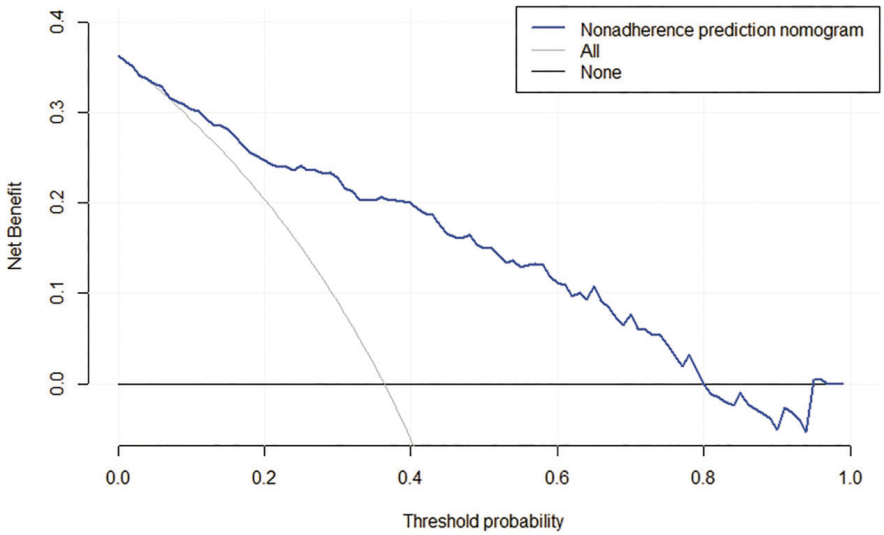

Fig. 5. Decision curve of AAV risk prediction model for pulmonary haemorrhage risk.
A: represents the assumption that there is no AAV combined with DAH decision curve;
B: represents the assumption of the model's decision curve, and the thin, thick and solid line represents the assumption that all patients have AAV combined with DAH.

(BALF) cytology, PLT and ESR were found to be significantly associated with AAV combined DAH (34).

There is a close relationship between AAV combined with DAH and haematuria. Research has shown that up to 70% of AAV patients have renal involvement, characterised histologically by immunodeficiency, focal and segmental necrotising glomerulonephritis (FSNGN). Most cases of AAV with DAH also have concurrent renal involvement, with microscopic haematuria and proteinuria accounting for 97% and 79%, respectively (35). It is speculated that this may be due to abnormal activation of the immune system in AAV patients, leading to the production of autoantibodies that deposit in the glomeruli, causing glomerular inflammation. These immune complexes activate the complement system, leading to an inflammatory response, which can cause dilation of the glomerular vessels (36), resulting in the formation of haematuria. Based on the above analysis, the area under the AUC curve in this study is 0.852 (95%CI: 0.801–0.903), which can still reach 0.824 in interval verification, with medium differentiation and high diagnostic and treatment value. However, there are still shortcomings in this study. Due to limited data, it is impossible to conduct external verification to simulate and prevent overfitting, and more data needs to be collected in the future for improvement. Therapeutic aspect: for severe renal impairment and diffuse alveolar haemorrhage, high-dose glucocorticoid combined with cyclophosphamide combined with plasma exchange is recommended, and impact dose of glucocorticoid combined with cyclophosphamide should be used in critical cases and there are also studies showing that rituximab is significantly better than cyclophosphamide for complete remission in the first 6 months of DAH (37, 38). The 2016 EULAR consensus recommendations, among others, proposed that plasma exchange can be utilised for the treatment of diffuse alveolar haemorrhage in ANCA-associated vasculitis (4).

Based on the above analysis, the area under the AUC curve in this study is 0.852 (95%CI: 0.801–0.903), which can still reach 0.824 in interval verification, with medium differentiation and high diagnostic and treatment value. However, there are still shortcomings in this study. Due to limited data, it is impossible to conduct external verification to simulate and prevent overfitting, and more data needs to be collected in the future for improvement.

Conclusion

In summary, age, HB, ESR, PLT, and haematuria are independent risk factors for DAH in AAV patients. Nomogram risk prediction model based on the above risk factors can be considered in clinical practice to reasonably assess the risk of DAH in AAV patients and targeted measures can be taken to reduce the incidence of AAV patients complicated with DAH.

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