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Preoperative clinical characteristics and risk assessment in Sun's modified classification of Stanford type A acute aortic dissection

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Abstract

Objectives This study aims to retrospectively analyze the clinical features of Stanford type A acute aortic dissection (TAAAD) based on Sun's modified classification, and to investigate whether the Sun's modified classification can be used to assess the risk of preoperative rupture.

Methods Clinical data was collected between January 2018 and June 2019. Data included patient demographics, history of disease, type of dissection according to the Sun's modified classification, time of onset, biochemical tests, and preoperative rupture.

Results A total of 387 patients with TAAAD who met the inclusion criteria of Sun's modified classification were included. There were more complex types, with 75, 151 and 140 patients in the type A1C, A2C and A3C groups, respectively. The age of the entire group of patients was 51.46 ± 12.65 years and 283 (73.1%) were male. The time from onset to the emergency room was 25.37 ± 30.78 h. There were a few cases of TAAAD combined with stroke, pericardial effusion, pleural effusion, and lower extremity and organ ischemia in the complex type group. The white blood cell count (WBC), neutrophil count (NEC) and blood amylase differed significantly between the groups. Three independent risk factors for preoperative rupture were identified: neutrophil count, blood potassium ion level, and platelet count. Binary logistic regression analysis showed that the Sun's modified classification could not be used to assess the risk of preoperative rupture in TAAAD.

Conclusion TAAAD was classified as the complex type in most patients. WBC, NEC and blood amylase were significantly different between the groups. NEC and serum potassium ion level were independent risk factors for preoperative rupture of TAAAD, while platelet count was its protective factor. More samples are needed to determine whether Sun's modified classification can be used to evaluate the risk of preoperative rupture.

Keywords Stanford type A, Modified classification, Acute aortic dissection, Aortic rupture, Risk factor

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Background

Acute aortic dissection (AAD) is a potential fatal disease. It is estimated that the risk of death per hour is 1-2%, and non-surgical treatment is related to the death of nearly 60% of patients [1]. Prompt surgical treatment for AAD has become the consensus of many scholars [2]. In 2005, Sun et al. [3] reported the application of a newly modified classification (Sun's modified classification) to determine the timing of surgery, develop a surgical plan, and predict a preliminary prognosis. Using the Sun's modified classification as a preoperative assessment of the degree of surgical risk, Sun's procedure has improved the success rate of open aortic dissection [3]. However, the preoperative clinical characteristics of the various types of modified classification of type A AAD(TAAAD) remain unclear, as does whether the Sun's modified classification has additional functions.

This study aims to summarize the clinical features of Stanford A acute aortic dissection (AAD) by Sun's modified classification through retrospective analysis, and to investigate whether Sun's modified classification can be used to assess the risk of preoperative rupture.

Methods

Patient enrollment

We enrolled patients diagnosed with TAAAD who were admitted to the Emergency Resuscitation Unit of Beijing Anzhen Hospital from January 2018 to June 2019. Their medical records were reviewed retrospectively. This study was approved by the Committee on Ethics of Biomedicine Research of Beijing Anzhen Hospital (2021148X).

Data collection

Clinical data was collected by standardized forms. Data included patient demographics, history of disease, TAAAD based on Sun's modified classification, time from onset to the emergency room (TOE), biochemical tests, and cause of death.

Definition of Sun's modified classification of TAAAD

Sun's modified classification of TAAAD is as follows: (1) type A1, A2 and A3 according to aortic root involvement (Fig. 1); (2) type C (complex) and type S (simple) according to the etiology and arch lesions. Type A1: normal sinotubular junction and its proximal end, no aortic valve insufficiency; Type A2: aortic sinus diameter < 3.5 cm, entrapment involving the right coronary artery, resulting in partial or complete detachment of the intima at its opening, and mild to moderate aortic valve insufficiency; Type A3: severe root involvement type, sinus diameter > 5.0 cm, or 3.5–5.0 cm in diameter, but sinotubular junction structure disrupted, with severe aortic valve insufficiency. Type C (any of the following): (1) primary endothelial rupture in the arch or distal to it, with retrograde dissection of the entrapment into the ascending aorta or proximal aortic arch; (2) aneurysm formation (> 50 cm in diameter) in the arch or distal to it; (3) entrapment or aneurysm formation in the cephalic vessels; (4) retrograde tearing of type A entrapment after thoracic aortic overmold stenting; (5) sleeve-like endothelial dissection and extensive intramural hematoma; (6) postoperative residual or new entrapment in aortic root or ascending aorta; and (7) etiology due to hereditary connective tissue disorders, like Marfan syndrome. Type S: primarily ruptured endothelial layer in the ascending aorta without any of the above-mentioned type C lesions.

Clinic diagnosis is based on the actual combination of various types, such as A1C.

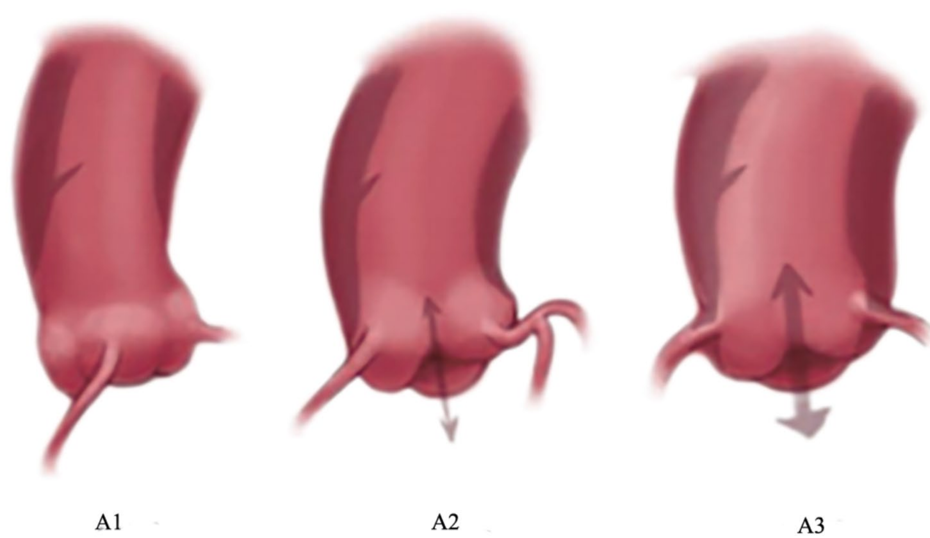

Fig. 1 TAAAD by Sun's modified classification

Definition of acute phase

The aortic dissection staging method of the 2014 European Society of Cardiology guidelines was used [4]: acute stage with onset time ≤ 14 days, subacute stage with onset time 15–90 days, and chronic stage with onset time > 90 days. In this study, the onset time of all cases were in the acute stage, that is, ≤ 14 days.

Statistical analysis

GraphPad Prism 9 software was used for data processing. Continuous variables are expressed as mean ± standard deviation or median and quartile ranges, depending on the normality of the distribution. Missing values were replaced by the mean or median of the variables, depending on their distribution. When the variables are normally distributed, the comparison of continuous variables between two groups shall be subject to t test by students. The Wilcoxon Ranking and Test are used when the variables are not normally distributed. Categorical variables were proportional and analyzed using Pearson's χ2 test or Fisher-Irwin test. In order to identify factors associated with the risk of rupture, significant variables were detected by simple logistic regression analysis and further analyzed by stepwise multivariate logistic regression. Probabilities (OR) and 95% confidence intervals (95% CI) were calculated to evaluate associations. All *P*-values were bilateral and $P<0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 638 patients with TAAAD admitted to the Emergency Resuscitation Unit of Anzhen Hospital from January 2018 to June 2019 were assessed. A total of 311 cases were excluded, of which 238 cases were not subjected to Sun's modified classification, 3 cases in which the time of onset was not specified in the history, 12 cases in which the time of onset was greater than 14 days, and 10 cases in which no blood test results were available.387 patients with TAAAD using Sun's modified classification met the inclusion criteria (Table 1). There were more complex types, with 75, 151 and 140 patients in the type A1C, A2C and A3C groups, respectively. There were only 5, 9 and 7 patients in the A1S, A2S and A3S groups, respectively.

The age of the entire group of patients was 51.46 ± 12.65 years, and 282 (73.87%) were male. There were no significant differences between the groups in terms of age and gender composition.

There were no statistical differences between the groups regarding history of hypertension, diabetes, coronary artery disease, chronic renal insufficiency, open heart surgery, and cardiac interventional procedures. However, none of the simple subgroups (A1S, A2S and A3S) had a history of diabetes. There were four patients with Marfan syndrome in the A3C group.

Clinical characteristics

All enrolled patients had the complaint of chest pain and were referred to our emergency resuscitation unit from other hospitals (primary care hospitals). All were treated with pharmacological interventions before entering our hospital. For this reason, we did not collect data on blood pressure, heart rate, and oxygen saturation on admission. Total of 9 cases were missing creatinine data and 19 cases were missing Calcium ion levels (Ca2+) data when evaluating the baseline characteristics of each Sun's Modified Classification subgroup. Missing values were replaced by the mean or median of the variables, depending on their distribution.

The mean of TO was 25.37 ± 30.78 h. Although the TOE in the A3S group was 52.67 ± 60.84 h, this was not significantly different compared with the other subgroups (Table 2).

There were a few cases of AAD combined with stroke (6 cases, including 4 in the A2C group), pericardial effusion (4 cases), pleural effusion (2 cases), and lower extremity and organ ischemia (3 cases) (Table 2).

The white blood cell count (WBC), neutrophil count (NEC) and blood amylase were significantly different between the groups. There were no significant differences in other blood test results. The WBC in the A2C

Table 1 Patient demographic data

	Total	A1C	A1S	A2C	A2S	A3C	A3S	*P*value
Number of patients	387	75	5	151	9	140	7	
Age (years)	51.46 ± 12.65	51.09 ± 10.71	61 ± 13.36	52.24 ± 11.69	57.78 ± 18.42	49.6 ± 13.79	60.83 ± 7.31	0.959
Male (%)	283 (73.13%)	57 (76%)	5 (100%)	104 (68.8%)	7 (77.7)	104 (76.4%)	5 (83.3%)	0.451
Hypertension (%)	220 (51.59%)	51 (68%)	3 (60%)	95 (62.91%)	4 (44.44%)	64 (47.06%)	3 (50%)	0.034
Diabetes	6 (1.57%)	0	0	5 (3.3%)	0	1 (0.74%)	0	0.405
CHD (%)	17 (4.45%)	0	1 (20%)	9 (5.96%)	0	7 (5.15%)	0	0.156
Chronic kidney disease (%)	7 (1.83%)	1 (1.33%)	0	3 (1.99%)	1 (11.11%)	2 (1.47%)	0	0.449
History of open heart surgery (%)	11 (2.88%)	2 (2.67%)	1 (20%)	4 (2.65%)	0	3 (2.21%)	1 (16.67%)	0.08
History of cardiac interventional procedure (%)	9 (2.36%)	0	0	7 (4.64%)	0	2 (1.47%)	0	0.29

Table 2 Preoperative characteristics in TAAAD with Sun's modified classification

Characteristics	Total	A1C	A1S	A2C	A2S	A3C	A3S	*P* value
Number of patients	387	75	5	151	9	140	7	
Time from onset of symptom to admission (h)	25.37 ± 30.78	27.58 ± 32.47	32 ± 27.71	22.07 ± 24.76	31.56 ± 42.78	25.98 ± 33.03	52.67 ± 60.84	0.192
Pericardial effusion (%)	4 (1.05%)	0	0	1 (0.67%)	0	2 (1.47%)	1 (16.67%)	0.008
Pleural effusion (%)	2 (0.52%)	0	1 (20%)	0	0	1 (0.74%)	0	< 0.0001
Limb deficit (%)	3 (0.79%)	1 (1.33%)	0	1 (0.67%)	0	1 (0.74%)	0	0.992
Stroke (%)	6 (1.57%)	1 (1.33%)	1 (20%)	4 (2.65%)	0	0	0	0.012
Ruptured AD (%)	34 (8.79%)	7 (9.43%)	0	11 (7.28%)	2 (22.22%)	13 (9.29%)	1 (14.29%)	0.375
WBC (×109/L)	12.71 ± 4.34	13.31 ± 3.62	10.87 ± 4.23	12.46 ± 3.79a	15.61 ± 9,56b	12.31 ± 4.65	21.23 ± 1.047	0.015
Neutrophils (×109/L)	10.74 ± 4.06	11.19 ± 3.50	9.41 ± 4.20	10.57 ± 3.59c	13.22 ± 8.68d	10.37 ± 4.29	19 ± 1.30	0.04
Lymphocytes (×109/L)	1.19 ± 0.57	1.25 ± 0.57	1.01 ± 0.30	1.14 ± 0.51	1.54 ± 0.93	1.19 ± 0.6	1.28 ± 0.32	0.57
Neutrophil/lymphocyte count ratio	11.29 ± 7.35	11.56 ± 8.57	9.24 ± 2.23	11.45 ± 7.02	12.63 ± 10.30	10.83 ± 6.91	15.51 ± 4.89	0.943
Platelets (×1012/L)	178.27 ± 65.27	187.44 ± 66.81	195.5 ± 25.85	176.75 ± 59.74	180.57 ± 104.62	175.91 ± 67.11	56.5 ± 9.19	0.192
APTT (s)	30.65 ± 4.52	30.43 ± 4.06	29.38 ± 0.88	30.47 ± 4.81	32.26 ± 6.06	30.88 ± 4.46	32.6 ± 5.66	0.908
PT (s)	13.47 ± 4.07	13.23 ± 3.99	12.68 ± 0.83	13.46 ± 4.49	13 ± 2.00	13.64 ± 3.87	15.2 ± 0.14	0.986
INR	1.20 ± 0.26	1.18 ± 0.35	1.15 ± 0.09	1.20 ± 0.40	1.15 ± 0.17	1.20 ± 0.34	1.33 ± 0.01	0.996
D-Dimer (ng/mL)	8197.75 ± 16742.02	9160.63 ± 16562.29	1103.5 ± 1058.19	8190.91 ± 14693.19	3279.71 ± 4318.11	8352.17 ± 19842.46	3933 ± 2316.48	0.8964
Lactate (mmol/L)	2.08 ± 2.31	1.86 ± 1.11	1.25 ± 0.58	2.26 ± 2.97	2.62 ± 2.43	1.91 ± 1.94	6.75 ± 0.21	0.064
Amylase (mmol/L)	64.06 ± 89.07	73.92 ± 100.80e	50.13 ± 27.65f	53.11 ± 38.87 g	123.18 ± 143.15 h	54.71 ± 39.21i	694.65 ± 611.29	< 0.0001
K+ (mmol/L)	4.02 ± 0.62	4.07 ± 0.72	3.75 ± 0.33	3.93 ± 0.56	3.72 ± 0.24	4.10 ± 0.59	4.98 ± 2.15	0.061
Ca2+ (mmol/L)	1.11 ± 0.06	1.12 ± 0.04	1.13 ± 0.03	1.11 ± 0.07	1.10 ± 0.03	1.12 ± 0.05	1.12 ± 0.18	0.743
Creatinine (mmol/L)	120.61 ± 148.68	119.50 ± 142.97	108.28 ± 61.57	126.09 ± 178.94	117.5 ± 66.09	113.62 ± 120.10	187.5 ± 91.10	0.985

(12.46±3.79×109/L) and A3C (12.31±4.65×109/L) groups were significantly different from that in the A3S group (21.23±1.047×109/L) ($P<0.05$). Similarly, the NEC in the A2C (10.57±3.59×109/L) and A3C (10.37±4.29×109/L) groups were significantly different from that in the A3S group (19±1.30×109/L) ($P<0.05$). The blood amylase levels in the remaining subgroups (A1C group: 73.92±100.80mmol/L; A1S group: 50.13±27.65mmol/L; A2C group: 53.11±38.87mmol/L; A2S group 123.18±143.15mmol/L; and A3C group: 54.71±39.21mmol/L) were significantly different from that in the A3S group (694.65±611.29 mmol/L) ($P<0.05$) (Table 2).

Risk factors for rupture in TAAAD with Sun's modified classification

We selected 566 of a total of 638 patients who met the TAAAD inclusion criteria. A total of 72 cases were excluded, of which 47 were diagnosed as aortic ulcers and intermural hematomas of the aorta on examination, 3 had no clear TOE in the history, 12 had an onset greater than 14 days, and 10 had no blood test results. There were 46 cases in the preoperative ruptured group and 520 cases in the preoperative unruptured group. (Table 3).

Patient age in the preoperative ruptured group was 56.2±12.1 years and was 51.6±12.4 years in the preoperative unruptured group. The difference between the two groups was statistically significant ($P=0.0181$). The comparison of the percentage of those aged≥65 years also showed statistical differences ($P=0.0440$) (Table 3).

TOE in the preoperative ruptured group (16.07±12.09 h) was slightly lower than TOE in the preoperative unruptured group (26.10±31.67 h). However, the differences were not statistically significant ($P=0.103$) (Table 3).

There was no statistically significant difference between the preoperative rupture group and the preoperative unruptured group in terms of history of hypertension, diabetes mellitus, coronary heart disease, chronic kidney

Table 3 Univariate analysis of preoperative rupture of TAAAD

	Preoperative rupture group	Preoperative unruptured group	*P*
Total	46	520	
Age (years)	56.15 ± 12.14	51.64 ± 12.38	0.0181
Age ≥ 65 years (%)	12 (26)	77 (14.8)	0.0440
Male (%)	31 (67.39)	378 (72.69)	0.4415
Hypertension (%)	22 (47.8)	142 (27.3)	0.0591
Diabetes	0	8 (1.5)	0.3969
CHD (%)	2 (4.3)	24 (4.6)	0.9338
Chronic kidney disease (%)	3 (6.5)	12 (2.3)	0.0881
History of Marfan syndrome (%)	0	5 (0.9)	0.5041
History of open-heart surgery (%)	1 (2.1)	9 (1.7)	0.8269
History of cardiac interventional procedure (%)	1 (2.1)	12 (2.3)	0.9537
Time from onset of symptom to admission (h)	16.07 ± 12.09	26.10 ± 31.67	0.103
WBC (×109/L)	13.84 ± 4.42	12.51 ± 4.32	0.1249
Neutrophils (×109/L)	11.89 ± 3.81	10.54 ± 4.07	0.0960
Lymphocytes (×109/L)	1.17 ± 0.74	1.19 ± 0.55	0.8829
Neutrophil/lymphocyte count ratio	13.45 ± 8.61	10.93 ± 6.94	0.0734
Platelets (×1012/L)	149.1 ± 76.76	178.1 ± 65.12	0.0277
Platelets ≤ 100 × 1012	5 (10.8)	28 (5.3)	0.1047
APTT (s)	30.89 ± 4.23	30.34 ± 4.47	0.5502
PT (s)	13.68 ± 2.18	13.25 ± 3.51	0.5389
INR	1.22 ± 0.2	1.18 ± 0.31	0.5308
D-Dimer (ng/mL)	8217 ± 10,086	7924 ± 15,926	0.9263
D-Dimer ≥ 10,000 ng/mL (%)	5 (10.8)	74 (14.2)	0.5283
Lactate (mmol/L)	2.66 ± 2.36	1.94 ± 2.16	0.1359
Amylase (mmol/L)	107.5 ± 184.9	65.02 ± 102.9	0.0599
K+ (mmol/L)	4.42 ± 0.74	3.95 ± 0.58	0.0002
Ca2+ (mmol/L)	1.13 ± 0.05	1.11 ± 0.06	0.2126
Creatinine (mmol/L)	130.1 ± 89.53	120.3 ± 142.6	0.7202
Pericardial effusion (%)	2 (4.3)	4 (0.7)	0.0231
Pleural effusion (%)	2 (4.3)	0	< 0.0001
Stroke (%)	0	5 (0.9)	0.5041
Limb deficit (%)	1 (2.1)	6 (1.1)	0.5485

Table 4 Univariate analysis of preoperative rupture of TAAAD with Sun's modified classification

	Preoperative rupture group	Preoperative unruptured group	P
Total	46	520	
A1C (%)	7 (15.2)	68 (13)	0.6815
A1S (%)	1 (2.1)	4 (0.7)	0.3291
A2C (%)	11 (23.9)	140 (26.9)	0.6582
A2S (%)	1 (2.1)	8 (1.5)	0.7412
A3C (%)	13 (28.2)	127 (24.4)	0.5631
A3S (%)	1 (2.1)	6 (1.1)	0.5485
Type C (%)	31 (67.4)	335 (64.4)	0.6865
Type S (%)	3 (6.52)	18 (3.47)	0.2926

Table 5 Significant risk factors for preoperative rupture of TAAAD

Variables	Coefficient B	Standard Error	Odds ratio	95% CI	P
Platelet count	-0.012	0.006	0.988	0.977–0.999	0.035
Potassium ion level	0.673	0.310	1.959	1.068–3.595	0.030
Neutrophil count	0.120	0.060	1.128	1.003–1.269	0.0451
Constants	-4.631	2.309	0.010		0.045

insufficiency, open-heart surgery, cardiac interventional procedures and Marfan syndrome ($P>0.05$) (Table 3).

There were 2 cases of pleural effusion (4.3%) in the preoperative rupture group and no cases of pleural effusion in the preoperative unruptured group. There were 2 cases (4.3%) of pericardial effusion in the preoperative ruptured group and 4 cases (0.7%) of pericardial effusion in the preoperative unruptured group. Both of these complication ratios, when compared between the two groups, were statistically different with P values less than 0.05.

Lower extremity and other organ ischemic disease was present in 1 (2.1%) and 6 (1.1%) cases in the ruptured and unruptured groups, respectively. Five (0.9%) cases of combined stroke were all found in the unruptured group. The two complication ratios mentioned above were not statistically different between the two groups, with p values greater than 0.05 (Table 3).

Platelet count was slightly reduced in the preoperative ruptured group (149.1±76.76×102/L) compared with the preoperative unruptured group (178.1±65.12×1012/L), the difference being statistically significant between the two groups ($P=0.0277$) (Table 3).

Further stratification of platelets at ≤100×1012 showed 5 cases (10.8%) in the preoperative ruptured group and 28 cases (5.3%) in the preoperative unruptured group. However, the difference between the two groups was not statistically significant. ($P=0.1047$) (Table 3).

The serum potassium ion level was 4.42±0.74 mmol/L in the preoperative rupture group and 3.95±0.58 mmol/L in the preoperative unruptured group, with statistically significant difference between the two groups ($P=0.0002$), suggesting that serum potassium ion level may be a risk factor for dissection rupture (Table 3).

The comparison of other blood indicators between the two groups showed no statistically significant difference.

Binary logistic regression analysis showed that Sun's modified classification could not be used to assess the risk of preoperative rupture in TAAAD ($P>0.05$) (Table 4.)

Multivariable analysis of all statistically significant factors using stepwise selection was performed to identify significant variables associated with aortic rupture in TAAAD cases (Table 5). The 10 variables initially screened for $P<0.10$ by univariate analysis were age, history of hypertension, history of chronic renal insufficiency, NEC, NLR, PLT, blood amylase level, potassium ion level (K+), combined pericardial effusion, and combined pleural effusion. A factor was considered to be possibly associated with rupture of the sandwich when a one-way analysis showed $P<0.10$. The determination of $P<0.10$ was to avoid eliminating some false negative variables. Univariate analysis prior to multifactorial analysis avoids losing possible independent correlates.

Based on previous studies, the age factor was added to the age≥65 years variable, and the remaining variables added were PLT≤100×1012. For the above measures, cut-off values were taken to calculate the percentage of positives, and then the $\chi 2$ test was performed. Whether or not the mezzanine ruptured was selected as the dependent variable (1=yes, 0=no), and the 10 covariates were brought into multifactorial two-category logistic regression analysis (age≥65years, 1=yes, 0=no; history of hypertension, 1=yes, 0=no; history of chronic renal insufficiency, 1=yes, 0=no; PLT≤100×1012, 1=yes, 0=no; combined pericardial effusion, 1=yes, 0=no; combined pleural effusion, 1=yes, 0=no).

Three independent risk factors were identified: neutrophil count (OR: 1.128; 95%CI, 1.003–1.269, $P=0.0451$), platelet count (OR: 0.988; 95%CI, 0.977–0.999; $P=0.035$), and potassium ion level (OR: 1.959; 95%CI, 1.068–3.595, P=0.030) (Fig. 2).

Discussion

Aortic dissection was the most serious disease in aortic diseases. Chronic aortic dissection, combined with massive and extensive aortic aneurysmal dilatation, and AAD based on an aneurysm are more common in China than in developed countries. The prevalence of hypertension in China is high, and the awareness and control rates are low. The age at onset of AAD is significantly lower than in other countries, and the life expectancy of patients after treatment is longer than in western countries [3, 5].

In 2005, Sun et al. [3] reported the application of a newly modified classification to determine the timing of surgery, develop a surgical plan, and predict a preliminary prognosis. The results showed that the in-hospital mortality rate of TAAAD was 4.6% (22/477) and the complication rate was 14.5% (69/477). However, the preoperative clinical characteristics of the various modified types of TAAAD are unclear.

According to the research results of the International Registry of Aortic Dissection (IRAD), the average age of AAD prevalence was 63 years, with 65% of males [5]. The present study showed that the age of AAD patients was 51.46±12.65 years and 73.87% were male, and no significant differences were observed when compared with other subgroups [6]. It is consistent with the results of China AD Registration Research (Sino-RAD) [7].

Some studies have shown that hypertensive status is the most common causative factor for AD, with 62-78% of patients having a history of hypertension [8–10]. Although in the present study, 57.59% of all AAD patients had a history of hypertension, this was lower than in previous studies, and the percentage of patients with hypertensive history in the A1C (68%) and A2C (62.9%) groups was high, which was consistent with the previous studies.

A history of connective tissue disease, such as Marfan syndrome, and previous aortic intervention or surgery is considered high risk factors for AAD [2, 4, 11]. In the present study, there were only 4 cases with Marfan syndrome, all in the A3C group (2.86%). Patients with a history of cardiac surgery (11 cases) and cardiac interventional procedures (9 cases) were mainly in the complex type groups (A1C, A2C and A3C).

As the anatomy of the aorta is altered after invasive manipulation, the tolerance to withstand the high velocity blood flow and shear forces on the vessel wall is reduced, and lacerations are often located in these weak points of the aortic wall. The location and morphology of the entrapment formed due to these factors are consistent with the characteristics of the complex type.

Pain is the most common clinical manifestation of AAD, and is often sudden and severe in the aortic travel or mapping region, and often persistent and unbearable. In our study, all patients had chest pain, which is not a necessary symptom of AAD and the frequency of painless coarctation varies between 5% and 15% [5, 12–14]. Particularly in terms of neurological sequelae of AD, several patients without significant pain have been reported [12, 13].

In the present study, there were 6 cases of AAD combined with new stroke, 4 of which were in the A2C group. Although these patients had symptoms such as headache, severe chest pain remained the chief complaint. We also identified other AAD comorbidities, such as 4 cases of pericardial effusion (1 A2C, 2 A3C and 1 A3S), 2 cases of pleural effusion (1 each in A1S and A3C), and 3 cases of lower limb ischemia (1 each in A1C, A2C and A3C), which were mainly in the complex type subgroups.

TOE was 25.37±30.78 h. All enrolled patients were transferred to our emergency resuscitation unit from other hospitals (hospitals where initial diagnosis was made). The time of initial diagnosis at other hospitals,

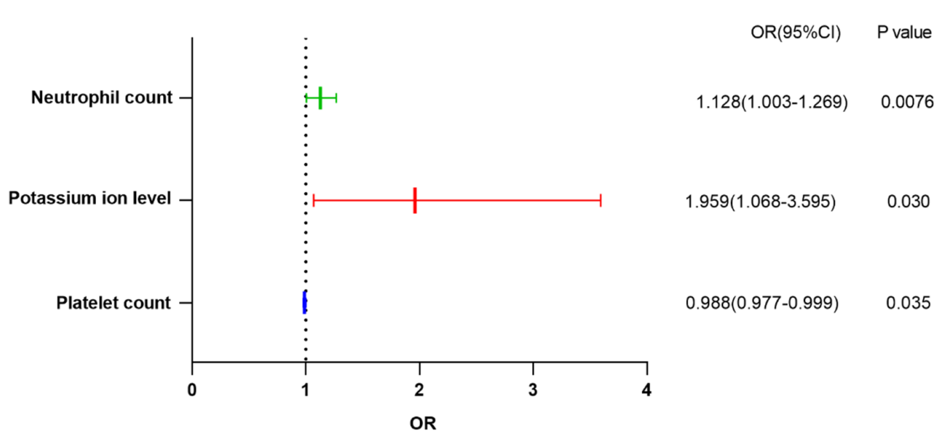

Fig. 2 Risk factors for preoperative rupture in patients with TAAAD

patient's family decision-making, and long-distance transfers were all major factors in prolonged TOE. Although the TOE in the A3S group was 52.67±60.84 h, this was not significantly different compared with the other subgroups. This may have been due to bias caused by the small sample size in the A3S group. A similar bias appeared in the between-group comparisons of lactate and blood amylase levels.

In this study, the rupture rate (8.79%) was lower than in a previous study by Afifi et al. (15.3%) [15]. which may have been attributed to the different time range of patient recruitment, as Afifi et al. recruited patients earlier than we did. Also, our rupture rate was lower than that of Li et al. (9.4%) [16] where patients were recruited during a longer period than in our study, and included both acute and subacute patients.

Afifi et al. [15] also showed risk factors associated with rupture in TAAAD cases: elderly age, female, aortic dilatation and cardiac arrest.

In the present study, although the proportion of males in the preoperative rupture group (67.39%) was slightly lower than that in the preoperative unruptured group (72.69%), the difference was not significant. Analysis of data from 1078 patients included in the International Registry of Acute Aortic Dissection (IRAD) allows us to know that imaging manifestations suggestive of rupture, such as periaortic hematoma and pleural or pericardial effusion, are predominantly in the female population. Hospital complications such as hypotension and pressure occlusion were also more common in women, resulting in higher in-hospital mortality. After adjustment for age and hypertension, female patients with AD were more likely to die (OR: 1.4, $P=0.04$), occurring mainly between 66 and 75 years of age [17]. In the present study, a univariate analysis of aortic coarctation suggested that age≥65 years was a possible risk factor for dissection rupture ($P=0.044$). However, further multifactorial logistic regression analysis indicated that age≥65 years could not serve as an independent risk factor for preoperative dissection rupture in patients with AAD.

This finding is similar to the results of the analysis of age as a whole (without stratification) as a risk factor for preoperative rupture of the dissection. This differs from previous studies. Kim et al. [18] carried out a competing risk analysis of 4654 ascending aortas with a maximum diameter of 40 –55 mm to identify independent risk factors for AD. In multivariable analysis, age was an independent predictor of AD rupture. This may have been caused by selection bias due to our selection of patients with only TAAAD.

The present study showed that NEC was an independent risk factor for AAD rupture (OR: 1.128; 95% CI, 1.003–1.269, $P=0.045$). This indicates that a one-unit increase in neutrophil count is associated with a 12.8% increased risk of intercalation rupture in AAD. Previous studies have reported that neutrophils present in the aortic adventitia within the first 12 h of aortic dissection and peak at 12 to 24 h after onset, rarely 2 days later [19]. Thus, neutrophil infiltration may occur after the onset of aortic dissection, which in turn may participate in poor remodeling of the aortic wall. Shohei Yoshida et al. [20] found neutrophil infiltration mainly in the outer membrane layer of aortic dissection samples. Histological analysis revealed that signal transduction and activators of transcription 3 (STAT3) was activated not in neutrophils but in other cells, and there was a positive correlation between neutrophil infiltration and STAT3 activation. The causal relationship between STAT3 activation and neutrophil infiltration is still unclear. Theoretically, the activation of STAT3 is due to the secretion of various cytokines by neutrophils and other inflammatory cells [21, 22], which in turn induce the expression of chemokines and promote cellular infiltration [23]. Similar to this finding, in mouse models of aortic dissection, deletion of the IL-6 gene or inhibition of STAT3 resulted in the inability of local Th17 cells to be significantly activated and reduced secretion of IL-17 [24], which is critical for neutrophil recruitment in aortic lesions [25]. However, the evidence of the direct relationship between neutrophil infiltration and STAT3 activation requires further study in the tissues of human aortic dissection.

Blood potassium levels were also an independent risk factor for AD rupture (OR: 1.959; 95% CI, 1.068–3.595, $P=0.030$). In the study by Chen et al. [19], univariate Cox regression analysis found that the range of blood potassium levels below 3.5–4.5 mmol/L was a risk factor for hospitalization and long-term death. After adjusting for age, sex, surgery, and other risk factors, potassium levels below the range of 3.5–4.5 mmol/L remained significantly associated with long-term mortality. Some scholars believe that the increase in blood potassium level is related to acute renal failure, while the decrease in blood potassium level may be related to arrhythmia in patients with potential heart diseases [26]. In the present study, multifactorial analysis showed that a previous history of chronic renal insufficiency was not an independent risk factor for the onset of AAD. Univariate analysis showed that the difference in creatinine levels between the preoperative ruptured group (130.1±89.53 mmol/L) and the preoperative unruptured group (120.3±142.6 mmol/L) was not statistically significant. Therefore, in this study, acute renal dysfunction due to chronic renal dysfunction and acute renal dysfunction induced by AAD did not affect the incidence of rupture in patients with AAD. In addition, univariate analysis of a history of coronary heart disease, open-heart surgery and cardiac interventional procedures showed no statistically significant differences between the preoperative ruptured and preoperative unruptured groups. Therefore, in the present study, high and low potassium levels were not strongly associated with renal function and potential heart diseases, and were not significantly influenced by renal function and potential heart diseases.

In the present study, the OR of platelets was <1, indicating that platelet count was a protective factor in AD. As platelets increased, patients had a reduced risk of AD. This may be due to the fact that patients with AAD exhibit a depleted coagulation state and a procoagulant state in the perioperative period. A decrease in platelets indicates a decrease in the major coagulation component, which implies an increased risk of bleeding, hence an increased risk of AD. Zindovic et al. [26] revealed that TAAAD was associated with the coagulation state. In the perioperative period in patients with AAD, systemic activation of coagulation and fibrinolysis, as well as inhibition of anticoagulant mechanisms, were observed. However, in the present study, the main indicators of coagulation, activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR) and D-dimer, were abnormal, suggesting that coagulation and fibrinolysis were activated. This is in agreement with the findings of Zindovic et al. [27]. However, in the univariate analysis of clamping rupture, it was shown that the differences in APTT, PT, INR, and D-dimer were not statistically significant between the preoperative ruptured and preoperative unruptured groups ($P > 0.05$), suggesting that APTT, PT, INR, or D-dimer levels are not possible risk factors for the development of AAD. In this regard, there are several reports related to the molecular research of the cardiac aorta [28–33].

Although combined pericardial effusion and pleural effusion were possible risk factors for the occurrence of AAD in the univariate analysis, they could not be used as independent risk factors for the occurrence of AAD as shown in the univariate regression analysis. This may be a bias caused by the lack of number of enrolled cases. However, it should be noted that the combined presence of pericardial effusion or pleural effusion signifies that AAD patients are in a very serious condition. This indicates that the patient's aorta is leaking or bleeding, the epicardium is very fragile, and the patient could die at any time due to an enlarged AAD tear. Wu et al. [8] applied random forest as a tool to predict in-hospital rupture of TAAAD. The results showed that aortic hematoma was the strongest predictor of pleural effusion ($P < 0.001$), while other indicators were also linked to a higher incidence of in-hospital dissection of the entrapment. Therefore, we highly recommend early and aggressive surgery for patients with AAD plus pleural effusion.

It should be noted that we conducted a preliminary regression analysis on whether Sun's refined typing could be used to assess the risk of preoperative rupture in AAD. Unfortunately, the P values were all greater than 0.05 and were not statistically significant. This indicates that Sun's modified classification cannot be used to assess the risk of preoperative rupture of TAAAD. This may be related to the small number of cases enrolled in each simplex subgroup. Therefore, we will expand the data collection in the next phase of the study, which will adopt a multicenter study.

However, the Sun's modified classification still has an important role in the assessment of surgical risk of TAAAD, the selection of surgical timing, design of the surgical plan, and the preliminary judgment of prognosis.

As a single-center retrospective analysis, this study has inherent limitations and biases, including a small number of cases in the rupture group, missing data on biochemical outcomes, and lack of prior treatment records.

Conclusion

In total, 387 patients with TAAAD met the inclusion criteria for Sun's modified classification, with more complex types than simple types. There were no significant differences among the groups in terms of age, gender, Marfan family history, history of hypertension, diabetes, coronary artery disease, chronic renal insufficiency, open heart surgery, cardiac interventional procedures, and TOE. There were a few cases of TAAAD combined with stroke, pericardial effusion, pleural effusion, and lower extremity ischemia, and were mainly distributed in the complex type groups. The WBC, NEC and blood amylase were significantly different between the groups. Potassium level, platelet count, age, sex, and pleural effusion were risk factors for TAAAD rupture. Further studies are needed to determine whether the Sun's modified classification can be used to assess the risk of pre-operative rupture of TAAAD.

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Author contributions
SS, CJL, TL, YZ and WZ participated the design, supervision and editing, and resources, writing of original draft, experimental implementation, and data statistics and analysis. All authors read and approved final manuscript.

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Data availability
The datasets used and/or analyzed in the present study are available from the. corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the local ethics committee of the Beijing Anzhen Hospital, Capital Medical University. All experiments were performed in accordance with relevant guidelines and regulations such as the Declaration of Helsinki and the patients signed the informed consent form and agreed to be published.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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