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Aortic diseases involving visceral artery: Clinical therapeutic management and related basic research

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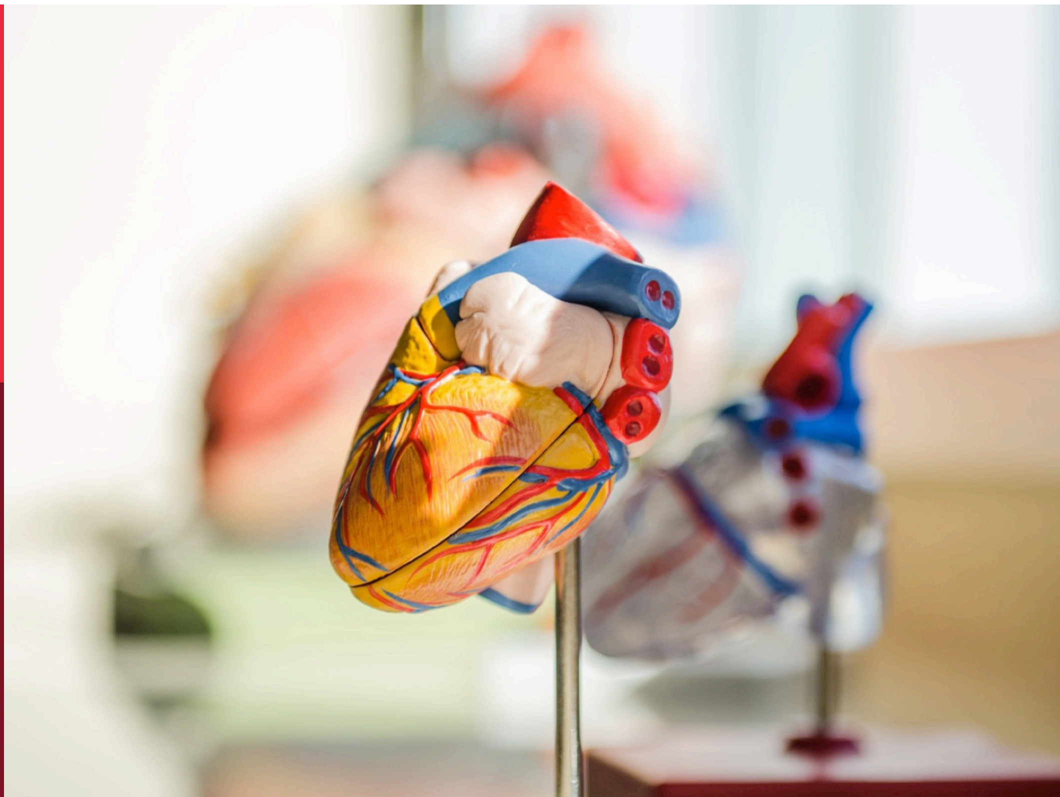

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Aortic diseases involving visceral artery: Clinical therapeutic management and related basic research

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Editorial: Aortic diseases involving visceral artery: clinical therapeutic management and related basic research

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Editorial on the Research Topic
Aortic diseases involving visceral artery: clinical therapeutic management and related basic research

Introduction

Aortic diseases involving visceral arteries mainly include true and post-dissection thoracoabdominal or abdominal aortic aneurysm (TAAA or AAA). Post-dissection aortic aneurysm is common in both type A and type B aortic dissection, even after successful coverage of the primary entry tears. False aortic aneurysm involving visceral arteries is relatively uncommon. The management of these complex aortic diseases is usually challenging due to involvement of visceral arteries. Several surgical treatment methods are used for these diseases, mainly including open surgical repair, hybrid surgery, and endovascular treatment.

True TAAA or AAA

Standard open repair for TAAA or AAA involving visceral arteries was usually associated with definite effect, large trauma, and high mortality and morbidity. With the development of surgical techniques and perioperative adjunctives, many studies suggest clinical results have been significantly improved in high-volume hospitals (1, 2). The in-hospital mortality was significantly decreased in the past three decades, as well as the rate of permanent spinal cord ischemia (2). Open surgical repair remains a valid treatment option for patients with long life expectancy.

In 1999, Quinones-Baldrich et al. first reported the hybrid surgery for a type IV TAAA (3). It involves sequentially bypassing the visceral arteries and using an uninvolved vessel for inflow to disconnect them from the aneurysmal aorta. Mortality after hybrid surgery is highly variable by center, but strongly affected by preoperative comorbidities and the centers' experience with the technique (4).

Ma et al. compared clinical outcomes after hybrid surgery with conventional open surgery. Although the age of the hybrid surgery group was significantly higher than that of the other group, perioperative mortality was low in the hybrid surgery group compared with conventional surgery group. Furthermore, the rates of postoperative complications such as renal failure, respiratory failure, and deep venous thrombosis following hybrid surgery were significantly lower than conventional open surgery. Hybrid surgery is technically feasible and associated with definite efficacy in selected cases. It simplifies the operation procedure and reduces the risks of mortality and morbidity in high-risk or high-age patients. Hybrid surgery may be a promising alternative to conventional open surgery in selected patients.

Endovascular aortic repair (EVAR) is associated with small trauma and rapid recovery. It mainly includes parallel stenting technique and fenestrated/branched endografts to preserve the visceral arteries. The use of parallel stenting is limited due to high risk of type IA endoleak, and the risk of stent collapse. The joint use covered stent graft and overlapped bare stents in the visceral artery segment demonstrated favorable mid-term clinical outcomes in type V TAAAs (5). Using of bifurcated abdominal aortic stent graft main body and docking two or three parallel covered stents in the short limb for the reconstruction of visceral arteries, known as "Octopus" technique, demonstrated promising mid-term outcomes for treating ruptured and symptomatic TAAAs (6).

Branched or fenestrated endograft can be custom-made, off-the-shelf, or physician-modified. For custom-made endografts, the manufacturing time limits their use. The shortcomings of physician-modified endografts include technical demanding, potential contamination risk, and damage of device integrity, as well as legal issues. A recent meta-analysis suggested the use of the off-the-shelf t-Branch multibranched endograft for endovascular TAAA repair was associated with high technical success rates and demonstrated to be safe and effective at early and mid-term follow-up (7). The primary use of a novel G-Branch multibranched (two inner branches and two outer branches) endograft also yielded good early and midterm outcomes (8). Treatment modality of TAAA or AAA involving visceral arteries is gradually shifted from conventional open surgery to endovascular repair in many countries (9).

PD-TAAA or PD-AAA

Studies with regard to open surgical repair for PD-TAAA or PD-AAA involving visceral arteries were relatively few in literature. Limited data showed conventional open surgery was more invasive than endovascular treatment, while it was also associated with acceptable rates of morbidity and mortality when it was performed in a specialized hospital. Long-term results were excellent and it should also be considered when evaluating less invasive alternatives (10). More studies are required to verify its safety and efficacy.

Post-dissection aortic aneurysms are increasingly being treated by endovascular repair. A large number of endovascular methods have been reported. Fenestrated/branched-EVAR (F/B-EVAR) is the most commonly used method (11). Other methods are usually associated with a small number of cases. F/B-EVAR can cover multiple tears regardless of sizes and preserve branch organ perfusion. However, the endografts usually need to be modified by physicians. It is technically demanding, which limits its widespread use. Spinal cord ischemia, endoleak, and stent or stent-graft occlusion of branch arteries are common complications. Other substitution methods are currently explored.

F/B-EVAR mainly focuses on the management of the true lumen, while management of false lumen and aortic tears has been attempted (12). Isolated management of the false lumen or tears seems to make it difficult to achieve satisfactory outcomes for PD-TAAA or PD-AAA (13). Several combined methods have been reported. They usually combine the management of two or three objectives (true lumen, false lumen, and aortic tears), such as "road block" strategy, "double splints" technique, and spot stenting combined with false lumen endovascular occlusive repair (14–16). The preliminary results of these techniques were acceptable, despite of the requirement for higher-grade evidence. One of the most important problems is how to occlude the false lumen and the tears safely and effectively. There have been no available specialized devices to date. New novel devices are anticipated to help resolve this issue in future, such as EndoSeal and Endopatch system (17, 18). Visceral arteries arising from the false lumen can be reconstructed with direct stent-graft placement via adjacent tears, reverse branch technique, iliac branched device, or *in situ* fenestration.

In conclusion, endovascular treatment is gradually become the mainstream treatment for true or post-dissection TAAA or AAA involving visceral arteries. Open surgery and hybrid surgery still are valid treatment options for selected patients, such as low-risk patients with long-life expectancy and those unfit for endovascular repair.

Author contributions

XD: Writing – original draft, Writing – review & editing. MW: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Oh AR, Lim SK, Sung K, Lee SM, Lee JH. Outcomes of open repair for descending thoracic and thoracoabdominal aortic aneurysm in recent 10 years: experience of a high-volume centre in Korea. *Eur J Cardiothorac Surg*. (2023) 64:ezad338. doi: 10.1093/ejcts/ezad338

2. Chiesa R, Rinaldi E, Kahlberg A, Tinaglia S, Santoro A, Colacchio G, et al. Outcomes following management of complex thoracoabdominal aneurysm by an open approach. *J Clin Med*. (2023) 12:3193. doi: 10.3390/jcm12093193

3. Quiñones-Baldrich WJ, Panetta TF, Vescera CL, Kashyap VS. Repair of type IV thoracoabdominal aneurysm with a combined endovascular and surgical approach. *J Vasc Surg*. (1999) 30:555–60. doi: 10.1016/s0741-5214(99)70084-4

4. Escobar GA, Oderich GS, Farber MA, de Souza LR, Quinones-Baldrich WJ, Patel HJ, et al. Results of the north American complex abdominal aortic debranching (NACAAD) registry. *Circulation*. (2022) 146:1149–58. doi: 10.1161/CIRCULATIONAHA.120.045894

5. Wang M, He Q, Yao C, Yin HH, Wang SM, Chang GQ. Treatment of high surgical risk thoracoabdominal aortic aneurysms with stent graft and multilayer bare stents joint technique: mid-long-term clinical results. *Ann Vasc Surg*. (2020) 63:108–16. doi: 10.1016/j.avsg.2019.06.041

6. Wang M, Yao C, Yin HH, Wang JS, Liao BY, Li ZL, et al. Endovascular treatment of ruptured or symptomatic thoracoabdominal and pararenal aortic aneurysms using octopus endograft technique: mid-term clinical outcomes. *J Endovasc Ther*. (2023) 30 (2):163–75. doi: 10.1177/15266028221075236

7. Chen Y, Liu Z, Wang S, D'Oria M, Zhang X, Bi J, et al. Systematic review and meta-analysis of short-term and mid-term outcomes after use of t-branch off-the-shelf multibranched endograft for elective and urgent treatment of thoracoabdominal aortic aneurysms. *J Endovasc Ther*. (2023):15266028231220322. doi: 10.1177/15266028231220322. [Epub ahead of print].

8. Zhang HP, Ge YY, Wang JB, Fan TT, Guo W. Off the shelf multibranched endograft for thoraco-abdominal and pararenal abdominal aortic aneurysms: a prospective, single centre study of the G-branch endograft. *Eur J Vasc Endovasc Surg*. (2024) 67:417–25. doi: 10.1016/j.ejvs.2023.11.005

9. Mohnot J, Wang YG, Yin K, Malas MB, Edwards NM, Dobrilovic N, et al. Changes in treatment patterns of thoracoabdominal aortic aneurysms in the United States. *JTCVS Open*. (2023) 16:48–65. doi: 10.1016/j.xjon.2023.08.019

10. Lin J, Liu W, Yang CW, Jian K, Xia Y, Peng H, et al. Early and mid-term outcomes of open thoracoabdominal aortic aneurysm repair after thoracic endovascular aortic repair. *BMC Cardiovasc Disord*. (2024) 24:182. doi: 10.1186/s12872-024-03837-8

11. He Y, Jia S, Sun G, Cao L, Wang X, Zhang H, et al. Fenestrated/branched endovascular repair for postdissection thoracoabdominal aneurysms: a systematic review with pooled data analysis. *Vasc Endovascular Surg*. (2020) 54:510–8. doi: 10.1177/1538574420927131

12. Li R, Liu Y, Jiang J. Case report: the application of amplatzer vascular plug to repair aortic dissection intimal tears and false lumen. *Front Cardiovasc Med*. (2023) 10:1337430. doi: 10.3389/fcvm.2023.1337430

13. Hofferberth SC, Nixon IK, Mossop PJ. Aortic false lumen thrombosis induction by embolotherapy (AFTER) following endovascular repair of aortic dissection. *J Endovasc Ther*. (2012) 19:538–45. doi: 10.1583/JEVT-12-3844R.1

14. Li Y, Li Z, Feng J, Feng R, Zhou J, Jing Z. A novel solution for distal dilation of chronic dissection after repair involving visceral branches: the road block strategy. *Front Cardiovasc Med*. (2022) 9:821260. doi: 10.3389/fcvm.2022.821260

15. Zeng Z, Feng R. Endovascular exclusion of tears in visceral segment in aortic dissection with endografts in false lumen and visceral artery. *Eur J Vasc Endovasc Surg*. (2020) 60(480):480. doi: 10.1016/j.ejvs.2020.05.002

16. Zhou M, Liu F, Shu X, Shi Z, Guo D, Wang L, et al. Spot stenting combined with false lumen endovascular occlusive repair for post-dissection abdominal aortic aneurysm. *J Endovasc Ther*. (2022) 29:705–10. doi: 10.1177/15266028211062564

17. Cao L, Zhang H, Guo W. First in man: sealing the distal re-entry tears of aortic dissection after thoracic endovascular aortic repair by an ENDOPATCH^{TM} system. *Eur Heart J*. (2023) 44:237. doi: 10.1093/eurheartj/ehac676

18. Ge Y, Zhang H, Guo W. First in man: blocking the false lumen backflow of aortic dissection after thoracic endovascular aortic repair by an off-the-shelf EndoSeal^{TM} system. *Eur Heart J*. (2024):ehae117. doi: 10.1093/eurheartj/ehae117. [Epub ahead of print].

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Risk factor prediction of severe postoperative acute kidney injury at stage 3 in patients with acute type A aortic dissection using thromboelastography

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Objective: Perioperative blood transfusions and postoperative drainage volume not only are the commonly recognized risk factors for acute kidney injury (AKI) but also are indirect indicators of coagulopathy in patients with acute type A aortic dissection (ATAAD). However, standard laboratory tests fail to accurately reflect and assess the overall coagulopathy profile in patients with ATAAD. Thus, this study aimed to explore the association between the hemostatic system and severe postoperative AKI (stage 3) in patients with ATAAD using thromboelastography (TEG).

Methods: We selected 106 consecutive patients with ATAAD who underwent emergency aortic surgery at Beijing Anzhen Hospital. All participants were categorized into the stage 3 and non-stage 3 groups. The hemostatic system was evaluated using routine laboratory tests and TEG preoperatively. We undertook univariate and multivariate stepwise logistic regression analyses to determine the potential risk factors for severe postoperative AKI (stage 3), with a special investigation on the association between hemostatic system biomarkers and severe postoperative AKI (stage 3). The receiver operating characteristic (ROC) curves were generated to assess the predictive ability of hemostatic system biomarkers for severe postoperative AKI (stage 3).

Results: A total of 25 (23.6%) patients developed severe postoperative AKI (stage 3), including 21 patients (19.8%) who required continuous renal replacement therapy (RRT). Multivariate logistic regression analysis demonstrated that the preoperative fibrinogen level (OR, 2.02; 95% CI, 1.03 to 3.00; $p = 0.04$), platelet function (MA level) (OR, 1.23; 95% CI, 1.09 to 1.39; $p = 0.001$), and cardiopulmonary bypass (CPB) time (OR, 1.01; 95% CI, 1.00 to 1.02; $p = 0.02$) were independently associated with severe postoperative AKI (stage 3). The cutoff values of preoperative fibrinogen and platelet function (MA level) for predicting severe postoperative AKI (stage 3) were determined to be 2.56 g/L and 60.7 mm in the ROC curve [area under the curve (AUC): 0.824 and 0.829; $p < 0.001$].

Conclusions: The preoperative fibrinogen level and platelet function (measured by the MA level) were identified as potential predictive factors for developing severe postoperative AKI (stage 3) in patients with ATAAD. Thromboelastography could be considered a potentially valuable tool for real-time monitoring and rapid assessment of the hemostatic system to improve postoperative outcomes in patients.

KEYWORDS

acute type A aortic dissection, acute kidney injury, thromboelastography (TEG), risk factor, continuous renal replacement therapy (CRRT)

Introduction

Acute kidney injury (AKI) has become a frequent and serious complication characterized by staggeringly high morbidity and mortality in patients with acute type A aortic dissection (ATAAD) after total arch replacement (TAR) combined with a frozen elephant trunk (FET) implant (1–3). Unlike in other cardiovascular surgeries, the incidence of AKI after thoracic aortic surgery is higher and varies considerably (4–7). However, some studies demonstrated that only patients with severe postoperative AKI (stage 3) had lower long-term survival—not patients with postoperative AKI (stages 1 and 2) (1, 2). Therefore, early identification and prompt prevention of potential risk factors for severe postoperative AKI (stage 3) play an important role in improving the overall prognosis of patients with ATAAD.

The majority of experts (3, 5) believe that excessive perioperative bleeding, blood transfusion, or postoperative drainage volume are currently identified as independent relevant risk factors for ATAAD-AKI. To some extent, the relationship between the hemostatic system (bleeding, transfusion, and drainage) and ATAAD-AKI has already been discussed in previous studies (8–10). However, there is a lack of uniform data regarding the association between hemostatic system biomarkers and severe postoperative AKI (stage 3) in patients with ATAAD. As it provided information not only about the dynamics of clot formation and clotting factors but also about the function of platelet and fibrinogen, thromboelastography (TEG) has been described as a prospective tool in patients undergoing non-complex cardiac surgery (11). Nevertheless, only a few studies have investigated the dynamics of the hemostatic system using TEG in the acute and complex settings of aortic dissection. Thus, the purpose of our study was to explore the incidence and risk factors for severe postoperative AKI (stage 3) among patients with ATAAD after emergency aortic surgery, with special emphasis on the relationship between the hemostatic system and the severity of postoperative AKI.

Material and methods

Study design

In this single-center prospective study, we analyzed the association between the hemostatic system and severe postoperative AKI (stage 3) in 106 patients with ATAAD who underwent aortic arch surgery using the preoperative routine laboratory test results and TEG analysis at Beijing Anzhen Hospital, Capital Medical University, China. The plasma fibrinogen concentration was tested using the Clauss method. A single team performed all procedures. The protocol of this study was approved by Anzhen Hospital's Ethics Committee (No. 2018004), and consent was obtained from the patients or their relatives.

Abbreviations: AKI, acute kidney injury; ATAAD, acute type A aortic dissection; AUC, area under the curve; CI, confidence interval; CPB, cardiopulmonary bypass; CT, computed tomography; eGFR, Estimated glomerular filtration rate; FDP, fibrinogen degradation products; FET, frozen elephant trunk; HCA, hypothermic circulatory arrest; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; OR, odds ratio; RBC, red blood cell; ROC, receiver operating characteristic; RRT, renal replacement therapy; sCr, serum creatinine; SD, standard deviation; TAR, total arch replacement; TEG, thromboelastography.

Patient population

From June 2020 to December 2021, a total of 106 patients with ATAAD per the Stanford classification were eligible for inclusion in the study at the Institute of Cardiac Surgery, Beijing Anzhen Hospital, Capital Medical University, China (Figure 1). All emergency TAR combined with a FET implant with cardiopulmonary bypass (CPB) involving moderate hypothermic circulatory arrest (HCA) with or without aortic valve operations were collected for further analysis. Patients were recruited consecutively on the condition that they agreed to provide informed consent. The exclusion criteria included congenital or acquired coagulative disorders, liver disease or abnormal liver function, preoperative use of anti-coagulants or antiplatelet drugs, death before planned surgery, preoperative chronic dialysis within the past month or emergency dialysis before surgery, and incomplete clinical data.

Measurements and variable definitions

The diagnosis of postoperative AKI stage 3 was based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (12): a threefold increase or more above baseline or an increase in serum creatinine (sCr) to $\geq$ 4.0 mg/dl ($\geq$ 353.6 mmol/l) or the initiation of renal replacement therapy (RRT) or, in patients under 18 years of age, a decrease in estimated glomerular filtration rate (eGFR) to <35 ml/min per 1.73 m^2 (Table 1). The diagnosis of ATAAD was confirmed by a contrast-enhanced computed tomography (CT) scan, with the onset of symptoms onset within 48 h. Intraoperative bleeding was defined as blood loss that was collected and quantified using intraoperative cell salvage and surgical gauze swabs. Continuous RRT was defined as the need for continuous hemofiltration or hemodialysis after surgery.

TEG analysis

After taking blood samples in the emergency department, the samples were immediately transferred to a clinical laboratory in our hospital. According to the manufacturer's instructions, professional staff performed TEG analysis using the TEG 5000 analyzer (Haemoscope, Niles, IL). The following EG parameters were tested: R time is the period from the initiation of the test to the initial fibrin formation (representing thrombus formation initiation). K time is the period from the beginning of clot formation until the amplitude of the curves reaches 20 mm (representing the dynamics of clot formation). Maximum amplitude (MA) is a direct measure of the highest point on the TEG curve (which represents platelet function). Theαangle is the angle between the line in the middle of the TEG tracing and tangential to the body of the TEG tracing (represents the kinetics of fibrin buildup and cross-linking).

Surgical procedures

Under standard anesthetic management, emergency aortic surgery refers to TAR using a tetra-furcate vascular graft in combination with the implantation of FET into the descending

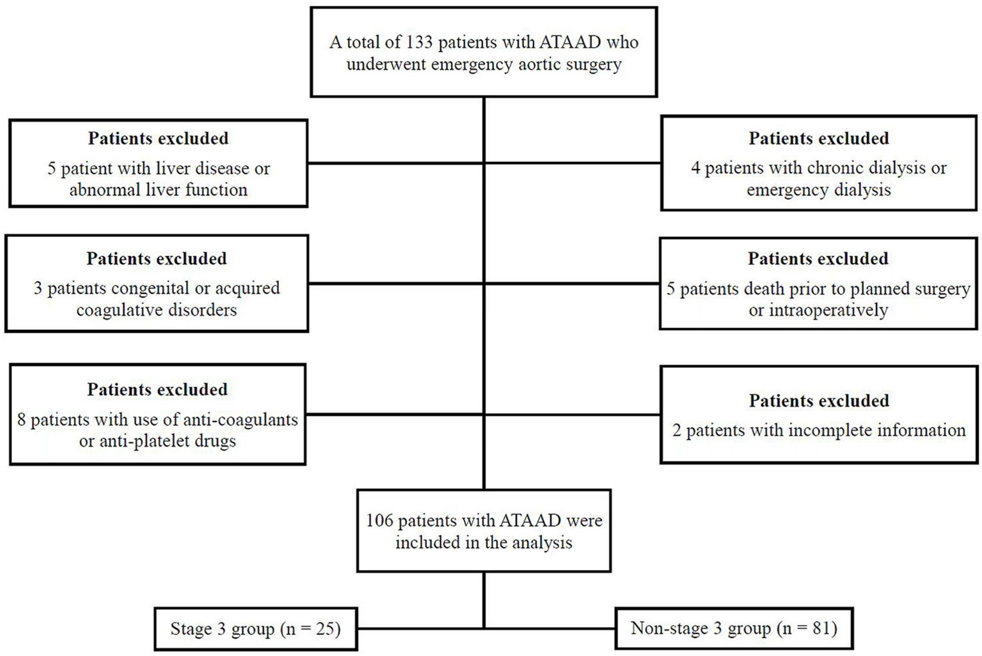

FIGURE 1
A flowchart of the study cohort.

aorta under moderate HCA. Briefly, the procedure involved cannulation of the right axillary artery and right atrium for CPB and selective antegrade cerebral perfusion [5–15 mL/(kg·min)] at a nasopharyngeal temperature of approximately 26–28°C. After systemic heparinization, the proximal aortic root operation was carried out based on the lesions of the aortic root during the cooling period. The sequence of aortic arch reconstruction was proximal descending aorta, left carotid artery, ascending aorta, left subclavian artery, and innominate artery. After the distal anastomosis was completed, CPB was restarted, and the patient was gradually rewarmed to a normal temperature. Other concomitant operations were conducted during the rewarming period. Upon completion of the repair and adequate rewarming, the patient was extubated from CBP.

TABLE 1 KDIGO stages of AKI according to sCr levels and urine output.

Stage	sCr	Urine output
1	1.5–1.9 times baseline or ≥ 0.3 mg/dL (≥26.5 mmol/l) increase	<0.5 ml/kg/h for 6-12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	> 3.0 times baseline or increase in sCr to ≥ 4.0 mg/dl (≥353.6 mmol/l) or initiation of RRT or in patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥24 h or anuria for ≥12 h

AKI, acute kidney injury; Egfr, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; sCr, serum creatinine.

Statistical analysis

The normality of the data distribution was tested using the Kolmogorov–Smirnov test. Continuous data with a normal distribution were expressed as mean ± standard deviation (SD), and continuous data with a non-normal distribution were expressed as median (25 and 75^{th} percentile); categorical variables were expressed as *n* (%). For comparison, independent sample *t*-tests or the Wilcoxon rank sum tests were analyzed for continuous variables. The chi-squared test or Fisher's exact test was used for categorical variables. The univariate logistic regression analysis was used to compare baseline characteristics between two groups for severe postoperative ATAAD-AKI (stage 3), and the multivariate stepwise logistic regression model was carried out to identify possible risk factors ($p < 0.01$) for severe postoperative ATAAD-AKI (stage 3). The receiver operating characteristic (ROC) curve was performed to further evaluate the predictive ability of risk factors for severe postoperative ATAAD-AKI (stage 3). For all analyses, a two-tailed value of p of < 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS 18.0 (SPSS, Inc., Chicago, IL).

Results

Incidence of postoperative ATAAD-AKI

Based on the KDIGO criteria, our study's incidence of postoperative ATAAD-AKI was 53.8% (57/106). Among them, the prevalence of severe ATAAD-AKI was 38.6% for stage 1 (22 cases), 17.5% for stage 2 (10 cases), and 43.9% for stage 3 (25 cases). In total, 21 patients (19.8%) needed continuous RRT after the operation. Renal malperfusion occurred in 14 patients (13.2%) preoperatively. Among them, four (28.6%) patients developed postoperative AKI. The mean age of patients with AKI was 48.2 ± 10.5 years, and the data involved 42 men and 15 women in the AKI group. Chest pain (94.4%) represents one of the most frequent symptoms in patients with ATAAD. Hypertension was confirmed in 84 out of the 106 patients. Only 6.6% of patients have Marfan syndrome. With regard to imaging data, the clot-filled false lumen appeared on enhanced CT in 65 patients. In addition, 79 patients suffered dissections extending below the diaphragm, and the remaining 27 patients had dissections terminating above the diaphragm (Table 2).

Baseline characteristics

Based on the KDIGO criteria, the patient population was divided into two groups: the stage 3 group and the non-stage 3 group. Patient baseline demographic information is presented in Table 2. Marfan syndrome was more common in the severe postoperative AKI (stage 3) group (16.0 vs. 3.7%, $p = 0.03$) according to the medical history. The preoperative routine laboratory tests between the two groups are also summarized in Table 2. The neutrophil ratio, fibrinogen degradation products (FDP), and D-dimer were higher in the severe postoperative AKI (stage 3) group compared to patients in the non-stage 3 group ($p = 0.001$, $p < 0.001$, and $p = 0.001$, respectively). Nevertheless, platelet counts and fibrinogen levels were relatively lower in the severe postoperative AKI (stage 3) group ($p = 0.008$ and $p < 0.001$, respectively). In addition, TEG parameters showed that the MA level (platelet function) was lower in the severe postoperative AKI (stage 3) group when compared to the non-AKI stage 3 group ($p < 0.001$). Other TEG parameters, such as R time, K time, andαangle, did not differ significantly between the two groups.

Surgical characteristics and postoperative outcomes

Patient surgical details are shown in Table 2. Our data demonstrated that operation time and CPB time were all prolonged in patients with severe postoperative AKI (stage 3) ($p = 0.004$ and $p = 0.002$). Regarding nasopharyngeal or rectal temperature, no significant differences were observed between the two groups. Notably, there was a higher intraoperative amount of red blood cells (RBC) in the severe postoperative AKI (stage 3) group than in the non-stage 3 groups ($p = 0.04$). Although there was a similarity with respect to in-hospital mortality between the two groups ($p = 0.07$), the postoperative complications were indeed more serious and complicated in patients with severe postoperative AKI (stage 3), such as a longer intensive care unit (ICU) stay, continuous RRT, severe hypoxemia, multi-organ failure, and sepsis ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.004$ and $p = 0.04$, respectively).

Changes in preoperative MA level (platelet function) and fibrinogen level among AKI groups according to the AKI stages

A clear distinction was observed in the preoperative MA level (platelet function) among the groups of patients with AKI when analyzed by the AKI stages in a general trend analysis ($p = 0.007$) (Figure 2). Similar to the overall analysis, the MA level (platelet function) was lower in postoperative AKI stage 3 compared with the stage 0, stage 1, and stage 2 groups ($p = 0.001$, $p = 0.004$, and $p = 0.041$, respectively). Moreover, there was also a significant distinction in preoperative fibrinogen levels among AKI groups in the overall trend analysis ($p < 0.001$) (Figure 3). Similarly, the preoperative fibrinogen level was lower in postoperative AKI stage 3 compared with other AKI stages ($p < 0.001$, $p = 0.001$, and $p = 0.006$, respectively).

Univariate and multivariate logistic regression analysis associated with independent risk factors for severe postoperative AKI (stage 3)

The preoperative characteristics, such as neutrophil ratio, platelet counts, fibrinogen level, FDP, D-Dimer, and MA level (platelet function), were associated with related risk factors for severe postoperative AKI (stage 3) in the univariate analysis ($p < 0.01$). Furthermore, the duration of the operation and CPB time in operative variables might be linked to the risk of severe postoperative AKI (stage 3) in univariate logistic regression analysis ($p < 0.01$). To address issues of collinearity, a multivariate stepwise logistic regression analysis was conducted to identify the risk factors of severe postoperative AKI (stage 3), and the results are summarized in Table 3. Among the potential risk factors determined by a univariate analysis ($p < 0.01$), independent risk factors for severe postoperative AKI (stage 3) in patients with ATAAD were the preoperative fibrinogen level [OR, 2.02; 95% confidence interval (CI), 1.03 to 3.00; $p = 0.04$], the MA level (platelet function) (OR, 1.23; 95% CI, 1.09 to 1.39; $p = 0.001$), and longer CPB time (OR, 1.01; 95% CI, 1.00 to 1.02; $p = 0.02$) in multivariate logistic regression analysis.

Predictive ability of a risk factor for severe postoperative AKI (stage 3)

The ROC curves were generated to explore the predictive ability and the cutoff value of risk factors for severe postoperative AKI (stage 3). As shown in Figure 4, the area under the curve (AUC) of the preoperative fibrinogen level and the MA level (platelet function) used for predicting severe postoperative AKI (stage 3) in patients with ATAAD were 0.824 (cutoff, 2.56 g/L; sensitivity, 81.3%; specificity, 76.0%; $p < 0.001$) and 0.829 (cutoff, 60.7 mm; sensitivity, 77.5%; specificity, 72.0%; $p < 0.001$), respectively.

Discussion

The key conclusion of this study was that the preoperative fibrinogen and MA levels (platelet function) were independent predictive indicators for risk factors associated with severe postoperative AKI (stage 3) in patients with ATAAD after TAR combined with a FET, and it emphasized the association between hemostatic system biomarkers and severe postoperative AKI (stage 3). To the best of our knowledge, this is the first research to investigate the relationship between hemostatic system biomarkers and the severity of postoperative AKI in patients with ATAAD

TABLE 2 Characteristics of the study patients with ATAAD at baseline.

Characteristics	Stage 3 (n = 25)	Non-stage 3 (n = 81)	*p*-value
Demographic data			
Age, year	50.2 ± 9.4	47.5 ± 10.8	0.26
Male, %	15 (60.0)	64 (79.0)	0.11
BMI, kg/m^2	27.3 ± 3.4	25.9 ± 3.9	0.11
Medical history			
Hypertension, %	23 (92.0)	61 (75.3)	0.07
Diabetes mellitus, %	1 (4.0)	6 (7.4)	0.55
Cerebrovascular disease, %	1 (4.0)	4 (4.9)	0.85
Coronary artery disease, %	0	6 (7.4)	0.17
Smoking history, %	14 (56.0)	35 (43.2)	0.26
Drinking history, %	9 (36.0)	14 (17.3)	0.45
Marfan syndrome, %	4 (16.0)	3 (3.7)	0.03
Preoperative condition			
Alanine amino transaminase, U/L	24.9 ± 5.8	33.4 ± 5.5	0.18
sCr, umol/L	94.5 ± 32.8	84.3 ± 27.9	0.13
eGFR, mL/(min·1.73m^2)	85.8 ± 12.4	84.7 ± 13.2	0.36
White blood cells, $\times 10^3$/mm^3	12.4 ± 3.7	11.0 ± 3.7	0.11
Neutrophil ratio, %	84.4 ± 5.1	77.9 ± 9.3	0.001
Hemoglobin, g/dL	132.1 ± 14	137.0 ± 16.9	0.19
Platelet counts, $\times 10^3$/mm^3	141.8 ± 40.7	185.0 ± 76.7	0.008
Fibrinogen level, g/L	2.3 ± 1.1	3.9 ± 1.6	<0.001
FDP, ug/mL	35.8 (18.7, 65.2)	11.7 (6.5, 27.4)	<0.001
D-Dimer, ng/mL	2378 (1918, 7726)	1085 (591, 2526)	0.001
LVEF, %	64.7 ± 5.3	62.0 ± 6.0	0.05
Aortic root size, mm	40.8 ± 7.3	41.0 ± 8.3	0.94
Ascend aorta size, mm	46.6 ± 7.1	45.4 ± 7.6	0.50
Aortic regurgitation, %	11 (44.0)	36 (44.4)	0.97
Renal malperfusion, %	4 (16.0)	10 (12.3)	0.64
TEG			
R time (min)	5.5 ± 1.6	5.9 ± 3.1	0.48
K time (min)	2.0 ± 0.9	1.7 ± 1.1	0.35
MA (mm)	55.7 ± 7.7	65.1 ± 6.8	<0.001
α angle (degree)	63.6 ± 7.3	67.1 ± 9.3	0.08
Operation details			
Bentall+TAR+FET, %	12 (48.0)	28 (34.6)	0.23
Combined with CABG, %	2 (8.0)	6 (7.4)	0.92
The duration of operation, hour	9.35 ± 2.0	8.1 ± 1.8	0.004
CPB time, min	242.0 ± 69.9	202.2 ± 49.0	0.002
Aortic cross clamp time, min	135.8 ± 39.8	120.9 ± 43.8	0.13
The duration of HCA, min	28.8 ± 7.0	26.5 ± 9.4	0.23
Nasopharyngeal temperature, °C	22.3 ± 1.4	23.2 ± 2.0	0.06
Rectal temperature, °C	25.1 ± 2.0	24.5 ± 2.4	0.45

(Continued)

TABLE 2 (Continued)

Characteristics	Stage 3 (n = 25)	Non-stage 3 (n = 81)	*p*-value
Intraoperative blood loss, mL	1592 ± 615	1462 ± 767	0.44
Intraoperative amount of plasma, mL	500 (0, 1000)	400 (100, 600)	0.25
Intraoperative amount of RBC, mL	600 (0, 750)	300 (0, 600)	0.04
24 h postoperative drainage	600 (380, 910)	650 (500, 925)	0.58
48 h postoperative drainage	1000 (725, 1195)	1050 (720, 1550)	0.49
Postoperative outcomes			
In-hospital mortality, %	4 (16.0)	4 (4.9)	0.07
Length of hospital, day	15 (12, 22)	14 (10, 17)	0.16
Length of ICU, day	8.0 (6, 12)	2 (1, 4)	<0.001
Continuous RRT, %	21 (84.0)	0	<0.001
Severe hypoxemia, %	18 (72.0)	21 (25.9)	<0.001
Reoperation for bleeding, %	3 (12.0)	5 (6.2)	0.34
Low cardiac output syndrome, %	2 (8.0)	4 (4.9)	0.56
Cerebral infarction or bleeding, %	2 (8.0)	7 (8.6)	0.75
Multi-organ failure, %	7 (28.0)	4 (4.9)	0.004
Sepsis, %	7 (28.0)	9 (11.1)	0.04

Results are expressed as n (%), mean ± SD or median (interquartile range). AKI, acute kidney injury; ATAAD, acute type A aortic dissection; BMI, body mass index; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; FET, frozen elephant trunk; FDP, fibrinogen degradation products; HCA, hypothermic circulatory arrest; ICU, intensive care unit; LVEF, left ventricular ejection fraction; MA, maximum amplitude; RBC, red blood cell; RRT, renal replacement therapy; sCr, serum creatinine; TAR, total arch replacement; TEG, Thromboelastography.

using TEG. With the aid of TEG parameters, early monitoring and identification of critically ill patients may be achieved for renal preventive and protective strategies.

The incidence of severe postoperative ATAAD-AKI (stage 3) in our study is 23.6% (25/106), and the required continuous RRT is 19.8% (21/106). A recently published investigation from Wang et al. (9) revealed that 23.8% of patients developed severe postoperative ATAAD-AKI (stage 3) after ATAAD surgery, including 16.6% of patients who received continuous RRT. Similarly, Chen et al. (7) also demonstrated that 47.9% of patients developed severe postoperative AKI (AKI stages 2 or 3) and 14.6% required continuous RRT. However, Ko (2) suggested that the incidence of developing severe postoperative AKI (stage 3) after aortic arch surgery was only 14%, and the rate of patients who needed continuous RRT was as low as 9%. The reason for these lower rates might be mainly attributed to the exclusion of emergency ATAAD surgery from that study. Due to the life-threatening aortic syndrome and the complexity of the urgent operation, it is unsurprising that the rates of severe postoperative AKI (AKI stage 3) and continuous RRT were up to 20% in our study. Increasing evidence suggests that increasing AKI severity is associated with an increase in mortality. Thus, TEG might be a suitable tool for early AKI diagnosis and the prediction of the need for RRT in patients with ATAAD.

The high mortality rate for emergency aortic surgery is challenging and is associated with high rates of perioperative bleeding and blood product transfusions (13, 14). Excessive perioperative bleeding and blood product transfusions represent one of the most common and feared complications in emergency aortic surgery. Massive blood transfusions are also considered an indirect marker of hemorrhage and a known risk factor for ATAAD-AKI (8, 10).

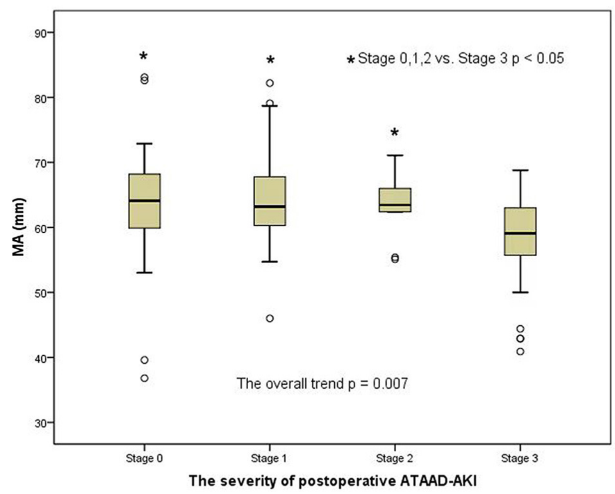

FIGURE 2
Changes in preoperative MA level (platelet function) among the AKI groups.

Growing evidence (2, 3, 15) indicates that perioperative transfusions of large amounts of RBC and plasma were designed to determine independent risk factors for AKI. In line with these studies, the intraoperative quantity of RBC was higher in our study's severe postoperative AKI (stage 3) group. In addition, patients with major bleeding on preoperative dual antiplatelet therapy had more postoperative AKI, which indirectly showed the relationship between bleeding and AKI (16).

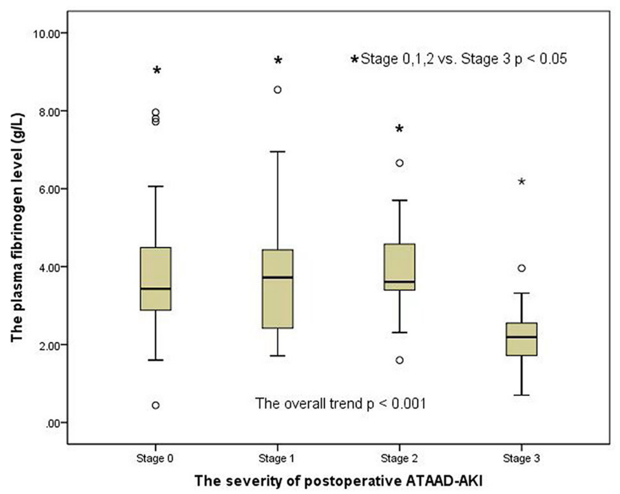

FIGURE 3
Changes in preoperative fibrinogen level among the AKI groups.

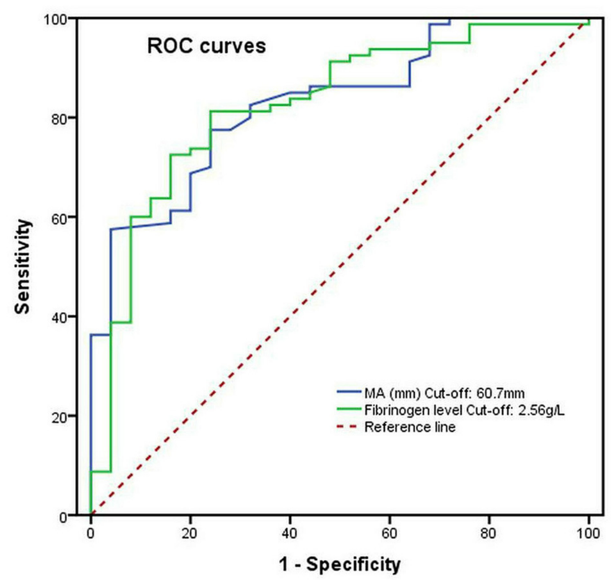

FIGURE 4
The preoperative MA level (platelet function) and fibrinogen level as predictive values of risk factors for severe postoperative AKI (stage 3) in patients with ATAAD by the ROC curve analysis.

TABLE 3 Risk factors for postoperative AKI (stage 3) in multivariate logistic regression analysis in patients with ATAAD.

Risk factors	OR	95% CI	*p*-value
Neutrophil ratio, %	1.07	0.94–1.21	0.32
Platelet counts, $\times 10^3/mm^3$	0.99	0.97–1.00	0.11
Low fibrinogen level, g/L	2.02	1.03–3.00	0.04
FDP, ug/mL	0.98	0.93–1.03	0.34
D-Dimer, ng/mL	1.01	0.98–1.04	0.33
Low MA (mm)	1.23	1.09–1.39	0.001
The duration of operation, hour	1.01	0.99–1.02	0.97
CPB time, min	1.01	1.00–1.02	0.02

AKI, acute kidney injury; ATAAD, acute type A aortic dissection; CI, confidence interval; CPB, cardiopulmonary bypass; FDP, fibrinogen degradation products; MA, maximum amplitude; OR, odds ratio.

Wang et al. (9) showed that the logistic regression model identified the 24-h drainage volume after an aorta repair operation as another independent risk factor for postoperative AKI stage 3. Additionally, the multivariate logistic regression analysis similarly revealed that 72-h drainage volume was an important predictor of postoperative ATAAD-AKI in an overweight patient with ATAAD (6). Excessive drainage volume can disrupt homeostasis, induce pro-inflammatory states, and increase oxidative stress, which will contribute to the pathogenesis of AKI (17). Therefore, decreasing postoperative drainage volume is considered essential and may reduce the incidence of postoperative AKI. Although the association between drainage volume and ATAAD-AKI was not directly established in our research, it appears that excessive bleeding and transfusion did not provide any benefits for patients with ATAAD.

HCA- and CPB-induced coagulopathy in aortic surgery is already a well-accepted clinical pathological condition (18–20). The impairment of the hemostatic system is already caused by the contact of blood flow with the non-endothelialized walls of the false lumen before emergency aortic surgery (19, 21). In light of the activation of the hemostatic system preoperatively, our study primarily described preoperative changes in the hemostatic system in patients with ATAAD. Similar to some previous studies (21, 22), our study's routine laboratory tests and TEG documented fibrinogen, platelet, and clotting factor consumption and, ultimately, coagulopathy in the early preoperative period of ATAAD. To date, no similar study has been performed in which data on the association between TEG parameters of changes in the hemostatic system and severe postoperative AKI (stage 3) were obtained.

It is widely known that platelets and fibrinogen are critical for clot formation and clot strength. Therefore, increasing emphasis has focused on the importance of platelets and fibrinogen in reducing blood loss and improving prognosis (19). Notably, many guidelines (23–25) have recommended the use of fibrinogen concentrate and platelets to correct early coagulopathy. Some previous studies (19, 21, 26) consistently reported that fibrinogen is directly responsible for clot strength and can compensate for platelet function. Indeed, the shortage of platelets and fibrinogen might lead to perioperative bleeding and blood product transfusions associated with postoperative AKI. Our research confirmed that the multivariate logistic regression analysis identified the preoperative fibrinogen level and the MA level (platelet function) as independent risk factors for severe postoperative AKI (stage 3) in patients with ATAAD. Thus, we have reasons to believe that there are predictable and quantifiable changes in TEG parameters for severe postoperative AKI (stage 3) in ATAAD.

Because of the interaction between a non-pulsatile flow and the activation of an inflammatory response, a few studies (2, 8, 27, 28) had already confirmed that CPB is associated with increased postoperative AKI. Moreover, Englberger et al. (29) discovered that every additional 10-min increase in CPB time would lead to a higher risk of postoperative ATAAD-AKI. Similarly, Wang et al. (9) also illustrated that prolonged CPB duration is an independent risk factor for developing severe postoperative ATAAD-AKI (stage

3). In contrast, Kim et al. (3) and Li et al. (5) discovered that HCA time is associated with a risk for ATAAD-AKI in multivariable analysis but not CPB. Amano et al. (30, 31) also concluded that the duration of HCA was recognized as a surgical risk factor for postoperative ATAAD-AKI. However, Roh et al. (8, 29, 32) did not find a relationship between HCA time and ATAAD-AKI. We believe that, despite the inconsistency of those conclusions, there was no doubt that renal medullary ischemia or reperfusion injury induced by CPB or HCA might be the most important pathophysiological change associated with ATAAD-AKI.

Early identification and management of the hemostatic system might be lifesaving (33). Nevertheless, the routine laboratory tests can only analyze factors in plasma and isolated components or fractions. Thus, it does not adequately evaluate the whole coagulation state in patients with ATAAD. At many major cardiovascular centers, TEG-guided perioperative bleeding management has been extensively used to monitor hemostasis and decrease the risk of bleeding (34, 35). This technology may provide an overall view of coagulation and detect platelet function (MA level) and fibrinogen function (αangle), which may be beneficial for patients with ATAAD. Although TEG has been proven to reduce transfusions in cardiac surgery, only a few studies have shown the predictive value of TEG (11, 36, 37). Nevertheless, the use of TEG as a tool to predict risk factors for severe postoperative AKI (stage 3) has been confirmed by our study. TEG measurements could supplement routine laboratory tests, but they do not negate the need for routine laboratory tests.

Study limitations

Several potential limitations of the present study should be discussed. First, the sample size of the study was small, and this study was conducted only in one institution, which may limit the applicability of our findings to other settings. Second, we could not identify the underlying mechanisms linking the hemostatic system to the development of ATAAD-AKI. Third, some potential bias may have been retained after the multivariate analysis. To verify these findings, larger and more comprehensive prospective multicenter studies are needed. Finally, further long-term follow-up studies are needed to better understand the association between the preoperative hemostatic system and postoperative ATAAD-AKI.

Conclusions

In conclusion, in the present study, we found that preoperative fibrinogen level and MA level were significantly associated with the risk of severe postoperative AKI (stage 3) in patients with ATAAD. The TEG may be an effective tool in identifying and assessing the risk factors for severe postoperative ATAAD-AKI (stage 3) in patients with ATAAD (stage 3).

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee at Anzhen Hospital (Institutional Review Board File No. 2018004). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Conception and design: X-LG, H-YL, H-JZ, and X-LW. Administrative support: H-YL and H-JZ. Provision of study materials or patients: MG and X-LW. Collection and assembly of data: X-LG, MG, and H-YL. Data analysis and interpretation: X-LG, LL, and X-LW. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Sasabuchi Y, Kimura N, Shiotsuka J, Komuro T, Mouri H, Ohnuma T, et al. Long-term survival in patients with acute kidney injury after acute type A aortic dissection repair. *Ann Thorac Surg.* (2016) 102:2003–9. doi: 10.1016/j.athoracsur.2016.05.006

2. Ko T, Higashitani M, Sato A, Uemura Y, Norimatsu T, Mahara K, et al. Impact of acute kidney injury on early to long-term outcomes in patients who underwent surgery for type A acute aortic dissection. *Am J Cardiol.* (2015) 116:463–8. doi: 10.1016/j.amjcard.2015.04.043

3. Kim WH, Park MH, Kim HJ, Lim HY, Shim HS, Sohn JT, et al. Potentially modifiable risk factors for acute kidney injury after surgery on the thoracic aorta: a propensity score matched case-control study. *Medicine.* (2015) 94:e273. doi: 10.1097/MD.0000000000000273

4. Tsai HS, Tsai FC, Chen YC, Wu LS, Chen SW, Chu JJ, et al. Impact of acute kidney injury on one-year survival after surgery for aortic dissection. *Ann Thorac Surg.* (2012) 94:1407–12. doi: 10.1016/j.athoracsur.2012.05.104

5. Li L, Zhou J, Hao X, Zhang W, Yu D, Xie Y, et al. The incidence, risk factors and in-hospital mortality of acute kidney injury in patients after surgery for acute type A aortic dissection: a single-center retrospective analysis of 335 patients. *Front Med (Lausanne).* (2020) 7:557044–51. doi: 10.3389/fmed.2020.557044

6. Zhao H, Pan X, Gong Z, Zheng J, Liu Y, Zhu J, et al. Risk factors for acute kidney injury in overweight patients with acute type A aortic dissection: a retrospective study. *J Thorac Dis.* (2015) 7:1385–90.

7. Chen X, Zhou J, Fang M, Yang J, Wang X, Wang S, et al. Incidence- and in-hospital mortality-related risk factors of acute kidney injury requiring continuous renal replacement therapy in patients undergoing surgery for acute type a aortic dissection. *Front Cardiovasc Med.* (2021) 8:749592. doi: 10.3389/fcvm.2021.749592

8. Helgason D, Helgadottir S, Ahlsson A, Gunn J, Hjortdal V, Hansson EC, et al. Acute kidney injury after acute repair of type A aortic dissection. *Ann Thorac Surg.* (2021) 111:1292–8. doi: 10.1016/j.athoracsur.2020.07.019

9. Wang Z, Ge M, Wang Z, Chen C, Lu L, Zhang L, et al. Identification of risk factors for postoperative stage 3 acute kidney injury in patients who received surgical repair for acute type A aortic dissection. *BMC Surg.* (2022) 22:75. doi: 10.1186/s12893-022-01526-x

10. Qiu Z, Chen L, Cao H, Zhang G, Xu F, Chen Q. Analysis of risk factors for acute kidney injury after ascending aortic replacement combined with open placement of triple-branched stent graft in type A aortic dissection: a new technique versus the traditional method in a single Chinese center. *Med Sci Monit.* (2015) 21:674–80. doi: 10.12659/MSM.892492

11. Wasowicz M, McCluskey SA, Wijeysundera DN, Yau TM, Meinri M, Beattie WS, et al. The incremental value of thrombelastography for prediction of excessive blood loss after cardiac surgery: an observational study. *Anesth Analg.* (2010) 111:331–8. doi: 10.1213/ANE.0b013e3181e456c1

12. Khwaja A, KDIGO. clinical practice guidelines for acute kidney injury. *Nephron Clin Pract.* (2012) 120:c179–84. doi: 10.1159/000339789

13. Evangelista A, Isselbacher EM, Bossone E, Gleason TG, Eusanio MD, Sechtem U, et al. Insights from the international registry of acute aortic dissection: A 20-year experience of collaborative clinical research. *Circulation.* (2018) 137:1846–60. doi: 10.1161/CIRCULATIONAHA.117.031264

14. Zindovic I, Sjögren J, Bjursten H, Björklund E, Herou E, Ingemansson R, et al. Predictors and impact of massive bleeding in acute type A aortic dissection. *Interact Cardiovasc Thorac Surg.* (2017) 24:498–505. doi: 10.1093/icvts/ivw425

15. Kindzelski BA, Corcoran P, Siegenthaler MP, Horvath KA. Postoperative acute kidney injury following intraoperative blood product transfusions during cardiac surgery. *Perfusion.* (2018) 33:62–70. doi: 10.1177/0267659117712405

16. Hansson EC, Geirsson A, Hjortdal V, Mennander A, Olsson C, Gunn J, et al. Preoperative dual antiplatelet therapy increases bleeding and transfusions but not mortality in acute aortic dissection type A repair. *Eur J Cardiothorac Surg.* (2019) 56:182–8. doi: 10.1093/ejcts/ezy469

17. Karkouti K, Wijeysundera DN, Yau TM, Callum JL, Cheng DC, Crowther M, et al. Acute kidney injury after cardiac surgery: focus on modifiable risk factors. *Circulation.* (2009) 119:495–502. doi: 10.1161/CIRCULATIONAHA.108.786913

18. Ranucci M, Baryshnikova E, Ciotti E, Ranucci M, Silvetti S. Hemodilution on cardiopulmonary bypass: thromboelastography patterns and coagulation-related outcomes. *J Cardiothorac Vasc Anesth.* (2017) 31:1588–94. doi: 10.1053/j.jvca.2017.04.014

19. Guan XL, Wang XL, Liu YY, Lan F, Gong M, Li HY, et al. Changes in the hemostatic system of patients with acute aortic dissection undergoing aortic arch surgery. *Ann Thorac Surg.* (2016) 101:945–51. doi: 10.1016/j.athoracsur.2015.08.047

20. Pan X, Lu J, Cheng W, Yang Y, Zhu J, Jin M. Pulmonary static inflation with 50% xenon attenuates decline in tissue factor in patients undergoing Stanford type A acute aortic dissection repair. *J Thoracic Dis.* (2018) 10:4368–76. doi: 10.21037/jtd.2018.06.95

21. Liu Y, Han L, Li J, Gong M, Zhang H, Guan X. Consumption coagulopathy in acute aortic dissection: principles of management. *J Cardiothorac Surg.* (2017) 12:50. doi: 10.1186/s13019-017-0613-5

22. Larsson M, Zindovic I, Sjögren J, Svensson PJ, Strandberg K, Nozohoor S, et al. prospective, controlled study on the utility of rotational thromboelastometry in surgery for acute type A aortic dissection. *Sci Rep.* (2022) 12:18950. doi: 10.1038/s41598-022-23701-z

23. Miceli A, Ranucci M, Glauber M. Fibrinogen concentrate as first-line hemostatic treatment for the management of bleeding in complex cardiac surgery. *J Thorac Cardiovasc Surg.* (2016) 151:383–4. doi: 10.1016/j.jtcvs.2015.09.023

24. Schochl H, Nienaber U, Hofer G, Voelckel W, Jambor C, Scharbert G, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Crit Care.* (2010) 14:R55. doi: 10.1186/cc8948

25. Schochl H, Nienaber U, Maegele M, Hochleitner G, Primavesi F, Steitz B, et al. Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. *Crit Care.* (2011) 15:R83. doi: 10.1186/cc10078

26. Velik-Salchner C, Haas T, Innerhofer P, Streif W, Nussbaumer W, Klingler A, et al. The effect of fibrinogen concentrate on thrombocytopenia. *J Thromb Haemost.* (2007) 5:1019–25. doi: 10.1111/j.1538-7836.2007.02481.x

27. Vekstein AM, Yerokun BA, Jawitz OK, Doberne JW, Anand J, Karhausen J, et al. Does deeper hypothermia reduce the risk of acute kidney injury after circulatory arrest for aortic arch surgery? *Eur J Cardiothorac Surg.* (2021) 60:314–21. doi: 10.1093/ejcts/ezab044

28. Xu S, Liu J, Li L, Wu Z, Li J, Liu Y, et al. Cardiopulmonary bypass time is an independent risk factor for acute kidney injury in emergent thoracic aortic surgery: a retrospective cohort study. *J Cardiothorac Surg.* (2019) 14:90. doi: 10.1186/s13019-019-0907-x

29. Englberger L, Suri RM, Greason KL, Burkhart HM, Thoralf M. Sundt 3rd, Daly RC, et al. *Deep hypothermic circulatory arrest is not a risk factor for acute kidney injury in thoracic aortic surgery J Thorac Cardiovasc Surg.* (2011) 141:552–8. doi: 10.1016/j.jtcvs.2010.02.045

30. Skotsimara G, Antonopoulos A, Oikonomou E, Papastamos C, Siasos G, Tousoulis D. Aortic wall inflammation in the pathogenesis, diagnosis and treatment of aortic aneurysms. *Inflammation.* (2022) 45:965–76. doi: 10.1007/s10753-022-01626-z

31. Amano K, Takami Y, Ishikawa H, Ishida M, Tochii M, Akita K, et al. Lower body ischaemic time is a risk factor for acute kidney injury after surgery for type A acute aortic dissection. *Interact Cardiovasc Thorac Surg.* (2020) 30:107–12. doi: 10.1093/icvts/ivz220

32. Roh GU, Lee JW, Nam SB, Lee J, Choi JR, Shim YH. Incidence and risk factors of acute kidney injury after thoracic aortic surgery for acute dissection. *Ann Thorac Surg.* (2012) 94:766–71. doi: 10.1016/j.athoracsur.2012.04.057

33. Chee YE, Liu SE, Irwin MG. Management of bleeding in vascular surgery. *Br J Anaesth.* (2016) 117:ii85–94. doi: 10.1093/bja/aew270

34. Girdauskas E, Kempfert J, Kuntze T, Borger MA, Enders J, Fassl J, et al. Thromboelastometrically guided transfusion protocol during aortic surgery with circulatory arrest: a prospective, randomized trial. *J Thorac Cardiovasc Surg.* (2010) 140:1117–24. doi: 10.1016/j.jtcvs.2010.04.043

35. Gorlinger K, Pérez-Ferrer A, Dirkmann D, Saner F, Maegele M, Pérez Calatayud AA, et al. The role of evidence-based algorithms for rotational thromboelastometry-guided bleeding management. *Korean J Anesthesiol.* (2019) 72:297–322. doi: 10.4097/kja.19169

36. Davidson SJ, McGrowder D, Roughton M, Kelleher AA. Can ROTEM thromboelastometry predict postoperative bleeding after cardiac surgery? *J Cardiothorac Vasc Anesth.* (2008) 22:655–61. doi: 10.1053/j.jvca.2008.07.002

37. Lee GC, Kicza AM, Liu KY, Nyman CB, Kaufman RM, Body SC. Does rotational thromboelastometry (ROTEM) improve prediction of bleeding after cardiac surgery? *Anesth Analg.* (2012) 115:499–506. doi: 10.1213/ANE.0b013e31825e7c39

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Use of the cardiopulmonary coupling index based on refined composite multiscale entropy for prognostication of acute type A aortic dissection

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Objectives: The aim of this study is to assess the influence of cardiopulmonary coupling (CPC) based on RCMSE on the prediction of complications and death in patients with acute type A aortic dissection (ATAAD).
Background: The cardiopulmonary system may be nonlinearly regulated, and its coupling relationship with postoperative risk stratification in ATAAD patients has not been studied.
Methods: This study was a single-center, prospective cohort study (ChiCTR1800018319). We enrolled 39 patients with ATAAD. The outcomes were in-hospital complications and all-cause readmission or death at 2 years.
Results: Of the 39 participants, 16 (41.0%) developed complications in the hospital, and 15 (38.5%) died or were readmitted to the hospital during the two-year follow-up. When CPC-RCMSE was used to predict in-hospital complications in ATAAD patients, the AUC was 0.853 ($p < 0.001$). When CPC-RCMSE was used to predict all-cause readmission or death at 2 years, the AUC was 0.731 ($p < 0.05$). After adjusting for age, sex, ventilator support (days), and special care time (days), CPC-RCMSE remained an independent predictor of in-hospital complications in patients with ATAAD [adjusted OR: 0.8 (95% CI, 0.68–0.94)].
Conclusion: CPC-RCMSE was an independent predictor of in-hospital complications and all-cause readmission or death in patients with ATAAD.

KEYWORDS
cardiopulmonary coupling, acute type a aortic dissection, prognostication, composite multiscale entropy, risk stratification

1. Introduction

Acute type A aortic dissection (ATAAD) is a cardiovascular emergency disease that can kill 1%–2% of untreated patients every hour following the onset of symptoms (1). Despite timely emergency and essential surgery in the hospital, the in-hospital mortality and complications of patients with acute aortic dissection are still high. Fortunately, thanks to advances in surgical technology and improvements in perioperative care, mortality has decreased over the past decade to 12% (2). Therefore, it is necessary to improve risk prediction for patients with a high risk of complications and death to make timely and appropriate interventions.

The concept of cardiopulmonary coupling (CPC) was advocated in 2005 (3). CPC is now a technique that can reflect the function of cardiopulmonary system action relation and coupling strength by calculating the cross-spectral power and coherence of respiratory tidal volume fluctuations and heart rate variability (HRV) (4). It may provide information on the quantitative presentation of a person's manifestations of cardiovascular autonomic nervous function.

Since the cardiopulmonary system may be regulated in a nonlinear way, a new coupling analysis technique is needed. In recent years, the multiscale entropy (MSE) algorithm has gained massive attention, especially in the cardiovascular and physiological fields (5). Norris et al. found that heart rate (HR) MSE within hours of admission predicted mortality occurring later in 3,154 trauma patients (6). Many studies have shown that MSE is a method that can be used to generate novel clinical prognostic biomarkers.

No known research has focused on exploring the relationship between the definition of CPC based on MSE and the complications and deaths of patients with ATAAD. Therefore, we propose the following hypotheses: the cardiopulmonary coupling index based on refined composite multiscale entropy (CPC-RCMSE) can be used for successful risk stratification in ATAAD patients.

2. Methods

2.1. Study design

This was a prospective cohort study involving all patients after aortic dissection at the First Affiliated Hospital of Wenzhou Medical University from September 2018 through September 2020 (ChiCTR1800018319). The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University.

The inclusion criteria were as follows: (1) patients aged 18–65 years; (2) patients who met the diagnostic criteria for acute type A aortic dissection and underwent surgery; and (3) patients or family members who voluntarily participated in the trial and signed informed consent. The exclusion criteria were as follows: (1) patients with chest and back deformity (including appearance and organic); (2) pacing patients; (3) patients with an ECG signal quality not up to standard; (4) patients in the terminal stage of chronic wasting disease; (5) patients in persistent coma; and (6) pregnant or nursing women.

2.2. CPC-RCMSE definitions

Electrocardiograph signals and respiratory waveforms were collected for more than 4 h on the first day after returning to the cardiac care unit. The CPC-RCMSE formula was described previously (7).

2.3. Primary outcome

The main end point was the occurrence of death, acute liver failure, acute renal failure, or ventilator-associated pneumonia composite end events in the hospital. The secondary endpoint was all-cause readmission or death at 2 years.

2.3.1. Statistical analysis

Continuous variables are expressed as the mean ± standard deviation (SD). Categorical variables are expressed as the number (percentage). Groups of continuous variables were compared using Student's t test or the Mann-Whitney U test, and groups of categorical variables were compared using the χ^2 test or Fisher's exact test.

Univariate logistic regression analysis was used to investigate the independent risk factors for the compound endpoint of complications in the hospital in patients with ATAAD. All variables significantly associated with in-hospital mortality were candidate variables in the stepwise multivariate analysis. Based on the results of the multivariate logistic regression analysis, we explored whether CPC-RCMSE is an independent predictor of complications in the hospital. A receiver operating characteristic (ROC) curve for CPC-RCMSE was generated. Survival curves were described by the Kaplan-Meier method and compared by the log-rank test. Statistical analyses were performed by SPSS 25.0 statistical software (SPSS Company, Chicago, IL) and the R language tool. In all analyses, $p < 0.05$ was statistically significant.

3. Results

3.1. Baseline characteristics

In this study, patients with aortic dissection were selected. The results are presented in **Table 1**. The average age of the study population was 53.6 ± 10.4 years. A total of 84.6% of the participants were male, 69.2% had hypertension, 16 (41.0%) developed complications in the hospital, and 15 (38.5%) died or were readmitted to the hospital during the two-year follow-up.

3.1.1. Independent prognostic factors

The univariate logistic analysis results are shown in **Table 2**. According to multivariate analysis, CPC-RCMSE was independently associated with in-hospital complications. After adjusting for age, sex, ventilator support (days), and special care time (days), CPC-RCMSE remained an independent predictor of in-hospital complications in patients with ATAAD [adjusted OR: 0.8 (95% CI, 0.68–0.94)]. In Model 2, CPC-RCMSE remained an independent risk factor for in-hospital complications after adjusting for age, sex, ventilator duration, special care time, cardioactive drugs, and vasoactive drugs [adjusted OR: 0.77 (95% CI, 0.63–0.95), $p < 0.05$].

3.2. ROC curve

As shown in **Figure 1**, when CPC-RCMSE was used to predict in-hospital complications in ATAAD patients, the AUC

TABLE 1 Baseline characteristics of aortic dissection patients.

Variable	CPC-RCMSE			*p*-value
	T1 < 19.71 (*n* = 13)	T2 ≥ 20.69 to <29.91 (*n* = 13)	T3 ≥ 30.03 to <37.35 (*n* = 13)	
Age	56.15 ± 9.44	52.85 ± 9.93	51.77 ± 11.89	0.544
Male	11 (84.62%)	12 (92.31%)	10 (76.92%)	0.855
Hypertension	9 (69.23%)	10 (76.92%)	8 (61.54%)	0.697
Diabetes	0 (0.00%)	1 (7.69%)	0 (0.00%)	1.000
Smoking	5 (38.46%)	7 (53.85%)	4 (30.77%)	0.476
Drinking	5 (38.46%)	6 (46.15%)	3 (23.08%)	0.458
Coronary heart disease	1 (8.33%)	1 (7.69%)	0 (0.00%)	0.760
Chest pain	10 (76.92%)	10 (76.92%)	11 (84.62%)	1.000
Back pain	7 (53.85%)	7 (53.85%)	9 (69.23%)	0.654
Osphyalgia	5 (38.46%)	3 (23.08%)	3 (23.08%)	0.603
Abdominal pain	3 (23.08%)	1 (7.69%)	0 (0.00%)	0.297
Ventilator support (days)	140.08 ± 143.19	71.69 ± 73.48	51.15 ± 35.40	0.102
Extracorporeal circulation time (min)	258.08 ± 41.32	270.85 ± 30.57	264.31 ± 61.60	0.579
Aortic cross clamp time (min)	158.46 ± 43.37	172.46 ± 37.68	182.54 ± 52.91	0.460
Admission SBP	132.62 ± 24.23	136.69 ± 17.68	141.69 ± 23.99	0.702
Admission DBP	71.23 ± 13.91	71.54 ± 21.66	74.38 ± 17.93	0.852
Postoperative SBP	130.31 ± 31.14	129.54 ± 26.77	139.00 ± 22.91	0.643
Postoperative DBP	70.08 ± 14.82	69.54 ± 10.44	72.69 ± 13.16	0.842
Postoperative mean arterial pressure	92.54 ± 21.22	89.08 ± 16.24	95.69 ± 16.47	0.653
LVEF (%)	61.55 ± 7.31	64.94 ± 5.82	63.73 ± 5.59	0.332
Hypothermic circulatory arrest (min)	26.69 ± 3.61	29.08 ± 7.01	29.54 ± 5.01	0.380
Special care time (days)	11.00 ± 8.42	7.92 ± 4.52	7.62 ± 4.43	0.501
Preoperative heart failure	1 (7.69%)	0 (0.00%)	1 (7.69%)	1.000
Preoperative pleural effusion	1 (7.69%)	4 (30.77%)	1 (7.69%)	0.321
Preoperative pericardial effusion	3 (23.08%)	2 (15.38%)	1 (7.69%)	0.855
Norepinephrine/dopamine	4 (30.77%)	3 (23.08%)	1 (7.69%)	0.477
Vascular Drug	8 (61.54%)	8 (61.54%)	8 (61.54%)	1.000
ACE inhibitor	0 (0.00%)	0 (0.00%)	1 (7.69%)	1.000
Calcium channel blocker	3 (23.08%)	4 (30.77%)	3 (23.08%)	0.874
Beta blocker	2 (15.38%)	4 (30.77%)	2 (15.38%)	0.689
Postoperative pericardial effusion				0.648
0	12 (92.31%)	10 (76.92%)	9 (69.23%)	
1	1 (7.69%)	2 (15.38%)	2 (15.38%)	
2	0 (0.00%)	1 (7.69%)	2 (15.38%)	
Postoperative pleural effusion				0.081
0	2 (15.38%)	0 (0.00%)	0 (0.00%)	
1	4 (30.77%)	8 (61.54%)	3 (23.08%)	
2	7 (53.85%)	5 (38.46%)	10 (76.92%)	
Hospital days	24.23 ± 7.58	21.31 ± 9.06	21.46 ± 7.42	0.267
In-hospital complications	11 (84.62%)	3 (23.08%)	2 (15.38%)	<0.001
Death	2 (15.38%)	1 (7.69%)	0 (0.00%)	0.760
Readmission	9 (69.23%)	2 (15.38%)	3 (23.08%)	0.008
Cardiac readmission	5 (38.46%)	0 (0.00%)	0 (0.00%)	0.003
All-cause readmissions and deaths	9 (69.23%)	3 (23.08%)	3 (23.08%)	0.020

LVEF, left ventricular ejection fraction; Vascular Drug, sodium nitroprusside/urapidil/lyceryl trinitrate; In-hospital complications included acute renal failure, acute liver failure, respiratory failure, pulmonary infection and death.

was 0.853 ($p < 0.001$). When CPC-RCMSE was used to predict all-cause readmission or death at 2 years, the AUC was 0.731 ($p < 0.05$).

3.3. Kaplan–Meier survival

As shown in **Figure 2**, the Kaplan-Meier curves showed significant survival outcomes for all-cause readmission or death at 2 years by CPC-RCMSE score. In patients with a higher CPC-RCMSE score, survival was better ($p < 0.0001$).

4. Discussion

In reviewing the literature, no data were found on the association between CPC-RCMSE and prognosis in ATAAD patients who have undergone surgery. Our findings highlight the

TABLE 2 Association of CPC-RCMSE with in-hospital complications.

Clinical variables	Univariate analysis		Model 1		Model 2	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age	1.04 (0.98–1.11)	0.19	0.98 (0.85–1.13)	0.79	0.98 (0.86, 1.12)	0.79
Male	0.10 (0.01–0.96)	<0.05	0.08 (0.00–4.32)	0.21	0.04 (0.00, 20.03)	0.30
Hypertension	0.96 (0.24–3.83)	0.96	–	–	–	–
Smoking	0.49 (0.13–1.89)	0.30	–	–	–	–
Drinking	0.71 (0.18–2.72)	0.61	–	–	–	–
Chest pain	0.63 (0.13–3.01)	0.56	–	–	–	–
Back pain	0.53 (0.14–1.96)	0.34	–	–	–	–
Osphyalgia	2.16 (0.52–8.90)	0.29	–	–	–	–
Abdominal pain	5.08 (0.48–54.03)	0.18	–	–	–	–
Ventilator support (days)†	5.10 (1.72–15.11)	<0.05	3.40 (0.67–17.22)	0.14	4.31 (0.61, 30.41)	0.14
Extracorporeal circulation time†	2.17 (0.06–82.94)	0.68	–	–	–	–
Aortic cross clamp time†	0.14 (0.01–1.81)	0.13	–	–	–	–
Admission SBP	0.99 (0.96–1.02)	0.71	–	–	–	–
Admission DBP	0.99 (0.95–1.03)	0.65	–	–	–	–
Postoperative DBP	1.00 (0.95–1.06)	0.86	–	–	–	–
LVEF†	0.58 (0.00–312.26)	0.87	–	–	–	–
Hypothermic circulatory arrest†	0.03 (0.00–1.63)	0.09	–	–	–	–
Special care time (days)†	8.67 (1.76–42.67)	<0.05	8.11 (0.55–120.46)	0.13	9.64 (0.56,164.44)	0.12
Preoperative heart failure	1.47 (0.08–25.32)	0.79	–	–	–	–
Preoperative pleural effusion	0.24 (0.02–2.58)	0.21	–	–	–	–
Preoperative pericardial effusion	1.54 (0.27–8.82)	0.63	–	–	–	–
Norepinephrine/dopamine	1.58 (0.33–7.56)	0.56	–	–	0.09 (0.00, 6.93)	0.27
Vascular Drug	0.68 (0.18–2.54)	0.57	–	–	0.38 (0.02, 8.79)	0.55
Calcium channel blocker	1.64 (0.38–6.97)	0.50	–	–	–	–
Beta blocker	0.40 (0.07–2.33)	0.31	–	–	–	–
CPC-RCMSE	0.82 (0.73–0.92)	<0.05	0.80 (0.68–0.94)	<0.05	0.77 (0.63, 0.95)	<0.05

Abbreviations as in Tables 1. †Log-transformed.
Model 1 was adjusted for age, Male, Ventilator support (days) †, Special care time (days) †,.
Model 2 was adjusted for age, Male, Ventilator support (days) †, Special care time (days) †, Vascular Drug, Norepinephrine/dopamine.

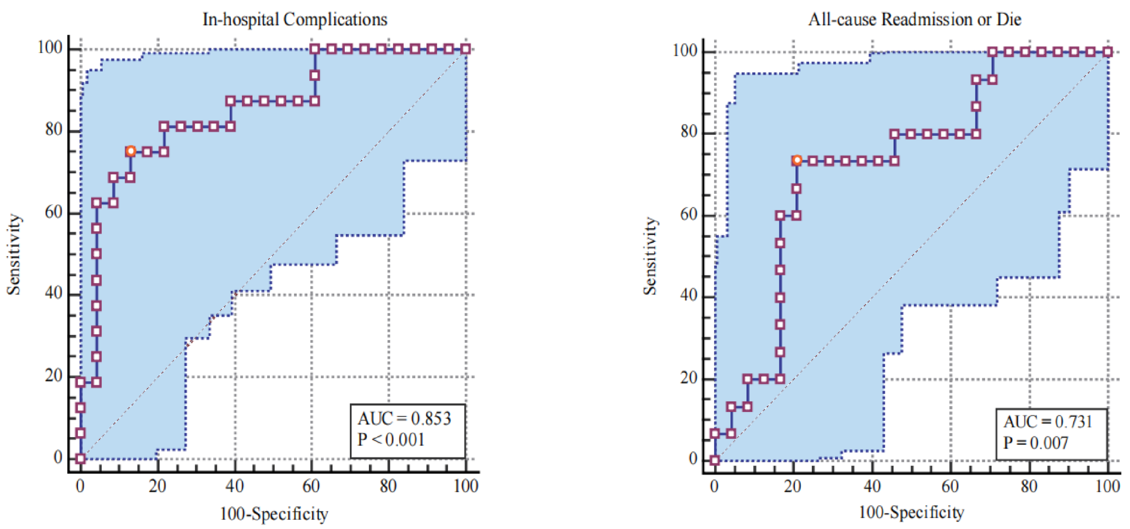

FIGURE 1
Receiving operating characteristic curves and corresponding AUCs for CPC-RCMSE.

prognostic importance for ATAAD. As expected, patients in the highest quintile of CPC-RCMSE had better outcomes. When CPC-RCMSE was used to predict the occurrence of postoperative complications in ATAAD patients, the AUC was 0.853 ($p <$ 0.001), indicating that CPC-RCMSE had a good ability to predict the occurrence of complications in the hospital. When CPC complexity was ≤21.2, the sensitivity was 75%, and the specificity was 86.7%. When CPC complexity was used to predict

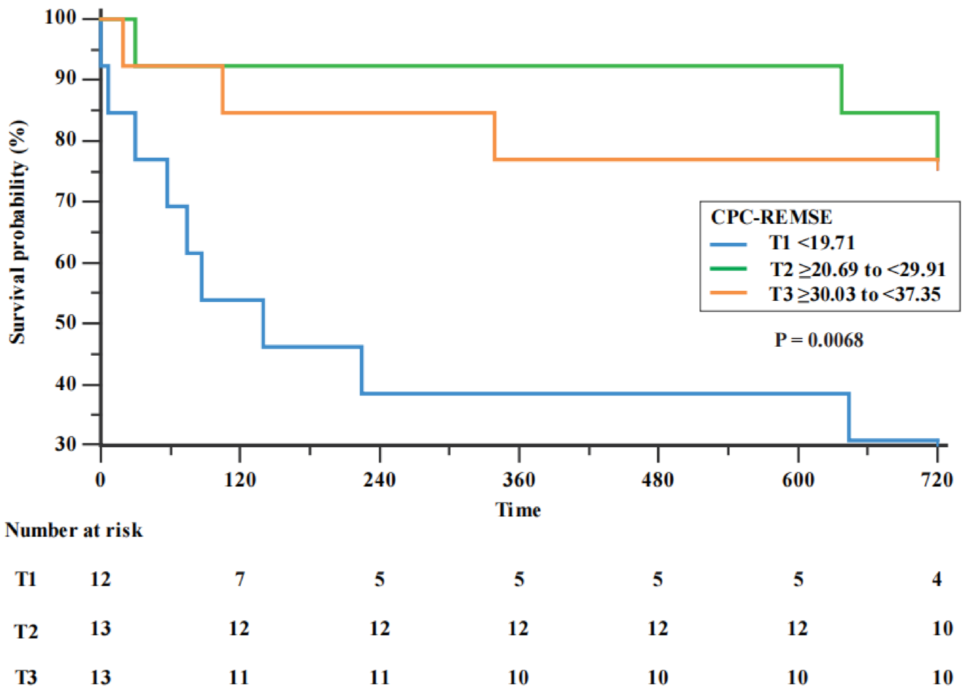

FIGURE 2
Kaplan–Meier survival by stage of CPC-RCMSE.

readmission and death, the AUC was 0.731 ($p < 0.05$), also indicating good differentiation ability. The results of multivariate analysis indicate the clinical prediction and risk stratification value of CPC-RCMSE.

CPC (3) is based on continuous ECG signals and uses Fourier transform technology to analyze two characteristics of the signal: (1) heart rate variation and (2) the fluctuation of ECG R wave amplitude caused by respiration. From a physiological point of view, CPC can identify the bistable properties of automatic NREM sleep state transitions. One state shows deep sleep features, and the other state exhibits shallow sleep features. Many studies (8, 9) have reported its clinical significance, such as the 24-hour Holter-based CPC analysis (10), which showed that the recurrence rate was lower in atrial fibrillation patients who had unstable sleep before radiofrequency ablation (HR: 0.32; 95% CI, 0.12–0.83).

The cardiopulmonary system likely performs complex regulation in a nonlinear manner. The development of nonlinear dynamics and information theory has made new progress in the study of information transmission among multivariate time series and can complement traditional linear symmetry analysis technology to provide more diagnostic and prognostic information (11, 12). Costa et al. (13) proposed an MSE algorithm to calculate SampEn over a certain scale to represent the complexity of a time series. Pilatia et al. (14) described the application of the MSE algorithm to cardiopulmonary coupling. In our study, we used new algorithms. The RCMSE algorithm reduces the chance of generating indefinite entropy and is more suitable for the application of short time series analysis, such as physiological time series (7). Our study provide evidence for CPC-RCMSE on the prediction of complications and death in patients with ATAAD. Notably, many algorithms have proved to have advantages in the analysis of physiological signals in different study population. In terms of Congestive Heart Failure patients, Liu C et al. (15) determined the differential RR interval time series signal (MSE_dRR) had better statistical stability and better discrimination. Azami H. et al. (16) points out that Refined Composite Dispersion Entropy (RCMDE) increased ability to find differences between physiological signs better than RCMSE. However, the above algorithm has not been tested in ATAAD patients. For this reason, we expect compare the advantages and disadvantages of different algorithms in ATAAD patients with larger samples in future studies.

The results of our study indicated that CPC-RCMSE was an independent risk factor for ATAAD. ATAAD patients were divided into three groups according to their CPC-RCMSE ($T1 < 19.71$; $T2 \geq 20.69$ to <29.91; $T3 \geq 30.03$ to <37.35). The Kaplan-Meier curves showed significant survival outcomes for all-cause readmission or death at 2 years by CPC-RCMSE score. In patients with lower CPC-RCMSE scores, survival was worse ($p < 0.0001$).

Additionally, we found that CPC-RCMSE was a strong independent predictor associated with in-hospital complications in our study population. When CPC complexity increased by 1 unit, the risk of hospital complications decreased by 20%. Clinical health care workers can be more targeted in meeting patient needs based on CPC-RCMSE scores to improve medical efficiency, shorten hospital stay, reduce care unit costs, and improve patient hospitalization outcomes.

5. Conclusions

CPC-RCMSE is an independent predictor of in-hospital complications in patients with ATAAD. CPC-RCMSE should be used more widely and routinely in the risk stratification of ATAAD patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Human Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Mao Z-J and Wen W-W: wrote the first draft of the manuscript. Han Y-C, Shen L-j and Dong W-h: performed data collection and follow-up. Mao Z-J and Xie Q-L contributed to the study design. Huang Z-Q and Xie Q-L guided the subsequent revisions of this article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Gawinecka J, Schönrath F, von Eckardstein A. Acute aortic dissection: pathogenesis, risk factors and diagnosis. *Swiss Med Wkly.* (2017) 147:w14489. doi: 10.4414/smw.2017.14489

2. Conway BD, Stamou SC, Kouchoukos NT, Lobdell KW, Khabbaz KR, Murphy E, et al. Improved clinical outcomes and survival following repair of acute type A aortic dissection in the current era. *Interact Cardiovasc Thorac Surg.* (2014) 19:971–6. doi: 10.1093/icvts/ivu268

3. Thomas RJ, Mietus JE, Peng CK, Goldberger AL. An electrocardiogram-based technique to assess cardiopulmonary coupling during sleep. *Sleep.* (2005) 28:1151–61. doi: 10.1093/sleep/28.9.1151

4. Lu M, Penzel T, Thomas RJ. Cardiopulmonary coupling. *Adv Exp Med Biol.* (2022) 1384:185–204. doi: 10.1007/978-3-031-06413-5_11

5. Thuraisingham RA, Gottwald GA. On multiscale entropy analysis for physiological data. *Phys A: Stat Mech Appl.* (2006) 366:323–32. doi: 10.1016/j.physa.2005.10.008

6. Riordan WP Jr, Norris PR, Jenkins JM, Morris JA Jr. Early loss of heart rate complexity predicts mortality regardless of mechanism, anatomic location, or severity of injury in 2178 trauma patients. *J Surg Res.* (2009) 156:283–9. doi: 10.1016/j.jss.2009.03.086

7. Wu S-D, Wu C-W, Lin S-G, Lee K-Y, Peng C-K. Analysis of complex time series using refined composite multiscale entropy. *Phys Lett A.* (2014) 378:1369–74. doi: 10.1016/j.physleta.2014.03.034

8. Sun QM, Xing L, Wang C, Liang W. Cardiopulmonary coupling analysis predicts early treatment response in depressed patients: a pilot study. *Psychiatry Res.* (2019) 276:6–11. doi: 10.1016/j.psychres.2019.04.002

9. Choi JH, Thomas RJ, Suh SY, Park IH, Kim TH, Lee SH, et al. Sleep quality change after upper airway surgery in obstructive sleep apnea: electrocardiogram-based cardiopulmonary coupling analysis. *Laryngoscope.* (2015) 125:1737–42. doi: 10.1002/lary.25101

10. Kim W, Na JO, Thomas RJ, Jang WY, Kang DO, Park Y, et al. Impact of catheter ablation on sleep quality and relationship between sleep stability and recurrence of paroxysmal atrial fibrillation after successful ablation: 24-hour holter-based cardiopulmonary coupling analysis. *J Am Heart Assoc.* (2020) 9:e017016. doi: 10.1161/JAHA.120.017016

11. Pincus SM. Approximate entropy as a measure of system complexity. *Proc Natl Acad Sci U S A.* (1991) 88:2297–301. doi: 10.1073/pnas.88.6.2297

12. Metin Akay. "Nonlinear Behavior of Heart Rate Variability as Registered after Heart Transplantation," in Nonlinear Biomedical Signal Processing, Dynamic Analysis and Modeling, IEEE, 2000, pp. 133–158, doi: 10.1109/9780470545379.ch5

13. Costa M, Goldberger AL, Peng CK. Multiscale entropy analysis of complex physiologic time series. *Phys Rev Lett.* (2002) 89:068102. doi: 10.1103/PhysRevLett.89.068102

14. Platiša MM, Radovanović NN, Kalauzi A, Milašinović G, Pavlović SU. Multiscale entropy analysis: application to cardio-respiratory coupling. *Entropy (Basel, Switzerland)* (2020) 22(9):1042. doi: 10.3390/e22091042

15. Liu C, Gao R. Multiscale entropy analysis of the differential RR interval time series signal and its application in detecting congestive heart failure. *Entropy.* (2017) 19:251. doi: 10.3390/e19060251

16. Azami H, Rostaghi M, Abasolo D, Escudero J. Refined composite multiscale dispersion entropy and its application to biomedical signals. *IEEE Trans Biomed Eng.* (2017) 64:2872–9. doi: 10.1109/TBME.2017.2679136

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Is valve-sparing aortic root replacement better than total aortic root replacement? An overview of reviews

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Background: Total aortic root replacement (TRR) is certainly beneficial for aortic root disease, but does it still have an advantageous prognosis for patients compared to valve-sparing aortic root replacement (VSRR)? An overview of reviews was conducted to assess each of their clinical efficacy/effectiveness.
Review methods: Systematic reviews (SRs)/Meta-analyses comparing the prognosis of TRR and VSRR in aortic root surgery were collected from 4 databases, all searched from the time of database creation to October 2022. Two evaluators independently screened the literature, extracted information and applied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) tool, Grading of Recommendations, Assessment, Development and Evaluations (GRADE), and Risk of Bias in Systematic Reviews (ROBIS) to evaluate the quality of reporting, methodological quality, risk of bias, and level of evidence of the included studies.
Main results: A total of 9 SRs/Meta-analyses were ultimately included. In terms of the reporting quality of the included studies, PRISMA scores ranged from 14 to 22.5, with issues mainly in reporting bias assessment, risk of study bias, credibility of evidence, protocol and registration, and funding sources. The methodological quality of the included SRs/Meta-analyses was generally low, with key items 2, 7, and 13 having major flaws and non-key items 10, 12, and 16. In terms of risk of bias assessment, the overall assessment of the included 9 studies was high-risk. The quality of the evidence was rated as low to very low quality for the three outcome indicators selected for the GRADE quality of evidence rating: early (within 30 days postoperatively or during hospitalization) mortality, late mortality, and valve reintervention rate.
Conclusions: VSRR has many benefits including reduced early and late mortality after aortic root surgery and reduced rates of valve-related adverse events, but the methodological quality of the relevant studies is low, and there is a lack of high-quality evidence to support this.
Systematic Review Registration: https://www.PROSPERO, identifier: CRD42022381330.

KEYWORDS
total aortic root replacement, valve-sparing aortic root replacement, aortic surgery, overview of reviews, systematic reviews

1. Introduction

TRR using a composite mechanical valve, as proposed by Bentall and De Bono in 1968 (1), has been a boon to many patients requiring surgery for aortic root disease. For more than 50 years, it has long been considered the "gold procedure" for aortic root disease, particularly type A aortic dissection and Marfan syndrome, because of its excellent early and late postoperative results (2, 3). However, the implementation of a mechanical prosthesis exposes patients to a cumulative risk of lifelong anticoagulation, hemodynamic restrictions, and an increased risk of thromboembolism. Even though bio-prosthesis implantation can minimize these risks, re-intervention would be an undesired result of bio-prosthesis degeneration (4–6).

Although TRR is the most common procedure performed during surgery for aortic root disease, the optimal management of the aortic valve at the time of root surgery remains highly controversial. The benefit of preserving the native aortic valve, particularly in some young patients with good aortic valve pathology, has been remarkable. This controversy has become more intense since the introduction of the reimplantation technique by David in 1992 (7) and the remodeling technique by Yacoub in 1983 (8). The superior early outcome, lower late cardiac-related mortality, and valve-related complications of VSRR have led to a strong preference (6, 9, 10). Because VSRR is so challenging, most studies have come from specialist cardiac centers. Some argue that the more technically demanding VSRR has a proportionally increased complication and mortality rate, both intraoperatively and postoperatively. In this way, the prognosis of patients who undergo VSRR is not necessarily better than those who opt for a composite mechanical or biological valve for TRR (11).

A large number of studies exist that have explored the early and late mortality and complications of TRR and VSRR, and several SRs/Meta-analyses have been published based on this. However, there is considerable heterogeneity in the original studies included in the various SRs/Meta-analyses in terms of year of publication, sample size, interventions/controls, and outcome indicators. In particular, the inconsistency of postoperative complication rates across different research has largely limited the application and dissemination of evidence-based evidence in clinical practice. Overview of reviews (Overviews) is a comprehensive approach to collecting systematic reviews on the etiology diagnosis, treatment, and prognosis of the same disease or health problem and conducting a comprehensive study (12). And this article aims to analyze the current published SRs/Meta-analyses on the prognosis of TRR compared to VSRR and provide a basis for clinical selection.

2. Materials and methods

The protocol for this overview was registered on PROSPERO (CRD42022381330) and is accessible on the PROSPERO website (https://www.crd.york.ac.uk/prospero/). The reporting of this overview of reviews adheres to the PRISMA 2020 criteria (13).

2.1. Search and study selection

PubMed, Embase, Web of science, and China National Knowledge Infrastructure (CNKI) databases were searched to collect SRs/Meta-analyses comparing survival, mortality, complications, and reoperation rates after VSRR versus TRR, all searched from the time of database creation to October 2022. In addition, references to the included literature were retrospectively included to supplement access to relevant literature. Searches were conducted using a combination of subject terms and free words. Terms include aortic valve-sparing, aortic valve preservation, aortic valve repair, aortic valve-sparing, VSRR, David procedure, remodeling, Yacoub, reimplantation, Bentall procedure, composite valve graft, valved conduit, CVG, total root replacement, aortic valve replacement, systematic review, meta-analysis, etc. The specific search strategy for PubMed, for example, is shown in Table 1.

2.2. Inclusion and exclusion criteria

SRs/Meta-analyses were included if:

(i) Review of studies on the clinical outcomes of TRR and VSRR.
(ii) Research into aortic root diseases, including but not limited to aortic dissection and Marfan syndrome.
(iii) Primary outcome indicators include early mortality (within 30 days of surgery or during hospitalization), mortality during follow-up, reoperation rates, thromboembolic events, endocarditis, and bleeding associated with aortic root and aortic valve lesions.

SRs/Meta-analyses were excluded if:

(i) Reviews, conference abstracts, case reports, and letters.

TABLE 1 The search strategy using pubmed as an example.

SET	QUERY
#1	aortic valve-preserving [Title/Abstract]
#2	aortic valve preservation [Title/Abstract]
#3	aortic valve repair [Title/Abstract]
#4	aortic valve-sparing [Title/Abstract]
#5	VSRR [Title/Abstract]
#6	David procedure [Title/Abstract]
#7	remoulding [Title/Abstract]
#8	remodeling [Title/Abstract]
#9	reimplantation [Title/Abstract]
#10	Yacoub [Title/Abstract]
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12	Bentall procedure [Title/Abstract]
#13	composite valve graft [Title/Abstract]
#14	valved conduit [Title/Abstract]
#15	CVG [Title/Abstract]
#16	total root replacement [Title/Abstract]
#17	aortic valve replacement [Title/Abstract]
#18	#12 OR #13 OR #14 OR #15 OR #16 OR #17
#19	#11 AND #18
#20	"Meta-Analysis as Topic" [Mesh]OR"Meta-Analysis"[Publication Type]
#21	meta analysis[Title/Abstract] OR meta analyses[Title/Abstract] OR meta-analysis[Title/Abstract] OR meta-analyses[Title/Abstract] OR metaanalysis [Title/Abstract] OR metanalysis[Title/Abstract] OR met-analysis[Title/Abstract]OR meta analyses[Title/Abstract]OR metanalyses[Title/Abstract] OR met-analyses[Title/Abstract] OR data pooling[Title/Abstract]OR data poolings[Title/Abstract]
#22	#20 OR #21
#23	systematic review[Title/Abstract] OR systematic reviews[Title/Abstract]
#24	#22 OR #23
#25	#19 AND #24

(ii) Duplicate publications or overlapping studies included.
(iii) Literature for which data could not be extracted or full text was not available.
(iv) Currently incomplete SRs/Meta-analyses.

2.3. Literature screening and data extraction

Two evaluators independently screened the literature, extracted information, and cross-checked it, consulting a third person to assist with any disagreements and contacting the authors to supplement any missing information where possible. The literature was screened by first reading the title and abstract and then, after excluding any irrelevant literature, further reading the full text to determine final inclusion. If multiple SRs/Meta-analyses existed for the same group of researchers, those with a relatively recent year of publication and containing more complete studies were selected for inclusion. Data extraction included the following: first author and year of publication, number of included studies, sample size, interventions, risk of bias assessment tools used, outcome indicators, PRISMA score (14) results, AMSTAR 2 (15) evaluation results and funding sources.

2.4. Assessment of included reviews

All of the evaluation methods were assessed independently by two researchers and then summarized. Any inconsistencies were resolved by consensus or by third-author adjudication.

2.4.1. Reporting quality

The PRISMA Statement (14) evaluates the quality of the reports included in the study using a total of 27 items, with each item being scored 1 for complete reporting, 0.5 for partial reporting, and 0 for no reporting, out of a total of 27 points, with a score of <15 being considered a relatively serious information deficiency in the systematic evaluation report, a score of 15–21 being considered some deficiency in the report, and a score of 21 or more being considered a relatively complete report. The PRISMA statement indicates that a report with a completeness level of <50% for each item is considered to be deficient.

2.4.2. Methodological quality

The AMSTAR 2 (15) scale was used to evaluate the methodological quality of the included studies. The scale contains 16 items, of which items 2, 4, 7, 9, 11, 13, and 15 are key items, and

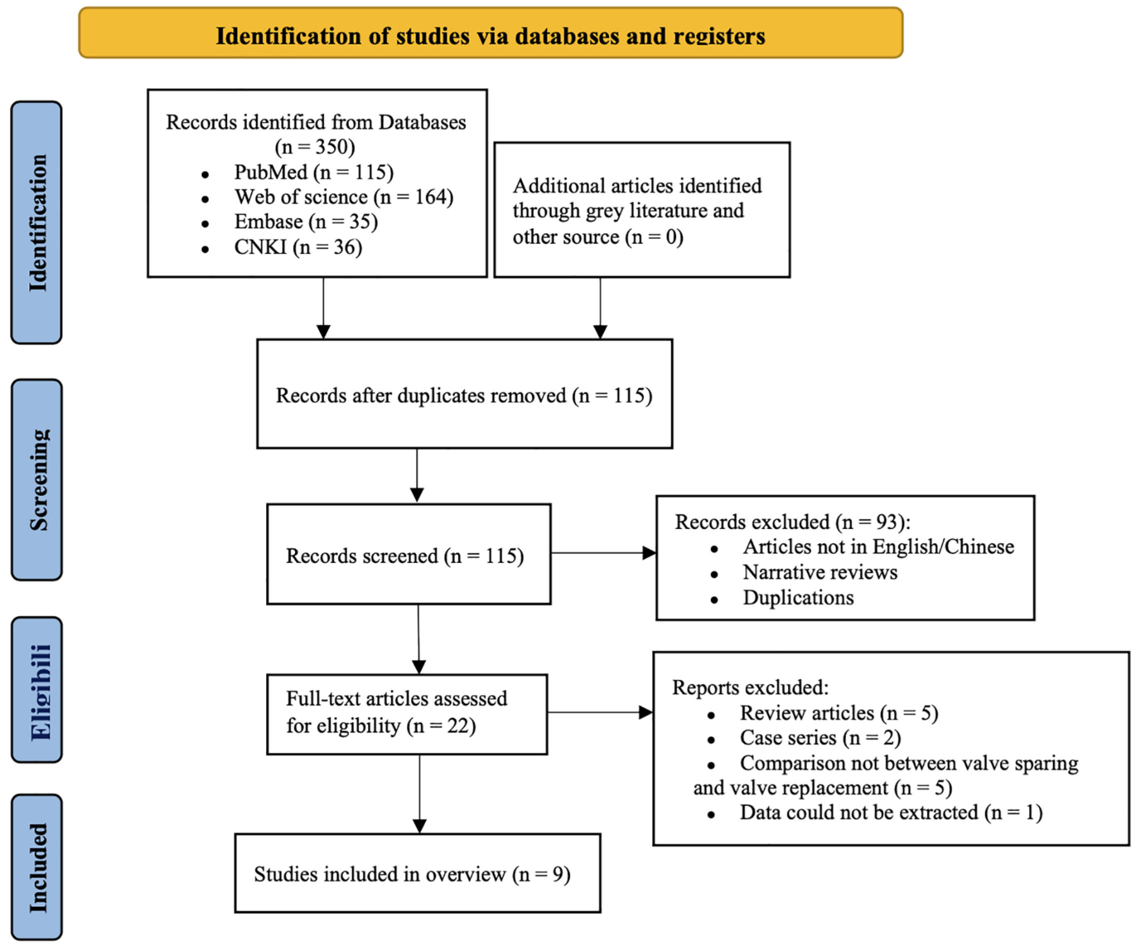

FIGURE 1
Flow diagram of the search and screening of the literature included in this study.

TABLE 2 Characteristics of the included systematic reviews and the score of PRISMA evaluation.

First author	Year	Intervention		No. of studies	Sample size	Included diseases or methods of operation	Outcomes
Soto	2021	VSRR	TRR	41	4,025	MFS and other connective tissue diseases	In-hospital and late mortality, stroke, bleeding, aortic insufficiency, endocarditis, thromboembolic events, arrhythmia, valve reintervention, freedom from valve reintervention
Burgstaller	2018	RAV	CVG	20	21,560	MFS	In-hospital deaths, mortality/survival during the follow-up period, reoperation related to aortic root and aortic valve diseases, reoperation rate because of bleeding, stroke rate, thromboembolism and pacemaker implantation during the hospital stay
Benedetto	2011	VSRR	TRR	11	13,850	MFS	Reintervention on the aortic valve, thromboembolic event, endocarditis
Elbatarny	2020	VSRR	CVG	26	6,218	Aortic root dilation	All-cause mortality, reoperation for bleeding, myocardial infarction, thromboembolism/stroke, reintervention, bleeding
Flynn	2017	VSRR	CVG	23	2,976	MFS	Endocarditis, thromboembolism, hemorrhagic complication and reoperation
Hu	2014	VSRR	TRR	7	690	MFS	Thromboembolism, endocarditis, long-term death, re-exploration, reoperation rates
Mosbahi	2018	RAV	CVG	27	3,058	Acute type A aortic dissection	In-hospital mortality, mortality/survival during the follow-up, and reoperation related to the AoR and/or aortic valve pathology during the follow-up, reoperation because of bleeding, incidence of stroke, thromboembolic events and incidence of permanent pacemaker implantation during hospital stay.
Salmasi	2019	VSRR	Bentall	34	7,313	Aortic root aneurysms	In-hospital or up to 30 days post-surgery death, incidence of complications and time spent in intensive care/hospital, survival at various intervals, rates of reintervention, echocardiographic parameters and functional class
Wu	2019	VSRR	Bentall	9	706	Acute type A aortic dissection	Early mortality, late mortality, re-exploration, thromboembolic/bleeding events, post-operative infective endocarditis and reintervention.

First author	Year	Quality assessment tool	Data-analysis method	Subgroup/ sensitivity analysis/meta-regression	Publication bias	Score of PRISMA evaluation
Soto	2021	Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria	Meta-analysis	No/No/No	No	22.5
Burgstaller	2018	Scottish Intercollegiate Guidelines Network (SIGN) Methodology checklist	Meta-analysis	No/No/Yes	Yes	18
Benedetto	2011	Not mentioned	Meta-analysis	Yes/No/Yes	No	15
Elbatarny	2020	Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria	Meta-analysis	Yes/Yes/Yes	Yes	20
Flynn	2017	Not mentioned	Meta-analysis	Yes/Yes/No	No	15
Hu	2014	Newcastle–Ottawa scale (NOS)	Meta-analysis	No/No/No	No	14

(*continued*)

TABLE 2 Continued

First author	Year	Intervention		No. of studies	Sample size	Included diseases or methods of operation	Outcomes
Mosbahi	2018	Scottish Intercollegiate Guidelines Network (SIGN) Methodology checklist	Meta-analysis	Yes/No/Yes	Possibly Yes	17.5	
Salmasi	2019	Newcastle–Ottawa scale (NOS)	Meta-analysis	Yes/No/Yes	No	20.5	
Wu	2019	Newcastle–Ottawa scale (NOS)	Meta-analysis	No/Yes/Yes	No	18.5	

RAV, reimplantation of the aortic valve; CVG, composite valve graft; TRR, total aortic root replacement; VSRR, valve sparing aortic root replacement.

the results are classified into three levels: satisfied, partially satisfied, and not satisfied. AMSTAR 2 scores of satisfied and partially satisfied ≥70% are considered to be a complete report of the items.

2.4.3. Evidence quality

GRADE (16) was used to evaluate the quality of evidence for different outcome indicators of the included studies, with downgrading factors including study limitations, inconsistency of findings, non-directness or indirectness (uncertainty about whether it is direct evidence), imprecision (insufficient precision or wide confidence intervals), and publication bias. The quality of the evidence was graded into four categories: high, moderate, low, and very low.

2.4.4. Risk of bias

The level of bias in each of the included SRs was assessed using the ROBIS tool (17), which helps to assess the level of bias in four domains: (1) eligibility criteria for each study; (2) study identification and selection; (3) data collection and study evaluation; and (4) overall synthesis and key findings. Within each domain, specific questions were used to determine the risk of bias, with bias rated as "low", "high" or "uncertain".

2.5. Data synthesis and application of software

Due to the heterogeneity between SRs, particularly between the TRR and VSRR groups, and the duplication of studies included in the individual RCTs, the selected SRs were analyzed descriptively only, rather than quantitatively synthesized. The data were summarized as percentages and frequencies for each of PRISMA, AMSTAR 2, GRADE, and ROBIS. The characteristics and results of each SR and these tools' results are presented in tables and figures using RStudio and Review Manager (RevMan).

3. Results

3.1. Literature selection and basic characteristics

The initial literature search identified 350 potential SRs/Meta-analyses. Duplicate publications were removed by filtering ($n = 235$). After screening all titles and abstracts, 93 articles were excluded and the remaining 22 articles were retrieved for further review. After screening 22 full-text articles, 13 SRs were excluded and 9 SRs/Meta-analyses (18–26) were ultimately included. The literature screening process and results are shown in **Figure 1**. The basic characteristics of the included studies are shown in **Table 2**.

3.2. Quality evaluation of the included studies

3.2.1. Reporting quality

The PRISMA (14) scores for the included studies ranged from 14 to 22.5 (**Table 2**). Of these, 1 study (23) scored 14 (reported relatively serious information deficiencies) and 7 studies (19–22, 24–26) scored ≤21 (reported some deficiencies). The PRISMA statement (14) items for which more than half of the studies were rated as "not satisfied" included: assessment of reporting bias, risk of study bias, credibility of evidence, protocol and registration, and funding source. PRISMA statement (14) items for which more than half of the studies were evaluated as "partially satisfied" included: a structured summary, inclusion/exclusion criteria, information sources, search strategy, data extraction, data items, synthesis of methods, and synthesis of results.

3.2.2. Methodological quality

The results of the AMSTAR 2 (15) evaluation showed that the methodological quality of all studies was "very low" (**Table 3**). A total of 5 items with AMSTAR 2 scores of ≥70% satisfied and partially satisfied indicated high quality. Of the 7 critical items in the AMSTAR 2 (15) quality assessment, item 2, item 7, and item 13 had significant deficiencies; the non-critical items with significant deficiencies were item 10, item 12, and item 16. The results for each item in the AMSTAR 2 quality assessment are shown in **Figure 2**.

3.2.3. Evidence quality

7 articles (18, 19, 21, 23–26) reporting early mortality were included, 3 (19, 21, 24) of which showed very low-quality evidence. 6 (18, 21–23, 25, 26) that reported late mortality, 5 (18, 21–23, 26) on valve re-intervention, and 3 (18, 21, 22) on bleeding were included, and they each showed the results of

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TABLE 3 Methodological quality assessment of included systematic reviews/meta-analyses by AMSTAR 2.

Item	First author and publication year									Compliance [n (%)]
	Soto 2021	Burgstaller 2018	Benedetto 2011	Elbatarny 2020	Flynn 2017	Hu 2014	Mosbahi 2018	Salmasi 2019	Wu 2019	
Item 1	Y	Y	Y	Y	Y	Y	Y	Y	Y	9 (100.00)
Item 2[a]	N	N	N	N	N	N	N	N	N	0 (0)
Item 3	Y	Y	Y	Y	N	N	N	N	N	4 (44.44)
Item 4[a]	PY	PY	PY	PY	PY	PY	PY	N	PY	8 (88.89)
Item 5	Y	N	N	Y	N	Y	Y	Y	N	5 (55.56)
Item 6	Y	N	N	Y	Y	N	N	Y	Y	5 (55.56)
Item 7[a]	N	N	N	N	N	N	N	N	N	0 (0)
Item 8	Y	PY	PY	PY	Y	PY	PY	PY	PY	9 (100.00)
Item 9[a]	Y	Y	N	Y	N	Y	Y	Y	Y	7 (77.78)
Item 10	Y	N	N	N	N	N	N	Y	Y	3 (33.33)
Item 11[a]	Y	Y	Y	Y	Y	Y	Y	Y	Y	9 (100.00)
Item 12	Y	Y	N	N	N	N	N	Y	N	3 (33.33)
Item 13[a]	Y	Y	N	N	N	N	N	Y	N	3 (33.33)
Item 14	Y	N	Y	Y	Y	Y	N	N	Y	6 (66.67)
Item 15[a]	Y	N	Y	N	Y	Y	N	Y	Y	6 (66.67)
Item 16	Y	N	Y	N	Y	N	N	N	N	3 (33.33)
Compliance [n (%)]	14 (87.50)	8 (50.00)	8 (50.00)	9 (56.25)	8 (50.00)	8 (50.00)	6 (37.50)	10 (62.50)	9 (56.25)	
Ranking of quality	Critical low	Critical low	Critical low	Critical low	Critical low	Critical low	Critical low	Critical low	Critical low	

[a]Critical items of AMSTAR 2; AMSTAR 2: A Measurement Tool to Assess Systematic Reviews 2; Y, yes; PY, partial yes; N, no. Item 1: did the research questions and inclusion criteria for the review include the components of population, intervention, comparison, and outcome (PICO)? Item 2: did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? Item 3: did the review authors explain their selection of the study designs for inclusion in the review? Item 4: did the review authors use a comprehensive literature search strategy? Item 5: did the review authors perform study selection in duplicate? Item 6: did the review authors perform data extraction in duplicate? Item 7: did the review authors provide a list of excluded studies and justify the exclusions? Item 8: did the review authors describe the included studies in adequate detail? Item 9: did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? Item 10: did the review authors report on the sources of funding for the studies included in the review? Item 11: if meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? Item 12: if meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? Item 13: did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? Item 14: did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? Item 15: if they performed quantitative synthesis, did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? Item 16: did the review authors report any potential sources of conflicts of interest, including any funding they received for conducting the review?.

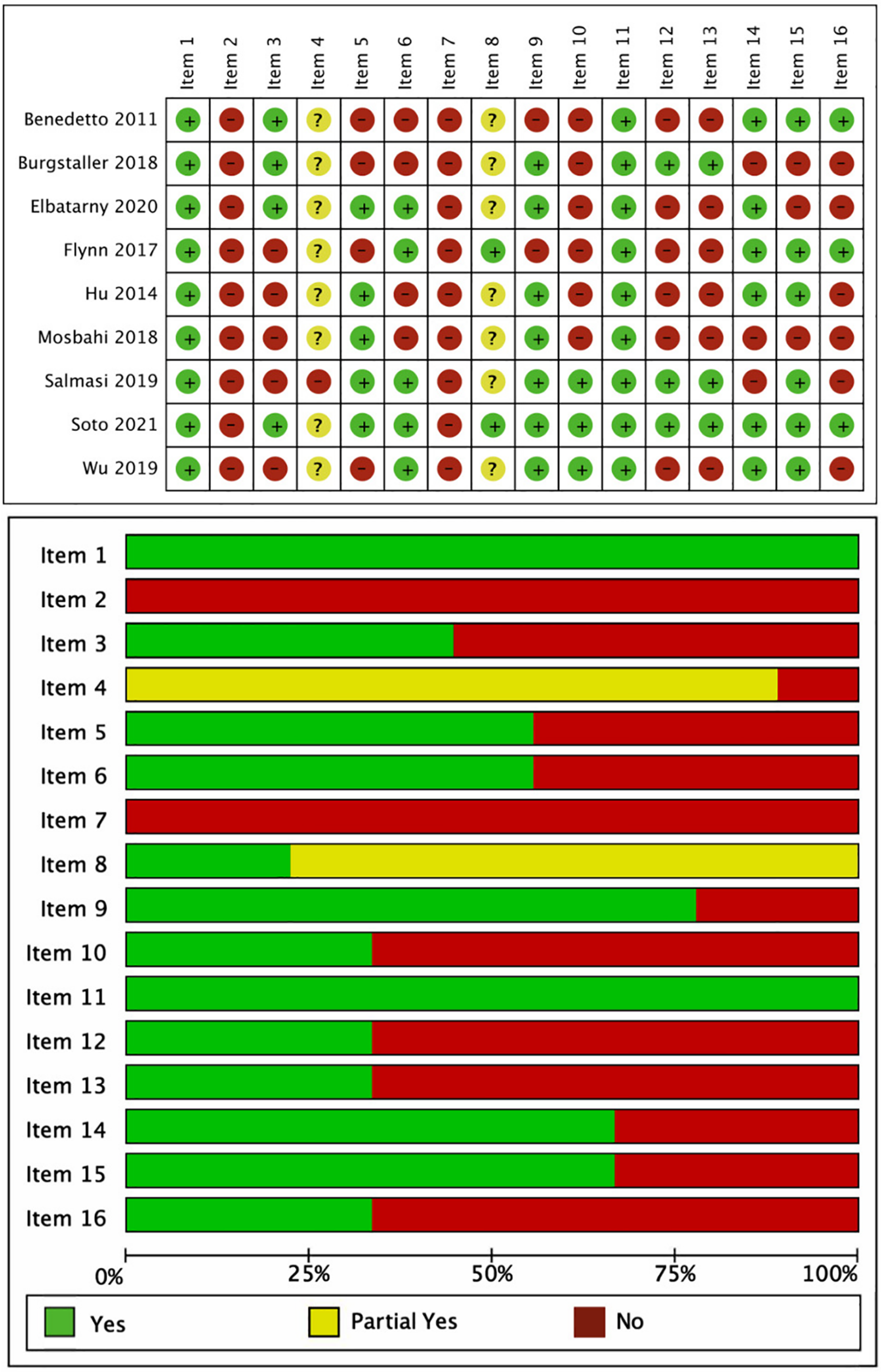

FIGURE 2
Results of the visualization quality evaluation of A Measurement Tool to Assess Systematic Reviews 2.

Elbatarny et al. (21) as very low-quality evidence. Except for the very low-quality evidence mentioned above, all were low-quality evidence. The main factors causing the downgrading of the quality of the evidence were Inconsistency, Indirectness, and Imprecision. The results are detailed in **Table 4** and **Figure 3**.

3.2.4. Risk of bias

In this overview, we did not implement the first stage of ROBIS, which was used to determine whether the proposed question and the target question matched. Using Domain-1 to assess the inclusion and exclusion criteria for each study, we found that

TABLE 4 Main results assessed by the grading of recommendations, assessment, development and evaluations.

Main results	First author/ Publication year	No. of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
Early mortality	Soto 2021	7	0	0	0	0	0	Low
	Burgstaller 2018	20	−1	0	0	0	−1	Very low
	Elbatarny 2020	26	−1	0	0	0	−1	Very low
	Hu 2014	3	0	0	0	0	0	Low
	Mosbahi 2018	27	−1	0	0	0	−1	Very low
	Salmasi 2019	33	0	0	0	0	0	Low
	Wu 2019	9	0	0	0	0	0	Low
Late mortality	Soto 2021	4	0	0	0	0	0	Low
	Elbatarny 2020	23	−1	0	0	0	−1	Very low
	Flynn 2017	8	0	0	0	0	0	Low
	Hu 2014	6	0	0	0	0	0	Low
	Salmasi 2019	24	0	0	0	0	0	Low
	Wu 2019	9	0	0	0	0	0	Low
Valve re-intervention	Soto 2021	5	0	0	0	0	0	Low
	Elbatarny 2020	26	−1	0	0	0	−1	Very low
	Flynn 2017	12	0	0	0	0	0	Low
	Hu 2014	6	0	0	0	0	0	Low
	Wu 2019	9	0	0	0	0	0	Low
Thomboembolic	Soto 2021	2	0	0	0	0	0	Low
	Flynn 2017	12	0	0	0	0	0	Low
	Hu 2014	4	0	0	0	0	0	Low
	Salmasi 2019	23	0	0	0	0	0	Low
Endocarditis	Soto 2021	3	0	0	0	0	0	Low
	Flynn 2017	11	0	0	0	0	0	Low
	Hu 2014	5	0	0	0	0	0	Low
	Wu 2019	9	0	0	0	0	0	Low
Bleeding	Soto 2021	4	0	0	0	0	0	Low
	Elbatarny 2020	9	−1	0	0	0	−1	Very low
	Flynn 2017	7	0	0	0	0	0	Low

77.8% (7/9) of the SRs/Meta-analyses (18–24) had a low risk of bias. Domain-2 examined the process of identifying, retrieving, and selecting literature in each SR and showed that all (18–26) were at high risk of bias. In Domain-3, data extraction and quality evaluation, 1 SR/Meta-analyses (18) with a low risk of bias and 8 SRs/Meta-analyses (19–26) with an uncertain risk of bias were identified. Domain-4 evaluated the overall results and the combined results of each study and showed that 4 studies (19–21, 24) had a high risk of bias and 5 studies (18, 22, 23, 25, 26) had an uncertain risk of bias. Of the 9 SRs/Meta-analyses (18–26) included, all were evaluated as high risk of bias. **Table 5** and **Figure 4** present the ROBIS results for each SR.

4. Discussion

The main objective of this overview is to assess and summarize the available clinical evidence through the currently published SRs/ Meta-analyses on VSRR and TRR. However, the currently available SRs/Meta-analyses were of unsatisfactory quality through our series of scale evaluations, suggesting that we need to be more cautious about further interpreting their results.

In terms of reporting quality, 1 (23) study had relatively serious information deficiencies (<15 points) and 7 (19–22, 24–26) had moderate deficiencies (≤21 points), mainly related to the evaluation of reporting bias, risk of study bias, credibility of evidence, protocol and registration, funding source, inclusion/ exclusion criteria, search strategy, data extraction, and synthesis of methods and results. Of course, the above-mentioned issues are also common problems with SRs/Meta-analyses at present, especially in terms of scheme and registration, which need our attention. If we make our scheme and register it before the study, it can make us more logical on the one hand, and on the other hand, it can be used by others to search for and find the problems in time, which is a very good pre-communication process. In addition, PICO criteria were not well represented in a significant number of included studies (19, 20, 22–24, 26), and most of the included studies did not provide a complete search formula. This is a reason to suspect that the original literature is missing.

In terms of methodological quality, key items 2 and 7 in all 9 included studies had serious deficiencies. Before the implementation of the systematic review, the authors did not clearly state the study methodology for the systematic review, did not state the existence of a written protocol or guidance document, and all studies did not provide a list of excluded literature. Only three studies (18, 19, 25) considered the risk of bias in the included studies when interpreting and discussing each outcome. These results suggested that the current SR/Meta-

Characteristics	No. of studies	Effect Measure	Effect Estimate	P–value
Early mortality				
Soto 2021	7	Risk Ratio	0.62 (0.22-1.74)	–
Burgstaller 2018	20	Odds Ratio	0.23 (0.09-0.55)	<0.01
Elbatarny 2020	26	Risk Ratio	0.65 (0.42-1.03)	–
Hu 2014	3	Risk Ratio	0.26 (0.05-1.23)	<0.05
Mosbahi 2018	27	Odds Ratio	0.33 (0.15-0.72)	<0.01
Salmasi 2019	33	Odds Ratio	0.51 (0.21-0.57)	<0.01
Wu 2019	9	Odds Ratio	0.34 (0.21-0.57)	–
Late mortality				
Soto 2021	4	Risk Ratio	0.35 (0.11-1.11)	–
Elbatarny 2020	23	Incident Rate Ratio	0.68 (0.54-0.87)	<0.01
Flynn 2017	8	Odds Ratio	0.26 (0.15-0.46)	<0.01
Hu 2014	6	Risk Ratio	0.37 (0.18-0.74)	<0.01
Salmasi 2019	24	Odds Ratio	0.67 (0.48-0.94)	<0.01
Wu 2019	9	Odds Ratio	0.34 (0.21-0.57)	–
Valve re–intervention				
Soto 2021	5	Risk Ratio	0.79 (0.31-1.98)	–
Elbatarny 2020	26	Incident Rate Ratio	1.15 (0.66-2.01)	0.62
Flynn 2017	12	Odds Ratio	0.89 (0.35-2.24)	0.80
Hu 2014	6	Risk Ratio	1.07 (0.35-3.27)	>0.05
Wu 2019	9	Odds Ratio	3.88 (1.66-9.06)	–
Thomboembolic				
Soto 2021	2	Risk Ratio	0.19 (0.03-1.13)	0.07
Flynn 2017	12	Odds Ratio	0.32 (0.16-0.62)	<0.01
Hu 2014	4	Risk Ratio	0.17 (0.05-0.57)	<0.01
Salmasi 2019	23	Odds Ratio	1.32 (0.77-2.24)	0.34
Endocarditis				
Soto 2021	3	Risk Ratio	0.13 (0.03-0.61)	0.01
Flynn 2017	11	Odds Ratio	0.27 (0.10-0.68)	<0.01
Hu 2014	5	Risk Ratio	0.31 (0.11-0.94)	<0.05
Wu 2019	9	Odds Ratio	0.71 (0.23-2.15)	–
Bleeding				
Soto 2021	4	Risk Ratio	0.51 (0.17-1.47)	–
Elbatarny 2020	9	Incident Rate Ratio	0.21 (0.11-0.42)	<0.01
Flynn 2017	7	Odds Ratio	0.18 (0.07-0.45)	<0.01

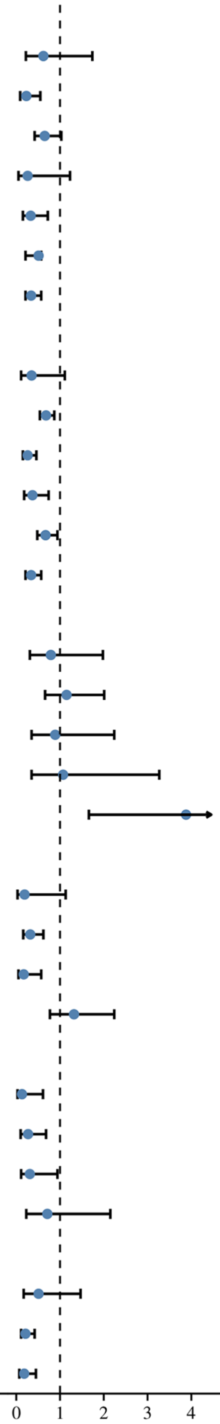

FIGURE 3
A summary of the 6 postoperative outcomes evaluated using Grading of Recommendations, Assessment, Development and Evaluations.

analyses of issues related to postoperative VSRR versus TRR were largely able to follow reporting norms, but methodological quality needs to be improved, and investigators still lack attention to protocol registration, provision of search strategies, and the risk of bias in included studies.

In terms of evidence quality, the included SRs/Meta-analyses were of low/very low quality, which may be due to the following reasons. First, the methodological quality of the included cohorts was uneven and subject to large bias. Second, the outcome indicators reported in the cohort studies were not comprehensive,

TABLE 5 Risk of bias of the included systematic reviews assessed by risk of bias in systematic reviews.

First author/ year	Phase 2				Phase 3
	1. Study eligibility criteria	2. Identification and selection of studies	3. Data collection and study appraisal	4. Synthesis and findings	Risk of bias in the review
Soto 2021	L	H	L	U	H
Burgstaller 2018	L	H	U	H	H
Benedetto 2011	L	H	U	H	H
Elbatarny 2020	L	H	U	H	H
Flynn 2017	L	H	U	U	H
Hu 2014	L	H	U	U	H
Mosbahi 2018	L	H	U	H	H
Salmasi 2019	H	H	U	U	H
Wu 2019	H	H	U	U	H

L, low risk; H, high risk; U, unclear risk.

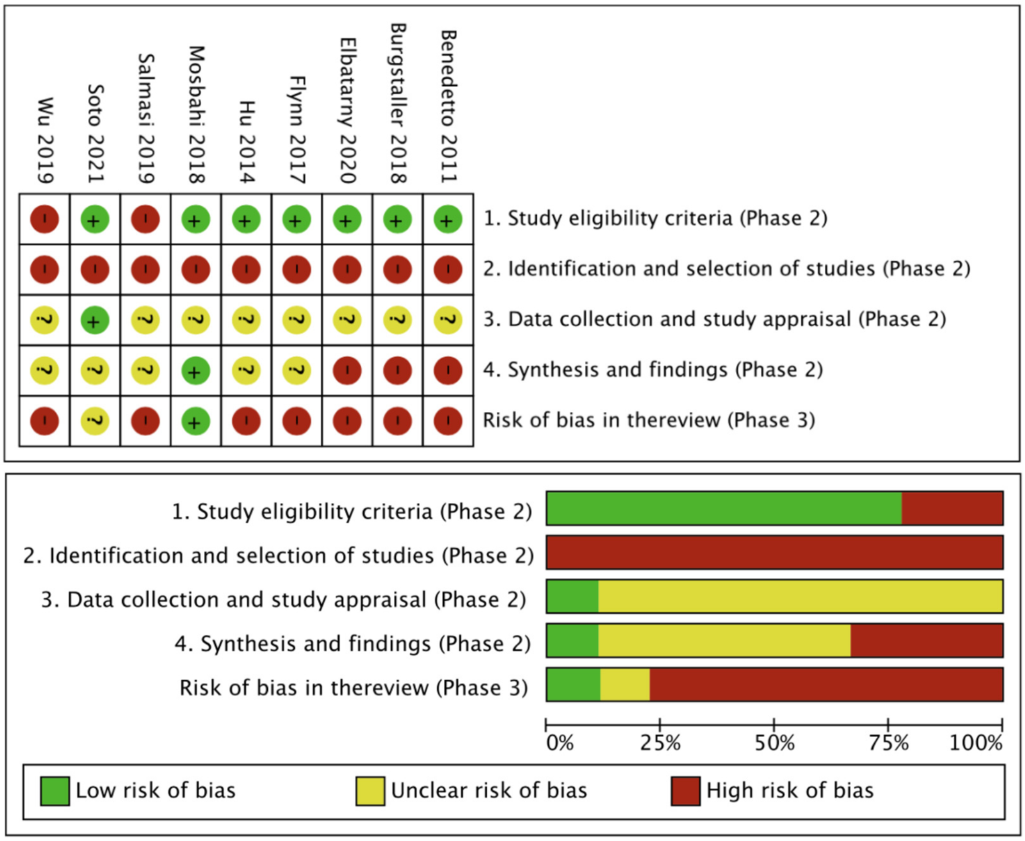

FIGURE 4
Visual analysis results of Risk of Bias in Systematic Reviews.

resulting in small sample sizes, wide confidence intervals, and imprecise results in some subgroups. Third, for publication bias reporting, some studies reported only the funnel plot, Egger's test, and Begg's test results for the primary outcome, which may have affected the credibility of other secondary outcomes.

As we know, both VSRR and TRR are different procedures for aortic root disease, and their biggest difference is whether the native aortic valve is preserved or not during the procedure. There is no denying that the VSRR is more difficult than the TRR. As mentioned in the 2022 American College of Cardiology/American Heart Association (ACC/AHA) guidelines (27), valve-preserving aortic root replacement is justified in patients undergoing aortic root replacement if the valve is suitable for repair and performed by an experienced surgeon on a multidisciplinary aortic team. In addition, the evaluation of the patient's aortic valve as well as the overall systemic condition is particularly important when performing VSRR. Through a review of the available literature, as well as our center's experience, VSRR is aggressively performed in patients with the following conditions: (i) good aortic valve pathology with high hope of preservation; (ii) young patients, especially women of reproductive age; and (iii) patients with contraindications to anticoagulation.

It is undeniable that in the secondary studies we included and in some original studies from large centers, patients who underwent VSRR had a longer time to cross-clamping and circulatory arrest than those who underwent TRR, yet the early and late mortality rates were lower in the VSRR group than those in the TRR group (28, 29). There were also very few complications in those receiving VSRR, especially the stroke rate during hospitalization, which was only half that of patients who received TRR (24). Several studies have shown a significant decrease in bleeding/embolic/endocarditis events to varying degrees as well (30–32). Beyond the above problems, the rate of valve re-intervention in patients undergoing VSRR is of real concern to everyone. Among the 5 included studies (18, 21–23, 26), only the re-intervention rate of VSRR was higher in the study by Wu et al. (26) and was approximately 4 times higher than that of patients in the TRR group. The rest of the studies did not differ from the TRR group of patients. However, this is quite acceptable given that the incidence of reintervention was only 3% higher in the VSRR group than in the TRR group in the study [VSRR: 4.9% (95% CI 0.008–0.090), TRR: 1% (95% CI 0.001–0.017)]. Therefore, we said that VSRR should be the first choice for patients if conditions permit.

5. Limitation

Although we have made a more detailed assessment and summary, we still cannot avoid some limitations. Firstly, multiple scales were used in the quality evaluation part of this study, and the subjectivity of the researchers in evaluating the literature could lead to bias and consequently affect the evaluation results. Secondly, SRs/Meta-analyses published more than 5.5 years were generally considered to have reduced timeliness, whereas the cycle of cardiovascular disease-related literature was even shorter (3 years) (33), and some of the studies in this review were published earlier and their contents need to be updated. Finally, there were differences in the level of centers and operators performing the VSRR procedure, and bias in the results was inherently unavoidable.

6. Conclusion

The current SRs/Meta-analyses point to many benefits of VSRR, including reduced early and late mortality after aortic root surgery and reduced incidence of valve-related adverse events, but the methodological quality of the relevant studies was low, and there was a lack of high-quality evidence to support them. Large-sample, multicenter clinical randomized controlled trials are necessary, and we need more rigorous and methodologically sound SRs/Meta-analyses to draw clear conclusions that can guide clinical practice.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

WW, TG, and ES wrote the main manuscript text. XZ, YS, SX, TS, and XH prepared figures and tables. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Bentall H, De Bono A. A technique for complete replacement of the ascending aorta. *Thorax*. (1968) 23(4):338–9. doi: 10.1136/thx.23.4.338

2. Gott VL, Greene PS, Alejo DE, Cameron DE, Naftel DC, Miller DC, et al. Replacement of the aortic root in patients with Marfan's syndrome. *N Engl J Med*. (1999) 340(17):1307–13. doi: 10.1056/nejm199904293401702

3. Kouchoukos NT, Marshall WG Jr, Wedige-Stecher TA. Eleven-year experience with composite graft replacement of the ascending aorta and aortic valve. *J Thorac Cardiovasc Surg*. (1986) 92(4):691–705. doi: 10.1016/S0022-5223(19)35873-8

4. Craver JM, Weintraub WS, Jones EL, Guyton RA, Hatcher CR Jr. Predictors of mortality, complications, and length of stay in aortic valve replacement for aortic stenosis. *Circulation*. (1988) 78(3 Pt 2):I85–90.

5. Christakis GT, Weisel RD, David TE, Salerno TA, Ivanov J. Predictors of operative survival after valve replacement. *Circulation*. (1988) 78(3 Pt 2):I25–I34.

6. Ouzounian M, Rao V, Manlhiot C, Abraham N, David C, Feindel CM, et al. Valve-sparing root replacement compared with composite valve graft procedures in patients with aortic root dilation. *J Am Coll Cardiol*. (2016) 68(17):1838–47. doi: 10.1016/j.jacc.2016.07.767

7. David TE, Feindel CM. An aortic valve-sparing operation for patients with aortic incompetence and aneurysm of the ascending aorta. *J Thorac Cardiovasc Surg*. (1992) 103(4):617–21; discussion 622. doi: 10.1016/S0022-5223(19)34942-6

8. Sarsam MA, Yacoub M. Remodeling of the aortic valve anulus. *J Thorac Cardiovasc Surg*. (1993) 105(3):435–8. doi: 10.1016/S0022-5223(19)34225-4

9. Coselli JS, Volguina IV, LeMaire SA, Sundt TM, Connolly HM, Stephens EH, et al. Early and 1-year outcomes of aortic root surgery in patients with Marfan syndrome: a prospective, multicenter, comparative study. *J Thorac Cardiovasc Surg*. (2014) 147(6):1758–66. doi: 10.1016/j.jtcvs.2014.02.021

10. Caceres M, Ma Y, Rankin JS, Saha-Chaudhuri P, Englum BR, Gammie JS, et al. Mortality characteristics of aortic root surgery in North America. *Eur J Cardiothorac Surg*. (2014) 46(5):887–93. doi: 10.1093/ejcts/ezu083

11. Miller DC. Aortic valve-sparing surgery: yes, but not for every patient and select the center very carefully. *J Am Coll Cardiol*. (2016) 68(17):1848–50. doi: 10.1016/j.jacc.2016.08.020

12. Becker LA, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.0.2. The cochrane collaboration (2009). Available at: www.cochrane-handbook.org.

13. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Br Med J*. (2021) 372:n71. doi: 10.1136/bmj.n71

14. La Moher D, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. (2009) 6(7): e1000097. doi: 10.1371/journal.pmed.1000097

15. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Br Med J*. (2017) 358:j4008. doi: 10.1136/bmj.j4008

16. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence–imprecision. *J Clin Epidemiol*. (2011) 64(12):1283–93. doi: 10.1016/j.jclinepi.2011.01.012

17. Whiting P, Savović J, Higgins JP, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: a new tool to assess risk of bias in systematic reviews was developed. *J Clin Epidemiol*. (2016) 69:225–34. doi: 10.1016/j.jclinepi.2015.06.005

18. Soto ME, Ochoa-Hein E, Anaya-Ayala JE, Ayala-Picazo M, Koretzky SG. Systematic review and meta-analysis of aortic valve-sparing surgery versus replacement surgery in ascending aortic aneurysms and dissection in patients with marfan syndrome and other genetic connective tissue disorders. *J Thorac Dis*. (2021) 13(8):4830–44. doi: 10.21037/jtd-21-789

19. Burgstaller JM, Held U, Mosbahi S, Stak D, Steurer J, Eckstein F, et al. A systemic review and meta-analysis: long-term results of the bentall versus the david procedure in patients with Marfan syndrome. *Eur J Cardiothorac Surg*. (2018) 54(3):411–9. doi: 10.1093/ejcts/ezy158

20. Benedetto U, Melina G, Takkenberg JJ, Roscitano A, Angeloni E, Sinatra R. Surgical management of aortic root disease in Marfan syndrome: a systematic review and meta-analysis. *Heart*. (2011) 97(12):955–8. doi: 10.1136/hrt.2010.210286

21. Elbatarny M, Tam DY, Edelman JJ, Rocha RV, Chu MWA, Peterson MD, et al. Valve-sparing root replacement versus composite valve grafting in aortic root dilation: a meta-analysis. *Ann Thorac Surg*. (2020) 110(1):296–306. doi: 10.1016/j.athoracsur.2019.11.054

22. Flynn CD, Tian DH, Wilson-Smith A, David T, Matalanis G, Misfeld M, et al. Systematic review and meta-analysis of surgical outcomes in Marfan patients undergoing aortic root surgery by composite-valve graft or valve sparing root replacement. *Ann Cardiothorac Surg*. (2017) 6(6):570–81. doi: 10.21037/acs.2017.11.06

23. Rui H, Zhiwei W, Xiaoping H, Hongbing W, Zhen Z. Effect of native aortic valve sparing aortic root reconstruction surgery on short- and long-term prognosis in Marfan syndrome patients: a meta-analysis. *Chin J Cardiol*. (2014) 42(5):433–8. doi: 10.3760/cma.j.issn.0253–3758.2014.05.018

24. Mosbahi S, Stak D, Gravestock I, Burgstaller JM, Steurer J, Eckstein F, et al. A systemic review and meta-analysis: bentall versus david procedure in acute type A aortic dissection. *Eur J Cardiothorac Surg*. (2019) 55(2):201–9. doi: 10.1093/ejcts/ezy266

25. Salmasi MY, Theodoulou I, Iyer P, Al-Zubaidy M, Naqvi D, Snober M, et al. Comparing outcomes between valve-sparing root replacement and the bentall procedure in proximal aortic aneurysms: systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg*. (2019) 29(6):911–22. doi: 10.1093/icvts/ivz211

26. Wu J, Huang Y, Qiu J, Saeed B, Yu C. Is valve-sparing root replacement a safe option in acute type A aortic dissection? A systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg*. (2019) 29(5):766–75. doi: 10.1093/icvts/ivz180

27. Isselbacher EM, Preventza O, Hamilton Black Iii J, Augoustides JG, Beck AW, Bolen MA, et al. 2022 ACC/AHA guideline for the diagnosis and management of aortic disease: a report of the American heart association/American college of cardiology joint committee on clinical practice guidelines. *J Am Coll Cardiol*. (2022) 80(24):e223–e393. doi: 10.1016/j.jacc.2022.08.004

28. Franke UF, Isecke A, Nagib R, Breuer M, Wippermann J, Tigges-Limmer K, et al. Quality of life after aortic root surgery: reimplantation technique versus composite replacement. *Ann Thorac Surg*. (2010) 90(6):1869–75. doi: 10.1016/j.athoracsur.2010.07.067

29. Lee H, Cho YH, Sung K, Kim WS, Park KH, Jeong DS, et al. Clinical outcomes of root reimplantation and bentall procedure: propensity score matching analysis. *Ann Thorac Surg*. (2018) 106(2):539–47. doi: 10.1016/j.athoracsur.2018.02.057

30. Halstead JC, Spielvogel D, Meier DM, Rinke S, Bodian C, Malekan R, et al. Composite aortic root replacement in acute type A dissection: time to rethink the indications? *Eur J Cardiothorac Surg*. (2005) 27(4):626–32; discussion 632–3. doi: 10.1016/j.ejcts.2004.12.059

31. Lewis CT, Cooley DA, Murphy MC, Talledo O, Vega D. Surgical repair of aortic root aneurysms in 280 patients. *Ann Thorac Surg*. (1992) 53(1):38–45; discussion 45–6. doi: 10.1016/0003-4975(92)90755-s

32. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The task force for the diagnosis and treatment of aortic diseases of the European society of cardiology (ESC). *Eur Heart J*. (2014) 35(41):2873–926. doi: 10.1093/eurheartj/ehu281

33. Shojania KG, Sampson M, Ansari MT, Ji J, Doucette S, Moher D. How quickly do systematic reviews go out of date? A survival analysis. *Ann Intern Med*. (2007) 147(4):224–33. doi: 10.7326/0003-4819-147-4-200708210-00179

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The controlling nutritional status score predicts postoperative mortality in patients with ruptured abdominal aortic aneurysm: a retrospective study

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Background: Ruptured abdominal aortic aneurysms (rAAAs) are challenging for vascular surgeons because they have a high mortality rate. In many diseases, nutritional status is closely associated with prognosis. The Controlling Nutritional Status (CONUT) screening tool score is a prognostic factor in some malignant and chronic diseases; however, the impact of nutritional status on rAAA has not yet been reported. In this study, we explored the relationship between the CONUT score and the postoperative prognosis of patients with rAAA.
Methods: This was a retrospective review of 39 patients with rAAA who underwent surgical treatment from March 2018 to September 2021 at one center. Patient characteristics, nutritional status (CONUT score), and postoperative status were recorded. The patients were divided into groups A and B based on the CONUT score. The baseline characteristics of the two groups were compared, and Cox proportional hazards and logistic regression analyses were used to determine independent predictors of mid-term mortality and complications, respectively.
Results: The overall mid-term mortality rate was 28.21% (11/39). Compared with group A, group B had higher intraoperative ($P = 0.047$) and mid-term mortality ($P = 0.033$) rates. The univariate analysis showed that age [hazard ratio (HR), 1.098; 95% confidence interval (CI), 1.019–1.182; $P = 0.014$], CONUT score (HR, 1.316; 95% CI, 1.027–1.686; $P = 0.03$), and surgical procedure (HR, 0.127; 95% CI, 0.016–0.992; $P = 0.049$) were associated with mid-term mortality, whereas the multivariate analysis showed that the CONUT score (HR, 1.313; 95% CI, 1.009–1.710; $P = 0.043$) was an independent predictor of mid-term mortality. The multivariate logistic regression analysis did not reveal any associations with complications. The Kaplan–Meier curves showed that group B had a lower mid-term survival rate (log-rank $P = 0.024$).
Conclusion: Malnutrition is closely associated with the prognosis of patients with rAAA, and the CONUT score can be used to predict mid-term mortality.

KEYWORDS

controlling nutritional status score, ruptured abdominal aortic aneurysm, prognosis, mid-term mortality, surgical complications

Introduction

Abdominal aortic aneurysm (AAA) is defined as an abdominal aorta diameter of >3 cm or ≥50% greater than the normal diameter as a result of irreversible pathological dilation (1). Ruptured AAA (rAAA), which is one of the most dangerous conditions in vascular surgery, has an extremely high mortality rate (1, 2) of up to 81% according to a recent report from the USA Preventive Services Task Force (3). The vast majority of deaths attributed to rupture occur before patients reach the operating room; however, the postoperative mortality rate still reportedly exceeds 40% (4). Some patients who reach the hospital alive forgo surgery because of the high cost, or they cannot undergo surgery because of the presence of serious comorbidities, including cardiovascular insufficiency.

AAA is a chronic degenerative disease of older individuals. Similarly, malnutrition is common in older patients with chronic diseases. In our clinical practice, we have observed that malnourished patients with rAAA have a high mortality rate. We therefore hypothesized that nutritional status is a prognostic factor in patients with rAAA.

The Controlling Nutritional Status (CONUT) tool for classifying nutritional status has attracted much attention recently (5). The CONUT score is a prognostic predictor in patients with some malignant or chronic diseases, such as end-stage liver disease (6) and acute heart failure (7). The CONUT score is also associated with disease activity in patients with lupus nephritis (8). In addition, the CONUT score is associated with prognosis and the treatment response in oncology (9–12). Most patients with rAAA have hypertension and are of an older age, which is consistent with the finding that a low CONUT score is directly associated with poor survival in older hospitalized patients with hypertension (13, 14).

The aim of this study was to evaluate the association between the CONUT score and prognosis, including death, in patients with rAAA. The CONUT score was calculated from preoperative laboratory test findings.

Methods

Study cohort

This was a single-center retrospective review of patients with rAAA. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Nanjing Drum Tower Hospital affiliated to Nanjing University School. All patients provided written informed consent for surgery.

From March 2018 to September 2021, 45 patients with rAAA were admitted to our center as emergency cases. Six of the 45 patients were not managed surgically because of their poor physical condition. Endovascular aneurysm repair (EVAR) was performed in 22 patients, and open surgical repair (OSR) was performed in 17 patients. The 39 patients with rAAA were divided into two groups (**Figure 1**) according to the cut-off CONUT score: group A (CONUT score of 0–7, $n = 25$) and group B (CONUT score of 8–12, $n = 14$).

Data collection and follow-up

We reviewed the clinical data of all patients, including their baseline characteristics (e.g., age, sex, comorbidities, smoking status, medication history); preoperative and postoperative laboratory findings (e.g., routine blood tests, coagulation function, liver and kidney function, postoperative B-type natriuretic peptide); surgical data (e.g., surgical method, surgical time, intraoperative blood transfusion, intraoperative blood loss); postoperative status (e.g., surgical complications, anesthesia recovery period, length of intensive care unit stay); and total hospitalization cost.

Postoperative follow-up mainly comprised regular physical examination and abdominal computed tomography. When the patient had stopped attending for follow-up, we contacted the patient or their family to determine their current status. Patients who were followed up at other institutions were contacted by telephone to obtain the required data.

Clinical endpoints

The primary endpoint was mid-term mortality. The secondary endpoints were surgical complications, including acute organ injury, bleeding, and ischemia–reperfusion; implant-related complications, including stent rupture, leakage, implant infection, and vascular occlusion; and reoperation.

Definitions

The CONUT scoring system was first proposed by de Ulibarri et al. in 2005 (5). The CONUT score is calculated by adding together the preoperative albumin concentration, lymphocyte count, and cholesterol concentration (**Table 1**). Patients were divided into four groups based on their CONUT scores. A CONUT score of 0–1 was classified as denoting a normal nutritional status, and CONUT scores of 2–4, 5–8, and 9–12 were classified as mild, medium, and severe malnutrition, respectively.

Statistical analysis

Normally distributed continuous variables are presented as the mean ± standard deviation. Non-normally distributed continuous variables are represented as the median [interquartile range (IQR)]. Categorical variables are presented as the number of patients (%). Independent and paired-samples t-tests, the Mann–Whitney U test, and analysis of variance were used for comparisons. The receiver operating characteristic (ROC) curve

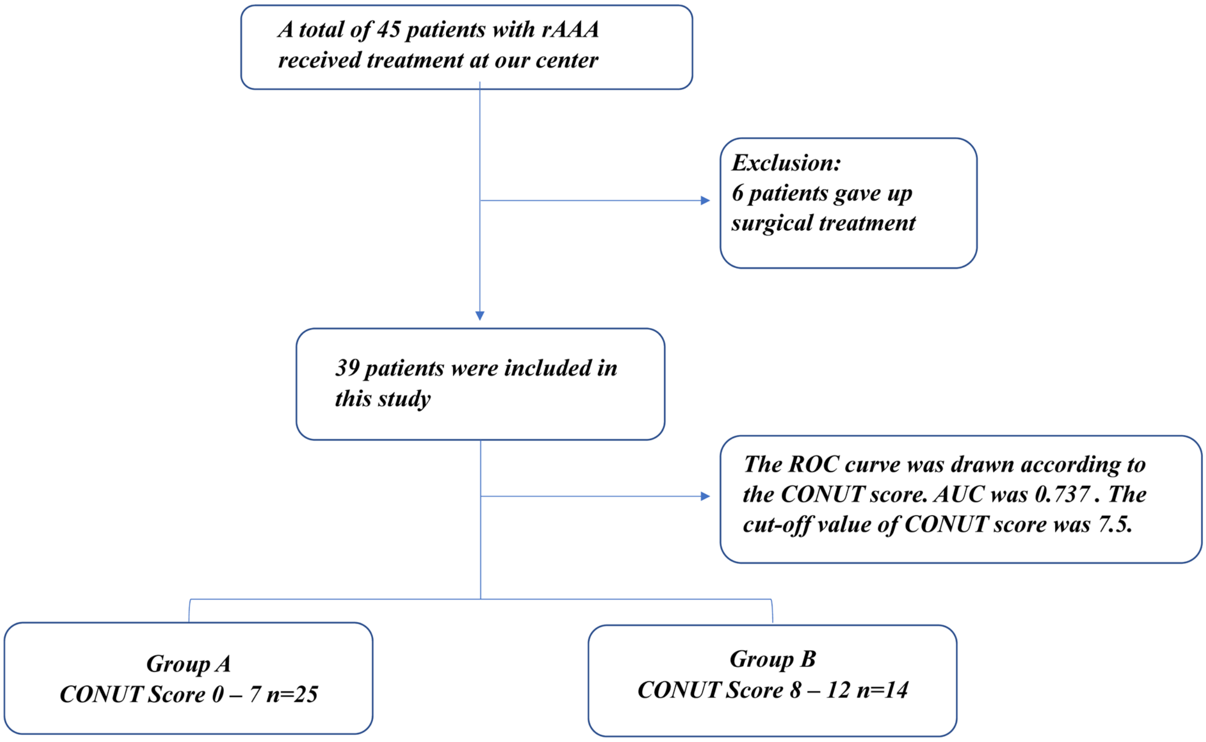

FIGURE 1
Flowchart of patients.

analysis was used to determine the cut-off value for the grouping. Survival rates were analyzed by the Kaplan–Meier method and the log-rank test. Correlations between patient characteristics and mortality were examined using Cox proportional hazards models. Surgical complications were analyzed by logistic regression. After the univariate analysis, any variable with a P value of <0.05 was entered into the multivariate analysis. All baseline characteristics, other studied variables, and comorbidities were incorporated into the Cox proportional hazards and logistic regression models to determine which factors were associated with mortality and postoperative complications. A P value of <0.05 was considered statistically significant. Data analysis was performed using SPSS 26.0 (IBM Corp., Armonk, NY, US).

TABLE 1 Controlling nutritional status (CONUT) scores.

Parameter	Score			
Serum albumin, g/dl	≥3.5	3.0–3.49	2.50–2.99	<2.5
Albumin score	0	2	4	6
Total cholesterol, mg/dl	>180	140–180	100–139	<100
Cholesterol score	0	1	2	3
Lymphocytes, count/ml	≥1,600	1,200–1,599	800–1,199	<800
Lymphocyte score	0	1	2	3
Nutritional status score	0–1 (normal status)	2–4 (low risk)	5–8 (medium risk)	9–12 (severe risk)

Results

Patients' characteristics

The study cohort comprised 39 patients with rAAA. According to the CONUT score, all patients had varying degrees of malnutrition; 16 of 39 patients had mild malnutrition (41.0%), 15 had medium malnutrition (38.5%), and 8 had severe malnutrition (20.5%). Eleven patients died during follow-up, and the ROC curve was drawn according to the CONUT score to predict the time of death (**Figure 2**). The area under the ROC curve was 0.737 (95% CI, 0.568–0.906; $P = 0.023$), the cut-off CONUT score for determining the grouping was 7.5, the sensitivity was 0.636, and the specificity was 0.75. The study cohort comprised 39 patients with rAAA divided into two groups (**Figure 1**) according to the cut-off CONUT score: group A (CONUT score of 0–7, $n = 25$) and group B (CONUT score of 8–12, $n = 14$).

The patients' characteristics are shown in **Table 2**. The mean age of the patients in group A was 66.12 ± 11.52 years and in group B was 69.57 ± 7.30 years ($P = 0.319$). Most of the patients were male. Interestingly, the absence of women in group B, the group with a worse nutritional status, may indicate that older men have a poorer nutritional status than women, similar to the findings of a previous report (13). The median CONUT score was 4 (IQR, 3–6) in group A and 9.5 (IQR, 8–10) in group B ($P < 0.001$). Significant differences in serum albumin and total cholesterol were observed between the two groups ($P < 0.001$). In

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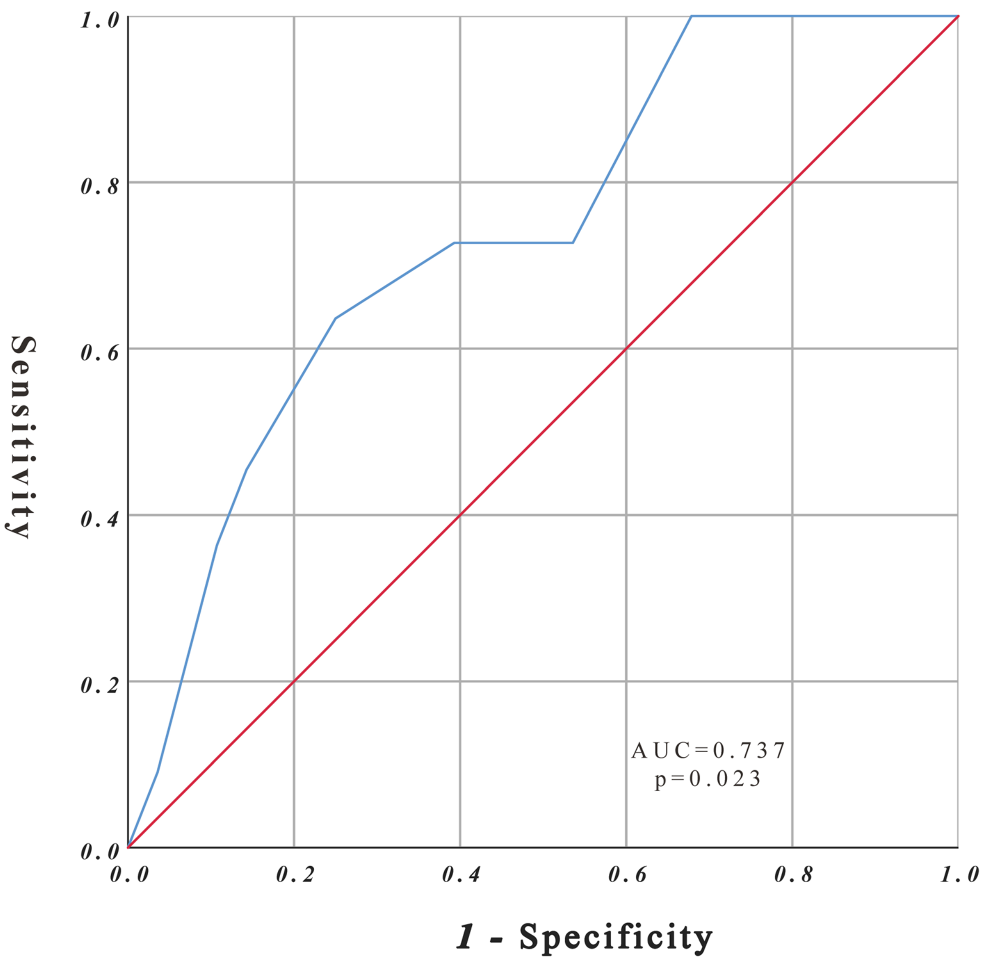

FIGURE 2
ROC curve analysis for survival rate.

addition, the postoperative estimated glomerular filtration rate was significantly lower in group B than in group A ($P = 0.009$), indicating that postoperative renal function was worse in group B. This may account for the higher mortality rate in group B than in group A. Finally, patients in group B had a longer length of hospital stay than those in group A ($P = 0.017$) because patients with a poor nutritional status tended to take longer to adjust their physical function after surgery. No significant differences in other basic characteristics were observed between the two groups.

Complications and reoperation

Postoperative complications were identified in 19 patients, including 13 patients in group A and 6 patients in group B (Table 3). The difference was not statistically significant ($P = 0.741$). In group A, one patient developed an unexplained pulmonary vein embolism on postoperative day 8, four had acute postoperative renal insufficiency, two had pleural effusion caused by cardiac insufficiency, one had gastrointestinal bleeding caused by a stress ulcer accompanied by pulmonary ischemia–reperfusion injury on postoperative day 2, one had epilepsy of unknown cause on postoperative day 3, and one developed an incisional hernia in the sixth postoperative month. In addition, there was one case of type II stent leakage on postoperative day 9. There was also one case of type II stent leakage 3 months postoperatively and one case of stent rupture 1 month postoperatively, which was identified on postoperative computed tomography at follow-up, and both of these cases required reoperation. Moreover, one patient developed implant infection 6 months after surgery, which progressed to fatal sepsis. In group B, three patients were diagnosed as having Kidney Disease Improving Global Outcomes 3 acute postoperative kidney injury that improved with treatment, one had intestinal ischemic necrosis and pulmonary edema, one had a bleeding tendency that improved after emergency platelet transfusion, and two had different degrees of lung ischemia–reperfusion injury. Two of these patients required reoperation for implant-related or other vascular complications. According to the univariate logistic regression analysis, hypertension and long-term preoperative use of hypotensive agents were associated with complications or reoperation. However, according to the multivariate analysis, there were no significant independent associations (Table 4), which may be attributable to the small sample size.

TABLE 2 Basic characteristics of included patients.

	Group A (*n* = 25)	Group B (*n* = 14)	*P*
Age, years	66.12 ± 11.52	69.57 ± 7.30	0.319
Sex, male/female	18/7	14/0	***0.036***
AAA diameter, cm	7.32 ± 3.38	7.52 ± 3.39	0.862
Surgical method			
EVAR	13 (52%)	5 (36%)	0.518
OSR	12 (48%)	9 (64%)	
CONUT score	4 (3–6)	9.5 (8–10)	***<0.001***
Comorbid disease			
Hypertension	21 (84%)	11 (79%)	0.686
DM	3 (12%)	0	0.54
Dyslipidemia	4 (16%)	1 (7%)	0.636
Stroke	1 (4%)	1 (7%)	1
Renal dysfunction	4 (16%)	3 (21%)	0.686
CAD	6 (24%)	3 (21%)	1
Prior arterial disease	5 (20%)	1 (7%)	0.391
Current smoker	16 (64%)	9 (64%)	1
Medication			
Depressor	17 (68%)	11 (79%)	0.713
Anticoagulants	11 (44%)	3 (21%)	0.187
Laboratory examination			
Serum albumin, mg/dl	34.15 ± 3.89	25.56 ± 2.57	***<0.001***
Total cholesterol, mg/dl	144.67 ± 31.62	105.93 ± 32.72	***0.001***
Lymphocyte count, 10^3 ml	1.2 (0.65–1.65)	0.8 (0.8–0.95)	0.061
WBC, 10^9/L	11.31 ± 5.38	10.45 ± 2.28	0.617
Hb, g/L	100.00 ± 21.79	98.36 ± 33.40	0.865
Plt, 109/L	122.00 ± 60.07	110.82 ± 77.81	0.648
CRP, mg/L	53.48 ± 40.53	71.97 ± 50.19	0.263
Postoperative eGFR, ml/min	79.10 ± 51.17	45.12 ± 19.62	***0.009***
Postoperative Cr, μmol/L	93.00 (55.10–194.90)	148.00 (117.00–230.70)	0.245
Postoperative PT, s	15.22 ± 6.52	14.05 ± 2.19	0.571
Postoperative Fibrinogen, g/L	2.48 ± 0.93	2.15 ± 0.92	0.341
Postoperative D-Dimer, mg/L	9.45 (3.67–21.06)	9.74 (6.38–13.37)	0.915
Postoperative BNP, pg/ml	79.00 (37.40–237.00)	70.65 (43.38–241.00)	0.959
Preoperative situation			
HR	85.92 ± 13.19	85.79 ± 11.81	0.975
SBP, mmHg	110.20 ± 26.97	106.21 ± 25.83	0.656
DBP, mmHg	66.56 ± 17.16	66.14 ± 16.70	0.942
Intraoperative situation			
Blood loss, ml	300 (150–2,675)	450 (100–4,250)	0.786
Blood transfusion, ml	1,650 (600–3,452)	2,822 (1,175–5,595)	0.335
Surgical time, h	3.10 ± 1.31	3.31 ± 1.79	0.665
Postoperative situation			
Anesthesia recovery period, h	16 (7–24)	42 (6.25–209.25)	0.07
ICU length of stay, d	2 (1–4.75)	6 (1.75–12.75)	***0.017***
Length of stay, d	12 (10–16)	14 (11–28)	0.24
Cost,¥	1,19,413.31 ± 59,434.46	1,58,214.32 ± 1,00,888.10	0.204

AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair; OSR, open surgical repair; CONUT, controlling nutritional status; DM, diabetes mellitus; CAD, coronary artery disease; WBC, white blood cell; Hb, hemoglobin; Plt, platelet; Cr, creatinine; PT, prothrombin time; INR, international standard ratio; eGFR, estimated glomerular filtration rate; BNP, type B natriuretic peptide; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; ICU, intensive care unit. Continuous variables are presented as the mean ± standard deviation if normally distributed or the median (interquartile range) if not normally distributed. Categorical variables are presented as the number of patients (%).
The bold values indices are statistical difference between the two group.

Intraoperative mortality

Five patients died during surgery (12.82%), and the analysis revealed a significant difference between group A and B (P = 0.047). Four patients in group B died of persistent hypotension that could not be resolved by blood transfusion and fluid rehydration. One patient in group A demonstrated iliac artery occlusion intraoperatively, prompting the surgeon to consider OSR. However, when informed of the situation, his family decided to cease active treatment.

TABLE 3 Patient's clinical end points.

	Group A (*n* = 25)	Group B (*n* = 14)	*P*
Follow-up time, months	17.16 ± 11.26	14.00 ± 13.69	0.442
Surgical success	24 (96%)	11 (79%)	0.123
Intraoperative mortality	1 (4%)	4 (29%)	***0.047***
Midterm mortality	4 (16%)	7 (50%)	***0.033***
Reoperation	5 (20%)	2 (14%)	1
Total complications	13 (52%)	6 (43%)	0.741
Surgical complications			
Acute organ injury	5 (20%)	3 (21%)	
Bleeding	1 (4%)	0	
Ischemia reperfusion	2 (8%)	2 (14%)	
Others	3 (12%)	2 (14%)	
Implant-related complications			
Stent rupture	1 (4%)	0	
Postoperative leakage	2 (8%)	0	
Implant infection	1 (4%)	0	
Vascular occlusion	0	1 (7%)	

The bold values indices are statistical difference between the two group.

TABLE 4 Logistic regression analysis of postoperative complications and reoperation.

Variable	Univariate analysis			Multivariate analysis		
	P	Odds ratio	95% CI	*P*	Odds ratio	95% CI
Age	0.482	0.977	0.916–1.042			
Sex	0.155	0.274	0.046–1.631			
CONUT score	0.835	1.025	0.813–1.291			
Surgical method	0.921	1.067	0.3–3.796			
AAA diameter	0.679	0.96	0.890–1.166			
Hypertension	0.043	10	1.070–93.437	0.224	6	0.335–107.420
DM	0.999					
Dyslipidemia	0.511	0.526	0.078–3.565			
Strok	0.999					
Renal dysfunction	0.313	2.5	0.422–14.828			
CAD	0.521	0.612	0.136–2.742			
Prior arterial disease	0.837	0.833	0.146–4.752			
Current smoker	0.306	2	0.531–7.539			
HR	0.346	0.975	0.925–1.028			
SBP	0.569	1.007	0.983–1.032			
DBP	0.704	1.007	0.970–1.047			
Hypotensor	0.045	4.8	1.034–22.293	0.585	1.8	0.219–14.801
Anticoagulants	0.719	0.786	0.212–2.918			
WBC	0.351	0.924	0.782–1.091			
Hb	0.573	0.992	0.966–1.020			
Plt	0.71	1.002	0.992–1.013			

AAA, abdominal aortic aneurysm; CONUT, controlling nutritional status; DM, diabetes mellitus; CAD, coronary artery disease; WBC, white blood cell; Hb, hemoglobin; Plt, platelet; Cr, creatinine; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Mid-term mortality

The mean duration of follow-up was 16.03 ± 12.11 months. The overall survival rate during follow-up was 71.79% (79.49% and 76.92% at 6 and 12 months, respectively) (**Figure 3**). The mean duration of follow-up in group A and group B was 17.16 ± 11.26 months and 14.00 ± 13.69 months, respectively. The difference between the two groups was not statistically significant ($P = 0.422$). However, on further analysis, we found that group B had a higher mid-term mortality rate than group A ($P = 0.033$).

In addition to intraoperative deaths, two patients in group A died of aneurysm rupture and another died of severe lung infection 14 months after surgery. Three patients in group B died at 4, 14, and 15 months after surgery for multiple-organ failure, severe pulmonary infection, and exacerbation of renal failure, respectively. Kaplan–Meier survival curves were constructed using the follow-up data. As shown in **Figure 4**, the survival rates were significantly lower in group B than in group A (log-rank, $P = 0.024$).

We used the Cox proportional hazards model to predict risk factors for mortality. The univariate analysis showed that age (HR, 1.098; 95% CI, 1.019–1.182; $P = 0.014$), CONUT score (HR, 1.316; 95% CI, 1.027–1.686; $P = 0.03$), and surgical procedure (HR, 0.127; 95% CI, 0.016–0.992; $P = 0.049$) were risk factors for mortality. The multivariate analysis using these three factors showed that the CONUT score (HR, 1.313; 95% CI, 1.009–1.710; $P = 0.043$) was an independent risk factor for mortality in patients with rAAA (**Table 5**).

Discussion

rAAAs are often lethal, with most deaths occurring because the patient does not make it to the operating room. Lindholt et al. found that the mortality rate of patients without surgical intervention could reach 100% (15). The latest Society for Vascular Surgery guidelines indicate that patients with rAAA require immediate emergency surgery, and the window for successful intervention is no more than 90 min (16, 17). Despite surgical treatment, the inpatient mortality rate is still as high as 40% (4). Our findings are consistent with these data. Six of the 45 patients who were admitted to our center for rAAA from March 2018 to September 2021 were unable to undergo surgical treatment because of their poor physical condition or financial factors. The remaining 39 patients underwent emergency surgery, and the postoperative mortality rate of these patients was 28.21% (11/39).

Previous attempts to identify prognostic factors in patients with rAAA have focused on surgical procedures. Several studies have shown that the annual decline in morbidity with rAAA in Europe and the United States over the past 20 years is closely related to the increasing proportion of patients undergoing EVAR (18, 19). Several randomized controlled trials have shown EVAR to be significantly superior to OSR in terms of early survival; however, there is no statistically significant difference in long-term survival between these procedures (20–22). Of note, both of these studies included patients with AAA, whether ruptured or unruptured. However, for rAAA alone, three recent large randomized controlled trials have found no clear evidence that EVAR is superior to OSR in terms of early survival (23–25). Interestingly, in the present study, we found that mid-term

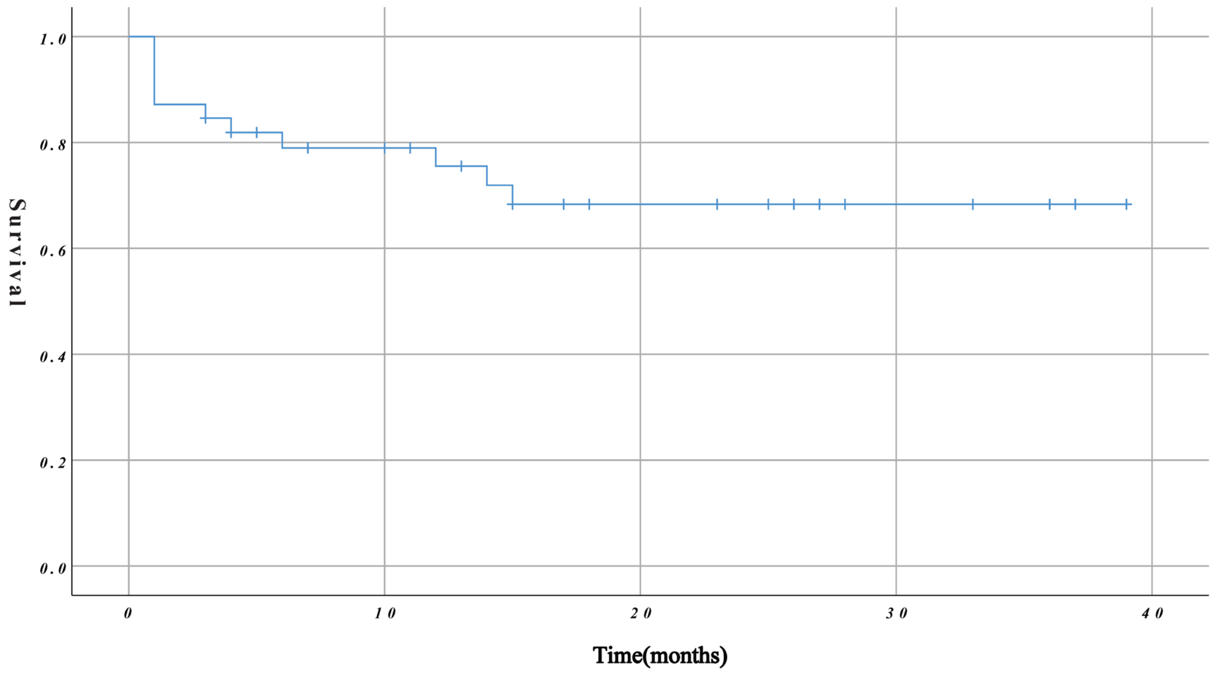

FIGURE 3
Kaplan–Meier curves for overall survival rate.

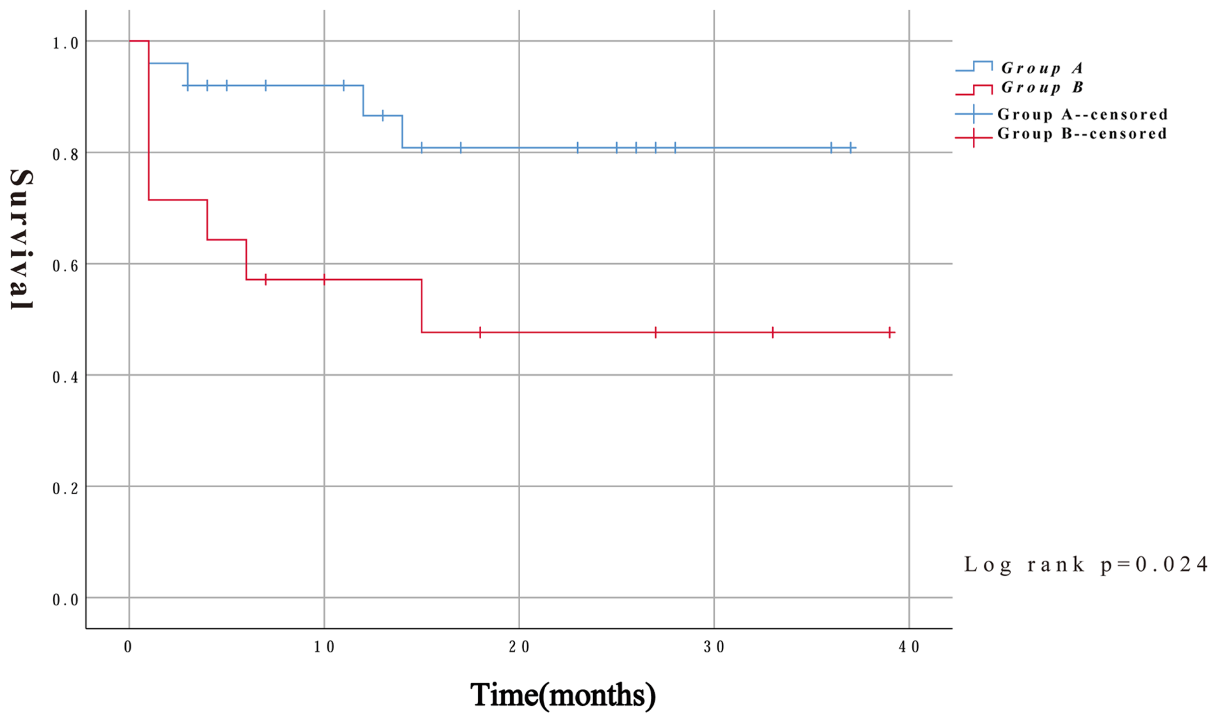

FIGURE 4
Kaplan Meier curves for midterm survival were compared among the two groups.

mortality of patients with rAAA was related to the surgical method ($P = 0.049$). Specifically, patients who underwent OSR had higher postoperative mortality than those who underwent EVAR. However, these results may be directly related to the small sample size or to subjective biases in the surgeons' choices of procedure.

In this retrospective analysis, we first proposed a correlation between nutritional status and the prognosis of patients with

TABLE 5 Cox regression analysis for risks of midterm mortality.

Variable	Univariate analysis			Multivariate analysis		
	P	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI
Age	0.014	1.098	1.019–1.182	0.083	1.074	0.991–1.165
Sex	0.308	0.035	0.000–21.768			
CONUT score	0.03	1.316	1.027–1.686	0.043	1.313	1.009–1.710
Surgical method	0.049	0.127	0.016–0.992	0.098	0.17	0.021–1.389
AAA diameter	0.135	0.949	0.684–1.052			
Hypertension	0.938	1.065	0.230–4.944			
DM	0.495	23.354	0.003–1,97,532.254			
Dyslipidemia	0.369	26.217	0.021–32,557.226			
Strok	0.748	0.713	0.091–5.609			
Renal dysfunction	0.975	1.024	0.221–4.744			
CAD	0.637	1.447	0.312–6.700			
Prior arterial disease	0.944	0.946	0.204–4.394			
Current smoker	0.106	0.279	0.059–1.312			
HR	0.253	0.968	0.916–1.023			
SBP	0.297	1.012	0.989–1.036			
DBP	0.294	1.02	0.983–1.058			
Hypotensor	0.424	0.535	0.116–2.480			
Anticoagulants/Antiplatelet	0.86	1.117	0.326–3.826			
WBC	0.659	1.036	0.886–1.212			
Hb	0.066	0.969	0.936–1.002			
Plt	0.596	1.003	0.991–1.015			

AAA, abdominal aortic aneurysm; CONUT, controlling nutritional status; DM, diabetes mellitus; CAD, coronary artery disease; WBC, white blood cell; Hb, hemoglobin; Plt, platelet; Cr, creatinine; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

rAAA. Nutritional status is a good indicator of both a patient's overall general condition and their immune and metabolic capacity. The CONUT screening tool score has been shown to predict the outcomes of malignant, chronic, and cardiovascular diseases (6, 7, 13, 14, 26). In this study, we found that 58.97% of patients with rAAA (23/39) had moderate or severe malnutrition, which may have been caused by prior massive bleeding from rAAA. The mid-term mortality of these patients was as high as 34.78% (8/23), which was much higher than that of patients who were at a normal or low risk (18.75%, 3/16). The univariate and multivariate analyses to identify predictors of mortality from any cause found that the CONUT score was an independent predictor of mid-term mortality (HR, 1.313; $P = 0.043$), suggesting that nutritional status influences the outcomes of patients undergoing surgical treatment for rAAA. Moreover, the logistic regression analysis showed that a high CONUT score was not associated with postoperative complications. The findings of previous studies investigating the correlations between the CONUT score and postoperative complications have been conflicting. Kodama et al. reported that the CONUT score predicts not only overall survival after OSR in patients with AAA, but also postoperative complications (27). Interestingly, in their study of radical hepatectomy for intrahepatic cholangiocarcinoma, Miyata et al. (28) found that a high CONUT score was associated with poorer postoperative overall survival, but not with postoperative complications, which is consistent with our findings.

Possible explanations for the high mortality rate among malnourished rAAA patients include the following. Malnutrition is often closely associated with frailty, which is defined as a clinically identifiable state of increased vulnerability and dysfunction (29, 30). Additionally, nutritional status partly reflects the development of inflammation (31–33), which promotes cytokine production and muscle catabolism, suppresses appetite, and lowers the albumin concentration (34). Reduced albumin may increase blood viscosity and activate platelets, leading to a deterioration in endothelial function (35). Furthermore, a previous study showed a relationship between nutritional status and C-reactive protein and interleukin-6 concentrations in humans (36). Moreover, the maximum diameter of AAA is positively correlated with the concentrations of interleukin-6, C-reactive protein, and other inflammatory factors (37). Cytokines secreted by inflammatory cells can damage tissues, causing the walls of blood vessels to become less elastic and eventually rupture (38). There have been no specific reports on the prognostic value of serum total cholesterol in cardiovascular disease, but low cholesterol is associated with a poor prognosis in a variety of cancers (39, 40). Therefore, it could be speculated that patients with a low total cholesterol concentration have a worse underlying condition and more comorbidities.

To the best of our knowledge, this is the first study to propose that nutritional status plays an important role in the prognosis of patients with rAAA, and that the CONUT score can predict mid-term mortality. In this study, malnutrition was common in patients with rAAA, and as malnutrition became more severe, mid-term mortality increased. Therefore, we suggest that clinicians should integrate the recognition of malnutrition into their daily practice and focus on nutritional health education for patients with AAA with the aim of reducing mortality.

This study has some limitations that should be noted. First, it was a single-center retrospective study. Furthermore, because most patients with rAAA die on the way to hospital, the study cohort was small. Second, updating our hospital's medical record system resulted in loss of case data from before March 2018. Additionally, because most of the patients were transferred from primary hospitals, we lacked some preoperative laboratory tests, despite attempting to collect as much information as possible through telephone follow-up. Therefore, we had no choice but to abandon some aspects of the preoperative examination and focus on postoperative data. Third, there was selection bias in the procedures performed, which were chosen mainly based on the personal judgment of the surgeon. Thus, we could not validly investigate the relationship between the surgical procedure and the prognosis of the patients. In addition, because of the rapid onset and urgency of rAAA, we lacked detailed preoperative imaging findings concerning the anatomical features of the aorta in some patients. Fourth, follow-up was limited; therefore, further studies are needed to understand the impact of nutritional status on long-term clinical outcomes. Finally, we did not compare the prognostic value of the scores obtained from other nutritional screening tools in these patients; however, a previous study showed that the CONUT score has good predictive performance in patients with AAA (27). To validate the effect of nutritional status on patient prognosis, further investigation in different clinical settings will be necessary. Therefore, we advocate that future studies should examine the potential role of nutritional status assessment. Further research is also needed to determine whether malnourished patients benefit from nutritional supplements.

Conclusion

rAAA has a high mortality rate, and nutritional status is associated with mid-term mortality. The score of the new nutritional screening tool, CONUT, is easy to determine in clinical practice. Based on our study, the CONUT score may play a prognostic role in rAAA. Clinicians should focus on patients' nutritional status and educate patients about good nutritional practices to improve their outcomes. Future large multi-center studies are needed to confirm our findings.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Nanjing Drum Tower Hospital affiliated to Nanjing University School. The patients/participants provided their written informed consent to participate in this study.

Author contributions

S-LY, L-LS, G-YX, ZL, A-MQ and X-QL conceived of the idea and were major contributors in writing the manuscript; S-LY, G-YX and W-DL collected the data; TT and S-LY performed the statistical analysis. All authors contributed to the interpretation of the results and critically reviewed the first draft. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Wanhainen A, Verzini F, Van Herzeele I, Allaire E, Bown M, Cohnert T, et al. Editor's choice - European society for vascular surgery (ESVS) 2019 clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysms. *Eur J Vasc Endovasc Surg*. (2019) 57(1):8–93. doi: 10.1016/j.ejvs.2018.09.020

2. Lesperance K, Andersen C, Singh N, Starnes B, Martin MJ. Expanding use of emergency endovascular repair for ruptured abdominal aortic aneurysms: disparities in outcomes from a nationwide perspective. *J Vasc Surg*. (2008) 47(6):1165. doi: 10.1016/j.jvs.2008.01.055

3. US Preventive Services Task Force, Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, et al. Screening for abdominal aortic aneurysm: US preventive services task force recommendation statement. *J Am Med Assoc*. (2019) 322 (22):2211–8. doi: 10.1001/jama.2019.18928

4. Karthikesalingam A, Holt PJ, Vidal-Diez A, Ozdemir BA, Poloniecki JD, Hinchliffe RJ, et al. Mortality from ruptured abdominal aortic aneurysms: clinical lessons from a comparison of outcomes in England and the USA. *Lancet*. (2014) 383(9921):963–9. doi: 10.1016/S0140-6736(14)60109-4

5. Ignacio de Ulibarri J, Gonzalez-Madrono A, de Villar NG, Gonzalez P, Gonzalez B, Mancha A, et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population. *Nutr Hosp*. (2005) 20(1):38–45.

6. Fukushima K, Ueno Y, Kawagishi N, Kondo Y, Inoue J, Kakazu E, et al. The nutritional index 'CONUT' is useful for predicting long-term prognosis of patients with end-stage liver diseases. *Tohoku J Exp Med*. (2011) 224(3):215–9. doi: 10.1620/tjem.224.215

7. Shirakabe A, Hata N, Kobayashi N, Okazaki H, Matsushita M, Shibata Y, et al. The prognostic impact of malnutrition in patients with severely decompensated acute heart failure, as assessed using the prognostic nutritional index (PNI) and controlling nutritional status (CONUT) score. *Heart Vessels*. (2018) 33(2):134–44. doi: 10.1007/s00380-017-1034-z

8. Ahn SS, Yoo J, Jung SM, Song JJ, Park YB, Lee SW. Comparison of the clinical implications among five different nutritional indices in patients with lupus nephritis. *Nutrients*. (2019) 11(7):1456. doi: 10.3390/nu11071456

9. Takagi K, Buettner S, Ijzermans JNM. Prognostic significance of the controlling nutritional status (CONUT) score in patients with colorectal cancer: a systematic review and meta-analysis. *Int J Surg*. (2020) 78:91–6. doi: 10.1016/j.ijsu.2020.04.046

10. Terasaki F, Sugiura T, Okamura Y, Ito T, Yamamoto Y, Ashida R, et al. The preoperative controlling nutritional status (CONUT) score is an independent prognostic marker for pancreatic ductal adenocarcinoma. *Updates Surg*. (2021) 73 (1):251–9. doi: 10.1007/s13304-020-00792-9

11. Zhang Y, Zhang X. Controlling nutritional status score, a promising prognostic marker in patients with gastrointestinal cancers after surgery: a systematic review and meta-analysis. *Int J Surg*. (2018) 55:39–45. doi: 10.1016/j.ijsu.2018.05.018

12. Shimose S, Kawaguchi T, Iwamoto H, Tanaka M, Miyazaki K, Ono M, et al. Controlling nutritional status (CONUT) score is associated with overall survival in patients with unresectable hepatocellular carcinoma treated with lenvatinib: a multicenter cohort study. *Nutrients*. (2020) 12(4):1076. doi: 10.3390/nu12041076

13. Cabre M, Ferreiro C, Arus M, Roca M, Palomera E, Serra-Prat M. Evaluation of CONUT for clinical malnutrition detection and short-term prognostic assessment in hospitalized elderly people. *J Nutr Health Aging*. (2015) 19(7):729–33. doi: 10.1007/s12603-015-0536-6

14. Sun XN, Luo LM, Zhao XQ, Ye P. Controlling nutritional status (CONUT) score as a predictor of all-cause mortality in elderly hypertensive patients: a prospective follow-up study. *BMJ Open*. (2017) 7(9):e015649. doi: 10.1136/bmjopen-2016-015649

15. Lindholt JS, Sogaard R, Laustsen J. Prognosis of ruptured abdominal aortic aneurysms in Denmark from 1994 to 2008. *Clin Epidemiol*. (2012) 4:111–3. doi: 10.2147/CLEP.S31098

16. Rokosh RS, Wu WW, Eskandari MK, Chaikof EL. Society for vascular surgery implementation of guidelines in abdominal aortic aneurysms: preoperative surveillance and threshold for repair. *J Vasc Surg*. (2021) 74(4):1053–4. doi: 10.1016/j.jvs.2021.04.068

17. Chaikof EL, Dalman RL, Eskandari MK, Jackson BM, Lee WA, Mansour MA, et al. The society for vascular surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. *J Vasc Surg*. (2018) 67(1):2–77 e2. doi: 10.1016/j.jvs.2017.10.044

18. Reite A, Soreide K, Ellingsen CL, Kvaloy JT, Vetrhus M. Epidemiology of ruptured abdominal aortic aneurysms in a well-defined Norwegian population with trends in incidence, intervention rate, and mortality. *J Vasc Surg*. (2015) 61 (5):1168–74. doi: 10.1016/j.jvs.2014.12.054

19. Parkinson F, Ferguson S, Lewis P, Williams IM, Twine CP, et al. Rupture rates of untreated large abdominal aortic aneurysms in patients unfit for elective repair. *J Vasc Surg*. (2015) 61(6):1606–12. doi: 10.1016/j.jvs.2014.10.023

20. United Kingdom EVAR Trial Investigators, Greenhalgh RM, Brown LC, Powell JT, Thompson SG, Epstein D, et al. Endovascular versus open repair of abdominal aortic aneurysm. *N Engl J Med*. (2010) 362(20):1863–71. doi: 10.1056/NEJMoa0909305

21. Lederle FA, Freischlag JA, Kyriakides TC, Padberg FT Jr, Matsumura JS, Kohler TR, et al. Outcomes following endovascular vs open repair of abdominal aortic aneurysm: a randomized trial. *J Am Med Assoc*. (2009) 302(14):1535–42. doi: 10.1001/jama.2009.1426

22. Patel R, Sweeting MJ, Powell JT, Greenhalgh RM, Investigators ET. Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial. *Lancet*. (2016) 388(10058):2366–74. doi: 10.1016/S0140-6736(16)31135-7

23. Desgranges P, Kobeiter H, Katsahian S, Bouffi M, Gouny P, Favre JP, et al. Editor's choice - ECAR (endovasculaire ou chirurgie dans les anevrysmes aorto-iliaques rompus): a French randomized controlled trial of endovascular versus open surgical repair of ruptured aorto-iliac aneurysms. *Eur J Vasc Endovasc*. (2015) 50 (3):303–10. doi: 10.1016/j.ejvs.2015.03.028

24. Powell JT, Sweeting MJ, Thompson MM, Ashleigh R, Bell R, Gomes M, et al. Endovascular or open repair strategy for ruptured abdominal aortic aneurysm: 30 day outcomes from IMPROVE randomised trial. *Brit Med J*. (2014) 348:f661. doi: 10.1136/bmj.f7661

25. Kapma MR, Dijksman LM, Reimerink JJ, de Groof AJ, Zeebregts CJ, Wisselink W, et al. Cost-effectiveness and cost-utility of endovascular versus open repair of ruptured abdominal aortic aneurysm in the Amsterdam acute aneurysm trial. *Brit J Surg*. (2014) 101(3):208–15. doi: 10.1002/bjs.9356

26. Kunimura A, Ishii H, Uetani T, Aoki T, Harada K, Hirayama K, et al. Impact of nutritional assessment and body mass index on cardiovascular outcomes in patients with stable coronary artery disease. *Int J Cardiol*. (2017) 230:653–8. doi: 10.1016/j.ijcard.2017.01.008

27. Kodama A, Takahashi N, Sugimoto M, Niimi K, Banno H, Komori K. Associations of nutritional status and muscle size with mortality after open aortic aneurysm repair. *J Vasc Surg*. (2019) 70(5):1585–93. doi: 10.1016/j.jvs.2019.01.049

28. Miyata T, Yamashita YI, Higashi T, Taki K, Izumi D, Kosumi K, et al. The prognostic impact of controlling nutritional status (CONUT) in intrahepatic cholangiocarcinoma following curative hepatectomy: a retrospective single institution study. *World J Surg*. (2018) 42(4):1085–91. doi: 10.1007/s00268-017-4214-1

29. Xue QL. The frailty syndrome: definition and natural history. *Clin Geriatr Med*. (2011) 27(1):1. doi: 10.1016/j.cger.2010.08.009

30. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. (2001) 56(3):M146–56. doi: 10.1093/gerona/56.3.M146

31. Raiten DJ, Ashour FAS, Ross AC, Meydani SN, Dawson HD, Stephensen CB, et al. Inflammation and nutritional science for programs/policies and interpretation of research evidence (INSPIRE). *J Nutr*. (2015) 145(5):1039s–108s. doi: 10.3945/jn.114.194571

32. Zabetakis I, Lordan R, Norton C, Tsoupras A. COVID-19: the inflammation link and the role of nutrition in potential mitigation. *Nutrients*. (2020) 12(5):1466. doi: 10.3390/nu12051466

33. Alwarawrah Y, Kiernan K, MacIver NJ. Changes in nutritional status impact immune cell metabolism and function. *Front Immunol*. (2018) 9:1055. doi: 10.3389/fimmu.2018.01055

34. Merker M, Felder M, Gueissaz L, Bolliger R, Tribolet P, Kagi-Braun N, et al. Association of baseline inflammation with effectiveness of nutritional support among patients with disease-related malnutrition A secondary analysis of a randomized clinical trial. *JAMA Netw Open*. (2020) 3(3):e200663. doi: 10.1001/jamanetworkopen.2020.0663

35. Joles JA, WillekesKoolschijn N, Koomans HA. Hypoalbuminemia causes high blood viscosity by increasing red cell lysophosphatidylcholine. *Kidney Int*. (1997) 52 (3):761–70. doi: 10.1038/ki.1997.393

36. Smidowicz A, Regula J. Effect of nutritional status and dietary patterns on human serum C-reactive protein and interleukin-6 concentrations. *Adv Nutr*. (2015) 6(6):738–47. doi: 10.3945/an.115.009415

37. Diehm N, Dick F, Schaffner T, Schmidli J, Kalka C, Di Santo S, et al. Novel insight into the pathobiology of abdominal aortic aneurysm and potential future treatment concepts. *Prog Cardiovasc Dis*. (2007) 50(3):209–17. doi: 10.1016/j.pcad.2007.05.001

38. Gitlin JM, Trivedi DB, Langenbach R, Loftin CD. Genetic deficiency of cyclooxygenase-2 attenuates abdominal aortic aneurysm formation in mice. *Cardiovasc Res*. (2007) 73(1):227–36. doi: 10.1016/j.cardiores.2006.10.015

39. Li JR, Zhang Y, Zheng JL. Decreased pretreatment serum cholesterol level is related with poor prognosis in resectable non-small cell lung cancer. *Int J Clin Exp Patho*. (2015) 8(9):11877–83.

40. Shin HJ, Roh CK, Son SY, Hoon H, Han SU. Prognostic value of hypocholesterolemia in patients with gastric cancer. *Asian J Surg*. (2021) 44 (1):72–9. doi: 10.1016/j.asjsur.2020.08.014

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Onset of pain to surgery time in acute aortic dissections type A: a mandatory factor for evaluating surgical results?

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Objective: An acute aortic dissection type A (AADA) is a rare but life-threatening event. The mortality rate ranges between 18% to 28% and mortality is often within the first 24 h and up to 1%–2% per hour. Although the onset of pain to surgery time has not been a relevant factor in terms of research in the field of AADA, we hypothesize that a patient's preoperative conditions depend on the length of this time.
Methods: Between January 2000 and January 2018, 430 patients received surgical treatment for acute aortic dissection DeBakey type I at our tertiary referral hospital. In 11 patients, the exact time point of initial onset of pain was retrospectively not detectable. Accordingly, a total of 419 patients were included in the study. The cohort was categorized into two groups: Group A with an onset of pain to surgery time < 6 h (n = 211) and Group B > 6 h (n = 208), respectively.
Results: Median age was 63.5 years (y) ((IQR: 53.3–71.4 y); (67.5% male)). Preoperative conditions differed significantly between the cohorts. Differences were detected in terms of malperfusion (A: 39.3%; B: 23.6%; P: 0.001), neurological symptoms (A: 24.2%; B: 15.4%; P: 0.024), and the dissection of supra-aortic arteries (A: 25.1%; B: 16.8%; P: 0.037). In particular, cerebral malperfusion (A 15.2%: B: 8.2%; P: 0.026) and limb malperfusion (A: 18%, B: 10.1%; P: 0.020) were significantly increased in Group A. Furthermore, Group A showed a decreased median survival time (A: 1,359.0 d; B: 2,247.5 d; P: 0.001), extended ventilation time (A: 53.0 h; B: 44.0 h; P: 0.249) and higher 30-day mortality rate (A: 25.1%; B: 17.3%; P: 0.051).
Conclusions: Patients with a short onset of pain to surgery time in cases of AADA present themselves not only with more severe preoperative symptoms but are also the more compromised cohort. Despite early presentation and emergency aortic repair, these patients show increased chances of early mortality. The "onset of pain to surgery time" should become a mandatory factor when making comparable surgical evaluations in the field of AADA.

KEYWORDS
aortic dissection, AADA, arch repair, time, pain

Abbreviations
AADA, Acute aortic dissection type A; BMI, Body mass index; IQR, Interquartile range; PVOD, Peripheral vascular occlusion disease; COPD, Chronic obstructive occlusion disease; FET, Frozen elephant trunk; SACP, Selective antegrade cerebral protection; CCT, Cranial computer tomography; TAA, Thoraco-abdominal aneurysm; TEVAR, thoracic endovascular aortic repair; EVAR, endovascular aortic repair; IRAD, International Registry of Acute Aortic Dissections; HCA, Hypothermic circulatory arrest; CABG, Coronary artery bypass graft; ECMO, Extracorporeal membrane oxygenation); LCA, Left coronary artery; RCA, Right coronary artery; CT, Computer tomography.

Introduction

An acute aortic dissection type A is a rare but life-threatening event (1, 2). This severe disease can have various manifestations. Following an initial intimal tear, blood is able to penetrate from the aortic lumen into the media layer, resulting in a separation of the aortic wall layers and the subsequent formation of a true and a false lumen. This process may result in either organ malperfusion and impairment or even in an aortic rupture. Acute aortic dissections Stanford type A (AADA) are reported with high perioperative mortality ranging from 18% to 28% and mortality within the first 24 h and up to 1%–2% per hour (3–6). Harris et al. found that a delay in time from diagnosis to surgery may be associated with a history of previous cardiac surgery, presentation without abrupt or any pain, and initial presentation to a nontertiary care hospital (7). However, results from the United Kingdom suggest that both short-term and long-term outcomes are significantly related to surgeons' experience (8).

Multiple publications present surgical outcomes following aortic repair in AADA. Nevertheless, is it essential to integrate the onset of pain to surgery time to evaluate and compare patients' preoperative conditions and, furthermore, to avoid selection bias? Existing studies calculate the time between onset and operation in days (9). Our department calculates it in hours.

It is common sense that a delayed diagnosis of aortic dissection will result in an increased mortality rate (10).

In our retrospective study we evaluated patients who received open aortic repair due to AADA in our department. We distinguished this cohort into two groups: one group under and one group above our median onset of pain to surgery time of 6 h.

We hypothesize that onset of pain to surgery time is a highly underrated factor in comparative evaluations regarding survival after aortic repair. Furthermore, we assume that a patient's preoperative conditions depend on this duration of time. But how should it be interpreted? The earlier the better?

Methods

Study population and study design

Between January 2000 and January 2018, 430 patients received surgical treatment due to acute aortic dissection DeBakey type I at our tertiary referral hospital. In 11 patients, the exact time point of initial onset of pain was retrospectively not detectable. Accordingly, a total of 419 patients (67.5% male; 63.5 years (y) median age; interquartile range (IQR) 53.3–71.4 y) were included in our study. All 430 patients were comers. Iatrogenic dissection and AADAs that occurred inside our hospital were not included in this study to prevent further selection bias.

DeBakey type II and III and chronic dissections were not included in this study. Due to the median onset of pain to surgery time of 6 h (h), we categorized the cohort in two groups: Group A with an onset of pain to surgery time < 6 h ($n = 211$) and Group B > 6 h ($n = 208$), respectively. Data were collected at our aortic outpatient clinic where patients were frequently seen after surgery. Furthermore, patients were actively contacted by a study nurse team. Individual consent was obtained from all patients to allow for further follow-up data collection. Follow-up data collection was ended and completed in February 2022. Our retrospective study was approved by our institutional ethics committee. Patients' preoperative characteristics are presented in **Tables 1, 2**.

TABLE 1 Patients' characteristics: IQR, interquartile range; BMI, body mass index; PVOD, peripheral vascular occlusion disease; COPD, chronic obstructive pulmonary disease.

Characteristics	Entire cohort	Onset of pain </= 6 h	Onset of pain > 6 h	*P*-value
Total patients	*n* = 419	*n* = 211	*n* = 208	
Age at surgery (years), median (IQR)	63.5 (53.3–71.4)	63.7 (53.1–71.5)	63.0 (53.6–71.1)	0.656
Sex male, *n* (%)	283 (67.5)	149 (70.6)	134 (64.4)	0.176
BMI, median (IQR)	26.2 (24.2–29.1)	26.1 (24.2–29.2)	26.3 (24.0–28.1)	0.574
Hypertension, *n* (%)	270 (64.4)	131 (62.1)	139 (66.8)	0.311
Diabetes mellitus, *n* (%)	29 (6.9)	15 (7.1)	14 (6.7)	0.879
PVOD, *n* (%)	18 (4.3)	7 (3.3)	11 (5.3)	0.320
COPD, *n* (%)	39 (9.3)	15 (7.1)	24 (11.5)	0.119
Coronary heart disease, *n* (%)	42 (10.0)	16 (7.6)	26 (12.5)	0.094
Hyperthyreosis, *n* (%)	3 (0.7)	1 (0.5)	2 (1.0)	0.621
Hypothyreosis, *n* (%)	33 (7.9)	15 (7.1)	18 (8.7)	0.557
Atrial fibrillation, *n* (%)	52 (12.4)	20 (9.5)	32 (15.4)	0.067
Marfan syndrome, *n* (%)	19 (4.5)	7 (3.3)	12 (5.8)	0.228
Pericardial tamponade, *n* (%)	162 (38.7)	91 (43.1)	71 (34.1)	0.059
Bicuspid aortic valve, *n* (%)	19 (4.5)	13 (6.2)	6 (2.9)	0.107
Preoperative intubation, *n* (%)	54 (12.9)	29 (13.7)	25 (12.0)	0.598
Mechanical resuscitation, *n* (%)	38 (9.1)	23 (10.9)	15 (7.2)	0.189
Cardiac reoperation, *n* (%)	14 (3.3)	5 (2.4)	9 (4.3)	0.265

TABLE 2 Preoperative data: CT, computed tomography; LCA, left coronary artery; RCA, right coronary artery; IQR, interquartile range.

Characteristics	Entire cohort	Onset of pain </= 6 h	Onset of pain > 6 h	*P*-value
Malperfusion, *n* (%)	132 (31.5)	83 (39.3)	49 (23.6)	**0.001**
Cerebral malperfusion, *n* (%)	49 (11.7)	32 (15.2)	17 (8.2)	**0.026**
Visceral malperfusion, *n* (%)	35 (8.4)	22 (10.4)	13 (6.3)	0.122
Renal malperfusion, *n* (%)	47 (11.2)	29 (13.7)	18 (8.7)	0.099
Limb malperfusion, *n* (%)	59 (14.1)	38 (18.0)	21 (10.1)	**0.020**
Hemiparesis, *n* (%)	26 (6.2)	13 (6.2)	13 (6.3)	0.970
Paraparesis, *n* (%)	15 (3.6)	10 (4.7)	5 (2.4)	0.198
Seizure, *n* (%)	6 (1.4)	3 (1.4)	3 (1.4)	1.000
Evidence of stroke CT, *n* (%)	26 (6.2)	16 (7.6)	10 (4.8)	0.239
Neurologic symptoms, *n* (%)	83 (19.8)	51 (24.2)	32 (15.4)	**0.024**
Dissection supra-aortic arteries, *n* (%)	88 (21.0)	53 (25.1)	35 (16.8)	**0.037**
Dissection LCA, *n* (%)	12 (2.9)	6 (2.8)	6 (2.9)	0.980
Dissection RCA, *n* (%)	41 (9.8)	26 (12.3)	15 (7.2)	0.078
Onset of pain prior to surgery (h), median (IQR)	6.0 (4.0–13.0)	4.0 (3.0–5.0)	13.0 (8.0–30.0)	**<.001**

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Definitions

Patients with AADA may either present specific symptoms like floating back pain, abdominal pain, neurological disabilities, signs of malperfusion, or unspecific symptoms. CT angiography remains the gold standard for diagnosis of this potentially lethal disease. The existence of a dissection membrane starting in the ascending aorta or even an intramural hematoma inside the aortic wall represents the radiographic equivalent of an AADA. The onset of pain to surgery time was defined as the time from the documented painful event until skin cut in the operation theater.

Patients who presented themselves with severe neurologic symptoms like apraxia, hemiplegia, or dysarthria without a performed cerebral CT scan prior to surgery and postoperative evidence of stroke were assigned to the preoperative stroke cohort. A stroke had to be verified by CT or magnetic resonance imaging (MRI).

Occlusion or complete false lumen perfusion was defined as malperfusion according to Sievers et al. (11) (TEM Aortic Dissection Classification stage M2 and M3 ((−), (+)). The diagnosis of dissection of the coronary arteries was detected either using coronary angiography or had to be visible intraoperatively. AADAs accidently induced during open heart surgery were defined as iatrogenic dissection. Dissections postoperatively detected using CT or MRI were defined as *persisting dissections*.

For the diagnosis of hypertension, diabetes mellitus, or chronic obstructive pulmonary disease (COPD) a preoperatively performed medical treatment was necessary.

Perioperative management and surgical technique

Our department provides emergency medical service to a population of approximately 2 million citizens. Longest distance of the ground- and helicopter-based patient transfer is around 100 km. According to our standard operating procedure, transfer to the operation theater must be performed promptly after diagnosis of AADA. Furthermore, we established a rapid response team of aortic surgeons, able to provide aortic repair 24/7 in case of AADA. These standardized procedures result in a median time from onset of pain to surgery of approximately 6 h.

According to our standard operating procedure, transfer to the operation theater must be performed promptly after diagnosis of AADA. To avoid early cardiac decompensation, intubation was not performed until all anesthesiological and surgical preparations were completed. This was followed by intubation and the establishment of full sternotomy extra-corporal circulation (ECC). Our cannulation technique in cases of AADA was previously published by our group (12, 13). We prefer direct aortic cannulation. Following the identification of the true lumen using transesophageal echocardiography, direct cannulation was performed. The left side of the heart was vented via the right upper pulmonary vein. The application of cardioplegia was performed directly into the coronary ostia and repeated every 30 min. Blood cardioplegia was used for myocardial protection. In 2010 we established the beating heart technique for extended arch surgery (14).

The root first technique was performed while cooling the patient. Concomitant procedures (e.g., CABG) were performed during cooling if necessary. In all cases of AADA with extended arch surgery, hypothermic circulatory arrest (temperatures between 22°C and 26°C) and bilateral selective antegrade cerebral perfusion were performed. The use of SACP varied based on the surgeon's decision on whether proximal arch repair was to be done.

Extended arch repair

From 2000 to 2010, the FET technique was performed using a custom-made Chavan-Haverich prosthesis followed by a prefabricated Chavan-Haverich hybrid graft (15, 16) (Curative GmbH, Dresden, Germany). From 2005 to 2010, the Jotec E-vita hybrid graft was used (17). The attachment of the supra-aortic arteries was performed using the island (*en bloc*) technique until 2010. Following the island technique, we switched to the four-branched frozen elephant trunk prosthesis (FET Vascutek Terumo, Terumo®, Glasgow, UK) (18, 19). We changed our strategy in 2007 from a straight graft with island technique to the branched Sienna™ graft (Terumo®, Glasgow, UK), even for total or hemi-arch replacement. The extensive use of branched aortic arch prostheses resulted in major technical developments. As a consequence of these changes, arch replacement was performed after completing cardiac and proximal aortic repair. Head vessels were anastomosed to the corresponding side branches of the graft at the end of the procedure.

Proximal arch repair

Limited aortic repair in terms of a proximal arch replacement was performed using established straight Dacron grafts.

Statistical analysis

SPSS 27 Statistics software (IBM Corp. released 2020; IBM SPSS Statistics for Windows, Version 27.0; Armonk, NY: IBM Corp.) was used for data analysis. A normal distribution of variables was calculated using the Kolmogorov–Smirnov test. Categorical variables are stated as absolute numbers (n) and proportions. Normally distributed continuous variables are stated as mean ± standard deviation, while continuous variables without normal distribution are stated as median and interquartile range (IQR). Fisher's exact test was used to detect differences in categorical variables. Differences in continuous variables were tested using the Mann-Whitney U test. Kaplan–Meier analysis and log rank were used for the evaluation of survival, and the log rank test was used to test for differences. We did not correct for multiple testing.

Results

Preoperative patient characteristics

Patient demographics are found in Table 1. Median age did not differ significantly between the groups (A: 63.7 y; B: 63.0 y; P: 0.656). The majority were male patients (A: 70.6%; B: 64.4%; P: 0.176). Hypertension was a dominant diagnosis in the patients' history (A: 62.1%; B: 66.8%; P: 0.311). Overall, medical history, including diabetes mellitus (A: 7.1%; B: 6.7%; P: 0.879) and PVOD (A: 3.3%; B: 5.3%; P: 0.320) were comparable in both cohorts. Group B showed higher COPD (A: 7.1%; B: 11.5%; P: 0.119), coronary heart disease (A: 7.6%; B: 12.5%; P: 0.094), and atrial fibrillation (A: 9.5%; B: 15.4%; P: 0.067). In contrast, pericardial tamponade (A: 43.1%; B: 34.1%; P: 0.059) and mechanical resuscitation (A: 10.9%; B: 7.2%; P: 0.189) occurred slightly but not significantly more often in patients with a painful event to surgery time <6 h.

Significant differences were detected in terms of malperfusion (A: 39.3%; B: 23.6%; P: 0.001), neurological symptoms (A: 24.2%; B: 15.4%; P: 0.024) and the dissection of supra-aortic arteries (A: 25.1%; B: 16.8%; P: 0.037). In particular, cerebral malperfusion (A: 15.2%; B: 8.2%; P: 0.026) and limb malperfusion (A: 18%; B: 10.1%; P: 0.020) were significantly increased in Group A. In addition, the incidence of isolated dissection of the right coronary artery was higher in this cohort (A: 12.3%; B: 7.2%; P: 0.078).

Intraoperative data

Intraoperative data are shown in Table 3. Operation time (A: 333.0 min; B: 323.0 min; P: 0.509), cardiopulmonary bypass time (A: 220.0; B: 213.0; P: 0.342), and aortic cross-clamp time (A: 124.0 min.; B: 323 min; P: 0.509) did not differ significantly between the two cohorts. Group A showed a higher demand for platelet concentrates (A: $n = 3.0$ (IQR: 2.0–4.0); B: $n = 2.0$ (IQR: 2.0–4.0); P: 0.011). The number of operations extended in terms of limited vs. total arch repair was comparable in both groups. Neither limited nor extended aortic arch repair showed significant differences. In keeping with an elevated dissection rate of RCA, CABG was more often performed in Group A (A: 19.9%; B: 14.9%; P: 0.177).

Postoperative data

Patients with a shorter "onset of pain to surgery time" presented a significantly decreased median survival time (A: 1,359.0 d; B: 2,247.5 d; P: 0.001), extended ventilation time (A: 53.0 h; B: 44.0 h; P: 0.249), and a higher 30-day mortality rate (A: 25.1%; B: 17.3%; P: 0.051). Furthermore, postoperative persisting visceral malperfusion (A: 4.7%; B: 0%; P: 0.002) and renal malperfusion (A: 8.1%; B: 1.4%; P: 0.001) occurred mostly in Group A (Table 4).

TABLE 3 Intraoperative data: SD, standard deviation; IQR, interquartile range; min, minute; HCA, hypothermic circulatory arrest time; CABG, coronary artery bypass graft; SACP, selective antegrade cerebral perfusion time.

Characteristics	Entire cohort	Onset of pain </= 6 h	Onset of pain > 6 h	*P*-value
Total patients	*n* = 419	*n* = 211	*n* = 208	
Total operation time (min), median (IQR)	329.0 (259.0–405.0)	333.0 (259.0–411.0)	323.0 (257.0–387.8)	0.509
Cardiopulmonary bypass time (min), median (IQR)	217.0 (168.0–286.0)	220.0 (168.0–289.0)	213.0 (168.0–281.0)	0.342
Aortic cross-clamp time (min), median (IQR)	126.0 (93.0–162.0)	124.0 (92.0–162.0)	128.5 (94.0–161.8)	0.947
HCA (hypothermic circulatory arrest) time (min), median (IQR)	36.0 (25.0–52.0)	36.0 (25.0–51.0)	36.0 (24.3–55.0)	0.686
SACP (selective antegrade cerebral perfusion) time (min), median (IQR)	33.0 (20.0–76.0)	32.0 (19.0–83.0)	38.0 (20.0–72.0)	0.615
Minimal core temperature (°C), median (IQR)	24.6 (22.2–26.0)	24.5 (q22.0–26.0)	24.6 (22.3–26.0)	0.528
Erythrocyte concentrates, median (IQR)	6.0 (4.0–10.0)	6.0 (4.0–10.0)	6.0 (3.3–10.0)	0.884
Fresh frozen plasma, median (IQR)	6.0 (4.0–10.0)	6.0 (4.0–10.0)	6.0 (4.0–10.0)	0.685
Platelet concentrates, median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	2.0 (2.0–4.0)	**0.011**
Arch replacement:				
Proximal arch replacement, *n* (%)	186 (44.4)	96 (45.5)	90 (43.3)	0.646
Subtotal arch replacement, *n* (%)	34 (8.1)	15 (7.1)	19 (9.1)	0.448
Total arch replacement, *n* (%)	35 (8.4)	18 (8.5)	17 (8.2)	0.895
Total arch replacement elephant trunk, *n* (%)	46 (11.0)	17 (8.1)	29 (13.9)	0.054
Total Arch replacement frozen elephant trunk, *n* (%)	118 (28.2)	65 (30.8)	53 (25.5)	0.226
Bio glue, *n* (%)	141 (33.7)	78 (37.0)	63 (30.3)	0.148
Aortic valve replacement:				
Biologic, *n* (%)	62 (14.8)	30 (14.2)	32 (15.4)	0.737
Mechanic, *n* (%)	66 (15.8)	32 (15.2)	34 (16.3)	0.740
Root involvement, *n* (%)	254 (60.6)	122 (57.8)	132 (63.5)	0.237
Bentall, *n* (%)	127 (30.3)	61 (28.9)	66 (31.7)	0.530
David, *n* (%)	97 (23.3)	49 (23.2)	48 (23.1)	0.972
Yacoub, *n* (%)	19 (4.5)	8 (3.8)	11 (5.3)	0.462
CABG, *n* (%)	73 (17.4)	42 (19.9)	31 (14.9)	0.177
ECMO, *n* (%)	18 (4.3)	9 (4.3)	9 (4.3)	0.975
Exitus in tabula, *n* (%)	12 (2.9)	6 (2.8)	6 (2.9)	0.980

TABLE 4 Postoperative data: SD, standard deviation; IQR, interquartile range; min, minute; CCT, cranial computed tomography.

Characteristics	Entire cohort	Onset of pain </= 6 h	Onset of pain > 6 h	*P*-value
Total patients	*n* = 419	*n* = 211	*n* = 208	
Survival time (days), median (IQR)	1,741.0 (80.0–3,223.0)	1,359.0 (24.0–2,786.0)	2,247.5 (309.5–3,740.0)	**0.001**
Ventilation time (h)	48.0 (21.0–136.0)	53.0 (23.0–146.0)	44.0 (20.0–110.8)	0.249
Intensive care unit (days), median (IQR)	4.0 (2.0–8.0)	4.0 (2.0–8.0)	4.0 (2.0–8.0)	0.784
Rethoracotomy, *n* (%)	69 (16.5)	37 (17.5)	32 (15.4)	0.553
Dialysis, *n* (%)	52 (12.4)	30 (14.2)	22 (10.6)	0.258
30-day mortality, *n* (%)	89 (21.2)	53 (25.1)	36 (17.3)	0.051
CCT stroke, *n* (%)	82 (19.6)	44 (20.9)	38 (18.3)	0.505
New-onset stroke, *n* (%)	35 (8.4)	18 (8.5)	17 (8.2)	0.895
Persisting cerebral malperfusion, *n* (%)	15 (3.6)	11 (5.2)	4 (1.9)	0.070
Persisting limb malperfusion, *n* (%)	11 (2.6)	5 (2.4)	6 (2.9)	0.742
Persisting visceral malperfusion, *n* (%)	10 (2.4)	10 (4.7)	0 (0.0)	**0.002**
Persisting renal malperfusion, *n* (%)	20 (4.8)	17 (8.1)	3 (1.4)	**0.001**

Long-term follow-up data

The completeness of follow-up was 98,8% and the mean follow-up time for the entire group is 5.7 ± 5.4 years (2,079.7 ± 1,958.6 days). Follow-up data can be found in Table 5. The ratio of re-operations and re-interventions was comparable. A comparison of long-term survival using Kaplan-Meier curves is given in Figure 1. Significant differences were found between the groups. In contrast to a mean survival of 9.8 years (onset of pain > 6 h) (IQR: 8.6–10.9), survival time was decreased in patients with a short onset of pain to surgery time (<6 h) at 8.3 years (IQR: 7.1–9.5y), (log rank, P: 0.141). The survival rate at one year after aortic repair was A: 63% and B: 76%; at two years A: 62% and B: 71%; and A: 58% and B: 69% four years after surgery.

Discussion

AADA is a catastrophic event characterized by a high mortality and a high urgency indication for surgical repair. Despite an extremely high early mortality rate of up to 35% in the first 24 h (20, 21), the duration from onset of pain to surgery has been a neglected topic in current AADA research. The comparability of early and long-term results requires reliable and almost identical preoperative conditions. Apart from the potentially high chance of selection bias due to the long time until aortic repair, we hypothesized that even a patient's preoperative status will differ significantly depending on the onset of pain to surgery time.

Nevertheless, an analysis from the International Registry of Acute Aortic Dissection (IRAD) indicates that the median time from emergency department presentation to a definitive diagnosis of acute aortic dissection is 4.3 h, with an additional 4 h between diagnosis and surgical intervention (22, 23). In comparison to IRAD data, in our department, patients with AADA received surgical treatment 6.0 h (median) following the initial painful event.

The time from "onset of pain" to surgery in acute aortic type A dissections depends on a variety of factors. Our department is well-established within the highly advanced German health care infrastructure. Clinical outcomes however depend on the diagnostic capacity of the referring center as well as on the speed of transportation and/or distance of travel. According to our data, patients' conditions from both cohorts varied substantially on admission to our hospital. Building on our thesis that strong clinical signs lead to a more rapid AADA diagnosis, Group A (<6 h) presented a higher incidence of independent risk factors

TABLE 5 Follow-up data: TAA, thoraco-abdominal aneurysm; TEVAR, thoracic endovascular aortic repair; EVAR, endovascular aneurysm repair.

Characteristics	Entire cohort	Onset of pain </= 6 h	Onset of pain > 6 h	*P*-value
Total patients	*n* = 419	*n* = 211	*n* = 208	
Secondary aortic operation, *n* (%)	52 (12.4)	22 (10.4)	30 (14.4)	0.215
Re-operation identical area, *n* (%)	16 (3.8)	7 (3.3)	9 (4.3)	0.590
Re-operation downstream aorta, *n* (%)	36 (8.6)	15 (7.1)	21 (10.1)	0.275
TAA repair, *n* (%)	9 (2.1)	5 (2.4)	4 (1.9)	1,000
Y prosthesis, *n* (%)	4 (1.0)	0 (0.0)	4 (1.9)	0.060
Descending repair, *n* (%)	18 (4.3)	7 (3.3)	11 (5.3)	0.346
Hybrid, *n* (%)	7 (1.7)	4 (1.9)	3 (1.4)	1,000
TEVAR, *n* (%)	12 (2.9)	7 (3.3)	5 (2.4)	0.575
EVAR, *n* (%)	5 (1.2)	5 (2.4)	0 (0.0)	0.061
Aortic fenestration (%)	2 (0.5)	1 (0.5)	1 (0.5)	1.000

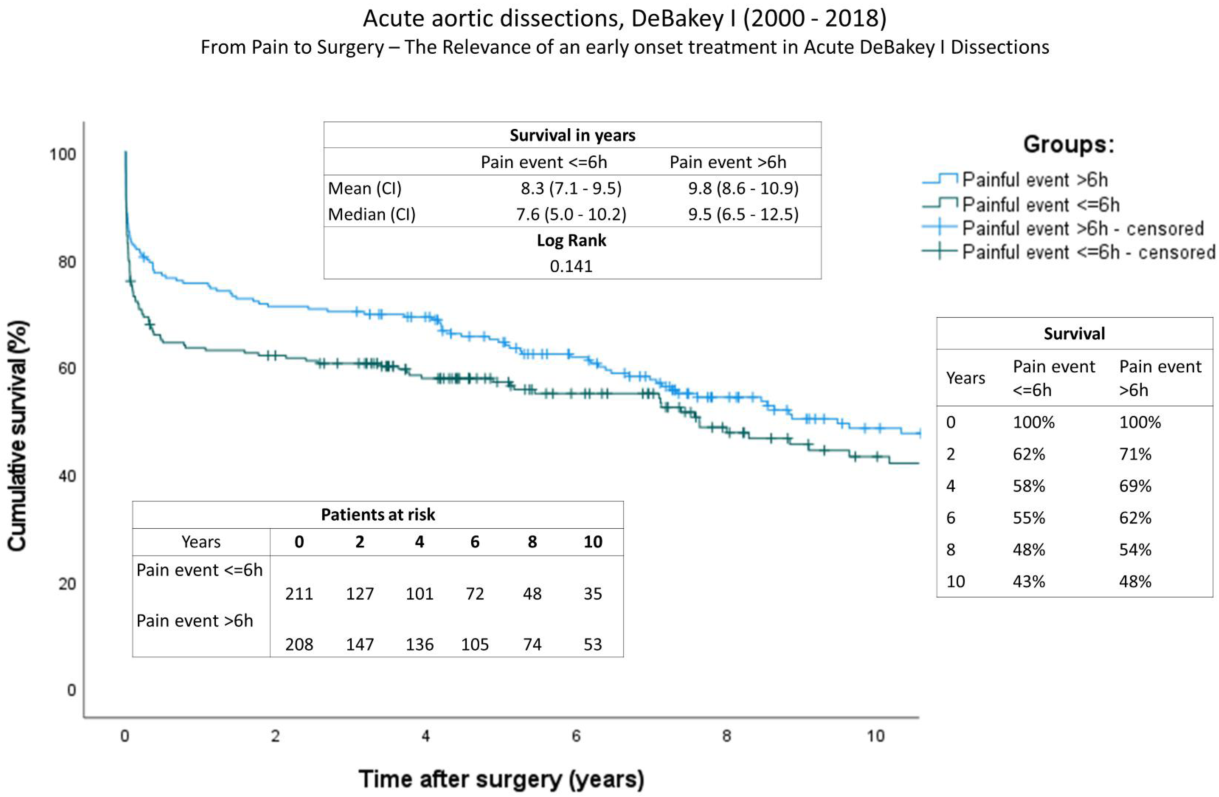

FIGURE 1
Survival: Kaplan-Meier curves showing survival of both groups (onset of pain <6 h; onset of pain >6 h). The x-axis denotes the time after operation.

for mortality, including pericardial tamponade (A: 43.1%; B: 34.1%; P: 0.059) and malperfusion (A: 39.3%; B: 23.6%; P: 0.001) (24). In particular, the increased incidence of cerebral malperfusion (A: 15.2%; B: 8.2%; P: 0.026) and limb malperfusion (A: 18.0%; B: 10.1%; P: 0.020) is consistent with more severe clinical symptoms. Furthermore, the high number of severe neurological symptoms (A: 24.2%; B: 15.4%; P: 0.024), which correlates with an increased incidence of the dissection of supra-aortic arteries (A: 25.1%; B: 16.8%; P: 0.037), is compatible with the thesis of early admission due to more severe symptoms.

There was no significant adjustment to the operative procedure observed in patients with aortic dissection <6 h. Even total operation time, cardiopulmonary bypass time, as well as aortic cross-clamp time, which are recognized as independent risk factors for mortality (25), were almost equally distributed in both groups.

Despite an equivalent surgical treatment, median survival time was significantly reduced (A: 1,359.0 d; B: 2,247.5 d; P: 0.001) and 30-day mortality (A: 25.1%; B: 17.3%; P: 0.051) increased in the cohort with the short onset of pain to surgery time (<6 h). This may be associated with the patient's assessed critically fatal conditions prior to surgery, with the consequence of a significantly reduced outcome despite comparable treatments.

These results correlate with a high rate of persisting visceral malperfusion (A: 4.7%; B: 0%; P: 0.002) and persisting renal malperfusion (A: 8.1%; B: 1.4%; P: 0.001) after surgery. According to the IRAD, malperfusion is the second most important cause of death after aortic dissection (20, 26, 27). There are two possible explanations for this remaining malperfusion. First, progress of the aortic dissection membrane of the downstream aorta between the initial CT scan and start of surgery, and second, the progress of the aortic dissection intraoperatively induced. Crawford et al. (27) previously described their observation that open aortic repair does not guarantee the restoration of distal perfusion as such, and end-organ malperfusion persists in up to 25% of patients, contributing to dismal operative outcomes (26). Nevertheless, only a minor number of malperfusions persist in patients with a longer time from pain onset to surgery. These results may imply an increased vulnerability of the aortic tissue during the early phase of AADA. To date, the existing literature needs to ask the relevant question of why patients with AADA show an elevated mortality rate during the first hours of disease occurrence, and whether an adjustment to their surgical therapy depending on the time factor is required. Until now, it was common sense that the early repair of aortic dissection would lead to a correction of malperfusion in most cases, while Goldberg et al. (28) suggested a better outcome when treating malperfusion first followed by a delayed repair of aortic dissection. The "malperfusion first" strategy is based on the fact that surgical repair can take a long time and persisting malperfusion may increase the chance of end-organ failure and aortic rupture (28). Finally, the question of whether an adjusted treatment is able to improve a patient's outcome or whether a patient's preoperative conditions are so limited that survival is independent of surgery remains unanswered.

Despite our results, the "early surgical treatment strategy" should remain the recommended algorithm in all cases to correct and prevent malperfusion or aortic rupture (29). However, whether this strategy includes the treatment of the more severely compromised patients should be clarified.

Nevertheless, our results also show that survival after an AADA depends on the health system infrastructure. Long transfer times due to geographic issues and prompt access to diagnostics and surgeon's skills are relevant factors for a patient's survival. It can be assumed that even in advanced healthcare systems, up to 20% of patients with AADA die before reaching a specialist center with surgical expertise for aortic surgery. Moreover, a diagnostic delay occurs in almost 40% of cases (30, 31).

According to our data, it cannot be denied that evidenced-based research in the field of AADA must consider the "onset of pain to surgery time" to avoid selection bias and to represent comparable results. Although this could be controversial, purely surgical results in terms of postoperative survival correlate positively with the onset of pain to surgery time: the longer the better.

Limitations

This is a retrospective study, and thus carries potential risks and biases linked to studies of this nature. Furthermore, decisions about the surgical procedure were individually made by the surgeon. Between the years 2000–2018, a total of 21 surgeons at our center performed surgical aortic repair in cases of AADA. Surgical skill levels may vary in this cohort. There were relevant changes regarding the total arch approach during the observed period of time. The use of different of prosthesis and surgical techniques may influence the study result. Our results confirm an increasing mortality rate in patients with a short onset of pain to surgery time. Nevertheless, strategies for the adjustment of a corresponding therapy were not evaluated. The number of patients who died before reaching the hospital is not documented. Knowledge of the exact number of patients who died preoperatively could influence the impact of the study.

Conclusion

Time is aorta. The prevention of high mortality due to AADA includes the development of a healthcare infrastructure for early diagnosis, referral, rapid hospital transfer, and well-trained aortic surgeons. In cases of AADA (where the onset of pain to surgery time is <6 h), patients present themselves not only with more severe preoperative symptoms but also are more compromised. Despite early presentation and emergency aortic repair, these patients show an increased chance of early mortality. The "onset of pain to surgery time" should become a required factor for making the surgical evaluation more comparable.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by This study is approved by the ethics comittee of the hanover medical school; Bernhard Schidt; No.: 10519_BO_K_2022. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors were involved in the conceptualization, data collection, data analysis, and writing the article. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Howard DP, Banerjee A, Fairhead JF, Perkins J, Silver LE, Rothwell PM, et al. Population-based study of incidence and outcome of acute aortic dissection and premorbid risk factor control: 10-year results from the Oxford vascular study. *Circulation*. (2013) 127(20):2031–7. doi: 10.1161/CIRCULATIONAHA.112.000483

2. Harris PD, Bowman FO Jr, Malm JR. The management of acute dissections of the thoracic aorta. *Am Heart J*. (1969) 78(3):419–22. doi: 10.1016/0002-8703(69)90048-9

3. Khan H, Hussain A, Chaubey S, Sameh M, Salter I, Deshpande R, et al. Acute aortic dissection type A: impact of aortic specialists on short and long term outcomes. *J Card Surg*. (2021) 36(3):952–8. doi: 10.1111/jocs.15292

4. Coady MA, Rizzo JA, Goldstein LJ, Elefteriades JA. Natural history, pathogenesis, and etiology of thoracic aortic aneurysms and dissections. *Cardiol Clin*. (1999) 17 (4):615–35. vii. doi: 10.1016/S0733-8651(05)70105-3

5. Trimarchi S, Nienaber CA, Rampoldi V, Myrmel T, Suzuki T, Mehta RH, et al. Contemporary results of surgery in acute type A aortic dissection: the international registry of acute aortic dissection experience. *J Thorac Cardiovasc Surg*. (2005) 129 (1):112–22. doi: 10.1016/j.jtcvs.2004.09.005

6. Chiappini B, Schepens M, Tan E, Dell' Amore A, Morshuis W, Dossche K, et al. Early and late outcomes of acute type A aortic dissection: analysis of risk factors in 487 consecutive patients. *Eur Heart J*. (2005) 26(2):180–6. doi: 10.1093/eurheartj/ehi024

7. Harris KM, Strauss CE, Eagle KA, Hirsch AT, Isselbacher EM, Tsai TT, et al. Correlates of delayed recognition and treatment of acute type A aortic dissection: the international registry of acute aortic dissection (IRAD). *Circulation*. (2011) 124 (18):1911–8. doi: 10.1161/CIRCULATIONAHA.110.006320

8. Bashir M, Shaw M, Field M, Kuduvalli M, Harrington D, Fok M, et al. Repair of type A dissection-benefits of dissection rota. *Ann Cardiothorac Surg*. (2016) 5 (3):209–15. doi: 10.21037/acs.2016.05.09

9. Zhang Y, Chen T, Chen Q, Min H, Nan J, Guo Z. Development and evaluation of an early death risk prediction model after acute type A aortic dissection. *Ann Transl Med*. (2021) 9(18):1442. doi: 10.21037/atm-21-4063

10. Zaschke L, Habazettl H, Thurau J, Matschilles C, Gohlich A, Montagner M, et al. Acute type A aortic dissection: aortic dissection detection risk score in emergency care —surgical delay because of initial misdiagnosis. *Eur Heart J Acute Cardiovasc Care*. (2020) 9(3_suppl):S40–7. doi: 10.1177/2048872620914931

11. Sievers HH, Rylski B, Czerny M, Baier ALM, Kreibich M, Siepe M, et al. Aortic dissection reconsidered: type, entry site, malperfusion classification adding clarity and enabling outcome prediction. *Interact Cardiovasc Thorac Surg*. (2020) 30(3):451–7. doi: 10.1093/icvts/ivz281

12. Khaladj N, Shrestha M, Peterss S, Strueber M, Karck M, Pichlmaier M, et al. Ascending aortic cannulation in acute aortic dissection type A: the Hannover experience. *Eur J Cardiothorac Surg*. (2008) 34(4):792–6. disussion 796. doi: 10.1016/j.ejcts.2008.05.014

13. Shrestha M, Martens A, Behrendt S, Maeding I, Koigeldiyev N, Haverich A. Is the branched graft technique better than the en bloc technique for total aortic arch replacement? *Eur J Cardiothorac Surg*. (2014) 45(1):181–6. discussion 186-7. doi: 10.1093/ejcts/ezt357

14. Martens A, Koigeldiyev N, Beckmann E, Fleissner F, Kaufeld T, Krueger H. Do not leave the heart arrested. Non-cardioplegic continuous myocardial perfusion during complex aortic arch repair improves cardiac outcome. *Eur J Cardiothorac Surg*. (2016) 49(1):141–8. doi: 10.1093/ejcts/ezv009

15. Karck M, Chavan A, Hagl C, Friedrich H, Galanski M, Haverich A. The frozen elephant trunk technique: a new treatment for thoracic aortic aneurysms. *J Thorac Cardiovasc Surg*. (2003) 125(6):1550–3. doi: 10.1016/S0022-5223(03)00045-X

16. Karck M, Chavan A, Khaladj N, Friedrich H, Hagl C, Haverich A. The frozen elephant trunk technique for the treatment of extensive thoracic aortic aneurysms: operative results and follow-up. *Eur J Cardiothorac Surg*. (2005) 28(2):286–90. discussion 290. doi: 10.1016/j.ejcts.2005.02.046

17. Jakob H, Tsagakis K, Pacini D, Di Bartolomeo R, Mestres C, Mohr F, et al. The international E-vita open registry: data sets of 274 patients. *J Cardiovasc Surg (Torino)*. (2011) 52(5):717–23. PMID: 21894139.

18. Shrestha M, Pichlmaier M, Martens A, Hagl C, Khaladj N, Haverich A. Total aortic arch replacement with a novel four-branched frozen elephant trunk graft: first-in-man results. *Eur J Cardiothorac Surg*. (2013) 43(2):406–10. doi: 10.1093/ejcts/ezs296

19. Shrestha M, Martens A, Kaufeld T, Beckmann E, Bertele S, Krueger H, et al. Single-centre experience with the frozen elephant trunk technique in 251 patients over 15 years. *Eur J Cardiothorac Surg*. (2017) 52(5):858–66. doi: 10.1093/ejcts/ezx218

20. Hagan PG, Nienaber CA, Isselbacher EM, Bruckman D, Karavite DJ, Russman PL, et al. The international registry of acute aortic dissection (IRAD): new insights into an old disease. *JAMA*. (2000) 283(7):897–903. doi: 10.1001/jama.283.7.897

21. Fann JI, Smith JA, Miller DC, Mitchell RS, Moore KA, Grunkemeier G, et al. Surgical management of aortic dissection during a 30-year period. *Circulation*. (1995) 92(9 Suppl):II113–21. doi: 10.1161/01.CIR.92.9.113

22. Lloyd-Jones DM. Cardiovascular health and protection against CVD: more than the sum of the parts? *Circulation*. (2014) 130(19):1671–3. doi: 10.1161/CIRCULATIONAHA.114.012869

23. Freundt M, Kolat P, Friedrich C, Salem M, Gruenewald M, Elke G, et al. Preoperative predictors of adverse clinical outcome in emergent repair of acute type A aortic dissection in 15 year follow up. *J Clin Med*. (2021) 10(22):5370–80. doi: 10.3390/jcm10225370

24. Hata M, Shiono M, Inoue T, Sezai A, Niino T, Funahashi M, et al. Preoperative cardiopulmonary resuscitation is the only predictor for operative mortality of type A acute aortic dissection: a recent 8-year experience. *Ann Thorac Cardiovasc Surg*. (2004) 10(2):101–5. PMID: 15209552.

25. Wang Z, Ge M, Chen T, Chen C, Zong Q, Lu L, et al. Independent risk factors and the long-term outcomes for postoperative continuous renal replacement treatment in patients who underwent emergency surgery for type a acute aortic dissection. *J Cardiothorac Surg*. (2020) 15(1):100. doi: 10.1186/s13019-020-01153-8

26. Dimagli A, Angelini GD. Time is aorta?": timeliness of surgical repair in type A aortic dissection. *J Card Surg*. (2022) 37(6):1661–3. doi: 10.1111/jocs.16412

27. Crawford TC, Beaulieu RJ, Ehlert BA, Ratchford EV, Black JH 3rd. Malperfusion syndromes in aortic dissections. *Vasc Med*. (2016) 21(3):264–73. doi: 10.1177/1358863X15625371

28. Goldberg JB, Lansman SL, Kai M, Tang GHL, Malekan R, Spielvogel D. Malperfusion in type A dissection: consider reperfusion first. *Semin Thorac Cardiovasc Surg*. (2017) 29(2):181–5. doi: 10.1053/j.semtcvs.2016.10.017

29. Bonser RS, Ranasinghe AM, Loubani M, Evans JD, Thalji NM, Bachet JE, et al. Evidence, lack of evidence, controversy, and debate in the provision and performance of the surgery of acute type A aortic dissection. *J Am Coll Cardiol*. (2011) 58 (24):2455–74. doi: 10.1016/j.jacc.2011.06.067

30. Shetty V, Shetty DP, Rao PV, Hosabettu PK, Subramanian S, Vikneswaran G, et al. Determinant of outcome in late presenting type A aortic dissection. *J Card Surg*. (2022) 37(6):1654–60. doi: 10.1111/jocs.16401

31. Pacini D, Leone A, Belotti LM, Fortuna D, Gabbieri D, Zussa C, et al. Acute type A aortic dissection: significance of multiorgan malperfusion. *Eur J Cardiothorac Surg*. (2013) 43(4):820–6. doi: 10.1093/ejcts/ezs500

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Operative experience on descending aorta with Takayasu Arteritis: a review

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Patients with Takayasu arteritis (TA) and descending aorta involvement often experience insidious onset and slow progression, leading to irreversible vascular lesions despite medication therapy. Surgical management plays a crucial role in resolving hemodynamic disturbances and has shown promise in improving the outcomes of this patient population, owing to significant advancements in surgical expertise. However, studies focusing on this rare disease are lacking. This review summarizes the characteristics of patients with stenosis in descending aorta, emphasizing surgical approaches, perioperative management, and disease outcomes. The operative approach depends on lesion location and extent. Existing studies have confirmed that the choice of surgical modality significantly influences postoperative complications and long-term prognosis in patients, highlighting the effectiveness of bypass surgery as a favorable option in clinical practice with a satisfactory long-term patency rate. To mitigate postoperative complications, it is advisable to conduct regular imaging follow-ups to prevent the deterioration of the condition. Notably, the occurrence of restenosis and pseudoaneurysm formation deserves particular attention due to their impact on patient survival. The use of perioperative medication remains a topic of debate, as previous studies have presented divergent perspectives. The primary objective of this review is to provide a comprehensive perspective on surgical treatment and offer customized surgical approaches for patients in this population.

KEYWORDS

surgery, descending aorta, takayasu arteritis, bypass suegery, endovascular treatment

Introduction

Takayasu arteritis (TA) is a nonspecific inflammatory disease of the aorta and its main branches, causing a range of arterial stenosis/occlusion or dilatation. Previous studies revealed that stenosis (93%) is the most frequent vascular presentation, and the abdominal aorta is the most frequent lesion location in the Asian population (1, 2). Patients with stenosis in the descending aorta (including the thoracic and abdominal aorta) may present life-threatening complications before 40, causing poor prognosis (3, 4). Surgical treatments are required in 18%–70% of all TA patients, with a substantial proportion experiencing stenosis in the descending aorta (5, 6).

Bypass surgery has been associated with a good long-term patency rate but is complex and requires a multidisciplinary approach. Endovascular therapy is less invasive and reproducible, but its patency rate is inferior to the former. Indeed, each method has pros and cons, which necessitates the tailored surgery design. It is imperative to evaluate each patient's condition individually, assess the surgical benefit and risks, and choose the appropriate surgical approach. A comprehensive evaluation of large systemic vessels is necessary to determine the optimal surgical approach. The utilization of advanced technology can assist in developing a precise surgical plan. In our center, for complex cases, we employ hemodynamic simulation to calculate pressures at various anatomical sites, identify optimal anastomosis locations, and re-evaluate the pressure to assess the effectiveness of the planned surgery. This approach allows us to validate the efficacy of the surgical intervention.

This article aims to present a comprehensive overview of current practices in the management of patients with descending aorta involvement. We will summarize the findings of previous studies, explore the impact of different surgical approaches on prognosis, and propose optimized management strategies for this specific patient population. We advocate that perioperative treatment and surgical modalities will continue to advance, offering hope and improved outcomes for these patients.

Methods

Considering the rarity of Takayasu arteritis, a comprehensive search was conducted to ensure that the objective reflects clinical practice. The study selection specifically focused on a population that underwent surgery targeting the descending aorta, which includes the thoracic and/or abdominal aorta. The research encompassed retrospective case-control analyses, case series, and case reports (**Table 1**). Studies that analyzed the outcomes of TA patients with multiple lesions, including thoracic and/or abdominal aortic stenosis, but were not exclusively focused on that specific aspect were marked "Null" in **Table 1**.

TABLE 1 Summary of surgery.

First author	Case	Surgery	Number	Follow-up	Patency rate	Survival rate	Complications	Reference
Miyata, T	32	Bypass Aortic patch	28 4	19.8 y	100%	Null	17 anastomotic aneurysms	(7)
Joh, J.-H.	2	Bypass Endarterectomy	1 1	4–75 m	100%	100%	1 migraine-like headache	(8)
Saadoun, D.	31	Surgery Endovascular treatment	18 13	6.5 y	Null	Null	Null	(9)
Lee, G.	14	Bypass Endovascular Treatment	5 9	3.2 y	100% 85.7%	100%	1 chylothorax, 1 aortic dissection and 1 aortic rupture	(10)
Lee, B.-B.	3	Endovascular treatment	3	46.8 m	Null	Null	Null	(11)
Labarca, C.	7	Bypass Endovascular treatment	2 5	10 y	Null	Null	Null	(6)
Kim, S. M.	10	Bypass Patch	9 1	60m	100%	100%	Null	(12)
Hinojosa, C. A.	2	Bypass	1 1	81m 46 m	100% 100%	100% 100%	Stenosis at aortic anastomosis 1 year after surgery	(13)
Setty, H. S. N.	10	Endovascular treatment	10	Null	Null	Null	Null	(14)
Hinojosa, C. A.	4	Bypass Aortic tube graft Endovascular treatment	2 1 1	Null	Null	Null	Null Recurrence at 11 months	(15)
Che, W.	48	Endovascular treatment	48	12 m	A total of 5 (10.9%) patients developed in-stent restenosis, which were resolved by reintervention (restenting in 3 patients and reangioplasty alone in 2 patients)	100%	1 patient developed retroperitoneal hemorrhage and one developed flow-limiting dissection that involved bilateral renal arteries perioperatively	(16)
Rosa Neto, N. S.	6	Bypass Endovascular treatment	4 2	Null	Null	100%	Null	(17)
Kim, Y. S.	9	Bypass	9	36.3 m	100%	5-year survival was 79 ± 13%.	3 patients with chylothorax, 1 patient with a wound problem, and 1 patient with bleeding due to pancreatic injury and mediastinitis	(18)
Diao, Y.	28	Bypass Endovascular treatment	11 17	48.5 ± 38.5 m	Null	Null	Null	(19)
Fan, L.	15	Endovascular treatment	15	2.88 y	Null	100%	thoracic aorta ($n = 5$, 13.9%), abdominal aorta ($n = 2$, 5.6%)	(20)
Joseph, G.	397	Endovascular treatment	397	34 m	98%	100%	Dissection 6.8% Rupture/PsA 3.3%	(21)

Null, the details of the data are not shown in the manuscripts.

Diagnostic criteria

The diagnostic criteria for Takayasu arteritis established by the American College of Rheumatology (ACR) in 1990 are widely accepted (22). However, these criteria were developed using a small sample size, limiting their generalizability and independent validation, impacting their applicability in clinical practice. In 1995, a modification to the diagnostic criteria was proposed, eliminating age restrictions. This modification resulted in an increased diagnostic sensitivity (92.5%) and specificity (95.0%) (23, 24). The most recent classification criteria for Takayasu arteritis developed jointly by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2022 have shown superior performance compared to the previous criteria. The 2022 criteria demonstrated a sensitivity of 93.8% and a specificity of 99.2%. These criteria were developed using a cohort of 316 TA patients and further validated using an independent dataset comprising an additional 146 TA patients from an international cohort (25). Notably, the 2022 criteria emphasized the importance of clinical symptoms, vascular physical examination findings, and vascular imaging in the classification of the disease. These criteria exhibited excellent performance across patients from different regions.

Demographics and angiographic patterns

Ascending aorta and aortic arch involvement is more commonly observed in patients from East Asia, while South Asian patients tend to exhibit a higher prevalence of abdominal aorta and renal artery involvement, and among Mexican patients, Numano V disease is the most frequently encountered subtype (26–28). Besides, gender plays a role in the distribution of vascular involvement in TA (29). In terms of vascular involvement in Takayasu arteritis, females are more commonly affected by thoracic aorta involvement, while males tend to have a higher susceptibility to abdominal aorta involvement (30, 31). Specifically, lesions in the abdominal aorta are diffusely distributed, with approximately 69% occurring in the suprarenal region, 23% in the juxtarenal region, and 8% in the infrarenal aorta (27). The Numano angiographic classification is widely utilized to categorize TA patients; however, it exhibits limitations in differentiating patients based on clinical presentation and formulating appropriate treatment plans (32). In this review, we focus on patients with descending aorta involvement (including Numano IIb, III, IV, V) as they often display similar clinical presentations and require similar surgical and medical approaches.

Signs and symptoms

The clinical presentation of Takayasu arteritis varies depending on the specific lesions involved. In patients with stenosis in the descending aorta, symptoms can arise from hypertension proximal to the aortic stenosis or hypotension distal to it. If the lower abdominal aorta is affected, claudication may be observed. Involvement of the suprarenal or juxtarenal aorta can lead to impaired renal perfusion and subsequent renal hypertension. Stenosis of the thoracic aorta can result in hypertension due to increased workload on the heart. Notably, hypertension is the most common symptom in TA patients with descending aorta involved with a prevalence of 60%–100%, probably associated with renal hypoperfusion or ischemia, stenosis of the descending aorta, severe aortic regurgitation, and reduced aortic compliance (12, 27, 33). If untreated, most patients die before 35 due to the complications of uncontrolled hypertension (3). Lower extremity claudication is the second most common symptom, presenting in 15%–50% of patients (4, 33). Other symptoms, including headache and syncope, can be observed in these patients (33). The formation of aneurysms (24%) is not rare in TA patients, and >50% of TA patients may develop aneurysms in the course of the disease. More importantly, multiple synchronous lesions (stenotic and aneurysmatic) may coexist in the same patients (34).

Hypertension, being the most prevalent symptom in Takayasu arteritis patients with descending aorta involvement, holds significant value as an indicator for assessing disease control and prognosis. However, the involvement of upper limb arteries may result in inaccurate blood pressure measurements, leading to delayed diagnosis and poor prognosis. For patients without bilateral upper limb arteries involved, the higher value from the arms is recorded; for patients with unilateral upper limb artery affected, the reading from the unaffected side is used; for patients with stenosis in bilateral upper limb arteries, the central blood pressure is collected to reflect the core blood pressure (35).

Assessment of disease activity

The definition of active disease in TA is based on the National Institutes of Health (NIH) guidelines (36, 37). Current acute-phase reactants used to assess disease activity include erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Elevated ESR is one of the strongest indicators of disease progression (15). However, it is important to note that vascular damage can progress without systemic inflammation. Current evidence suggests that 30%–40% of patients may appear clinically stable (in quiescence) but can still be confirmed to be in the active phase based on surgical histopathology findings (5, 33, 38).

[18F] Fluorodeoxyglucose combined positron emission and computed tomography (18F-FDG-PET-CT) and magnetic resonance imaging (MRI) can assess arterial inflammation by measuring the degree of vessel wall edema. These imaging examinations can confirm vascular wall inflammation, especially in patients with normal levels of inflammation markers (38, 39).

It should be borne in mind that 18F-FDG-PET-CT cannot accurately distinguish arteritis from metabolically active vascular remodeling due to the lack of inflammatory cell selectivity. However, new means of imaging examination have emerged to address this limitation. One such approach involves targeting macrophage activation, as macrophages play a significant role in inflammatory infiltrates. The somatostatin receptor subtype-2 (SST2), expressed on activated macrophages, has been identified as a biomarker for vasculitis. A recent study demonstrated that SST2 positron emission tomography (PET)/magnetic resonance imaging (MRI) showed potential in defining disease activity in TA patients with a more sensitive and accurate diagnosis (40).

Contrast-enhanced ultrasound (CEUS) is also a promising approach to assessing disease activity. A previous study showed that the severe stenosis depicted by CEUS in the carotid artery wall was correlated with vascular inflammation detected by PET/CT (41–44). Given the convenience of CEUS imaging, we introduced CEUS imaging as a routine in surveillance protocol.

Imaging

Imaging assessment primarily focuses on the aorta and its major branches in diagnosing Takayasu arteritis. While various imaging modalities are available, angiography remains the cornerstone for diagnosing TA. Computed tomographic arteriography (CTA), magnetic resonance angiography (MRA), and digital subtraction angiography (DSA) are the most frequently preoperative study used to define anatomy, which can facilitate the assessment of the extent and severity of the arterial injury (45). CTA is the imaging modality of choice for diagnosing and monitoring Takayasu arteritis in nearly 60% of patients. The widespread availability, cost-effectiveness, and superior image resolution compared to MRA account for the popularity of CTA. Its accessibility, affordability, and ability to provide detailed and high-quality images make CTA an invaluable tool in the evaluation and management of TA patients during both the diagnostic and follow-up stages.

Doppler ultrasonography (Doppler US) is also used to quantify the severity of luminal narrowing as a less invasive approach. Reports indicate that among TA patients who received imaging assessment, 58.8% underwent CTA, while 29.9% underwent MRA, and Doppler ultrasonography was used in 11.3% of all patients (46).

Current evidence suggests that 18F-FDG-PET-CT facilitates early diagnosis in 7% of patients and may improve prognosis (15, 47). PET-CT has also become a diagnostic test for assessing arterial inflammation and monitoring the response to immunomodulatory therapy (6, 48). Repeat PET-CT should be considered to confirm disease activity during this period.

The EULAR 2018 guidelines suggest that if the patient presents with recurrent or new symptoms, regular imaging assessment is needed during follow-up (49). Among these imaging methods, MRI is the most frequently used for follow-up because it avoids the use of radiation (46).

Cardiovascular manifestations

As the most common symptom, hypertension is one of the most valued indicators to assess disease control and prognosis. However, the involvement of upper limb arteries may result in inaccurate blood pressure measurements, leading to delayed diagnosis and poor prognosis.

Heart involvement is not rare in TA patients, emphasizing the need for conducting electrocardiograms (ECGs). It is now understood that congestive heart failure induced by stenosis lesions in descending aorta is the main cause of death in patients with Takayasu arteritis (50). Another symptom, aortic regurgitation, is present in 13% to 44% of cases due to increased afterload on the heart (51, 52). Thus, ECG is recommended as a routine examination in all TA patients to reflect valvular and atrioventricular abnormalities. The ejection fraction, the aortic regurgitation, the diameter of the ascending aorta, the diameter of the aortic sinus, the aortic valve annular diameter, and the left ventricular end-diastolic diameter have been reported as indicators in previous studies (53, 54). ECG can also be used for follow-up examination since surgery can mitigate TA-related hypertension and relieve left ventricular hypertrophy (18).

Coronary involvement is a commonly observed lesion in patients with Takayasu arteritis. When there is suspicion of coronary stenosis, state-of-the-art CT coronary angiography has emerged as a reliable non-invasive method (55, 56). This imaging technique offers high isotropic spatial resolution ranging from 0.23 mm to 0.35 mm, while maintaining a low radiation dose profile. CT coronary angiography provides detailed visualization of the coronary arteries, aiding in the assessment of coronary stenosis in TA patients with accuracy and precision.

Management

Surgical treatment

Severe stenosis, defined as a narrowing of 70% or more, can result in hemodynamic disturbances that lead to symptomatic end-organ ischemia. In such cases, surgical interventions are crucial in addressing stenosis in the descending aorta and its visceral artery branches. The indications for TA patients with descending aorta involvement mainly include refractory hypertension, cardiac ischemia, aortic regurgitation, and extremity claudication. In order to optimize patient outcomes, preoperative blood pressure control is recommended, aiming to maintain blood pressure within the normal range. However, if hypertension is primarily caused by a significant narrowing of the descending aorta, surgical intervention is preferred regardless of the patient's hypertension status. While it is generally advisable to avoid surgery during the acute phase of the disease, if patients are in a critical condition, surgery becomes necessary (17).

Aortic stenosis can often involve adjacent visceral arteries, with the splanchnic and renal arteries being common coexisting lesions (27). About 80% of patients with abdominal aortic stenosis also exhibit renal artery stenoses (27, 57). Renal reconstructions are usually performed in patients with decreased renal function or refractory renovascular hypertension. Mesenteric reconstructions are conducted in patients with abdominal pain or other related symptoms. However, although more than 50% of patients present with splanchnic occlusive lesions, only 6% experienced symptomatic bowel ischemia, suggesting prophylactic treatment is required to improve splanchnic stenosis (27).

The location and extent of the lesion should be taken into account during the selection of the surgical procedure. To date, no standard therapy is applicable to all patients. Methods for aortic reconstruction include bypass surgery, interposition graft, patch angioplasty, and endovascular therapy (12). Bypass procedures may be favored in patients having too extensive coarctation segments or complex lesions (15). In other cases with short coarctation, arterial patch, interposition graft, and endovascular therapy may be attractive (58) (**Figure 1**).

Endovascular technologies (including angioplasty and stent-graft repair) are suitable for localized stenoses distant from the renal, celiac, and superior mesenteric arteries. These minimally invasive procedures are advantageous for young patients since they can be repeated and may obviate the need for open surgery. In particular, endovascular interventions allow luminal dilation in children with a developing aorta without interfering with the vessels. The first percutaneous transluminal angioplasty(PTA) for a patient with abdominal aortic coarctation was performed in 1983 (59). However, due to the relatively high failure rate, balloon angioplasty alone is less effective than stent-graft repair (60, 61). It is widely recognized that endovascular therapy has certain inherent limitations. For instance, the arterial wall may become weakened following balloon angioplasty, resulting in aneurysm formation in 5% to 20% of cases (62, 63). Furthermore, the elastic fibers disruption in the media vessel wall and vascular fibrosis in the adventitia contribute to poor patient response to both endovascular therapies, leading to restenosis rates in 25% to 60% of cases (58, 64–66). Moreover, vessel stiffness can limit endovascular therapy's effectiveness, resulting in under-dilatation and risk of stent graft rupture (67).

Aorta endarterectomy is indicated for young patients with short and isolated segment (4, 8, 68). Butcher and his colleagues first reported a satisfactory result in cases with aortoiliac arterial occlusion treated by endarterectomy (69). However, endarterectomy is not recommended for TA patients. Theoretically, aortic endarterectomy addresses only the intimal fibrosis, while fibrosis in the adventitial or periadventitial layers may persist, posing a challenge to treatment efficacy (27). While it may offer the possibility of a thoracoabdominal bypass in the later stages of life, it is widely considered a standby option.

Considering that the TA patients are relatively young, long-term durability is a vital factor in choosing surgical approaches, leading to bypass surgery as the most frequent choice in TA with descending aorta involvement (26). This approach can resolve extensive arteriopathy by an ingenious surgical design, such as using a sequential bypass to re-establish the blood supply of the ischemic organs. Some studies also revealed that the need for open surgery remains, even when percutaneous procedures presented with an increasing and widening ambit (21). To date, several techniques for extra-anatomic bypass have been proposed.

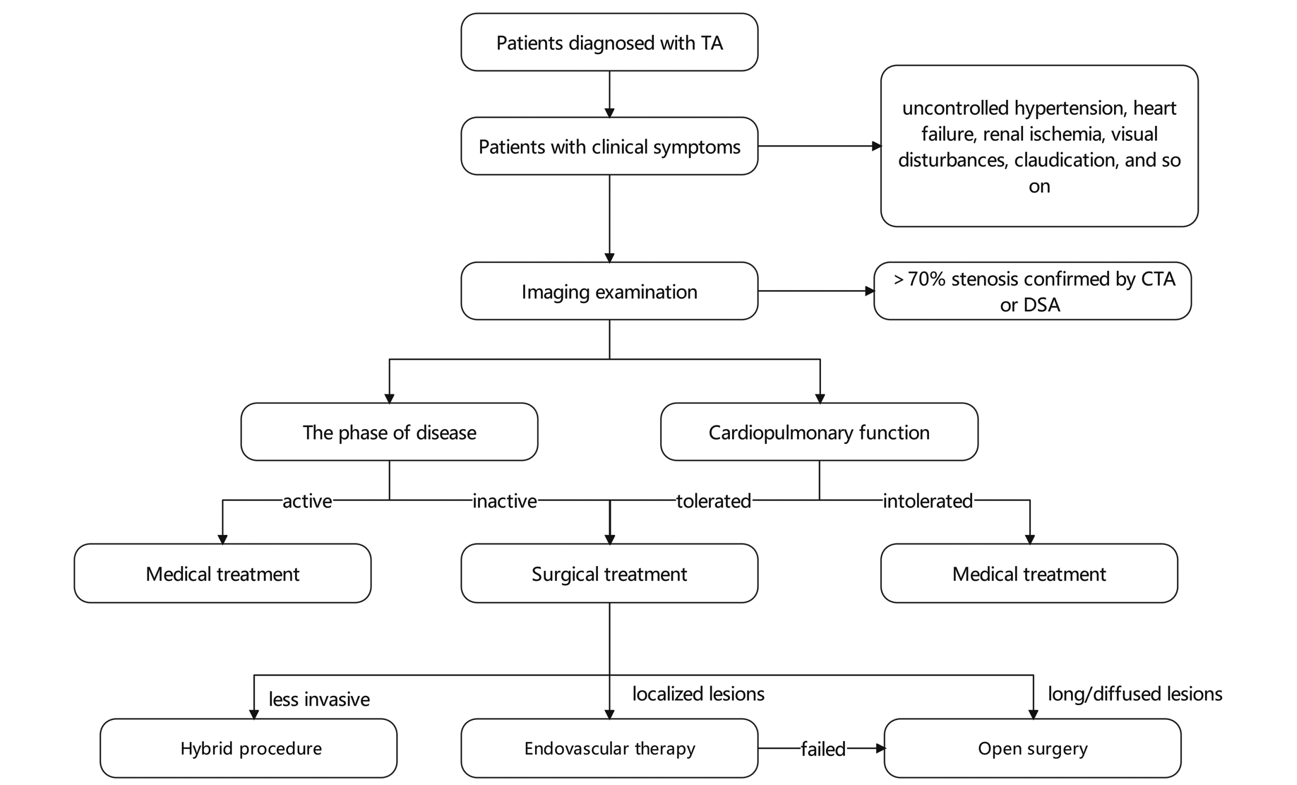

FIGURE 1
The treatment algorithm of TA patients.

The left posterolateral thoracotomy enables the procedure to be performed on the ascending aorta, aortic arch, and entire descending aorta. However, some studies have raised concerns about potential complications, including massive bleeding, paraplegia, and chylothorax (70–72). Median sternotomy was first reported by Vijayanagar R. et al. (73) in 1980. The benefits and disadvantages of this surgical modality have been established. Optimal operative exposure for the entire descending aorta can be achieved. It also allows simultaneous cardiac procedures or reoperation to be conducted. However, the requirement of both thoracotomy and laparotomy poses a great challenge to patients' cardiorespiratory functions, making it more appropriate for younger patients. For elderly patients, aorta-femoral bypass is a better option to augment the vascular bed and retrograde renal blood flow with a lower risk of damaging the collateral circulation.

Considering the chronic inflammatory state of patients, open surgery can be overly invasive. However, there is evidence supporting the use of hybrid aortic repair as a more favorable option in a less invasive way for complex lesions. This approach involves bypassing the supra-aortic vessels or debranching the visceral or renal arteries before performing stent grafting on the aortic arch and descending aorta. Joseph G. et al. (21) proposed that about 80% patients treated with surgical procedures underwent also endovascular procedures. Hybrid aortic repair offers advantages such as shorter operation time, reduced surgical complexity, and increased success rates. It is particularly beneficial for patients with a heavily calcified aorta (74–76).

Regarding the choice of the anastomotic site, the utilization of supra celiac bare area for distal anastomosis was first reported by Wukasch D. C. et al. in 1977, which featured reduced bleeding and decreased incidence of complications due to the short course of the graft (77, 78). However, it should be noted that this less invasive approach may have certain drawbacks. For instance, inadequate exposure may be an issue in patients with abdominal obesity or barrel-shaped thorax, and managing bleeding from the distal anastomosis may be challenging. As an alternative, an ascending-to-infrarenal abdominal aortic bypass may be considered. Although longer grafts increase the risk of complications from adjacent organs, the long midline incision facilitates exposure of the whole length of the descending aorta, making anastomosis and hemostasis easier (79). More importantly, the ascending-to-infrarenal abdominal aortic bypass can also provide significant antegrade flow to permit optimal renal perfusion, which relieves renovascular hypertension (4). According to the current literature, the double-suture aortic anastomotic technique is applied to prevent postoperative anastomotic aneurysms (80).

A statistically significant difference in restenosis rates has been reported between different graft materials. Polytetrafluoroethylene (PTFE) grafts demonstrated a superior patency rate to Dacron grafts at a 7-year follow-up (100% vs. 58%, $P = 0.005$) (58). The graft diameter was consistent with the mean diameter of descending aorta. A 14 mm–16 mm graft was deemed sufficient for most women, while an average man required a 16 mm–18 mm graft for adequate perfusion (27). Notably, oversized grafts compared to the aorta have been recommended in children to accommodate future growth (4, 27, 64).

Perioperative medications

Corticosteroids are generally the first-line treatment to control the disease activity, and cytotoxic drugs are added for those patients with disease progression on steroid therapy (64). However, the optimal timing for initiating immunosuppressive therapy upon confirmation of the diagnosis remains a subject of debate. Hinojosa C. A. et al. (15) believed that administering the immunosuppressive drugs as early as possible could arrest disease progression and reverse early clinical symptoms. Perera and colleagues proposed a similar finding that immunosuppression before the endovascular intervention significantly improved results ($P = 0.001$) (45). In contrast, Young Su Kim and co-workers formulated that fibrosis and calcification are predominantly disease-specific alterations rather than vascular wall inflammation for those in the chronic inactive phase, which means using immunosuppressive agents such as cytotoxic agents or steroids is unnecessary (18).

Similarly, no consensus has been reached on the efficacy of postoperative medication use. Some authors postulated that the restenosis rate is lower with post-surgical immunosuppressive treatment, while others argued that there were no differences among patients treated with or without corticosteroids (5, 81, 82). A previous study indicated that for patients on medication therapy, 93% in the open surgery group and 86% in the interventional procedure group exhibited good long-term patency (45). However, other studies showed there was no difference between groups (47, 83).

Previous studies reached an agreement regarding antiplatelet agent use since the TA-related hypercoagulable state can lead to arterial ischemic events, and patients can benefit from anticoagulant therapy (39, 84).

In recent years, the pathogenesis of TA has been better understood, which has led to the development of targeted biotherapies aimed at inhibiting signaling pathways. Recent studies have shown promising results for biological disease-modifying agents (bDMARDs), such as TNF-α inhibitors and IL-6 inhibitors, as well as targeted synthetic disease-modifying agents (tsDMARDs), such as JAK inhibitors75–80. Although limited evidence exists for some bDMARDs, such as Rituximab, Abatacep, and Ustekinumab, they also require further investigation (85–87).

Complications and prognosis

The prognosis of TA is heavily influenced by the presence or severity of complications. A study from the late 1980s, conducted at a time when diagnostic imaging and medical treatments were less advanced, found that most patients with descending aorta involvement would not survive past the age of 35 years (3). It has been established that graft-related complications, including restenosis and anastomotic aneurysms, are the most common complications after surgery (88). Other study also proposed that peri-interventional dual antiplatelet therapy, concurrent surgery, and technical failure were predictors for complications ($P < 0.05$) (20).

Several studies have revealed that the most common complication in both open and endovascular groups is restenosis, and patients who underwent endovascular procedures showed a higher rate of restenosis ($P < .001$). The patency rate of surgical bypass varied from 64 to 100%, while that of PTA ranged from 29% to 83% (5, 7, 58, 82, 89–91). Consistently, our prior retrospective study, which examined 116 TA patients who received surgery or endovascular interventions (such as PTA and stent-graft repair), revealed that both surgical approaches were effective and safe. However, open surgical repair was found to be more suitable for complex lesions due to its longer durability (19). Moreover, other factors are related to restenoses, such as hypertension ($P = 0.01$), dyslipidemia ($P = 0.01$), and high-dose steroids ($P = 0.012$) (6).

It has been reported that pseudoaneurysms at the anastomotic site occur with an incidence of 12.2%, 21.2%, and 37.3% in the 10-year, 20-year, and 30-year follow-ups, respectively (12). This complication probably results from hypertension and the degradation of graft materials (92). Notably, most patients presented with no symptoms or signs and were detected incidentally, which led to devastating results. Therefore, even though the patients showed no signs of anastomotic aneurysms, regular follow-ups are needed (27).

It is widely thought that postoperative complications are associated with disease activity. However, the association between postoperative complications and disease activity has been controversial. Kim, S. M. et al. (12) thought disease activity could affect outcomes and long-term survival. However, Fields C. E. et al. (5) found that long-term survival was not affected by disease activity, supported by findings reported by Weaver F. A. et al. (93).

Studies reported that the overall survival rate at 20 years was 62.3%–73.5% (7, 12) and death was mainly attributed to cardiovascular events (7, 50). Among these, the incidence of congestive heart failure-induced death ranged from 3% to 40% (7, 10). Further investigation also revealed that the risk factors for heart failure include pulmonary hypertension, aortic valve or coronary artery involvement, onset age >38 years, and serum tumor necrosis factor (TNF)-α concentration >10 pg/ml (54).

Ishikawa K. et al. (94) identified four predictors for mortality risk factors: complications (retinopathy, secondary hypertension, aortic regurgitation, and aneurysmal formation), the pattern of the clinical course, age, and year of diagnosis. Other studies confirmed that postoperative hypertension ($P = 0.028$), type of disease ($P = 0.0142$), age at operation ($P = 0.0052$), and presence of an aneurysmal lesion ($P = 0.0106$) were significantly associated with postoperative events and survival rate (7, 33).

Discussion

The need for multiple vascular surgeries involving both endovascular and surgical procedures is not uncommon in TA patients due to the prolonged duration of the disease. **Table 1** presents several studies highlighting the surgical management of descending aorta stenosis associated with TA. Most patients benefit from the correction of abnormal hemodynamics and the relief of hypertension. Current evidence suggests that 74%–90% of patients experience improvement in hypertension-related symptoms after the surgery (3, 27, 33). Surgery also played a role in relieving left ventricular burden. A study revealed that almost all patients demonstrated improved cardiac function, with some cases showing significant enhancements in interventricular septal diameter (IVSD, $P = 0.016$) and left ventricular mass index (LVMI, $P = 0.017$) (18). An updated retrospective study from our research team also demonstrated that surgery could significantly improve the prognosis of patients.

Taketani T. et al. (33) reported that after surgical treatment, the overall survival and event-free survival rate were 62.3% and 58.4% at 20-year follow-up, and postoperative hypertension was a significant predictor of event-free survival ($P = 0.028$). Kalangos A. et al. (58) demonstrated the safety and effect of the surgery, with hypertension being controlled and cardiac function returning to normal postoperatively. Stanley J. C. et al. (27) assessed the outcomes of different operative treatments in patients with abdominal aortic coarctation (4 were diagnosed with inflammatory aortitis) and found that more than 90% of patients benefit from surgery. The above studies overlap in their assertion that surgery is safe and effective for TA in all arterial areas. Herein, we focused on patients with descending aorta involvement and comprehensively analyzed the surgical methods and clinical outcomes of this patient population. We aimed to review the relevant literature in detail and summarize the unique characteristics of these patients.

With significant inroads achieved in surgical techniques, multidisciplinary decision-making, targeted biotherapies, and comprehensive postoperative monitoring and treatment, surgeries can be performed with low morbidity and improved quality of life (58). In addition, a deeper understanding of the pathophysiology of arterial reconstruction in TA patients helps to reduce surgical complications.

Preoperative evaluation is critical in guiding surgical decisions regarding the method and timing of interventions in TA patients. Despite their relatively young age, TA patients often present with severe cardiac, renal, and pulmonary complications due to the insidious nature of the disease and its atypical clinical manifestations. The involvement of multiple arterial bifurcations further adds to the complexity of the condition. As a result, comprehensive medical evaluations are essential prior to surgery. These evaluations encompass various aspects, such as assessing vascular lesions, determining disease activity, evaluating cardiopulmonary function, and overall disease status. While erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are commonly used as acute-phase indicators in TA, it should be noted that these serum markers may not always accurately reflect vascular wall inflammation. In fact, approximately 30%–40% of patients in the active phase of the disease may exhibit normal ESR and/or CRP levels (26). More importantly, combining clinical presentation, serum markers, and imaging examinations such as PET-CT and MRI is crucial for accurately assessing disease activity in TA patients, especially when acute-phase reactants exhibit poor sensitivity during periods of low disease activity.

The presence of nonspecific symptoms often leads to delayed diagnosis of TA, resulting in disease progression and the occurrence of ischemic events. Early diagnosis and prompt treatment are essential in order to improve the prognosis of patients with TA (95).

Besides, although the indications for surgery have not been definitively established, we advocate the safety and efficacy of surgical intervention. Prior to 1988, the average life expectancy of patients with atypical TA was only 35 years, likely due to less advanced and effective diagnostic techniques that led to delayed treatment (96). Kalangos A. et al. (58) revealed that patients couldundergo reconstructive procedures with satisfactory midterm and long-term outcomes regardless of the extent and severity of vascular lesions. We also demonstrated in another article that surgical revascularization is superior in relieving symptoms and improving the prognosis compared to conservative treatment. Moreover, given that these patients are complicated with coexisting renal and splanchnic artery occlusion, surgery aims to restore the renal and splanchnic artery flow based on the symptoms.

More importantly, the inconsistency of findings may be attributed to different follow-up duration. It has long been thought that at least a 20-year follow-up is mandatory to reflect the impact of surgical therapy since about 10% of patients were treated with secondary surgeries in the late stages of follow-up (5, 27). However, the debate regarding the choice of surgical options remains unsettled due to the limited number of studies with long-term follow-up, varying prognoses among patients, and inconsistent durations of follow-up.

It should be borne in mind that TA is a rare disease, and it is challenging to obtain a large cohort of patients undergoing surgical treatment. Further research is required to confirm the efficacy and safety of these procedures, which will enable us to offer improved treatment options for patients with TA.

Conclusion

The ongoing advancements in surgical techniques establish surgery as a viable treatment option for TA. While more studies are required to establish definitive criteria for surgical indications, existing data indicate that most patients can benefit from surgery.

Author contributions

YF conducted relevant literature and wrote the article, and YC designed the article and revised it. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Seyahi E. Takayasu arteritis: an update. *Curr Opin Rheumatol.* (2017) 29(1):51–6. doi: 10.1097/BOR.0000000000000343

2. Vanoli M, Daina E, Salvarani C, Sabbadini MG, Rossi C, Bacchiani G, et al. Takayasu's arteritis: a study of 104 Italian patients. *Arthritis Rheum.* (2005) 53 (1):100–7. doi: 10.1002/art.20922

3. Cohen JR, Birnbaum E. Coarctation of the abdominal aorta. *J Vasc Surg.* (1988) 8 (2):160–4. doi: 10.1016/0741-5214(88)90404-1

4. Hetzer R, Absi D, Miera O, Solowjowa N, Schulz A, del Maria Javier MF, et al. Extraanatomic bypass technique for the treatment of midaortic syndrome in children. *Ann Thorac Surg.* (2013) 96(1):183–9. doi: 10.1016/j.athoracsur.2013.03.025

5. Fields CE, Bower TC, Cooper LT, Hoskin T, Noel AA, Panneton JM, et al. Takayasu's arteritis: operative results and influence of disease activity. *J Vasc Surg.* (2006) 43(1):64–71. doi: 10.1016/j.jvs.2005.10.010

6. Labarca C, Makol A, Crowson CS, Kermani TA, Matteson EL, Warrington KJ. Retrospective comparison of open versus endovascular procedures for takayasu arteritis. *J Rheumatol.* (2016) 43(2):427–32. doi: 10.3899/jrheum.150447

7. Miyata T, Sato O, Koyama H, Shigematsu H, Tada Y. Long-term survival after surgical treatment of patients with Takayasu's Arteritis. *Circulation.* (2003) 108 (12):1474–80. doi: 10.1161/01.CIR.0000089089.42153.5E

8. Joh J-H, Kim D-K, Park K-H, Kim D-I. Surgical management of Takayasu's Arteritis. *J Korean Med Sci.* (2006) 21(1):20–4. doi: 10.3346/jkms.2006.21.1.20

9. Saadoun D, Lambert M, Mirault T, Resche-Rigon M, Koskas F, Cluzel P, et al. Retrospective analysis of surgery versus endovascular intervention in takayasu arteritis: a multicenter experience. *Circulation.* (2012) 125(6):813–9. doi: 10.1161/CIRCULATIONAHA.111.058032

10. Lee GY, Jeon P, Do YS, Sung K, Kim DI, Kim YW, et al. Comparison of outcomes between endovascular treatment and bypass surgery in takayasu arteritis. *Scand J Rheumatol.* (2014) 43(2):153–61. doi: 10.3109/03009742.2013.822096

11. Lee B-B, Laredo J, Neville R, Villavicencio JL. Endovascular management of takayasu arteritis: is it a durable option? *Vascular.* (2009) 17(3):138–46. doi: 10.2310/6670.2009.00012

12. Kim SM, Jung IM, Han A, Min SI, Lee T, Ha J, et al. Surgical treatment of middle aortic syndrome with takayasu arteritis or midaortic dysplastic syndrome. *Eur J Vasc Endovasc Surg.* (2015) 50(2):206–12. doi: 10.1016/j.ejvs.2015.04.032

13. Hinojosa CA, Anaya-Ayala JE, Torres-Machorro A, Lizola R, Laparra-Escareno H. Middle aortic syndrome in Takayasu's Arteritis: report of two surgical cases. *Ann Vasc Surg*. (2016) 34:270.e13–e17. doi: 10.1016/j.avsg.2015.12.015

14. Setty HSN, Rao M, Srinivas KH, Srinivas BC, Usha MK, Jayaranganath M, et al. Clinical, angiographic profile and percutaneous endovascular management of Takayasu's Arteritis—a single centre experience. *Int J Cardiol*. (2016) 220:924–8. doi: 10.1016/j.ijcard.2016.06.194

15. Hinojosa CA, Anaya-Ayala JE, Gomez-Arcive Z, Laparra-Escareno H, Torres-Machorro A, Lizola R. Factors associated with need for revascularisation in non-coronary arterial occlusive lesions secondary to Takayasu's Arteritis. *Eur J Vasc Endovasc Surg*. (2017) 54(3):397–404. doi: 10.1016/j.ejvs.2017.05.020

16. Che W, Xiong H, Jiang X, Dong H, Zou Y, Yang Y, et al. Stenting for middle aortic syndrome caused by takayasu arteritis-immediate and long-term outcomes. *Catheter Cardiovasc Interv*. (2018) 91(S1):623–31. doi: 10.1002/ccd.27492

17. Rosa Neto NS, Shinjo SK, Levy-Neto M, Pereira RMR. Vascular surgery: the main risk factor for mortality in 146 takayasu arteritis patients. *Rheumatol Int*. (2017) 37(7):1065–73. doi: 10.1007/s00296-017-3656-y

18. Kim YS, Cho YH, Sung K, Kim D-K, Chung S, Park TK, et al. Clinical outcome of extraanatomic bypass for midaortic syndrome caused by takayasu arteritis. *Ann Thorac Surg*. (2020) 109(5):1419–25. doi: 10.1016/j.athoracsur.2019.08.032

19. Diao Y, Yan S, Premaratne S, Chen Y, Tian X, Chen Z, et al. Surgery and endovascular management in patients with Takayasu's Arteritis: a ten-year retrospective study. *Ann Vasc Surg*. (2020) 63:34–44. doi: 10.1016/j.avsg.2019.07.009

20. Fan L, Yang L, Wei D, Ma W, Lou Y, Song L, et al. Clinical scenario and long-term outcome of childhood takayasu arteritis undergoing 121 endovascular interventions: a large cohort over a fifteen-year period. *Arthritis Care Res (Hoboken)*. (2021) 73(11):1678–88. doi: 10.1002/acr.24387

21. Joseph G, Thomson VS, Attumalil TV, Mathen PG, Anandaraj AM, George OK, et al. Outcomes of percutaneous intervention in patients with takayasu arteritis. *J Am Coll Cardiol*. (2023) 81(1):49–64. doi: 10.1016/j.jacc.2022.10.024

22. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, et al. The American college of rheumatology 1990 criteria for the classification of takayasu arteritis. *Arthritis Rheum*. (1990) 33(8):1129–34. doi: 10.1002/art.1780330811

23. Sharma BK, Jain S, Suri S, Numano F. Diagnostic criteria for takayasu arteritis. *Int J Cardiol*. (1996) 54(Suppl):S141–7. doi: 10.1016/S0167-5273(96)88783-3

24. de Souza AWS, de Carvalho JF. Diagnostic and classification criteria of takayasu arteritis. *J Autoimmun*. (2014) 48-49:79–83. doi: 10.1016/j.jaut.2014.01.012

25. Grayson PC, Ponte C, Suppiah R, Robson JC, Gribbons KB, Judge A, et al. 2022 American college of rheumatology/EULAR classification criteria for takayasu arteritis. *Ann Rheum Dis*. (2022) 81(12):1654–60. doi: 10.1136/ard-2022-223482

26. Petrovic-Rackov L, Pejnovic N, Jevtic M, Damjanov N. Longitudinal study of 16 patients with Takayasu's Arteritis: clinical features and therapeutic management. *Clin Rheumatol*. (2009) 28(2):179–85. doi: 10.1007/s10067-008-1009-7

27. Stanley JC, Criado E, Eliason JL, Upchurch GR, Berguer R, Rectenwald JE. Abdominal aortic coarctation: surgical treatment of 53 patients with a thoracoabdominal bypass, patch aortoplasty, or interposition aortoaortic graft. *J Vasc Surg*. (2008) 48(5):1073–82. doi: 10.1016/j.jvs.2008.05.078

28. Joseph G, Goel R, Thomson VS, Joseph E, Danda D. Takayasu arteritis: jACC focus seminar 3/4. *J Am Coll Cardiol*. (2022) 81(2):172–86. doi: 10.1016/j.jacc.2022.09.051

29. Zhang Z, Wang W, Zhou M, Lu PYJ, Li Y, Chen Y. An observational study of sex differences in takayasu arteritis in China: implications for worldwide regional differences. *Ann Vasc Surg*. (2020) 66:309–17. doi: 10.1016/j.avsg.2019.12.007

30. Watanabe Y, Miyata T, Tanemoto K. Current clinical features of new patients with takayasu arteritis observed from cross-country research in Japan: age and sex specificity. *Circulation*. (2015) 132(18):1701–9. doi: 10.1161/CIRCULATIONAHA.114.012547

31. Lim AY, Lee GY, Jang SY, Gwag HB, Choi SH, Jeon ES, et al. Gender differences in clinical and angiographic findings of patients with takayasu arteritis. *Clin Exp Rheumatol*. (2015) 33(2 Suppl 89):132–37.

32. Hata A, Noda M, Moriwaki R, Numano F. Angiographic findings of takayasu arteritis: new classification. *Int J Cardiol*. (1996) 54(Suppl):S155–63. doi: 10.1016/S0167-5273(96)02813-6

33. Taketani T, Miyata T, Morota T, Takamoto S. Surgical treatment of atypical aortic coarctation complicating Takayasu's Arteritis–experience with 33 cases over 44 years. *J Vasc Surg*. (2005) 41(4):597–601. doi: 10.1016/j.jvs.2005.01.022

34. Comarmond C, Biard L, Lambert M, Mekinian A, Ferfar Y, Kahn J-E, et al. Long-Term outcomes and prognostic factors of complications in takayasu arteritis: a multicenter study of 318 patients. *Circulation*. (2017) 136(12):1114–22. doi: 10.1161/CIRCULATIONAHA.116.027094

35. Qi Y, Yang L, Zhang H, Liang E, Song L, Cai J, et al. The presentation and management of hypertension in a large cohort of takayasu arteritis. *Clin Rheumatol*. (2018) 37(10):2781–8. doi: 10.1007/s10067-017-3947-4

36. Hoffman GS, Ahmed AE. Surrogate markers of disease activity in patients with takayasu arteritis. A preliminary report from the international network for the study of the systemic vasculitides (INSSYS). *Int J Cardiol*. (1998) 66:Suppl 1. doi: 10.1016/S0167-5273(98)00181-8

37. Hoffman GS. Takayasu arteritis: lessons from the American national institutes of health experience. *Int J Cardiol*. (1996) 54(Suppl):S99–102. doi: 10.1016/S0167-5273(96)88778-X

38. Jiang L, Li D, Yan F, Dai X, Li Y, Ma L. Evaluation of takayasu arteritis activity by delayed contrast-enhanced magnetic resonance imaging. *Int J Cardiol*. (2012) 155(2):262–7. doi: 10.1016/j.ijcard.2010.10.002

39. Wang H, Lai B, Wu X, Han T, Chen H. Late diagnosis of Takayasu's Arteritis with repeated attacks of heart failure and uncontrolled hypertension due to abdominal aortic thrombosis: case report and review of the literature. *Blood Press*. (2015) 24(6):333–9. doi: 10.3109/08037051.2015.1049423

40. Tarkin JM, Wall C, Gopalan D, Aloj L, Manavaki R, Fryer TD, et al. Novel approach to imaging active takayasu arteritis using somatostatin receptor positron emission tomography/magnetic resonance imaging. Circulation. *Cardiovascular Imaging*. (2020) 13(6):e010389. doi: 10.1161/CIRCIMAGING.119.010389

41. Lottspeich C, Dechant C, Köhler A, Tischler M, Treitl KM, Treitl M, et al. Assessment of disease activity in takayasu arteritis: potential role of contrast-enhanced ultrasound. *Ultraschall in Der Medizin (Stuttgart, Germany: 1980)*. (2019) 40(5):638–45. doi: 10.1055/a-0817-5423

42. Germanò G, Macchioni P, Possemato N, Boiardi L, Nicolini A, Casali M, et al. Contrast-Enhanced ultrasound of the carotid artery in patients with large vessel vasculitis: correlation with positron emission tomography findings. *Arthritis Care Res (Hoboken)*. (2017) 69(1):143–9. doi: 10.1002/acr.22906

43. Wang Y, Wang Y-H, Tian X-P, Wang H-Y, Li J, Ge Z-T, et al. Contrast-enhanced ultrasound for evaluating arteritis activity in takayasu arteritis patients. *Clin Rheumatol*. (2020) 39(4):1229–35. doi: 10.1007/s10067-019-04698-9

44. Li Z, Zheng Z, Ding J, Li X, Zhao Y, Kang F, et al. Contrast-enhanced ultrasonography for monitoring arterial inflammation in takayasu arteritis. *J Rheumatol*. (2019) 46(6):616–22. doi: 10.3899/jrheum.180701

45. Perera AH, Youngstein T, Gibbs RGJ, Jackson JE, Wolfe JH, Mason JC. Optimizing the outcome of vascular intervention for takayasu arteritis. *Br J Surg*. (2014) 101(2):43–50. doi: 10.1002/bjs.9372

46. Keleşoğlu Dinçer AB, Kılıç L, Erden A, Kalyoncu U, Hazirolan T, Kiraz S, et al. Imaging modalities used in diagnosis and follow-up of patients with Takayasu's Arteritis. *Turk J Med Sci*. (2021) 51(1):224–30. doi: 10.3906/sag-2005-70

47. Ohigashi H, Haraguchi G, Konishi M, Tezuka D, Kamiishi T, Ishihara T, et al. Improved prognosis of takayasu arteritis over the past decade–comprehensive analysis of 106 patients. *Circ J*. (2012) 76(4):1004–11. doi: 10.1253/circj.CJ-11-1108

48. Wong SPY, Mok CC, Lau CS, Yip ML, Tam LS, Ying KY, et al. Clinical presentation, treatment and outcome of Takayasu's Arteritis in southern Chinese: a multicenter retrospective study. *Rheumatol Int*. (2018) 38(12):2263–70. doi: 10.1007/s00296-018-4150-x

49. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis*. (2020) 79(1):19–30. doi: 10.1136/annrheumdis-2019-215672

50. Numano F. Differences in clinical presentation and outcome in different countries for Takayasu's Arteritis. *Curr Opin Rheumatol*. (1997) 9(1):12–5. doi: 10.1097/00002281-199701000-00003

51. Honig HS, Weintraub AM, Gomes MN, Hufnagel CA, Roberts WC. Severe aortic regurgitation secondary to idiopathic aortitis. *Am J Med*. (1977) 63(4):623–33. doi: 10.1016/0002-9343(77)90208-X

52. Isomura T, Hisatomi K, Yanagi I, Shimada S, Uraguchi K, Aoyagi S, et al. The surgical treatment of aortic regurgitation secondary to aortitis. *Ann Thorac Surg*. (1988) 45(2):181–5. doi: 10.1016/S0003-4975(10)62433-2

53. Cheng X, Li Z, Dang A, Lv N, Chang Q, Song Y, et al. Different treatment options for takayasu arteritis patients with moderate-to-severe aortic regurgitation: long-term outcomes. *Rheumatol (Oxford, England)*. (2021) 60(7):3134–43. doi: 10.1093/rheumatology/keaa647

54. Wang Y-J, Ma L-L, Liu Y, Yan Y, Sun Y, Wang Y-S, et al. Risk assessment model for heart failure in Chinese patients with Takayasu's Arteritis. *Clin Rheumatol*. (2021) 40(10):4117–26. doi: 10.1007/s10067-021-05745-0

55. Amano J, Suzuki A. Coronary artery involvement in Takayasu's Arteritis. Collective review and guideline for surgical treatment. *J Thorac Cardiovasc Surg*. (1991) 102(4):554–60. doi: 10.1016/S0022-5223(20)31426-4

56. Yuan S-M, Lin H-Z. Coronary artery involvements in takayasu arteritis: systematic review of reports. *Gen Thorac Cardiovasc Surg*. (2020) 68(9):883–904. doi: 10.1007/s11748-020-01378-3

57. Graham LM, Zelenock GB, Erlandson EE, Coran AG, Lindenauer SM, Stanley JC. Abdominal aortic coarctation and segmental hypoplasia. *Surgery*. (1979) 86(4):519–29. doi: 10.5555/uri:pii:0039606079901946

58. Kalangos A, Christenson JT, Cikirikcioglu M, Vala D, Buerge A, Simonet F, et al. Long-term outcome after surgical intervention and interventional procedures for the

management of Takayasu's Arteritis in children. *J Thorac Cardiovasc Surg*. (2006) 132 (3):656–64. doi: 10.1016/j.jtcvs.2006.04.020

59. Nanni GS, Hawkins IF, Alexander JA. Percutaneous transluminal angioplasty of an abdominal aortic coarctation. *AJR. Am J Roentgenol*. (1983) 140(6):1239–41. doi: 10.2214/ajr.140.6.1239

60. Ballweg J, Liniger R, Rocchini A, Gajarski R. Use of palmaz stents in a newborn with congenital aneurysms and coarctation of the abdominal aorta. *Catheter Cardiovasc Interv*. (2006) 68(4):648–52. doi: 10.1002/ccd.20749

61. Eliason JL, Passman MA, Guzman RJ, Naslund TC. Durability of percutaneous angioplasty and stent implantation for the treatment of abdominal aortic coarctation: a case report. *Vasc Surg*. (2001) 35(5):397–401. doi: 10.1177/153857440103500511

62. Ovaert C, Benson LN, Nykanen D, Freedom RM. Transcatheter treatment of coarctation of the aorta: a review. *Pediatr Cardiol*. (1998) 19(1):27–44. doi: 10.1007/s002469900243

63. O'Laughlin MP, Perry SB, Lock JE, Mullins CE. Use of endovascular stents in congenital heart disease. *Circulation*. (1991) 83(6):1923–39. doi: 10.1161/01.CIR.83.6.1923

64. Petrovic-Rackov L, Pejnovic N, Jevtic M. Refractory rapidly progressive Takayasu's Arteritis successfully treated with surgery. *Clin Rheumatol*. (2007) 26 (10):1787–9. doi: 10.1007/s10067-006-0522-9

65. Saxena A, Kothari SS, Sharma S, Juneja R, Srivastava S. Percutaneous transluminal angioplasty of the aorta in children with nonspecific aortoarteritis: acute and follow-up results with special emphasis on left ventricular function. *Catheter Cardiovasc Interv*. (2000) 49(4):419–24. doi: 10.1002/(SICI)1522-726X (200004)49:4<419::AID-CCD15>3.0.CO;2-I

66. Deyu Z, Lisheng L, Ruping D, Haiying W, Guozhang L. Percutaneous transluminal renal angioplasty in aortoarteritis. *Int J Cardiol*. (1998) 66(Suppl 1): S205–11. doi: 10.1016/S0167-5273(98)00170-3

67. Hiraya D, Sato A, Watabe H, Hoshi T, Ieda M. Axillofemoral bypass to improve congestive heart failure for atypical aortic coarctation complicating takayasu arteritis. *ESC Heart Failure*. (2020) 7(5):3184–8. doi: 10.1002/ehf2.12855

68. Kim DI, Huh SH, Lee BB. Aortic endarterectomy in Takayasu's Arteritis and Leriche's Syndrome. *J Cardiovasc Surg (Torino)*. (2002) 43(5):751.

69. Butcher HR, Jaffe BM. Treatment of aortoiliac arterial occlusive disease by endarterectomy. *Ann Surg*. (1971) 173(6):925–32. doi: 10.1097/00000658-197106010-00010

70. Jacob T, Cobanoglu A, Starr A. Late results of ascending aorta-descending aorta bypass grafts for recurrent coarctation of aorta. *J Thorac Cardiovasc Surg*. (1988) 95 (5):782–7. doi: 10.1016/S0022-5223(19)35688-0

71. Tsukube T, Yoshimura M, Matsuda H, Okada K, Matsukawa R, Hino Y, et al. Rib-cross thoracotomy for replacement of the thoracoabdominal or total descending aorta. *J Vasc Surg*. (2003) 37(1):219–21. doi: 10.1067/mva.2003.49

72. Okada K, Tanaka A, Munakata H, Matsumori M, Morimoto Y, Tanaka Y, et al. Extended replacement of aortic arch aneurysms through left posterolateral thoracotomy. *Eur J Cardiothorac Surg*. (2009) 35(2):270–5. doi: 10.1016/j.ejcts.2008.09.048

73. Vijayanagar R, Natarajan P, Eckstein PF, Bognolo DA, Toole JC. Aortic valvular insufficiency and postductal aortic coarctation in the adult. Combined surgical management through median sternotomy: a new surgical approach. *J Thorac Cardiovasc Surg*. (1980) 79(2):266–8. doi: 10.1016/S0022-5223(19)37983-8

74. Obitsu Y, Koizumi N, Saiki N, Kawaguchi S, Shigematsu H. Long-term result of hybrid procedure for an extensive thoracic aortic aneurysm in takayasu arteritis: a case report. *J Cardiothorac Surg*. (2010) 5:28. doi: 10.1186/1749-8090-5-28

75. Okonogi S, Ohki S, Obayashi T, Yasuhara K, Nagasawa A, Miki T. Single-stage hybrid procedure for ruptured calcified thoracic aortic aneurysm caused by Takayasu's Arteritis. *Gen Thorac Cardiovasc Surg*. (2021) 69(3):610–3. doi: 10.1007/s11748-020-01513-0

76. Liu Z, Zhou M, Liu C, Qiao T, Huang D, Zhang M, et al. Hybrid procedures for thoracoabdominal aortic pathologies. *Vascular*. (2013) 21(4):205–14. doi: 10.1177/1708538113478772

77. Wukasch DC, Cooley DA, Sandiford FM, Nappi G, Reul GJ. Ascending aorta-abdominal aorta bypass: indications, technique, and report of 12 patients. *Ann Thorac Surg*. (1977) 23(5):442–8. doi: 10.1016/S0003-4975(10)64164-1

78. Kumar MV, Choudhary SK, Talwar S, Gharde P, Sahu M, Kumar S, et al. Extraanatomic bypass to supraceliac abdominal aorta for Complex thoracic aortic obstruction. *Ann Thorac Surg*. (2016) 101(4):1552–7. doi: 10.1016/j.athoracsur.2015.10.080

79. Wang R, Sun L-Z, Hu X-P, Ma W-G, Chang Q, Zhu J-M, et al. Treatment of complex coarctation and coarctation with cardiac lesions using extra-anatomic aortic bypass. *J Vasc Surg*. (2010) 51(5):1203–8. doi: 10.1016/j.jvs.2009.12.027

80. Oishi K, Mizuno T, Fujiwara T, Kuroki H, Yashima M, Takeshita M, et al. Surgical strategy for inflammatory thoracic aortic aneurysms in the endovascular surgery era. *J Vasc Surg*. (2022) 75:1. doi: 10.1016/j.jvs.2021.06.479

81. Park MC, Lee SW, Park YB, Lee SK, Choi D, Shim WH. Post-interventional immunosuppressive treatment and vascular restenosis in Takayasu's Arteritis. *Rheumatol (Oxford, England)*. (2006) 45(5):600–5. doi: 10.1093/rheumatology/kei245

82. Tyagi S, Gupta MD, Singh P, Shrimal D, Girish MP. Percutaneous revascularization of sole arch artery for severe cerebral ischemia resulting from takayasu arteritis. *J Vasc and Int Radiol: JVIR*. (2008) 19(12):1699–703. doi: 10.1016/j.jvir.2008.09.017

83. Ham SW, Kumar SR, Rowe VL, Weaver FA. Disease progression after initial surgical intervention for takayasu arteritis. *J Vasc Surg*. (2011) 54(5):1345–51. doi: 10.1016/j.jvs.2011.04.044

84. Akazawa H, Ikeda U, Yamamoto K, Kuroda T, Shimada K. Hypercoagulable state in patients with Takayasu's Arteritis. *Thromb Haemostasis*. (1996) 75(5):712–6. doi: 10.1055/s-0038-1650353

85. Pazzola G, Muratore F, Pipitone N, Crescentini F, Cacoub P, Boiardi L, et al. Rituximab therapy for takayasu arteritis: a seven patients experience and a review of the literature. *Rheumatol (Oxford, England)*. (2018) 57(7):1151–5. doi: 10.1093/rheumatology/kex249

86. Langford CA, Cuthbertson D, Ytterberg SR, Khalidi N, Monach PA, Carette S, et al. A randomized, double-blind trial of Abatacept (CTLA-4Ig) for the treatment of takayasu arteritis. *Arth & Rheumatol (Hoboken, N.J.)*. (2017) 69(4):846–53. doi: 10.1002/art.40037

87. Terao C, Yoshifuji H, Nakajima T, Yukawa N, Matsuda F, Mimori T. Ustekinumab as a therapeutic option for takayasu arteritis: from genetic findings to clinical application. *Scand J Rheumatol*. (2016) 45(1):80–2. doi: 10.3109/03009742.2015.1060521

88. Miyata T. The Asia pacific meeting for vasculitis and ANCA workshop 2012: surgical treatment for Takayasu's Arteritis. *Clin Exp Nephrol*. (2014) 18(2):296–300. doi: 10.1007/s10157-013-0894-5

89. Reddy E, Robbs JV. Surgical management of Takayasu's Arteritis in children and adolescents. *Cardiovasc J Afr*. (2007) 18(6):393–6. doi: 10.10520/EJC2306

90. Liang P, Hoffman GS. Advances in the medical and surgical treatment of takayasu arteritis. *Curr Opin Rheumatol*. (2005) 17(1):16–24. doi: 10.1097/01.bor.0000146607.65808.37

91. Jung JH, Lee YH, Song GG, Jeong HS, Kim J-H, Choi SJ. Endovascular versus open surgical intervention in patients with Takayasu's Arteritis: a meta-analysis. *Eur J Vasc Endovasc Surg*. (2018) 55(6):888–99. doi: 10.1016/j.ejvs.2018.02.030

92. Berdat PA, Göber V, Carrel T. Extra-anatomic aortic bypass for complex (re-) coarctation and hypoplastic aortic arch in adolescents and adults. *Interact Cardiovasc Thorac Surg*. (2003) 2(2):133–7. doi: 10.1016/S1569-9293(02)00122-6

93. Weaver FA, Kumar SR, Yellin AE, Anderson S, Hood DB, Rowe VL, et al. Renal revascularization in takayasu arteritis-induced renal artery stenosis. *J Vasc Surg*. (2004) 39(4):749–57. doi: 10.1016/j.jvs.2003.12.022

94. Ishikawa K, Maetani S. Long-term outcome for 120 Japanese patients with Takayasu's Disease. Clinical and statistical analyses of related prognostic factors. *Circulation*. (1994) 90(4):1855–60. doi: 10.1161/01.CIR.90.4.1855

95. Clarkson PM, Nicholson MR, Barratt-Boyes BG, Neutze JM, Whitlock RM. Results after repair of coarctation of the aorta beyond infancy: a 10 to 28 year follow-up with particular reference to late systemic hypertension. *Am J Cardiol*. (1983) 51(9):1481–8. doi: 10.1016/0002-9149(83)90661-6

96. Gross RE. Surgical correction for coarctation of the aorta. *Surgery*. (1945) 18:673–8. doi: 10.5555/uri:pii:003960604590290X

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IFABP levels predict visceral malperfusion in the first hours after open thoracoabdominal aortic repair

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Introduction: Intestinal ischemia after open thoracoabdominal aortic repairs, is a rare but devastating complication, associated with high mortality. Notoriously challenging to diagnose, visceral malperfusion necessitates immediate surgical attention. Intestinal fatty acid-binding protein (IFABP) has been proposed as a biomarker for the diagnosis of intestinal wall damage. In this prospectively conducted, observational study we evaluated the diagnostic capacity of IFABP levels in patients' serum and their correlation with visceral malperfusion.
Methods: 23 patients undergoing open thoracoabdominal aortic repairs were included in this study and 8 of them were diagnosed postoperatively with visceral malperfusion—defined as a partial or complete thrombotic occlusion of the superior mesenteric artery and/or the coeliac trunk. IFABP levels and laboratory parameters often associated with intestinal ischemia (leucocytes, CRP, PCT and lactate) were measured at baseline, directly postoperatively, and at 12, 24 and 48 h after surgery. Postoperative visceral malperfusion—as revealed in CT angiography—was assessed and the predictive ability of IFABP levels to detect visceral malperfusion was evaluated with receiver-operator curve analysis.
Results: Patients with visceral malperfusion had a relevant risk for a fatal outcome ($p = .001$). IFABP levels were significantly elevated directly postoperatively and at 12 h after surgery in cases of visceral malperfusion. High IFABP concentrations in serum detected visceral malperfusion accurately during the first 12 h after surgery, with the maximum diagnostic ability achieved immediately after surgery (AUC 1, Sensitivity 100%, Specificity 100%, $p < .001$).
Conclusion: We conclude, that IFABP measurements during the first postoperative hours after open thoracoabdominal aortic surgery can be a valuable tool for reliable and timely detection of visceral malperfusion.

KEYWORDS
intestinal ischemia, visceral malperfusion, thoracoabdominal aorta, open aortic repair, postoperative management, aortic aneurysm

1. Introduction

Open surgical treatment of thoracoabdominal aortic aneurysms (TAAA) often requires reconstruction of the viscerorenal aortic segment, alongside with aortic cross-clamping and exposure to extracorporeal circulation, which may impair the integrity of the intestinal wall (1). With an incidence of 3% (2) to 9% (3) visceral malperfusion and intestinal ischemia are relatively rare, but devastating complications in fields of TAAA surgery, associated with high mortality rates [50%–90% (4)]. Furthermore, these cases are often accompanied by systemic inflammatory response and sepsis, as well as intestinal necrosis requiring surgical treatment. However, fluctuations in patient's fluid homeostasis, cardiopulmonal instability and deep sedation during the first postoperative hours may mask clinical and laboratory symptoms and signs of visceral malperfusion and hinder clinical suspicion and diagnosis.

A promising biomarker strongly associated with the incidence of bowel ischemia is intestinal fatty acid-binding protein (IFABP) (5). This 15 kDa protein is expressed in the cytoplasm of mature enterocytes found at the end of the intestinal villi (6). This area of the gut wall is the most distant from the intestinal capillary network and, as such, it bears the highest risk to be the first to succumb to malperfusion (7). Under the premise of this mechanism, many studies have investigated the clinical applicability and reliability of IFABP for the diagnosis of intestinal necrosis (1, 5, 6). The focus of its clinical relevance is placed on the detection of mesenteric ischemia affecting the small intestine, since the concentration of the protein is in this segment twenty times higher than in the large intestine (8). In the settings of open abdominal and thoracoabdominal aortic surgery, we demonstrated that elevation of IFABP after surgery and on the first postoperative day could reliably detect intestinal necrosis (1).

Expanding on the findings of this previous work, in this prospectively conducted study we investigated the dynamic changes of IFABP levels in patients' serum during the first postoperative hours after open TAAA repair and its correlation with the diagnosis of visceral malperfusion.

2. Patients and methods

2.1. Study design

In this observational study conducted at a single center, 23 patients who underwent open TAAA reconstructions between January 2019 and February 2023 were included. The study protocol was reviewed and approved by the ethic committee of the University Hospital Aachen (EK010/19) and designed according to the Declaration of Helsinki and the STROBE criteria. The apriori study protocol describing material acquisition was registered at clinicaltrials.gov/ct2/show/NCT04087161. Patients provided written informed consent before participating in the study. Pregnant women and those under 18 years of age were excluded. All included cases were elective, with patent coeliac trunk and superior mesenteric arteries at the time of the operation. Digital medical records and clinical charts were used to collect data on patients' medical history and demographic details.

2.2. Surgery

The surgical procedure for TAAA reconstructions, including the reconstruction of the visceral aortic segment, has been previously described in the literature (9). Exposure of the thoracoabdominal aorta was achieved through thoracolaparotomy. The abdominal aorta was approached transperitoneally. In all included cases a femoral-femoral cannulation via the left femoral vessels was applied. After the proximal aortic clamp was placed, the extracorporeal circulation was initiated to provide distal aortic perfusion. The time interval starting from the placement of the proximal aortic clamp until its removal at the end of the reconstruction, is later referred to as "cross-clamping time". During the reconstruction of the visceral aortic segment, selective perfusion of all visceral arteries was achieved via extracorporeal circulation, enabling a flow of at least 500 ml/min per catheter. CUSTODIOL® solution (HTK, Dr. Franz Köhler Chemie GmbH, Bensheim, Germany) was infused into both kidney arteries, and the mean arterial pressure was kept at 90 mmHg or higher throughout the procedure. Mild systemic hypothermia (32°C–33°C), cerebrospinal fluid drainage and intraoperative monitoring of motor-evoked potentials were implemented as protective measures to reduce the risk of spinal cord ischemia and postoperative neurologic deficits.

2.3. Measurements

To measure IFABP concentrations in serum, blood samples were collected from patients at baseline, immediately after surgery, and at 12, 24, and 48 h postoperatively. The samples were stored at −80°C after centrifugation, and IFABP concentrations were calculated using ELISA (RayBio® Human FABP2 ELISA Kit, RayBiotech, Norcross, USA) according to the manufacturer's recommendations. After all reagents and samples were prepared, 100 µl of sample were added in each well and were incubated for 2.5 h at room temperature. Then, 100 µl of the prepared biotin antibody were added to each well and were allowed to incubate for 1 h, before 100 µl Streptavidin solution were added. After further 45 min of incubation at room temperature, 100 µl of TMB One-Step Substrate Reagent were added. After 30 min of incubation at room temperature, the reaction was arrested with 50 µl of Stop Solution and the microplate was immediately read at 450 nm with the Tecan Spark 10 M Luminescence Multi Mode Microplate Reader (Tecan, Männedorf, Switzerland). The intra-assay coefficient of variation was 10%, and the inter-assay coefficient was 12%. The normal values for circulating IFABP in healthy, non-obese population is 4.8 ng/ml [Interquartile range 3.7–8] (10).

Routine laboratory parameters, including leucocyte count, levels of procalcitonin (PCT) and C-reaction protein (CRP) were obtained at baseline and at 12, 24 and 48 h postoperatively. Lactate was measured in arterial blood collected in a heparinized plastic syringe. The collected sample was immediately analyzed in the blood gas analyzer ABL90 Flex (Radiometer, Brønshøj, Denmark).

2.4. Endpoints

The primary endpoint and focus of this study was postoperative visceral malperfusion and its correlation with IFABP levels in serum. Patients with reduced arterial flow to mesenterium, because of acute partial or complete thrombotic occlusion of the superior mesenteric artery and/or coeliac trunk, as revealed by angiographic scan, were diagnosed with visceral malperfusion (11). In cases of only partial occlusion of the visceral arteries, patients with moderate or high grade stenosis were included in the "visceral malperfusion" group. Examples of CT-angiograms of included patients with partial and complete occlusions of the visceral arteries are presented in **Supplementary Figure S1**. The diagnosis of visceral malperfusion was based solely on angiographic findings in the computer tomography scan, regardless of laboratory parameters and clinical presentation. The patients with clinical suspicion of intestinal ischemia, elevated serum lactate and angiographic confirmation of visceral malperfusion required surgical revision.

Secondary endpoints were the associations of visceral malperfusion and adverse events during the postoperative phase. The diagnostic criteria for multi-organ dysfunction syndrome (MODS) was fulfilled when two or more vital organ systems failed (12). Sepsis was diagnosed in patients with active infection and an increase of their daily Sequential Organ Failure Assessment (SOFA)-Score by 2 points or more in comparison to the previous day (13). According to the Berlin definition, the diagnosis of acute respiratory distress syndrome (ARDS) was applied (14). Patients without a history of liver disease and a spontaneous international normalized ratio >1.5 accompanied with acute onset of jaundice were diagnosed with acute liver injury (15). Renal replacement therapy (RRT) was initiated in cases of severe metabolic acidosis and hyperkaliaemia, anuria and refractory volume overload (16).

2.5. Statistics

The absolute frequencies and percentages of the total sample are used to report categorical variables, while mean (±standard deviation) is used to present continuous variables. In the results, significance levels are indicated by (*) for $p < .05$, (**) for $p < .01$, and (**) for $p < .001$, with a 95% confidence interval (CI). Correlations of visceral malperfusion and postoperative complications and patient demographics were tested using univariable, logistic regression. IFABP serum levels were logarithmically transformed to achieve a normal distribution and one-way ANOVA was used to test for correlations between IFABP serum levels and the onset of visceral malperfusion. The diagnostic capacity of serum lactate and IFABP levels was evaluated using receiver-operating-characteristics (ROC) analysis and the optimal cut-offs were obtained with the Youden-Index. Data analysis was performed using the SPSS software (SPSS Inc., Chicago IL) and graphics were created with the GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, California USA).

3. Results

There were 23 patients ($n = 20$ men) included in this study with a mean age of 51.5 ± 11.7 years. 8 of these patients were diagnosed with visceral malperfusion during the postoperative phase. The details of the patients' comorbidities are displayed in **Table 1**. The onset of visceral malperfusion was not associated with any comorbidities and it was independent from both aortic cross-clamping time and duration of surgery, although we observed a statistically insignificant trend for longer procedures in the visceral malperfusion group (535 ± 92.5 min vs. 490 ± 103.1 min, $p = .21$). The most common reconstruction was type II repairs (Crawford classification). Postoperatively, patients with visceral malperfusion required in 50% of the cases a re-laparotomy for surgical revision of the visceral bypasses. The 4 patients in the visceral malperfusion group, that were not surgically revised presented partial thrombosis of the SMA. Two of these cases were treated conservatively with therapeutic anticoagulation and the other two succumbed to circulatory arrest before surgical revision. Resection of intestinal segments was necessary in 3 cases (38%). MODS and acute liver injury were significantly more common in these patients (MODS: 63% vs. 5%, $p < .001$; acute liver injury: 50% vs. 5%, $p = .002$). We also observed a trend for the onset of sepsis but without statistical significance (Sepsis: 63% vs. 32%, $p = .14$).

IFABP serum levels were postoperatively elevated in all patients, however at admission in the ICU the increase was ten-fold in patients with visceral malperfusion (154.4 ± 11.4 ng/ml vs. 14.9 ± 8.7 ng/ml, $p = .02$) and persisted for the first 12 h (125.6 ± 163.8 vs. 9.2 ± 8.4, $p = .01$) (**Figure 1**). Among these patients, we found a trend for higher IFABP levels in cases that necessitated intestinal resection, however without statistical significance (IFABP at 12 h: 224.9 ± 247 vs. 66.1 ± 67.8; $p = .21$) (**Supplementary Table S1**; **Supplementary Figure S2**). We observed a dynamic decrease in the subsequent time points. Serum lactate, C-reactive protein (CRP), procalcitonin (PCT) and leucocytes—all markers routinely examined in case of suspicion of visceral malperfusion—displayed only a trend of elevation during the early postoperative phase, without reaching statistical significance (**Table 2**).

ROC-Curve analysis for IFABP levels postoperatively revealed high diagnostic accuracy for visceral malperfusion during the first 12 h. The maximum accuracy was reached at patient's admission on ICU (AUC = 1, Sensitivity 100%, Specificity 100%, $p < .001$ for a cut-off of 32 ng/ml). Persistent elevation of IFABP levels 12 h postoperatively could still accurately predict visceral malperfusion (AUC = .835, Sensitivity 95.5%, Specificity 75%, $p = .006$ for a cut-off value of 21.7 ng/ml). In comparison, the clinically established lactate levels in serum did not reach an equivalent diagnostic capacity postoperatively with a maximum AUC of.784 (Sensitivity 87.5%, Specificity 60%, $p = .02$) at 12 and 24 h (**Table 3**).

4. Discussion

4.1. Dynamic of IFABP levels

IFABP levels did not differ between the two groups at baseline. Directly after surgery IFABP was elevated in both groups—albeit tenfold higher in the visceral malperfusion group—and declined in all subsequent time points. This dynamic can be understood through the physiologic expression of IFABP in mature

TABLE 1 Patient demographics and postoperative details.

	No visceral malperfusion ($n = 15$)	Visceral malperfusion ($n = 8$)	p-value
Demographics			
Age (years)	51.5 ± 11.7	48.8 ± 16.4	.95
Men	16 (73)	4 (50)	.26
Obesity	2 (9)	1 (13)	.79
Body mass index (kg/m^2)	23.4 ± 2.4	26.3 ± 6.2	.46
Smoking	7 (32)	2 (25)	.73
Chronic obstructive pulmonary disease	5 (23)	2 (25)	.9
Hypertension	15 (68)	8 (100)	.1
Chronic kidney disease (eGFR <60 ml/min/1.73 m^2)	10 (46)	5 (63)	.43
Type of TAAA			.7
I	1 (5)	2 (25)	
II	10 (46)	2 (25)	
III	5 (23)	2 (25)	
IV	5 (23)	1 (13)	
V	1 (5)	1 (13)	
Duration of surgery (minutes)	490 ± 103.1	535 ± 92.5	.21
Cardiopulmonary bypass time (minutes)	141.5 ± 51.1	156.62 ± 37.7	.52
Postoperative data			
30-day-mortality	0 (0)	3 (38)	.1
Intestinal resection	0 (0)	3 (38)	.002**
Surgical revision of the visceral bypass	0 (0)	4 (50)	<.001***
Intensive care unit stay (days)	30.2 ± 31.6	41.3 ± 38.4	.2
Hospital stay (days)	43.7 ± 27.4	64.1 ± 47.1	.42
Pneumonia	13 (59)	7 (88)	.2
Acute respiratory distress syndrome	10 (46)	5 (63)	.43
Sepsis	7 (32)	5 (63)	.14
Multi-organ dysfunction syndrome	1 (5)	5 (63)	<.001***
Acute liver injury	1 (5)	4 (50)	.002**
Renal replacement therapy	12 (55)	7 (88)	.1
Apoplex	4 (18)	1 (13)	.72
Delirium	9 (41)	2 (25)	.44

TAAA, thoracoabdominal aortic aneurysm; eGFR, estimated glomerular filtration rate.
** for p <.01 and *** for p <.001.

enterocytes, which reside at the tip of the intestinal villi and are the first to succumb under ischemic conditions, leaking IFABP in circulation (17). The reasons for the ischemic injury of the gut wall are multifactorial and although surgical techniques—like distal aortic perfusion and selective visceral perfusion—have been optimized to safeguard mesenteric oxygen supply during reconstruction of the viscerorenal segment, enterocyte damage cannot be eliminated altogether.

Firstly, aortic-cross clamping, opening the aneurysm sack and connection of the selective, visceral perfusion cannulas to provide volume-controlled blood flow to the intestine may cause a short period of absolute ischemia of the gut wall (1). Although, the time of this maneuver is sought to be brought to a minimum, it can still cause damage to the integrity of the gut wall. The selective perfusion of the visceral vessels as well as the maintenance of distal aortic perfusion deliver protection against intestinal ischemic injury (18). Yet, insults of the microcirculatory network are still possible (19) and some authors argue that selective visceral perfusion on its own does not provide adequate oxygenation of the bowel during the reconstruction of the viscerorenal aortic segment (18, 20, 21). In fact a point of discussion is the "unnatural" laminar flow generated from the extracorporeal circulation, which may limit the mucosal microcirculation (22) and disadvantage the microvascular perfusion (23). The implementation of pulsatile flow in the extracorporeal circulation circuit in the setting of cardiac surgery, may arguably preserve microcirculation and endorgan integrity (22), however some authors argue that pulsatile flow offers no significant advantage concerning organ perfusion or inflammatory response (24). Currently, in the field of selective visceral perfusion during open TAAA repairs, the implementation of pulsatile flow has not found widespread applicability. All patients included in this study received both selective visceral perfusion and distal aortic perfusion as per protocol with a laminar flow pattern and we did not observe a significant correlation of CBP time and the onset of visceral ischemia (141.5 ± 51.1 min vs. 156.62 ± 37.7 min, $p = .52$), supporting the notion that the protective measures provided sufficient oxygenation to the intestine during aortic reconstruction.

However, tissue injury of the gut wall suffers a second hit during reperfusion after completion of the reconstruction and re-initiation of pulsatile blood flow (25). In a previous work of our group, we described that clinical presentation of ischemia-reperfusion-injury of the intestine may greatly vary from patient to patient and is a

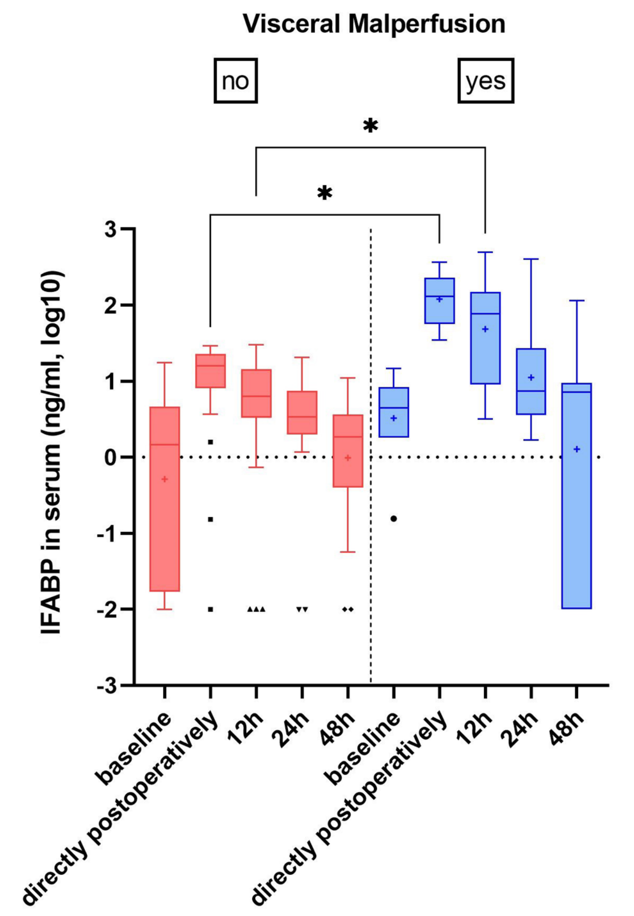

FIGURE 1
IFABP levels in serum.

dynamic event with both local and systemic consequences (26). Thus, the secretion of IFABP in the blood stream peaks at the end of the surgery, as the aftermath of the necrosis of the mature enterocytes of at the tip of the villi, although the vitality of the intestine seems macroscopically uncompromised.

These observations are in accordance with the previous study on IFABP in open TAAA repair patients, which described a significant elevation of IFABP during and after extra-corporeal circulation (1). IFABP is cleared through the kidneys and its levels physiologically decline in the early postoperative phase (27).

4.2. Clinical significance of IFABP serum levels

IFABP has gained the attention of researchers as a minimal invasive tool for the diagnostic algorithm of intestinal ischemia, which can be clinically easily missed (28). Sun et al. report in their meta-analysis a pooled sensitivity of 80% and pooled specificity of 85% for detecting acute mesenterial ischemia (28). However, they also report relevant heterogeneity of the included patients in their study, which may limit the interpretation of the results. Among the included studies, both vascular and non-vascular types of acute intestinal ischemia were included, which might have influenced the heterogeneity of the study cohort. Nuzzo et al. found IFABP not applicable for detecting acute mesenteric ischemia in their cross-sectional study for both arterial and venous intestinal infarction at the time of the admission in the emergency department (6). They report higher IFABP levels in cases of late phase intestinal necrosis, but without statistical significance. This finding is in line with the observations of Schellekens et al., who also did not find significant alterations of IFABP serum concentration between mucosal and transmural bowel ischemia (29).

Although Nuzzo et al. selected their patient cohort carefully and excluded patients with bowel strangulation, the clinical manifestation of acute mesenteric ischemia in an emergency setting may still account for high variability and confounding. The patient cohort presented in our study is homogenous, treated by the same

TABLE 2 Dynamics of leucocytes, CRP, PCT, lactate and IFABP in serum.

	No visceral malperfusion ($n = 15$)					Visceral malperfusion ($n = 8$)				
	Baseline	Admission ICU	12 h	24 h	72 h	Baseline	Admission ICU	12 h	24 h	72 h
Leucocytes (/nl)	7.3 ± 3.2	-	9.1 ± 3.5	10.7 ± 3.6	10.9 ± 3.7	9.5 ± 3.4	-	10.6 ± 2.2	11.7 ± 3.3	12.4 ± 4.1
CRP (mg/L)	23.3 ± 66.1	-	93.5 ± 47.8	240.4 ± 49.2	260.6 ± 62.5	56.3 ± 108.3	-	93.8 ± 69.1	212.8 ± 122.8	215.3 ± 85.4
PCT (ng/ml)	-	-	12.4 ± 12.7	13.9 ± 14.1	10.6 ± 11.4	-	-	32.5 ± 41.4	23.3 ± 37.8	25.3 ± 36.7
Lactate (mmol/L)	.9 ± 1.2	3.2 ± 4.4	2.3 ± 1.8	1.6 ± 1.1	1.1 ± .5	.6 ± .2	4.2 ± 3.9	5.5 ± 5.5	5 ± 7.7	2.4 ± 2.5
IFABP (ng/ml)	2.8 ± 4	14.9 ± 8.7	9.2 ± 8.4	4.9 ± 4.5	2.3 ± 2.4	5 ± 4.9	154.4 ± 111.4	125.6 ± 163.8	59.7 ± 139.3	17.6 ± 39.2

CRP, C-reactive protein; PCT, procalcitonin; IFABP, intestinal-fatty acid binding protein.

TABLE 3 ROC-curve analysis for IFABP and lactate in serum.

	IFABP					Lactate				
	AUC	*p*-value	Cut-off	Sensitivity (%)	Specificity (%)	AUC	*p*-value	Cut-off	Sensitivity (%)	Specificity (%)
Baseline	.636	.26	4.23	72.7	50	.585	.48	.55	50	63.6
Admission ICU	1	<.001	32	100	100	.6	.4	2.15	75	50
12 h	.835	.006	21.7	90.1	75	.784	.02	2.05	87.5	60
24 h	.733	.05	11.2	95.5	50	.784	.02	1.5	87.5	65
48 h	.54	.74	6	95.5	50	.71	.09	1.3	62.5	70

surgeon according to a standardized operative protocol and similar pathophysiologic mechanisms for the onset of visceral malperfusion. The reported 100% sensitivity and 100% specificity for high IFABP levels directly postoperatively and significant diagnostic accuracy up to the 12 h postoperatively (AUC.835, Sensitivity 90%, Specificity 75%, $p = .006$) indicate the relevance of IFABP serum levels as an adjutant to the detection of visceral malperfusion and may warrant further clinical and radiographic evaluation. We speculate that the increase of routinely monitored IFABP levels during the first hours after surgery may justify an early CT-angiogram to confirm the diagnosis of visceral malperfusion and plan the potential revision without delay.

This study is limited mainly through the small number of included patients. Open TAAA repairs are relatively rare procedures in the current era of endovascular surgery and visceral malperfusion itself is a rare complication. However, the observed differences of the IFABP dynamic between the two groups were statistically highly significant and therefore reliable. Moreover, although our surgical protocol included selective perfusion of the visceral arteries as a measure to minimize the ischemic time of the viscera, there was a small interval of absolute ischemia starting from the clamping of the viscerorenal segment until the identification and cannulation of the visceral ostia. We did not include this time interval in our study protocol, since it was kept under 5 min in all presented cases. A further weak point of this project is the heterogeneity of the investigated endpoint “visceral malperfusion”: in some patients, this would mean a partial thrombotic occlusion of the mesenteric circulation and in other cases complete transmural necrosis with necessary resection of intestinal segments. Yet, the pathomechanisms of the reported visceral malperfusion underlie the similar principles and necessitate thorough clinical evaluation, making the measurements of IFABP in patients’ serum a valuable tool in the arsenal of both the vascular surgeon and the intensivist.

5. Conclusion

In conclusion, IFABP serum levels could reliably and accurately predict visceral malperfusion in patients after open TAAA repair. Visceral malperfusion may signify impending intestinal necrosis and elevated serum concentrations of IFABP during the first 12 h postoperatively could be an alarm sign for further clinical and radiographic evaluation of the patients at risk.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethic Committee of the University Hospital Aachen (EK010/19). The patients/participants provided their written informed consent to participate in this study.

Author contributions

PD, CB, MJ, ME, and AG contributed to conception and design of the study. CB organized the database. PD performed the statistical analysis. PD wrote the first draft of the manuscript. HK, JF, MJ, ME, and AG wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1200967/full#supplementary-material

References

1. Vermeulen Windsant IC, Hellenthal FA, Derikx JP, Prins MH, Buurman WA, Jacobs MJ, et al. Circulating intestinal fatty acid-binding protein as an early marker of intestinal necrosis after aortic surgery: a prospective observational cohort study. *Ann Surg*. (2012) 255(4):796–803. doi: 10.1097/SLA.0b013e31824b1e16

2. Achouh PE, Madsen K, Miller CC 3rd, Estrera AL, Azizzadeh A, Dhareshwar J, et al. Gastrointestinal complications after descending thoracic and thoracoabdominal aortic repairs: a 14-year experience. *J Vasc Surg*. (2006) 44(3):442–6. doi: 10.1016/j.jvs.2006.05.018

3. Zarkowsky DS, Inman JT, Sorrentino TA, Hiramoto JS, Vartanian SM, Eichler CM, et al. Contemporary experience with paravisceral aortic aneurysm (PVAAA) repair in a tertiary center. *Ann Vasc Surg*. (2021) 75:368–79. doi: 10.1016/j.avsg.2021.01.109

4. Kudo T. Surgical complications after open abdominal aortic aneurysm repair: intestinal ischemia, buttock claudication and sexual dysfunction. *Ann Vasc Dis*. (2019) 12(2):157–62. doi: 10.3400/avd.ra.19-00038

5. Kayali F, Sarodaya V, Shah HI, Hayat MY, Leung MST, Harky A. Predicting outcomes of mesenteric ischemia postcardiac surgery: a systematic review. *J Card Surg*. (2022) 37(7):2025–39. doi: 10.1111/jocs.16516

6. Nuzzo A, Guedj K, Curac S, Hercend C, Bendavid C, Gault N, et al. Accuracy of citrulline, I-FABP and D-lactate in the diagnosis of acute mesenteric ischemia. *Sci Rep*. (2021) 11(1):18929. doi: 10.1038/s41598-021-98012-w

7. Gollin G, Marks C, Marks WH. Intestinal fatty acid binding protein in serum and urine reflects early ischemic injury to the small bowel. *Surgery*. (1993) 113(5):545–51.

8. Pelsers MM, Namiot Z, Kisielewski W, Namiot A, Januszkiewicz M, Hermens WT, et al. Intestinal-type and liver-type fatty acid-binding protein in the intestine. Tissue distribution and clinical utility. *Clin Biochem*. (2003) 36(7):529–35. doi: 10.1016/S0009-9120(03)00096-1

9. Mommertz G, Sigala F, Langer S, Koeppel TA, Mess WH, Schurink GW, et al. Thoracoabdominal aortic aneurysm repair in patients with marfan syndrome. *Eur J Vasc Endovasc Surg*. (2008) 35(2):181–6. doi: 10.1016/j.ejvs.2007.10.013

10. Seethaler B, Basrai M, Neyrinck AM, Nazare J-A, Walter J, Delzenne NM, et al. Biomarkers for assessment of intestinal permeability in clinical practice. *Am J Physiol Gastrointest Liver Physiol*. (2021) 321(1):G11–G7. doi: 10.1152/ajpgi.00113.2021

11. Kamman AV, Yang B, Kim KM, Williams DM, Michael Deeb G, Patel HJ. Visceral malperfusion in aortic dissection: the Michigan experience. *Semin Thorac Cardiovasc Surg*. (2017) 29(2):173–8. doi: 10.1053/j.semtcvs.2016.10.002

12. Rossaint J, Zarbock A. Pathogenesis of multiple organ failure in sepsis. *Crit Rev Immunol*. (2015) 35(4):277–91. doi: 10.1615/CritRevImmunol.2015015461

13. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *J Am Med Assoc*. (2016) 315(8):801–10. doi: 10.1001/jama.2016.0287

14. Meyer NJ, Gattinoni L, Calfee CS. Acute respiratory distress syndrome. *Lancet*. (2021) 398(10300):622–37. doi: 10.1016/S0140-6736(21)00439-6

15. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul J-L, et al. EASL clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. (2018) 69(1):182–236. doi: 10.1016/j.jhep.2018.03.019

16. Bagshaw SM, Wald R. Strategies for the optimal timing to start renal replacement therapy in critically ill patients with acute kidney injury. *Kidney Int*. (2017) 91(5):1022–32. doi: 10.1016/j.kint.2016.09.053

17. Pelsers MMAL, Hermens WT, Glatz JFC. Fatty acid-binding proteins as plasma markers of tissue injury. *Clin Chim Acta*. (2005) 352(1-2):15–35. doi: 10.1016/j.cccn.2004.09.001

18. Waked K, Schepens M. State-of the-art review on the renal and visceral protection during open thoracoabdominal aortic aneurysm repair. *J Vis Surg*. (2018) 4:31. doi: 10.21037/jovs.2018.01.12

19. Kalder J, Ajah D, Keschenau P, Kennes LN, Tolba R, Kokozidou M, et al. Microcirculatory perfusion shift in the gut wall layers induced by extracorporeal circulation. *J Vasc Surg*. (2015) 61(2):497–503. doi: 10.1016/j.jvs.2013.10.070

20. Kunihara T, Shiiya N, Wakasa S, Matsuzaki K, Matsui Y. Assessment of hepatosplanchnic pathophysiology during thoracoabdominal aortic aneurysm repair using visceral perfusion and shunt. *Eur J Cardiothorac Surg*. (2009) 35(4):677–83. doi: 10.1016/j.ejcts.2008.12.016

21. Hanssen SJ, Derikx JP, Vermeulen Windsant IC, Heijmans JH, Koeppel TA, Schurink GW, et al. Visceral injury and systemic inflammation in patients undergoing extracorporeal circulation during aortic surgery. *Ann Surg*. (2008) 248(1):117–25. doi: 10.1097/SLA.0b013e3181784cc5

22. O'Neil MP, Fleming JC, Badhwar A, Guo LR. Pulsatile versus nonpulsatile flow during cardiopulmonary bypass: microcirculatory and systemic effects. *Ann Thorac Surg*. (2012) 94(6):2046–53. doi: 10.1016/j.athoracsur.2012.05.065

23. Tan A, Newey C, Falter F. Pulsatile perfusion during cardiopulmonary bypass: a literature review. *J Extra Corpor Technol*. (2022) 54(1):50–60. doi: 10.1182/ject-50-60

24. Voss B, Krane M, Jung C, Brockmann G, Braun S, Günther T, et al. Cardiopulmonary bypass with physiological flow and pressure curves: pulse is unnecessary! *Eur J Cardiothorac Surg*. (2010) 37(1):223–32. doi: 10.1016/j.ejcts.2009.05.050

25. Katseni K, Chalkias A, Kotsis T, Dafnios N, Arapoglou V, Kaparos G, et al. The effect of perioperative ischemia and reperfusion on multiorgan dysfunction following abdominal aortic aneurysm repair. *Biomed Res Int*. (2015) 2015:598980. doi: 10.1155/2015/598980

26. Doukas P, Hellfritsch G, Krabbe H, Frankort J, Jacobs MJ, Gombert A, et al. Onset of adverse abdominal events due to intestinal ischemia-reperfusion injury after aortic cross-clamping is associated with elevated HSP70 Serum levels in the early postoperative phase. *Int J Mol Sci*. (2022) 23(23):1–2. doi: 10.3390/ijms232315063

27. Sekino M, Funaoka H, Sato S, Okada K, Inoue H, Yano R, et al. Intestinal fatty acid-binding protein level as a predictor of 28-day mortality and bowel ischemia in patients with septic shock: a preliminary study. *J Crit Care*. (2017) 42:92–100. doi: 10.1016/j.jcrc.2017.07.012

28. Sun D-L, Cen Y-Y, Li S-M, Li W-M, Lu Q-P, Xu P-Y. Accuracy of the serum intestinal fatty-acid-binding protein for diagnosis of acute intestinal ischemia: a meta-analysis. *Sci Rep*. (2016) 6:34371. doi: 10.1038/srep34371

29. Schellekens D, Reisinger KW, Lenaerts K, Hadfoune M, Olde Damink SW, Buurman WA, et al. SM22 A plasma biomarker for human transmural intestinal ischemia. *Ann Surg*. (2018) 268(1):120–6. doi: 10.1097/SLA.0000000000002278

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Debranching abdominal aortic hybrid surgery for aortic diseases involving the visceral arteries

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Objective: Aortic diseases involving branches of the visceral arteries mainly include thoracoabdominal aortic aneurysm (TAAA), aortic dissection (AD) and abdominal aortic aneurysm (AAA). The focus of treatment is to reconstruct the splanchnic arteries and restore blood supply to the organs. Commonly used methods include thoracoabdominal aortic replacement, thoracic endovascular aortic repair and hybrid approaches. Hybrid surgery for aortic disease involving the visceral arteries, consisting of visceral aortic debranching with retrograde revascularization of the celiac trunk and renal arteries and using stent grafts, has been previously described and may be considered particularly appealing in high-risk patients. This study retrospectively analyzed recorded data of patients and contrasted the outcomes with those of a similar group of patients who underwent conventional open repair surgery.

Methods: Between 2019 and 2022, 72 patients (52 men) with an average age of 61.57 ± 8.66 years (range, 36–79 years) underwent one-stage debranching abdominal aortic hybrid surgery. These patients, the hybrid group, underwent preoperative Computed Tomographic Angiography (CTA) and had been diagnosed with aortic disease (aneurysm or dissection) involving the visceral arteries and were at high risk for open repair. The criteria used to define these patients as high-risk group who are in the need of hybrid treatment were American Society of Anesthesiologists (ASA) class 3 or 4. In all cases, we accomplished total visceral aortic debranching through a previous visceral artery retrograde revascularization with synthetic grafts (customized Y or four-bifurcated grafts), and aortic endovascular repair with one of two different commercially produced stent grafts (Medtronic® and Lifetech®). In some cases, we chose to connect the renal artery to the artificial vessel with a stent graft (Viabahn) and partly or totally anastomosed. We analyzed the results and compared the outcomes of the hybrid group with those of a similar group of 46 patients (36 men) with an average age 54.15 ± 12.12 years (range, 32–76). These 46 patients, the conventional open group, were selected for having had thoracoabdominal aortic replacement between 2019 and 2022.

Results: In the hybrid group, 72 visceral bypasses were completed, and endovascular repair was successful in all cases. No intraoperative deaths occurred. Perioperative mortality was 2.78%, and perioperative morbidity was 9.72% (renal insufficiency in 1, unilateral renal infarction in 5, Intestinal ischemia in 1). At 1-month postoperative CTA showed 2 endoleaks, one of which was intervened. At follow-up, there were unplanned reoperation rate of 4.29% and 5 (7.14%) deaths. The remaining patients' grafts were patent at postoperative CTA and no endoleak or stent graft migration had occurred. In the conventional open group, 1 died intraoperatively, 4 died perioperatively, perioperative mortality was 10.87% and complications were respiratory failure in 5, intestinal paralysis/necrosis in 4, renal insufficiency in 17, and paraplegia in 2. At follow-up, 5 (12.20%) patients presented with synthetic grafts hematoma 4 (9.76%) patient died, and 6 (14.63%) patients required unplanned reoperation intervention.

Conclusion: Hybrid surgery is technically feasible in selected cases. For aortic diseases involving the visceral arteries, the application of hybrid abdominal aorta debranching can simplify the operation process, decrease the risks of mortality and morbidity in high-risk and high-age populations and decrease the incidence of various complications while achieving ideal early clinical efficacy. However, a larger series is required for valid statistical comparisons, and longer follow-ups are necessary to evaluate the long-term efficacy of hybrid surgery.

KEYWORDS

aortic disease, visceral artery, thoracoabdominal aortic replacement, endovascular aortic repair, hybrid surgery

Introduction

The visceral arterial branches mainly involve the renal arteries, the celiac trunk artery and the superior mesenteric artery (1). Aortic diseases involving branches of the visceral arteries mainly include thoracoabdominal aortic aneurysm (TAAA), aortic dissection (AD) and abdominal aortic aneurysm (AAA) (2–4). A common feature of a classic TAAA, as well as some diseases such as AD and AAA, is that the diseases may involve the visceral arteries and, in the surgical procedure, reconstruction of these visceral arterial branches is possible. Currently, the main modalities for the treatment of abdominal aortic disease are thoracoabdominal aortic replacement, endovascular aortic repair (EVAR) and hybrid approaches (5).

Since its first description in 1955, open repair has been considered the gold standard of treatment for aortic diseases and remains among the most difficult surgical approach due to the associated vital structures, such as the mesenteric/renal branches and the segmental arteries involved in the lesion (6). For aortic diseases involving the visceral artery branches, it is necessary to reconstruct the visceral artery branches while treating the aortic disease (7). Due to the long operation time and extensive trauma, various serious perioperative complications, such as internal organ ischemia, massive intraoperative hemorrhage, paraplegia, renal failure, and infection, are possible and the risk of mortality is high (8, 9).

Another alternative approach to traditional open repair is EVAR with endograft techniques (10). There is no doubt that a total endovascular approach would benefit patients with aortic diseases, but individualized stents may take years to become widely available (11). Treatment modalities consisting of visceral parallel graft (chimney/snorkel) techniques with off-the-shelf devices have a greater probability of causing complications such as endoleaks and displacements, so EVAR is now more beneficial for treating subrenal aortic diseases (12, 13). Three-dimensional, laser and customized branch/bifurcation stent grafts are now available for the treatment of TAA (14–17).

Hybrid approaches consisting of visceral aortic debranching with retrograde revascularization of the mesenteric, coeliac trunk and renal arteries and aortic lesion exclusion using commercially available stent grafts have been described in several reports (18, 19). This study analyzed recorded data of a series of high-risk patients with a history of aortic surgery who underwent hybrid repair for aortic diseases at some institutes in the last 4 years and compared the outcomes in this group with those in a similar group of patients who underwent conventional open repair for aortic diseases. The aim of this paper is to introduce a relatively less invasive surgical approach for patients who may have had total thoracoabdominal aortic replacement in the past.

Patients and methods

Between 2019 and 2022, 72 patients (52 men) with a mean age of (61.57 ± 8.66) years (range, 36–79 years) underwent a one-stage debranching abdominal aortic hybrid procedure at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Changhai Hospital, Naval Medical University, and other centres. These patients, the hybrid group, underwent preoperative Computed Tomographic Angiography (CTA) (**Figure 1**) and had been diagnosed with aortic disease (aneurysm or dissection) involving the visceral arteries. The group was assessed preoperatively as being at high risk and the criteria used to define these at-risk groups in need of hybrid surgery were American Society of Anesthesiologists (ASA) Level 3 or 4. At the same time, we selected a similar group of 46 patients (36 men) who had undergone thoracoabdominal aortic replacement between 2019 and 2022 as the conventional open group, whose mean age was (54.15 ± 12.12) years (range, 32–76 years). We analyzed the results and compared these results with the hybrid group. The aim of this study was to describe how to use the hybrid procedure in high-risk and high-age populations.

Hybrid group

Beginning in 2019, 72 high-risk patients underwent one-stage stent graft repair with visceral aortic debranching and prior retrograde revascularization of visceral arteries. The criteria we

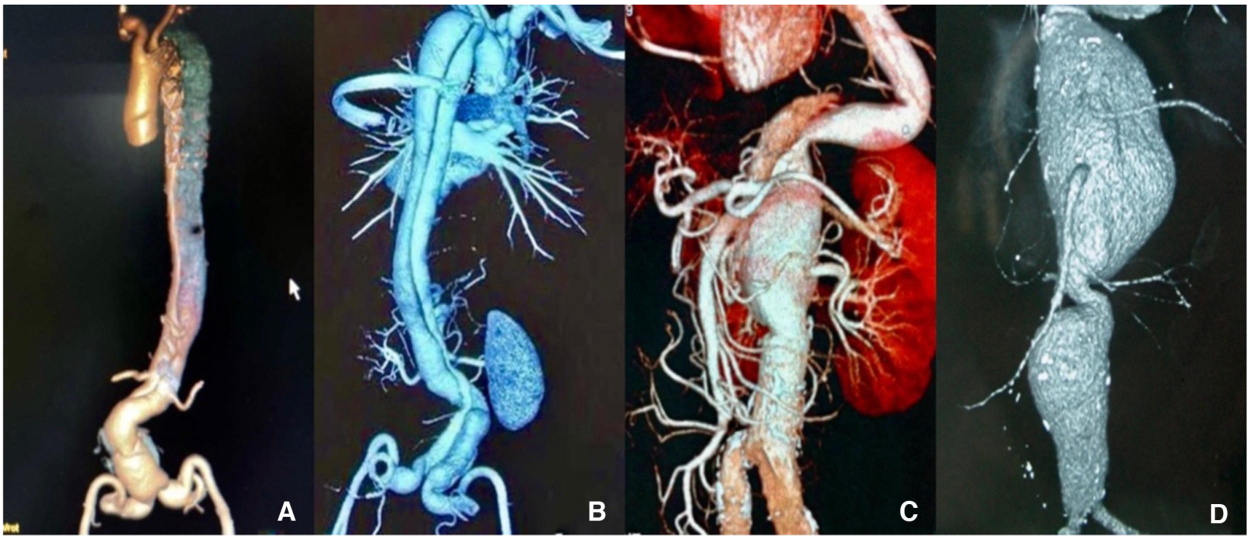

FIGURE 1
(A,B) Preoperative computed tomography angiography (CTA) scan shows thoracoabdominal aortic dissection (TAAD). (C,D) CTA shows thoracoabdominal aortic aneurysm (TAAA). The images show that all lesions of the aorta involve the visceral arteries.

used to define these patients as being at high risk for conventional repair were American Society of Anesthesiologists (ASA) class 3 or 4.

All patients underwent a one-stage procedure performed in the operating room. All patients were operated on under general anesthesia with tracheal intubation. The abdominal aorta, common iliac arteries, and the first 2 cm from the origin of the common hepatic artery, superior mesenteric artery, and renal arteries were exposed, when needed, through a transperitoneal midline approach with the patient in a supine position. Synthetic grafts with diameters of 6 or 8 mm and 10 were used in all patients. We preferably used customized Y grafts or separated bypass grafts, or both, and four-bifurcated grafts for each recipient vessel. In some cases, we accomplished total visceral aortic debranching through a previous visceral artery retrograde revascularization with four-bifurcated grafts.

There are two inflow site options: the prograde route (diversion from the ascending aorta) and the retrograde route (diversion from the iliac artery and distal abdominal aorta). We generally choose the retrograde route. The choice of inflow site for retrograde visceral artery bypass grafting was based on the extent of the lesion, the presence of prior abdominal aortic repair, and the quality of the walls of the native aorta and iliac arteries. The proximal segment of this iliac artery was blocked, an incision of approximately 10 mm was made in the wall of the iliac artery, and this incision was continuously anastomosed end-to-side with the opening of the two-branch artificial vessel. Each stitch needs to be tightened to avoid twisting, stenosis and anastomotic leakage due to improper placement of the artificial vessel.

Reconstruction of the outflow pathways allowed reconstruction of the visceral arterial branches. All the donor vessels were anastomosed end-to-side (**Figure 2**).

For celiac trunk revascularization, the graft was routed through the middle of the omental sac, either behind or in front of the pancreas, an arteriotomy was made in the common hepatic artery or the splenic artery, and an end-to-side anastomosis was made. If the proximal abdominal trunk is not tied, a type 2 endoleak can develop, so it is essential to prevent spinal cord ischemia and eliminate the need for cerebrospinal drainage to the same extent as in the open branch technique.

An end-to-side anastomosis of the superior mesenteric artery was made next to the flexor ligament. During the operation, part of the flexor ligament should be preserved, the duodenum should not be excessively dissected, and the formation of an acute angle between the bridge vessels and the superior mesenteric artery should be avoided after mesenteric repositioning.

When anastomosis of the renal artery was required for reconstruction, the kidney was wrapped in ice slush before and during renal artery cross-clamping and the temperature was lowered from 15°C to 18°C. An end-to-end anastomosis was performed when the renal artery was deep, and an end-to-side anastomosis was performed when the renal artery was shallow. To save time in reconstructing the renal artery, we usually used a Viabahn (GORE®) with a diameter of 6 or 7 mm and a length of 10 cm (depending on the diameter of the involved renal artery as measured by the preoperative CTA) that connected the artificial vessel to the renal artery. Renal warm ischemia time was limited to 2 min with Viabahn, so ice slush was not used for renal hypothermia (20). A bypass graft (6 mm in diameter) was sutured to the Y graft, which underwent end-to-side anastomosis with the iliac artery. A guidewire was introduced into the presutured graft over which the Viabahn was advanced. An opening was made in the anterior wall of the renal artery, and the guidewire was introduced distal to the renal artery. The Viabahn was then advanced through the guidewire into the renal artery to a certain distance as measured by preoperative CTA. A silk knot or suture was used to secure the stent to the outside of the artificial vessel.

In all the reconstructions, the grafted vessels were ligated proximally to prevent retrograde perfusion of the sac after

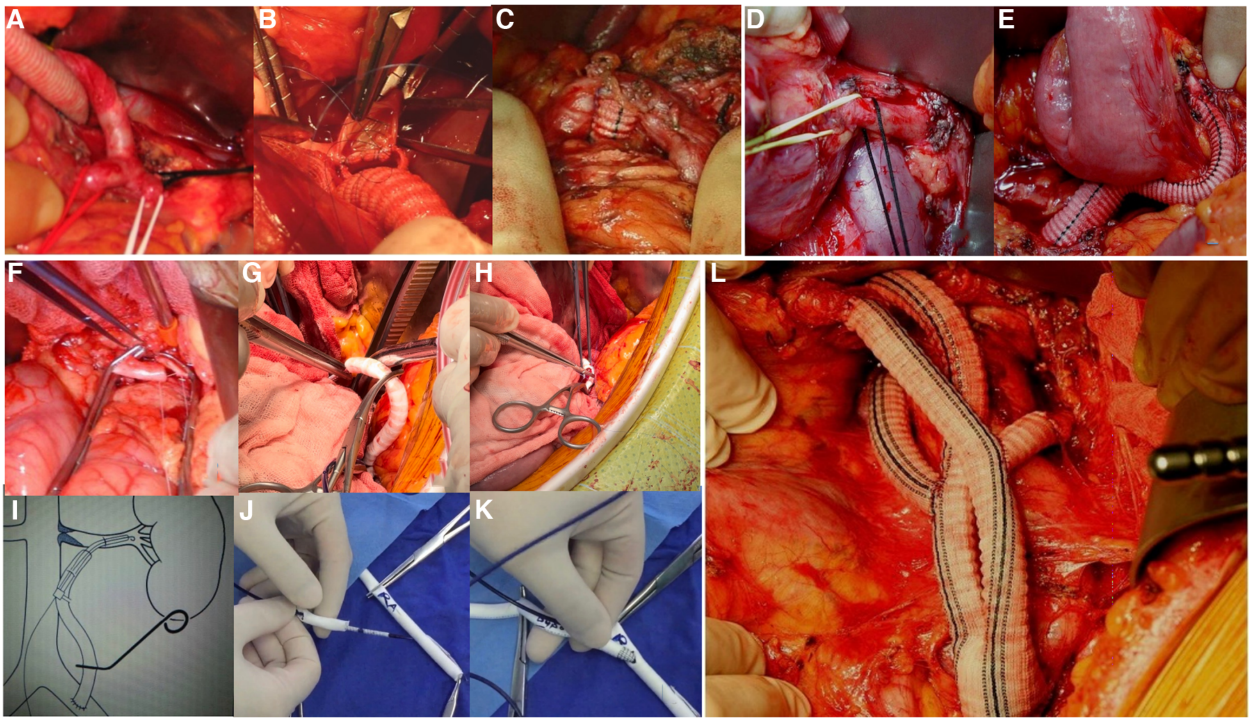

FIGURE 2
(A–C) Intraoperative photographs show details of the reconstructed celiac trunk. (D,E) Intraoperative photographs show the reconstruction of the superior mesenteric artery. (F) The photograph shows an end-to-side anastomosis of the renal artery. (G,H) Intraoperative photographs show a Viabahn was used to connect the graft to the renal artery, secured with sutures on the outside of the graft. (I) Diagram of the reconstructed renal artery with Viabahn. (J,K) Demonstration of the reconstructed renal artery with Viabahn. A guidewire is introduced into the pre-sutured graft and the Viabahn is advanced. An opening is made in the anterior wall of the renal artery and the guidewire is introduced into the distal end of the renal artery. Viabahn is then advanced through the guidewire into the renal artery for release. (L) Intraoperative photograph shows the reconstruction of the visceral arterial branches is finished.

endovascular exclusion of the aneurysm. The grafts were then covered with retroperitoneum or an omental flap whenever possible.

The access vessel for endograft insertion was the common femoral artery (exposed through an inguinal incision). Two stent grafts (Medtronic® and Lifetech®) were used, and 1–3 stent grafts were deployed in each patient. Complete aortography was performed after deployment of the endografts (**Figure 3**).

All patients were transferred to the intensive care unit (ICU) after the operation. Antiplatelet therapy (aspirin) was begun on the first postoperative day and was maintained for at least 3 months. Sensation and movement of the lower extremities, postoperative morbidity and short-term mortality were recorded. CTAs were performed at 3, 6, or 12 months after the operation in all the survivors and were carefully compared with the preoperative total CTAs to evaluate renal artery patency, to assess the stent and bypass grafts, and to identify renal infarction, bleeding at the anastomosis, and stent-grafter elated complications, such as migration, kinking, or fracture.

Conventionally treated group

From the entire series of patients who had undergone thoracoabdominal aortic replacement after 2019, we selected 46 patients (36 men) who had undergone prior aortic surgery (19.57% ascending, 15.22% descending, and 2.17% abdominal aortic repair) and had an ASA classification of 3 or 4.

All procedures were performed electively. Cell salvage, rapid infusers, and transfusion were used. All patients were operated on under general anesthesia, tracheal intubation and respiratory ventilation.

The surgery was performed from the left posterolateral 6th or 7th intercostal space to the inferior border of the costal arch and continued to the left rectus abdominis muscle. Depending on the extent of the lesion, the surgery can extend to the iliac fossa, allowing the opening of the diaphragm to expose and explore the thoracoabdominal aorta. Distal aortic perfusion with left atrial femoral artery bypass or hypothermic visceral perfusion with or without cerebrospinal fluid drainage was routinely used (21). Four branches of aortic grafts with diameters of 26 and 28 mm (branch diameter of 8 or 10 mm) were used in all patients. Reconstruction of the proximal aorta, visceral artery branches, and distal aorta was accomplished after sequential segmental block. End-to-end anastomosis was performed between these arteries and the graft. In some patients, the arterial wall containing the opening of the celiac trunk, superior mesenteric artery, and right renal artery could be directly anastomosed to the sidewall of the graft, and an end-to-side anastomosis of the left renal artery was performed separately. The patent intercostal arteries below the 8th thoracic vertebra were reconstructed, and

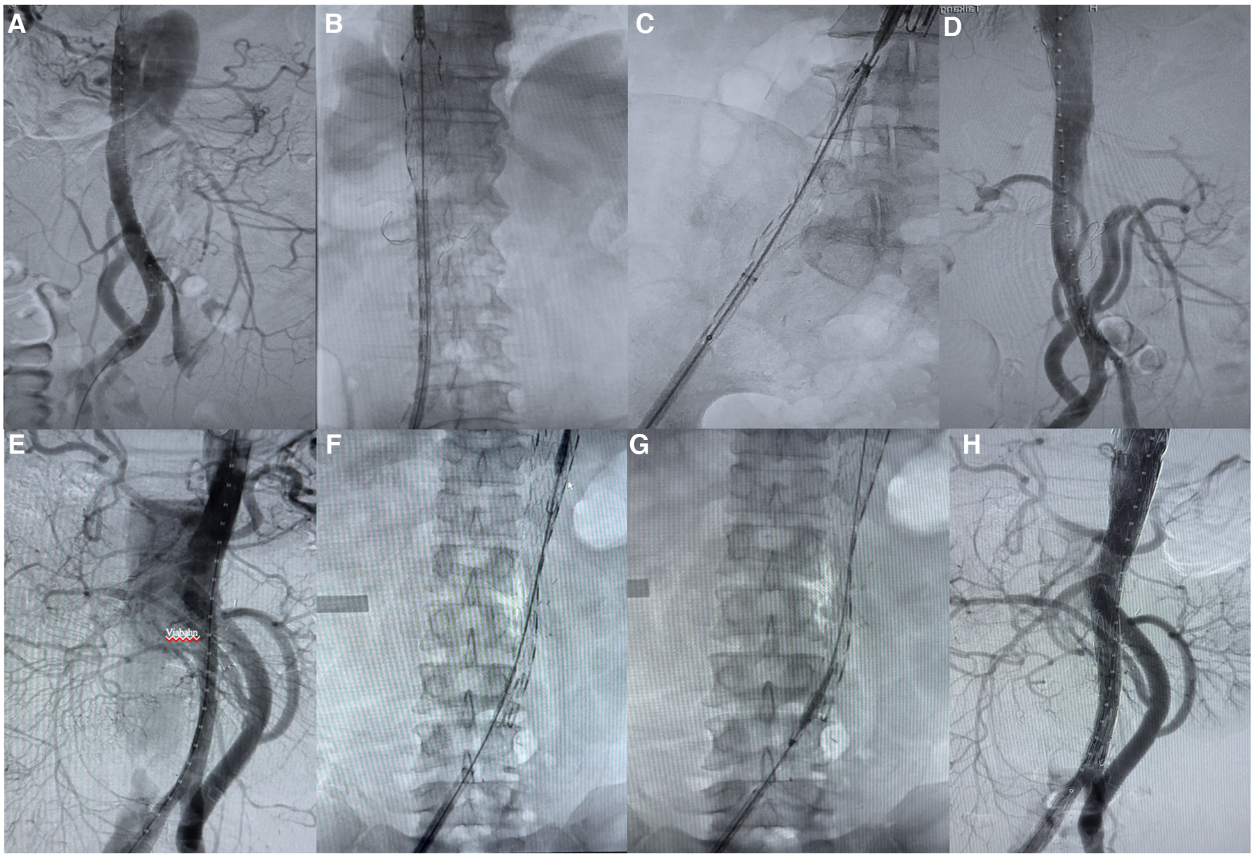

FIGURE 3
Complete endovascular repair of aortic disease. (A–D) Renal arterial reconstruction without Viabahn. (E–H) Renal arterial reconstruction with Viabahn.

the remaining occluded intercostal arteries were sutured. In cases of dissection/aneurysm involving the abdominal aortic bifurcation and below, the graft branches were anastomosed downward to the iliac artery.

Patients were evaluated with postprocedural CTA at 3, 6 and 12 months and yearly thereafter. Clinical follow-up was also conducted every 6 months. We analyzed the outcomes in our patients, reporting the results and methods.

Results

Hybrid group

Debranching abdominal aortic hybrid surgery of aortic diseases involving visceral arteries in all 72 patients. No intraoperative deaths occurred. Because we performed this procedure on some of our patients at other heart centers, we lost some of the patient data from the procedure. By analyzing the perioperative data of 72 patients, we mainly analyzed the incidence of postoperative complications and mortality.

The hybrid repair was clinically successful in 70 (97.22%) of 72 patients (**Figure 4**). Two patients died postoperatively for a mortality rate of 2.78%: one related to disseminated or diffuse intravascular coagulation (DIC) and one from ruptured aneurysm. Other postoperative complications included acute renal failure in one patient (1.39%) that resolved without dialysis that was considered as occlusion of the bridge vessel on one side and failure of revascularization on the other side, 5 patients (6.94%) presented with unilateral renal infarction considered to be bridge vessel occlusion, and one (1.39%) presented with left hemicolectomy necrosis considered the inferior mesenteric artery was not revascularized because of high regurgitant pressure.

During the follow-up period patients had one bridge vessel occlusion requiring unplanned reoperation (A patient was found to have renal artery occlusion due to VB displacement during the 5-years post-operative review. After dilatation with a balloon, the renal artery was recanalized.), two endoleaks requiring unplanned reoperation management (unplanned reoperation rate of 4.29%), one pulmonary infection due to aneurysm compression, and 5 (7.14%) deaths. In total, there were even 7 (9.72%) surgical and aneurysm-related deaths.

Conventionally treated group

One intraoperative death occurred. The mean procedure time was 398 ± 143 min. A mean of 5.4 ± 6.4 U of packed red blood cells was transfused for a median blood loss of 1852 ± 2124 ml. There were 4 postoperative deaths. Perioperative mortality was

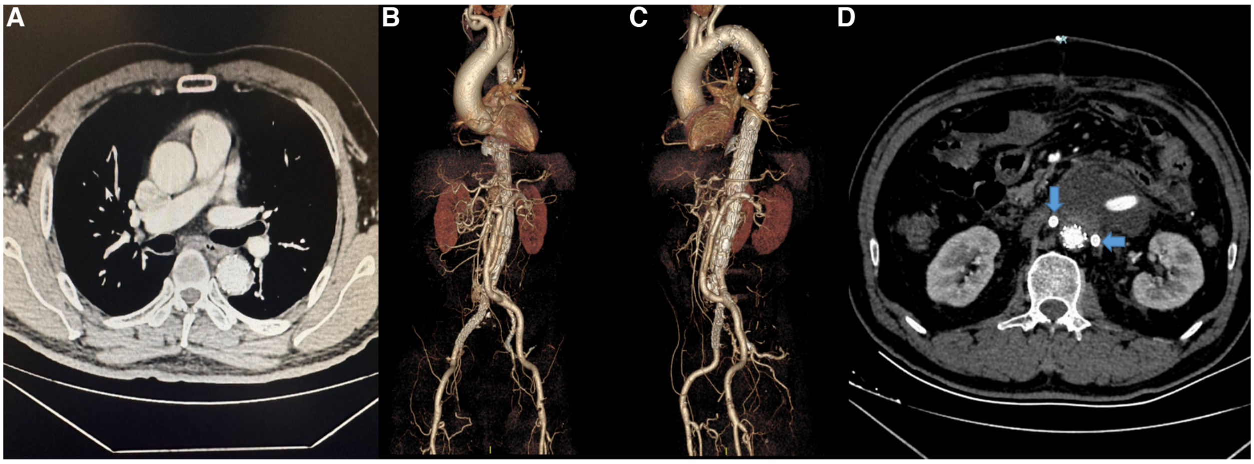

FIGURE 4
(A–C) The CTA and 3-dimensional reconstruction of patient after surgery. (D) The bilateral renal arteries (arrows) were patent.

10.87%. Perioperative complications included 2 patients with permanent paraplegia, 4 with intestinal paralysis/necrosis, 4 patients with unilateral renal infarction, 4 with venous thrombosis (one of which was a pulmonary embolism), 17 with renal failure, 7 with surgical site infection, 2 with graft infection, and 19 with pulmonary infection and 5 with respiratory failure. All patients were admitted to the intensive care unit, where the stayed for a mean of 4.30 ± 3.35 days.

At post-discharge follow-up, there were 4 (9.76%) deaths here, 6 (14.63%) patients required unplanned reoperation intervention (2 of EVAR, 2 of chest wall debridement and suturing, 1 of thoracotomy hemostasis and 1 of abdominal hemostasis), and 5 (12.20%) patients presented with synthetic grafts hematoma. The overall surgical and aneurysm-related death rate was 19.57%.

The age of the hybrid group was significantly higher than that of the conventional group, as the hybrid surgery was used preferentially on people who were at high-risk or of high-age (61.57 ± 8.66, 54.15 ± 12.12; respectively; $p < 0.05$). The rates of complication such as renal failure, respiratory failure, and lower extremity thrombosis within 30 days of hybrid surgery were also significantly lower in the hybrid surgery group than in the conventional surgery group ($p < 0.05$) (**Table 1**). Although there was no significant difference in mortality and unplanned reoperation rates between the hybrid and conventional treatment groups, the desired results were achieved in an older age group.

TABLE 1 Outcomes.

	Hybrid group	Conventionally treated group	p
Perioperative period			
Death	2/72 (2.78%)	5/46 (10.87%)	0.0696
Paraplegia	0/72 (0.00%)	2/46 (4.35%)	0.0743
Renal failure	1/72 (1.39%)	17/46 (36.96%)	<0.0001
Unilateral renal infarction	5/72 (6.94%)	4/46 (8.70%)	0.7267
Intestinal paralysis/ necrosis	1/72 (1.39%)	4/46 (8.70%)	0.0546
Respiratory failure	0/72 (0.00%)	5/46 (10.87%)	0.0043
Deep venous thrombosis	0/72 (0.00%)	4/46 (8.70%)	0.0109
Postoperative follow-up			
Death	5/70 (7.14%)	4/41 (9.76%)	0.6264
Unplanned reoperation	3/70 (4.29%)	6/41 (14.63%)	0.0539
Surgical/aneurysm-related deaths	7/72 (9.72%)	9/46 (19.57%)	0.1277

Discussion

The main aortic diseases involving the visceral arterial branches, including the renal arteries, celiac trunk and superior mesenteric artery, are TAAA, AD and AAA. TAAAs remains a challenging clinicopathology involving the visceral arteries, although it accounts for only 7%–15% of all aortic and peripheral aneurysms (22). TAAAs are mostly caused by aortic degeneration and have poor prognoses, with a 42%–70% probability of untreated rupture after diagnosis and an average survival time of 3 years (23). AAD refers to an aortic dissection involving the aorta below the diaphragm and is divided into two main types (24–26). The first type is an isolated abdominal aortic dissection (IAAD), which involves rupture of the abdominal aorta only and accounts for approximately 1%–4% of all aortic dissection cases. The other type is secondary thoracic aortic coarctation, which results from the continuation of the lesion into the abdominal aorta following an aortic tear, which is more common. A common characteristic of these lesions is their involvement with the visceral branch arteries, so it may be necessary to reconstruct these visceral artery branches during surgery. The choice of treatment depends primarily on the pathology of the aneurysm, the extent of the lesion and the patient's condition.

Thoracoabdominal aortic replacement is still one of the most difficult surgical approaches due to the associated vital structures, such as the visceral/renal branches and the segmental arteries involved in the lesion. First reported by Etheredge in 1955, open surgery has been the preferred treatment for this type of aortic disease, especially TAAA (6). Open surgery is not only traumatic, as it requires an incision of the chest, abdomen, and diaphragm, it also requires cardiopulmonary bypass, thereby leading to coagulation disorders (27, 28). Recent reports from high-volume aortic centers have shown that the mortality rate after open repair in young patients (younger than age 50 years) ranges from 3% to 6%, and the mortality rate in older patients remains 8%–17% (29, 30). Since Crawford proposed the inclusion technique for the treatment of TAAA in 1978, the outcome of the surgery has improved significantly due to the use of adjunctive procedures, including selective visceral perfusion, distal aortic perfusion and cerebrospinal fluid drainage (31–34). Despite advances in surgical technique, spinal cord protection and postoperative intensive care support, patients undergoing open surgery still have a 30-day mortality rate of 7%–17% (35). Fifty percent of patients have a significant risk of complications, including cardiac ischemia, pulmonary events, hemorrhage, spinal cord ischemia and acute renal failure (8, 36). Even though these outcomes are poor, selective repair remains necessary, since the 2- and 5-year mortality rates of patients who do not undergo an operation are 76% and more than 95%, respectively (37).

Another alternative approach to traditional thoracoabdominal aortic replacement is endovascular aortic repair (EVAR) with stent grafts. Using a stent graft, Parodi pioneered the minimally invasive treatment of abdominal aortic aneurysms in 1991 (38). In 1994, Dake performed a thoracic endovascular aneurysm repair to successfully treat a descending aortic aneurysm (39). EVAR can be performed percutaneously using a transfemoral method, avoiding thoracoabdominal incisions, diaphragm division, left heart or cardiopulmonary bypass and cross-clamping of the aorta. There is uninterrupted aortic flow and perfusion of the internal organs and lower limb vessels during the procedure. EVAR therefore radically reduces the physiological demands, the risk of end organ ischemia, blood loss, fluid requirements and the need for transfusion products. EVAR is a suitable treatment for older, weaker and higher risk patients who have been previously regarded as unsuitable candidates for open surgery. In the last decade, the number of EVARs has doubled, and its feasibility has already been demonstrated (40, 41). With the progress of EVAR, more abdominal aortic diseases involving the visceral arteries can be treated with these methods, including visceral parallel graft (chimney/snorkel) techniques, multibranched stent graft and fenestrated techniques (42). When the coeliac trunk, superior mesenteric and renal arteries are from a nonaneursymal implantation site, a simple hole (fenestration) in the stent graft is sufficient. When these arteries arise from the aneurysm, flow must be carried across the aneurysm through branches of the stent graft. Despite these advances, there are shortcomings and other anatomical limitations. Small vessels, such as the intercostal arteries, cannot be reconstructed by endovascular methods in most cases, raising concerns that extensive aortic coverage may increase the risk of spinal cord injury (43). Some papers have shown that compared to open surgical repair, endovascular aortic repair and subrenal endovascular repair is associated with better quality of life indicators at 1 year postoperatively (44). Three-dimensional, laser and customized branch/bifurcation stent grafts have been introduced for the treatment of TAA. These new technologies are constantly advancing to facilitate better individualized treatment (14–17). There is no doubt that a total endovascular approach would benefit patients in poor conditions (45, 46).

Hybrid surgery, a combination of open and endovascular techniques, for the treatment of aortic disease has been suggested to reduce surgical injury and improve outcomes, especially in high-risk patients, and was first reported in 1999 (47). The hybrid surgery provides sufficient anchorage for EVAR through open visceral artery reconstruction and "transfer" from the diseased aorta to the healthier aorta. Thus, hybrid surgery can be widely used in patients with paravisceral aneurysms (48). Compared to traditional thoracoabdominal aortic replacement, hybrid repair avoids the need for thoracotomy, extracorporeal perfusion, and supraceliac aortic clamping, and therefore, hemodynamics is more stable intraoperatively and there is less risk of causing an ischemia-reperfusion injury to the visceral organs (49). It significantly decreases postoperative pain and the incidence of pulmonary complications in patients with underlying pulmonary diseases (50). The disadvantage is that it still requires laparotomy. For abdominal obesity, exposure of the superior mesenteric artery and coeliac trunk is difficult, intraoperative damage to the pancreatic duct may lead to the formation of postoperative pancreatic cysts, and damage to the portal vein may lead to postoperative bleeding. In addition, postoperative intestinal obstruction or swelling may affect the patient's respiration (51). Although hybrid repair was developed as a less invasive approach than traditional open surgery, the 30-day mortality rate after hybrid techniques in many reports is disappointingly high (e.g., operative mortality, 3.6%–12.5% and renal failure, 20%), which has been attributed to the use of the technique in patients who are unsuitable or considered to be high-risk open surgery patients (50, 52). Although hybrid surgery has been debated, its efficacy and safety in treating aortic disease has been recognized in the 2017 Clinical Practice Guidelines of the European Society for Vascular Surgery (Class IIa/C evidence) (53).

In fact, several patients selected for hybrid surgery are not suitable for open repair because they have severe medical comorbidities. Another benefit of hybrid surgery is that it can be used in emergencies or for patients with acute cases of ruptured TAAAs or TAADs with poor perfusion who have severe respiratory or cardiac disease and are unlikely to survive open repair. There are no other repair options, with current endovascular techniques, for these patients because there are no available fenestrated stent grafts for narrow true lumens, branch stents that can be easily introduced into small spaces that limit maneuverability, branch arteries fed by the false lumen, and no distal healthy anchor zone. In our surgical practice, we consider elective hybrid surgery for patients who are unable to undergo major thoracoabdominal procedures, who have connective tissue disorders and whose anatomy does not allow EVAR.

Since 2019, we have performed debranching abdominal aortic hybrid surgery on 72 patients with aortic disease involving the visceral arteries, using the Viabahn for some of them.

Preoperative CTA showed that all patients had lesions involving the abdominal aorta and visceral arteries. A transabdominal abdominal approach is usually performed to expose the entire abdominal aorta and target vessels. Retrograde extra-anatomic bypass of the abdominal axis, superior mesenteric artery, and bilateral renal arteries is performed by using the iliac artery as the inflow port. In patients with aortic coarctation resulting in iliac artery disease, subrenal aortic replacement is considered. However, one clear disadvantage of anastomosis of the branches is the renal ischemia time. Standard suture anastomosis in renal arteries inevitably requires a long renal ischemic time of 25 min (54). Although hybrid surgery reduced the renal ischemic time to approximately 10 min, we found that the Viabahn reduced the renal ischemic time further by avoiding the need for a suture anastomosis and extensively exposing the renal artery (55). Our limited experience has shown that the Viabahn technique is workable and effective in all planned procedures, regardless of the anatomical location or quality of the visceral vessels.

The aims of our study were to to introduce a relatively less invasive surgical approach for patients in high-risk and high-age populations and to compare the differences between thoracoabdominal aortic replacement and hybrid surgery for aortic disease involving the visceral arteries in terms of mortality and complication rates (e.g., renal failure, unilateral renal infarction, intestinal paralysis/necrosis, respiratory failure, and deep venous thrombosis). There are very few studies that have compared these two methods. We present a hybrid surgery using the Viabahn for the treatment of the renal artery, which prevents stenosis of the renal artery anastomosis, avoids the need for ice chips, and shortens the length of renal artery decortication and the time of renal ischemia. As seen in our statistics, the rate of transient renal failure after hybridization was significantly lower. However, the rates of unilateral renal infarction and mortality at the follow-up visit following hybrid surgery were not significantly different from those following conventionally open surgery. During the follow-up period, three patients who underwent hybrid surgery underwent unplanned reoperation for reasons that included bridge vessel occlusion and endoleak.

It is evident that debranching abdominal aortic hybrid surgery also has limitations. First, endoleaks are an important cause of failure, and lesion development can lead to retrograde tearing of the dissection or enlargement and rupture of the aneurysm. Second, the current option for the inflow site is mainly a retrograde path, which has the risk of distant anastomotic stenosis and even branch occlusion. Viabahn's dislodgement or movement is one of the few undesirable occurrences. This can lead to an associated renal infarction with renal artery occlusion. Finally, the most important concern is that open repair is a major, technically challenging approach, particularly when complete visceral and/or renal revascularization is needed. The abdominal complications associated with an incision of the abdomen is a concern for doctors.

We also consider how to avoid these problems in our management. First, we ligate or suture the proximal end of the visceral artery during the debranching operations and then select an adequate anchorage as well as a stent graft of an appropriate size. Next, we performed a separation anterior to the left renal fascia and anastomosis of the synthetic grafts in the left iliac artery. The advantage of this is that the exposure is adequate, the anastomosis is more favorable, and the synthetic grafts are less prone to distortion. Finally, and most importantly, the Viabahn is used to perform a "no stitching anastomosis" of the aortic branches of the renal viscera in the debranching procedure. This tool avoids exposure and the need for anastomosis, which are technically demanding, reduces the interruption of blood and simplifies the procedure. However, we securely fix the Viabahn by suturing or tying knots from the outside where the Viabahn and the graft are in contact.

Hybrid surgery has the advantages of both EVAR and thoracoabdominal aortic replacement. The role of endovascular techniques in the treatment of aortic disease continues to develop. Hybrid surgery does not replace conventional open surgery but offers an option for high-risk patients who may be denied treatment. The long-term efficacy of hybrid surgery has yet to be elucidated, and patients still require routine surveillance to monitor for endoleak development. However, limited studies have shown results and outcomes that are favorable to hybrid surgery.

The biggest limitation of our study is the sample size of the hybrid group, as patients underwent surgery in different cities, leading to missing data and preventing a complete comparison of the metrics during surgery. The quality of the study was also limited by the asynchronous nature of the two groups, the economic status of the patients and the retrospective nature. Studies with a large series of patients with detailed medical histories and a longer follow-up are necessary to provide meaningful statistics for debranching abdominal aortic hybrid surgery for aortic diseases involving the visceral arteries and visceral artery reconstructions with the Viabahn.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (Institutional Review Board document number TJ-JRB20230516). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conception and design: XW, XF, and CC. Analysis and interpretation: XM, SL, CC, and XF. Data collection: BQ, YF, and XF. Writing the article: XM, QZ, CC, and YF. Critical revision of the article: CC and XF. Final approval of the article: CC and XF. Statistical analysis: YF, WA, MAT and XM. Overall responsibility:

XM, YF, CC, and XF. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Kabbani LS, Criado E, Jr UG, Patel HJ, Eliason JL, Rectenwald J, et al. Hybrid repair of aortic aneurysms involving the visceral and renal vessels. *Ann Vasc Surg.* (2010) 24(2):219–24. doi: 10.1016/j.avsg.2009.08.007

2. Cochennec F, Marzelle J. Les syndromes aortiques aigus [acute aortic syndromes]. *Presse Med.* (2018) 47(2):140–52. doi: 10.1016/j.lpm.2018.02.001

3. Smith TA, Gatens S, Andres M, Modrall JG, Clagett GP, Arko FR. Hybrid repair of thoracoabdominal aortic aneurysms involving the visceral vessels: comparative analysis between number of vessels reconstructed, conduit, and gender. *Ann Vasc Surg.* (2011) 25(1):64–70. doi: 10.1016/j.avsg.2010.06.004

4. Yamaguchi H, Murata S, Onozawa S, Sugihara F, Hayashi H, Kumita SI. Strategy for the treatment of spontaneous isolated visceral artery dissection. *Eur J Radiol Open.* (2018) 6:9–15. doi: 10.1016/j.ejro.2018.11.003

5. Rosenblum JM, Chen EP. Thoracoabdominal aortic aneurysm repair: open, endovascular, or hybrid? *Gen Thorac Cardiovasc Surg.* (2019) 67(1):175–9. doi: 10.1007/s11748-017-0820-y

6. Etheredge SN, Yee J, Smith JV, Schonberger S, Goldman MJ. Successful resection of a large aneurysm of the upper abdominal aorta and replacement with homograft. *Surgery.* (1955) 38(6):1071–81. doi: 10.1016/0371-1951(55)80039-2

7. Li Y, Li Z, Feng J, Feng R, Zhou J, Jing Z. A novel solution for distal dilation of chronic dissection after repair involving visceral branches: the roadblock strategy. *Front Cardiovasc Med.* (2022) 9:821260. doi: 10.3389/fcvm.2022.821260

8. Khoury MK, Acher C, Wynn MM, Acher CW. Long-term survival after descending thoracic and thoracoabdominal aortic aneurysm repair. *J Vasc Surg.* (2021) 74(3):843–50. doi: 10.1016/j.jvs.2021.02.048

9. Polanco AR, D'Angelo AM, Shea NJ, Allen P, Takayama H, Patel VI. Increased hospital volume is associated with reduced mortality after thoracoabdominal aortic aneurysm repair. *J Vasc Surg.* (2021) 73(2):451–8. doi: 10.1016/j.jvs.2020.05.027

10. Patel R, Sweeting MJ, Powell JT, Greenhalgh RM, EVAR trial investigators. Endovascular versus open repair of abdominal aortic aneurysm in 15-years' follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial. *Lancet.* (2016) 388(10058):2366–74. doi: 10.1016/S0140-6736(16)31135-7

11. Kheirelseid EA, Gardiner R, Haider SN, Martin Z, Colgan MP, O'Neill SM, et al. Endovascular repair of thoracoabdominal aortic aneurysm (TAAA): early experience. *Ir J Med Sci.* (2014) 183(2):153–60. doi: 10.1007/s11845-013-0974-2

12. Eagleton MJ, Follansbee M, Wolski K, Mastracci T, Kuramochi Y. Fenestrated and branched endovascular aneurysm repair outcomes for type II and III thoracoabdominal aortic aneurysms. *J Vasc Surg.* (2016) 63(4):930–42. doi: 10.1016/j.jvs.2015.10.095

13. Pecoraro F, Pfammatter T, Mayer D, Frauenfelder T, Papadimitriou D, Hechelhammer L, et al. Multiple periscope and chimney grafts to treat ruptured thoracoabdominal and pararenal aortic aneurysms. *J Endovasc Ther.* (2011) 18(5):642–9. doi: 10.1583/11-3556.1

14. Chuter TA, Gordon RL, Reilly LM, Goodman JD, Messina LM. An endovascular system for thoracoabdominal aortic aneurysm repair. *J Endovasc Ther.* (2001) 8(1):25–33. doi: 10.1177/152660280100800104

15. Zymvragoudakis V, Saha P, Gkoutzios P, Zayed H, Abisi S. Use of the off-the-shelf pre-cannulated E-nside endograft to overcome anatomical challenges in urgent complex endovascular aortic repair. *Ann Vasc Surg.* (2022) 79:441.e1–e7. doi: 10.1016/j.avsg.2021.07.045

16. Arakawa M, Sumikura H, Okamura H, Miyagawa A, Homma A, Yamaguchi A. A three-dimensional biomodel of type A aortic dissection for endovascular interventions. *J Artif Organs.* (2022) 25(2):125–31. doi: 10.1007/s10047-021-01294-0

17. Qin J, Wu X, Li W, Ye K, Yin M, Liu G, et al. Laser fenestration of aortic arch stent grafts for endovascular treatment of retrograde type A dissection. *Int J Cardiol.* (2021) 328:69–74. doi: 10.1016/j.ijcard.2020.12.011

18. Benrashid E, Wang H, Andersen ND, Keenan JE, McCann RL, Hughes GC. Complementary roles of open and hybrid approaches to thoracoabdominal aortic aneurysm repair. *J Vasc Surg.* (2016) 64(5):1228–38. doi: 10.1016/j.jvs.2016.04.022

19. Huang B, Yuan D, Zhao J, Ma Y. Hybrid treatment of a thoracoabdominal aortic aneurysm in China: report of the first successful case. *Surg Today.* (2012) 42(12):1219–24. doi: 10.1007/s00595-012-0164-2

20. Simmons MN, Schreiber MJ, Gill IS. Surgical renal ischemia: a contemporary overview. *J Urol.* (2008) 180(1):19–30. doi: 10.1016/j.juro.2008.03.022

21. Papadimas E, Tan YK, Qi Q, Ng JJ, Kofidis T, Teoh K, et al. Left heart bypass versus circulatory arrest for open repair of thoracoabdominal aortic pathologies. *ANZ J Surg.* (2020) 90(12):2434–40. doi: 10.1111/ans.16287

22. Bickerstaff LK, Pairolero PC, Hollier LH, Melton LJ, Van Peenen HJ, Cherry KJ, et al. Thoracic aortic aneurysms: a population-based study. *Surgery.* (1982) 92(6):1103–8. doi: 10.1055/s-0029-1245288

23. LeMaire SA, Price MD, Green SY, Zarda S, Coselli JS. Results of open thoracoabdominal aortic aneurysm repair. *Ann Cardiothorac Surg.* (2012) 1:286–92. doi: 10.3978/j.issn.2225-319X.2012.08.16

24. Trimarchi S, Tsai T, Eagle KA, Isselbacher EM, Froehlich J, Cooper JV, et al. Acute abdominal aortic dissection: insight from the international registry of acute aortic dissection (IRAD). *J Vasc Surg.* (2007) 46(5):913–9. doi: 10.1016/j.jvs.2007.07.030

25. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, et al. 2014 ESC guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The task force for the diagnosis and treatment of aortic diseases of the European society of cardiology (ESC). *Eur Heart J.* (2014) 35(41):2873–926. doi: 10.1093/eurheartj/ehu281

26. Zlatanovic P, Dragas M, Cvetkovic S, Dimic A, Mitrovic A, Vujcic A, et al. Open surgical treatment of acute spontaneous isolated abdominal aortic dissection. *Ann Vasc Surg.* (2021) 74:525.e13–e21. doi: 10.1016/j.avsg.2021.02.035

27. Coselli JS, Bozinovski J, LeMaire SA. Open surgical repair of 2286 thoracoabdominal aortic aneurysms. *Ann Thorac Surg.* (2007) 83:S862–4; discussion: S890–2. doi: 10.1016/j.athoracsur.2006.10.088

28. Conrad MF, Crawford RS, Davison JK, Cambria RP. Thoracoabdominal aneurysm repair: a 20-year perspective. *Ann Thorac Surg.* (2007) 83:S856–61; discussion: S890–2. doi: 10.1016/j.athoracsur.2006.10.096

29. Coselli JS, Amarasekara HS, Green SY, Price MD, Preventza O, de la Cruz KI, et al. Open repair of thoracoabdominal aortic aneurysm in patients 50 years old and younger. *Ann Thorac Surg*. (2017) 103:1849–57. doi: 10.1016/j.athoracsur.2016.09.058

30. Tanaka A, Sandhu HK, Affi RO, Miller CC 3rd, Ray A, Hassan M, et al. Outcomes of open repairs of chronic distal aortic dissection anatomically amenable to endovascular repairs. *J Thorac Cardiovasc Surg*. (2021) 161(1):36–43.e6. doi: 10.1016/j.jtcvs.2019.09.083

31. Crawford ES, Snyder DM, Cho GC, Roehm JO. Progress in treatment of thoracoabdominal and abdominal aortic aneurysms involving celiac, superior mesenteric, and renal arteries. *Ann Surg*. (1978) 188:404–10. doi: 10.1097/00000658-197809000-00016

32. Coselli JS, Conklin LD, LeMaire SA. Thoracoabdominal aortic aneurysm repair: review and update of current strategies. *Ann Thorac Surg*. (2002) 74:S1881–4. doi: 10.1016/S0003-4975(02)04139-5

33. Coselli JS. The use ofleft heart bypass in the repair of thoracoabdominal aortic aneurysms: current techniques and results. *Semin Thorac Cardiovasc Surg*. (2003) 15:326–32. doi: 10.1053/S1043-0679(03)00090-X

34. Quinones-Baldrich WJ. Descending thoracic and thoracoabdominal aortic aneurysm repair: 15-year results using a uniform approach. *AnnVasc Surg*. (2004) 18:335–42. doi: 10.1007/s10016-004-0033-6

35. Frederick JR, Woo YJ. Thoracoabdominal aortic aneurysm. *Ann Cardiothorac Surg*. (2012) 1:277–85. doi: 10.1007/978-3-642-00418-6_2292

36. Cowan JA Jr, Dimick JB, Henke PK, Huber TS, Stanley JC, Upchurch GR Jr. Surgical treatment of intact thoracoabdominal aortic aneurysms in the United States: hospital and surgeon volume-related outcomes. *J Vasc Surg*. (2003) 37(6):1169–74. doi: 10.1016/S0741-5214(03)00085-5

37. Crawford ES, De Natale RW. Thoracoabdominal aortic aneurysm: observations regarding the natural course of the disease. *J Vas Surg*. (1986) 3:578–82. doi: 10.1016/0741-5214(86)90281-8

38. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. *Ann Vasc Surg*. (1991) 5(6):491–9. doi: 10.1007/BF02015271

39. Dake MD, Miller DC, Semba CP, Mitchell RS, Walker PJ, Liddell RP. Transluminal placement of endovascular stent-grafts for the treatment of descending thoracic aortic aneurysms. *N Engl J Med*. (1994) 331(26):1729–34. doi: 10.1056/NEJM199412293312601

40. Greenberg RK, West K, Pfaff K, Foster J, Skender D, Haulon S, et al. Beyond the aortic bifurcation: branched endovascular grafts for thoracoabdominal and aortoiliac aneurysms. *J Vasc Surg*. (2006) 43:879–86. doi: 10.1016/j.jvs.2005.11.063

41. Han Y, Zhang S, Zhang J, Ji C, Eckstein HH. Outcomes of endovascular abdominal aortic aneurysm repair in octogenarians: meta-analysis and systematic review. *Eur J Vasc Endovasc Surg*. (2017) 54(4):454–63. doi: 10.1016/j.ejvs.2017.06.027

42. Tenorio ER, Dias-Neto MF, Lima GBB, Estrera AL, Oderich GS. Endovascular repair for thoracoabdominal aortic aneurysms: current status and future challenges. *Ann Cardiothorac Surg*. (2021) 10(6):744–67. doi: 10.21037/acs-2021-taes-24

43. Maurel B, Delclaux N, Sobocinski J, Hertault A, Martin-Gonzalez T, Moussa M, et al. The impact of early pelvic and lower limb reperfusion and attentive peri-operative management on the incidence of spinal cord ischemia during thoracoabdominal aortic aneurysm endovascular repair. *Eur J Vasc Endovasc Surg*. (2015) 49(3):248–54. doi: 10.1016/j.ejvs.2014.11.017

44. Kärkkäinen JM, Sandri GA, Tenorio ER, Macedo TA, Hofer J, Gloviczki P, et al. Prospective assessment of health-related quality of life after endovascular repair of pararenal and thoracoabdominal aortic aneurysms using fenestrated-branched endografts. *J Vasc Surg*. (2019) 69(5):1356–1366.e6. doi: 10.1016/j.jvs.2018.07.060

45. Oderich GS, Ribeiro M, Hofer J, Wigham J, Cha S, Chini J. Prospective, nonrandomized study to evaluate endovascular repair of pararenal and thoracoabdominal aortic aneurysms using fenestrated-branched endografts based on supraceliac sealing zones. *J Vasc Surg*. (2017) 65(5):1249–1259.e10. doi: 10.1016/j.jvs.2016.09.038

46. Gallitto E, Faggioli G, Melissano G, Fargion A, Isernia G, Lenti M. Preoperative and postoperative predictors of clinical outcome fenestrated and branched endovascular repair for complex abdominal and thoracoabdominal aortic aneurysms in an Italian multicenter registry. *J Vasc Surg*. (2021) 74(6):1795–1806.e6. doi: 10.1016/j.jvs.2021.04.072

47. Quiñones-Baldrich WJ, Panetta TF, Vescera CL, Kashyap VS. Repair of type IV thoracoabdominal aneurysm with a combined endovascular and surgical approach. *J Vasc Surg*. (1999) 30(3):555–60. doi: 10.1016/S0741-5214(99)70084-4

48. Bell KE, Lopez AC. Hybrid repair of thoracoabdominal aneurysms: a combined endovascular and open approach. *J Vasc Nurs*. (2008) 26(4):101–8. doi: 10.1016/j.jvn.2008.09.001

49. Tanaka A, Oderich GS, Estrera AL. Total abdominal debranching hybrid thoracoabdominal aortic aneurysm repair versus chimneys and snorkels. *JTCVS Tech*. (2021) 10:28–33. doi: 10.1016/j.xjtc.2021.08.002

50. Yang G, Zhang M, Muzepper M, Du X, Wang W, Liu C, et al. Comparison of physician-modified fenestrated/branched stent-grafts and hybrid visceral debranching plus stent-graft placement for complex thoracoabdominal aortic aneurysm repair. *J Endovasc Ther*. (2020) 27(5):749–56. doi: 10.1177/1526602820934466

51. Ljungman C, Wanhainen A, Kragsterman B, Nyman R, Ericksson LG, Eriksson . Propositions for refinement of the hybrid surgical technique for treatment of thoraco-abdominal aortic aneurysm. *Scand J Surg*. (2008) 97(2):174–7. doi: 10.1177/145749690809700221

52. Arnaoutakis DJ, Scali ST, Beck AW, Kubilis P, Huber TS, Martin AJ. Comparative outcomes of open, hybrid, and fenestrated branched endovascular repair of extent II and III thoracoabdominal aortic aneurysms. *J Vasc Surg*. (2020) 71(5):1503–14. doi: 10.1016/j.jvs.2019.08.236

53. Riambau V, Böckler D, Brunkwall J, Cao P, Chiesa R, Coppi G. Editor's choice—management of descending thoracic aorta diseases: clinical practice guidelines of the European society for vascular surgery (ESVS). *Eur J Vasc Endovasc Surg*. (2017) 53(1):4–52. doi: 10.1016/j.ejvs.2016.06.005

54. Chiesa R, Kahlberg A, Mascia D, Tshomba Y, Civilini E, Melissano G. Use of a novel hybrid vascular graft for sutureless revascularization of the renal arteries during open thoracoabdominal aortic aneurysm repair. *J Vasc Surg*. (2014) 60:622e30. doi: 10.1016/j.jvs.2014.03.256

55. Hughes GC, Barfield ME, Shah AA, Williams JB, Kuchibhatla M, Hanna JM. Staged total abdominal debranching and thoracic endovascular aortic repair for thoracoabdominal aneurysm. *J Vasc Surg*. (2012) 56(3):621–9. doi: 10.1016/j.jvs.2011.11.149

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Endovascular repair of thoracic aortic disease with isolated left vertebral artery and unfavorable proximal landing zone using fenestrated castor stent-graft

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Objective: The main purpose of this study was to evaluate the safety and efficacy of Castor single-branched stent-graft combined with fenestrated technique in treatment of thoracic aortic disease (TAD) with unfavorable proximal landing area (PLZ) and isolated left vertebral artery (ILVA).

Methods: From January 2018 to March 2022, 8 patients with TAD (6 patients with type B aortic dissections, 1 patient with type B intramural hematomas, and 1 patient with thoracic aortic aneurysm) underwent thoracic endovascular aortic repair with fenestrated Castor stent-graft due to the existence of ILVA and unfavorable PLZ. Demographic characteristics, surgical details, postoperative complications, follow-up and postoperative CTA imaging results were collected and analyzed.

Results: The primary technical success rate was 100%. The mean operation time was 115 min (range, 70–180 min). All the left subclavian arteries (LSAs) and ILVAs of the eight patients were revascularized by fenestrated Castor stent-grafts. During the follow-up period, no deaths and complications were observed. No internal leakage, aortic rupture, retrograde type A dissection were found on computed tomography angiography. All of the LSAs and ILVAs maintained patency without stenosis.

Conclusion: Castor single-branched stent-graft implantation combined with fenestration technique may be safe and feasible for TAD patients with ILVA and unfavorable PLZ.

KEYWORDS

isolated left vertebral artery, unfavorable proximal landing zone, castor single-branched stent-graft, fenestrated technique, thoracic aortic disease

Introduction

Thoracic endovascular aortic repair (TEVAR) has been increasingly used for the treatment of various thoracic aortic disease (TAD), including type B aortic dissection (TBAD), intramural hematoma (IMH), penetrating ulcer, thoracic aortic aneurysm, traumatic aortic injury due to its advantages of high safety, less trauma and fewer postoperative complications (1). However, the success of TEVAR largely depends on the sealing of the proximal landing zone (PLZ), which requires that the length of the PLZ is at least 2.0 cm (2). Therefore, for patients with unfavorable PLZ, the proximal stent-graft inevitably needs to cover LSA. Isolated left vertebral artery (ILVA) directly originates from the aortic arch, usually between the left common carotid artery and left subclavian artery (LSA) (3). It is the second most common anatomical variant in the variation of the superior aortic trunk, with an incidence of 0.79%–8% (3–7). TAD with unfavorable PLZ and ILVA is rare. If the circle of Willis is incomplete and the LSA and ILVA are handled improperly, it may lead to an increased risk of postoperative complications such as subclavian steal syndrome, left upper limb ischemia and stroke (8,9).

The stented elephant trunk technique has been reported to treat complicated TBAD with ILVA and unfavorable PLZ (10), but high technical difficulty and mortality rate restrict its application. In addition, TEVAR combined with carotid-subclavian bypass (CSbp) and ILVA transposition was also widely used for treating this special condition, but the trauma was massive (11,12). Fortunately, methods for reconstructing supra-arch branches in TEVAR have developed rapidly, including chimney technique, periscope technique, fenestrated technique and single-branched stent-graft implantation. With these techniques, an adequate proximal landing area and supra-arch branches reconstruction could be realized. In this study, we shared our experience of using Castor single-branched stent-graft combined with fenestrated technique in treatment of TAD patients with ILVA and unfavorable PLZ, which may reduce the complexity and difficulty of surgery. We hope that our experience can provide an additional choice for cardiovascular surgeons to deal with this supra-arch variation, which may be less invasive, safe and effective.

Materials and methods

This is a single-center observational study. From January 2018 to March 2022, a total of 8 TAD patients with ILVA underwent TEVAR in our center (**Figure 1**). In this small series, there were 6 patients with TBAD, 1 patient with type B IMH, and 1 patient with thoracic aortic aneurysm. As the opening of LSA was involved by TAD in the eight patients, Castor single-branched stent-graft was applied to obtain adequate PLZ and reconstruct LSA. To reserve the ILVA, Castor single-branched stent-graft was fenestrated prior to implantation. Demographic characteristics, comorbidities, surgical details, postoperative conditions and follow-up results were collected and analyzed. This study was approved by the Ethics Committee of Shandong University Qilu Hospital. Because this is a retrospective study and the data are anonymous, we waived informed consent for this study.

TEVAR procedure

The Castor stent-graft used in this study was the first single-branched stent-graft in China (9). It was with an integrated

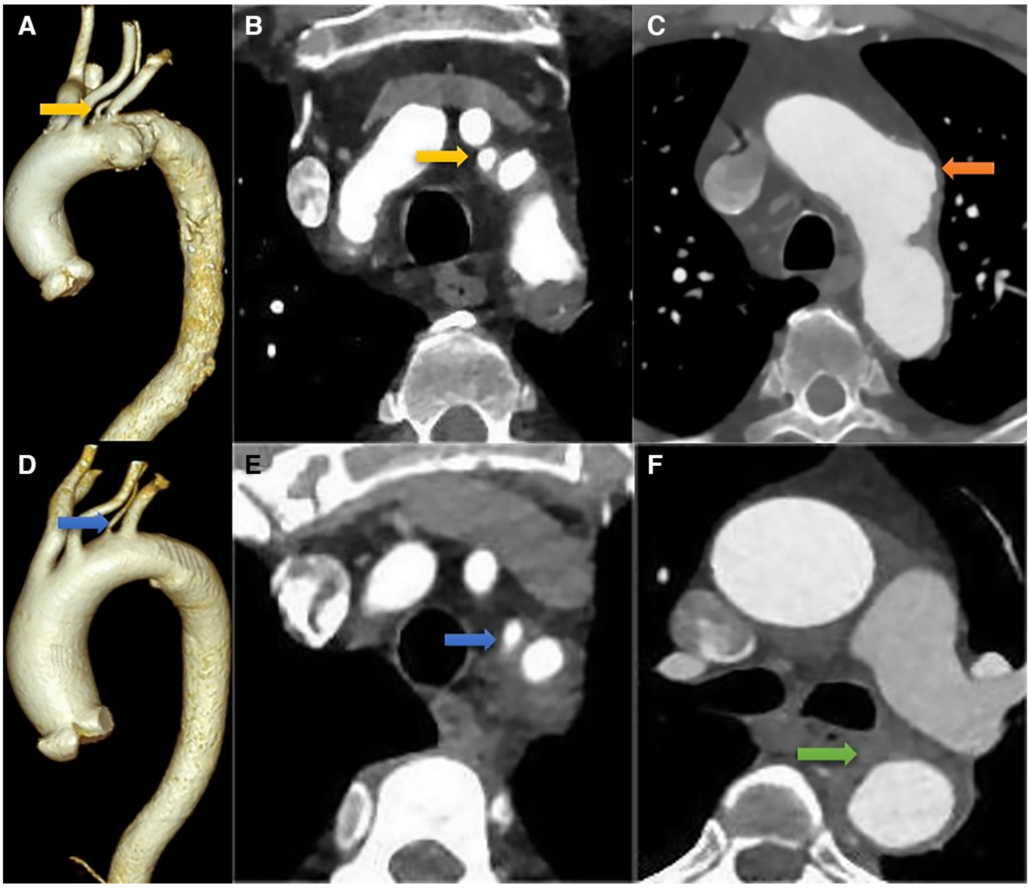

FIGURE 1
Preoperative CTA. (A–C) in a patient with thoracic aortic aneurysm, the ILVA (the yellow arrow) and aortic aneurysm (the orange arrow) are evident on the cross-sectional and three-dimensional reconstruction images; (D–F) in a patient with type B intramural hematoma, the ILVA (the blue arrow) and intramural hematoma (the green arrow) can be clearly seen from the cross-sectional and three-dimensional reconstruction images.

design of the main body and branch. All TEVAR procedures were performed under general anesthesia in the hybrid operating room by two experienced surgeons. The distance between LSA and ILVA, diameters of aortic zone 2, distal landing zone and the location of LSA and ILVA opening were obtained from preoperative computed tomography angiography (CTA). Usually, the right femoral artery (RFA) was chosen as the main approach. The details of the operation were as follows: first, the proximal part of Castor single-branched stent-graft was partially released from the sheath on the operation table. According to the aortic parameters obtained for preoperative CTA, including the relative location of LSA and ILVA, the size of ILVA opening, a fenestration was performed at an appropriate position (**Figure 2A**). The fenestration should be sutured firmly and circularly to achieve a smooth edge. The sutures around the stent-graft were tightened to avoid its deformation. The stent-graft was reinstalled and returned to the delivery sheath. Next, the RFA was exposed and two 6-F sheaths were inserted percutaneously into the left brachial artery (LBA) and left femoral artery (LFA), respectively. A 5-F pigtail catheter with a guidewire (catheter A) was pushed through the true lumen from the LFA to the ascending aorta. Angiography was subsequently performed to show the situation of the supra-arch branches and confirm the measurements obtained from CTA (**Figure 2B**). Then, another 5-F catheter (catheter B) was introduced from the LBA to the RFA through the true lumen along with a guidewire, and it was drawn out from the RFA and placed externally as a traction catheter. The third pigtail catheter with a guidewire (catheter C) was led from RFA to the ascending aorta and replaced with a super stiff guidewire. The traction wire of the branch was threaded into catheter B from RFA to LBA. Thereafter, the main body of the Castor single-branched stent-graft was delivered to the thoracic aorta along the super stiff guidewire, while the catheter B and the traction wire of the branch were moved simultaneously with the main body of delivery system. The position of the stent-graft was constantly adjusted to ensure the branch stent-graft was in good alignment with the LSA. Afterwards. the outer sheath and the soft sheath were removed, and the branch stent-graft was dragged into the LSA by pulling the traction wire. Finally, the main and branch grafts were released by pulling the trigger wire and the traction wire, respectively. Angiography was performed immediately to evaluate the stent-graft position, endoleak, LSA and ILVA perfusion (**Figure 2C**). All patients were given aspirin (100 mg/day) after operation to prevent thrombosis of the single-branched stent at least 6 months.

Definition and main results

Primary technical success was defined as successful stent deployment without conversion to open surgery or death, patency of LSA with ILVA without significant stenosis, and no obvious signs of endoleak. Postoperative stroke was determined by brain CT or MRI scan. The main manifestations of spinal cord ischemia were distal weakness of lower limbs and intermittent claudication. The main symptoms of left upper limb ischemia were pulseless of left arm, intermittent claudication of left arm and cold shoulder sensation.

The follow-up results were obtained by telephone interview and at outpatient clinic visits. Primary outcomes during the follow-up included early (<30 days) survival, late survival, freedom from aortic-related mortality, the patency of LSA and ILVA. Furthermore, endoleak, retrograde type A dissection, aortic

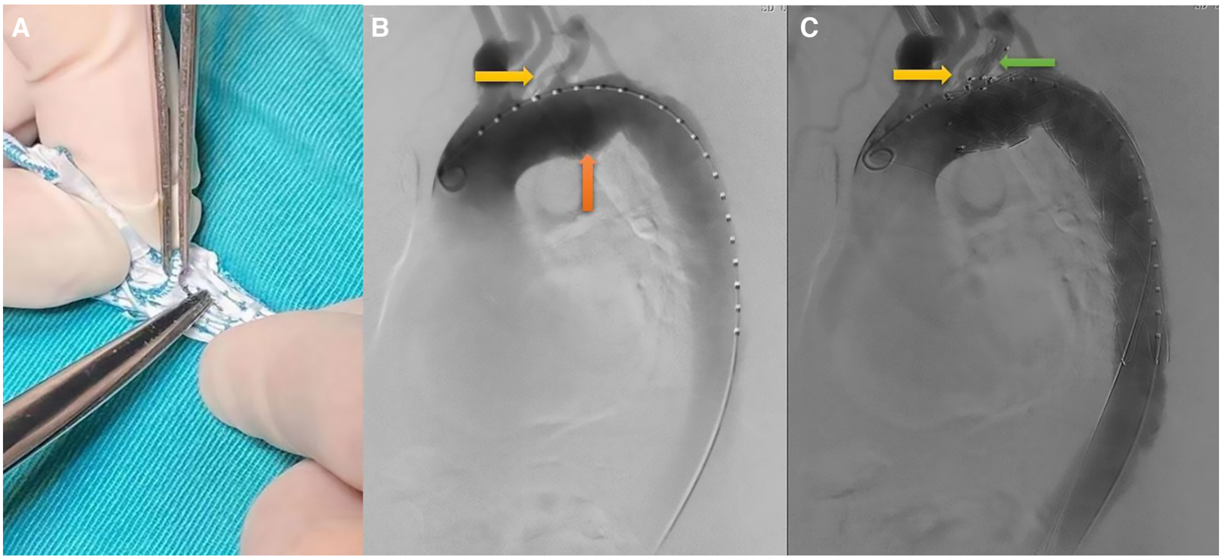

FIGURE 2
TEVAR procedure. (A) on-the-table fenestration; (B) preoperative angiography showed that isolated left vertebral artery (the yellow arrow) and aortic aneurysm (the orange arrow); (C) preoperative angiography showed that both ILVA (the yellow arrow) and LSA (the green arrow) were reconstructed.

rupture, stent-graft fracture and displacement were also evaluated from postoperative CTA.

Statistical analysis

Statistical analysis SPSS 26.0 (IBM, Armonk, New York, USA) was used for statistical analysis. Continuous variables are presented as mean ± SD and range. Categorical variables were presented as frequencies and percentages.

Results

Demographics and clinical characteristics

From January 2018 to March 2022, a total of 8 patients with TAD and ILVA underwent TEVAR in our center. Six (75.0%) patients were male, and the median age was 62.5 years old (range, 41 to 75 years old). The most common comorbidities are hypertension (62.5%). Four (50.0%) patients had smoking history, and 2 (25.0%) patients were diagnosed with COPD. According to preoperative CTA, there were 1 (12.5%) case of left vertebral artery dominant, 4 (50.0%) cases of right vertebral artery dominant, and 3 (37.5%) cases of symmetrical vertebral artery dominant. Additional details of patient characteristics were listed in **Table 1**.

Details of the procedure

TEVAR was performed in all patients, and the technical success rate was 100%. For each patient, the length of stent-graft main body was 200 mm and the length of the branch part was 25 mm. The median proximal stent-graft diameter was 34 mm (range, 30–36 mm). The median expansion ratio of proximal stents was 12.5% (range, 6.3%–15.4%). The median operation time was 115 min (range, 70–180 min). All the LASs and ILVAs were reconstructed. There was no endoleak during surgery.

TABLE 1 Baseline clinical characteristics of patients (*n* = 8).

Variables	Median or No.	Range or %
Age, years	62.5	41–75
Gender, male	6	75
Hypertension	5	62.5
CAD	1	12.5
Diabetes	2	25.0
COPD	2	25.0
CKD	0	0
Smoking	4	50.0
Drinking	4	50.0
Type of arch		
Type I	3	37.5
Type II	4	50.0
Type III	1	12.5
Dominant vertebral artery		
Left dominant	1	12.5
Right dominant	4	50.0
Symmetrical dominant	3	37.5
Bovine aortic arch	0	0

CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

Early and late outcomes

The median duration of hospital stay was 8 days (range, 3–13 days). No postoperative complications were observed in the eight patients, including stoke, spinal cord ischemia, left upper limb ischemia, AKI and puncture complication. There were no in-hospital deaths.

The median duration of follow-up was 48 months (range, 6–72 months). No neurological complications were observed during follow-up. The long-term survival rate was 100%. All of the LSAs and ILVAs maintained patency without stenosis (**Figure 3**). In addition, no endoleak, aortic rupture, and retrograde type A aortic dissection were observed in the eight patients. None of them required further intervention. More details were shown in **Table 2**.

Discussion

ILVA has been increasingly recognized as the second most common aortic arch branch variation, with an incidence of 0.79%–8% in general population (3–7). In patients with TBAD, the frequency of this anomaly is 3.6%, suggesting that ILVA may be related to the occurrence of TBAD (13). However, there were no clear guidelines whether ILVA should be reconstructed during surgery. In the most previous studies, the authors stated that the ILVA should be preserved (14,15). The left vertebral artery is an important component of the vertebrobasilar artery, which accounts for two fifths of the blood flow of the posterior cerebral artery (16). The posterior cerebral artery is the basic component of the Willis circle. It has been reported that the frequency of a complete Willis circle was 42% in the Western population. However, the frequency of a complete Willis circle in Chinese population was only 27% (17,18). Coverage of ILVA may increase the risk of spinal cord injury and postoperative stroke. However, some surgeons did not reconstruct the ILVA regularly (13). In their view, the ILVA was not necessarily reconstructed if it was with hypoplasia or thin size. Considering a high incidence of an incomplete circle of Willis in the Chinese population and the absence of cerebral artery CTA in an emergency, we regularly reconstructed the ILVA.

Several studies have reported the results of different surgical procedures for thoracic aortic disease and ILVA (10–12), including open surgery, hybrid surgery and total TEVAR. Zhu et al. (10) reported that seven patients with TBAD and ILVA underwent the stented elephant trunk procedure (open surgery). No deaths and postoperative complications were observed in the early term. Yang et al. (12) reviewed thirteen patients with thoracic aortic disease and ILVA using TEVAR with ILVA transposition and carotid-subclavian bypass (hybrid surgery). No

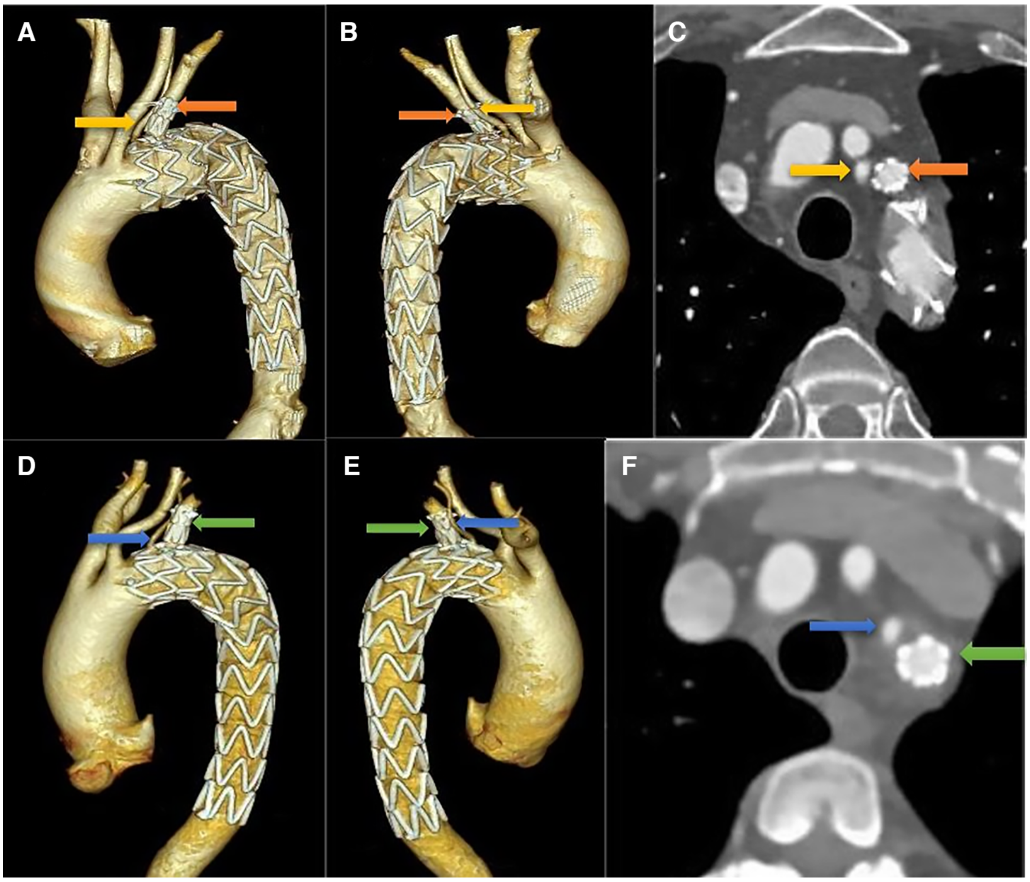

FIGURE 3
Follow-up CTA imaging. (A–C) in a patient with thoracic aortic aneurysm, both ILVA and LSA maintained patency without stenosis on three-dimensional reconstruction and cross-sectional images; (D–F) the same results can be seen in a patient with type B intramural hematoma.

deaths were observed in a mean follow-up of 22 months (range, 13–29 months). No complications were observed during the follow-up, including neurologic deficits, bypass occlusion and ILVA stenosis. Open surgery and hybrid surgery had shown satisfactory outcomes in treating the patients with thoracic aortic disease and ILVA. However, considering the massive trauma of these surgical methods, we attempted a less invasive approach, which is total TEVAR.

Total TEVAR for the thoracic aortic disease has been the mainstream treatment for its encouraging outcomes and less invasiveness. A length of 2.0 cm PLZ is essential for the success of total TEVAR. However, total TEVAR of thoracic aortic disease with ILVA and unfavorable PLZ was rarely reported. Ding et al. (13) reported 9 TBAD patients with ILVA treated with zone-2 TEVAR combined with LSA chimney technique. In order not to cover ILVA, the chimney stents were all bare stents. Neurologic deficits and chimney stent occlusions were not observed during surgery and follow-up, but complications such as immediate type I endoleak, type II endoleak and occlusion of the ILVA origin occurred. In our study, Castor single-branched stent-graft implantation combined with fenestration technique was used for treating patients with thoracic disease and ILVA. During the follow-up, all of the LSAs and ILVAs maintained patency without stenosis, no endoleak, aortic rupture and retrograde type A aortic dissection were observed in the eight patients. Based on excellent results, Castor single-branched stent-graft combined with fenestrated technique may be safe and feasible for repairing thoracic aortic disease with ILVA and insufficient PLZ.

It is considered that fenestrated or single-branched stent technique may lead to the risk of endoleak due to groove formation (12). However, previous published studies showed that the incidence of endoleak after Castor single-branched stent-graft implantation was low (19,20). Actually, single-branched stent-graft is more consistent with the design concept of anatomic correction. The anchoring effect of its branch part reduces the risk of stent displacement and endoleak (21). In 2004, McWilliams et al. first applied the in-situ fenestration technique of a thoracic stent-graft. to preserve LSA and demonstrated its feasibility (22). Since then, fenestration techniques have been developed continuously, mainly including in-situ fenestration and on-the-table fenestration. Currently, this technique has been applied in clinical practice through several preoperative and intraoperative methods classified as (1) mechanical, such as wires and hollow needles, and (2) physical, including laser and radiofrequency perforation (23). The incidence of endoleak in the early stage of fenestration is 0%–

TABLE 2 Early and late outcomes of thoracic aortic disease with ILVA after TEVAR ($n = 8$).

Variables	Median or No.	Range or %
Early outcomes		
Technical success	8	100
Operation time, min	115	70–180
Proximal stent-graft diameter, mm	34	30–36
Expansion ratio of proximal stent	0.125	0.063–0.154
Immediate type IA endoleak	0	0
Hospital stays, days	8	3–13
Stroke	0	0
Spinal cord ischemia	0	0
Ischemic symptoms of the left arm	0	0
AKI	0	0
Puncture complication	0	0
Death	0	0
Late outcomes		
Follow-up, months	48	6–72
Paraplegia	0	0
Stroke	0	0
Reintervention	0	0
Death	0	0
Patency rate of LSA	8	100
Patency rate of ILVA	8	100
Retrograde type A dissection	0	0
Aortic rupture	0	0
Endoleak	0	0
Stent-graft fracture and displacement	0	0

AKI, acute kidney injury; ILVA, isolated left vertebral artery; LSA, left subclavian artery.

3.2% described in the previous study (24). In fact, in cases of aortic arch disease that involved only the inner curve of the aorta, the selection of on-the-table fenestration technique can help reduce the incidence of endoleak after TEVAR (25). However, in our study, no endoleak of fenestration was observed during surgery and follow-up, which may be due to the small size of fenestration and healthy aortic wall surrounding the ILVA opening. Although the fenestrated technique may affect the long-term durability of the stent-graft, the early and mid-term results are still satisfactory whether in external pre-fenestration or in-situ fenestration (24–26). It is worth mentioning that computational fluid dynamics method based on patient-specific CTA images has been widely applied to evaluate the efficacy of complex TEVAR (27). Quantitative analysis of computational hemodynamics would be conducive to revealing the physiological effect of Castor single-branched stent-graft on the thoracic aortic disease with unfavorable PLZ and ILVA. Therefore, we are considering a related computational hemodynamics study in eight patients in the future.

Of course, our study still has some limitations. First, it is a single-center retrospective study with a small sample size. Second, the follow-up time was relatively short, and the long-term effect still needs further follow-up. Third, our study lacks relevant study on computational fluid dynamics, which needs to be further improved in the future. Finally, we lacked a comparison with open or hybrid surgery. These features and the limited experience with these anatomical variants do not allow us to make definitive recommendations from clinical or technical aspects. However, the surgical approach we have employed has hardly been reported in previous studies. We hope that larger registries or studies will confirm its feasibility and safety in addressing this challenge in the future.

Conclusion

Our limited experience indicates that single-branch stent-graft combined with fenestrated technique may be a safe and feasible treatment for TAD with ILVA and unfavorable PLZ. It can provide surgeons with an attractive choice due to its less invasiveness and good short-term effects. However, the durability and long-term effects of the technique needs to be further evaluated. Future studies with larger sample sizes and longer follow-up are warranted to confirm this finding.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Shandong University Qilu Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XZ designed the study. ZW prepared the first draft of the paper. ZW and CF were responsible for statistical analysis of the data. ZW and CF designed the methodology for searching. HS, DW, XM, XB and CL performed the data collection. All authors took part in revising it critically for important intellectual content; agreed to submit to the current journal; and agree to be accountable for all aspects of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Czerny M, Pacini D, Aboyans V, Al-Attar N, Eggebrecht H, Evangelista A, et al. Current options and recommendations for the use of thoracic endovascular aortic repair in acute and chronic thoracic aortic disease: an expert consensus document of the European society for cardiology (ESC) working group of cardiovascular surgery, the ESC working group on aorta and peripheral vascular diseases, the European association of percutaneous cardiovascular interventions (EAPCI) of the ESC and the European association for cardio-thoracic surgery (EACTS). *Eur J Cardiothorac Surg*. (2021) 59(1):65–73. doi: 10.1093/ejcts/ezaa268

2. Yoon WJ, Mell MW. Outcome comparison of thoracic endovascular aortic repair performed outside versus inside proximal landing zone length recommendation. *J Vasc Surg*. (2020) 72(6):1883–90. doi: 10.1016/j.jvs.2020.03.033

3. Lazaridis N, Piagkou M, Loukas M, Piperaki ET, Totlis T, Noussios G, et al. A systematic classification of the vertebral artery variable origin: clinical and surgical implications. *Surg Radiol Anat*. (2018) 40(7):779–97. doi: 10.1007/s00276-018-1987-3

4. Magklara EP, Pantelia ET, Solia E, Panagouli E, Piagkou M, Mazarakis A, et al. Vertebral artery variations revised: origin, course, branches and embryonic development. *Folia Morphol (Warsz)*. (2021) 80(1):1–12. doi: 10.5603/FM. a2020.0022

5. Popieluszko P, Henry BM, Hsieh WC, Saganiak K, Pękala PA, et al. A systematic review and meta-analysis of variations in branching patterns of the adult aortic arch. *J Vasc Surg*. (2018) 68(1):298–306.e10. doi: 10.1016/j.jvs.2017.06.097

6. Tsiouris C, Lazaridis N, Piagkou M, Hsieh WC, Saganiak K, Pękala PA, et al. The left-sided aortic arch variants: prevalence meta-analysis of imaging studies. *Surg Radiol Anat*. (2022) 44(5):673–88. doi: 10.1007/s00276-022-02945-4

7. Woraputtaporn W, Ananteerakul T, Iamsaard S, Namking M. Incidence of vertebral artery of aortic arch origin, its level of entry into transverse foramen, length, diameter and clinical significance. *Anat Sci Int*. (2019) 94(4):275–9. doi: 10. 1007/s12565-019-00482-6

8. Saremi F, Hassani C, Lin LM, Lee C, Wilcox AG, Fleischman F, et al. Image predictors of treatment outcome after thoracic aortic dissection repair. *Radiographics*. (2018) 38(7):1949–72. doi: 10.1148/rg.2018180025

9. Fang C, Wang C, Liu K, Pang X. Early outcomes of left subclavian artery revascularization using castor single-branched stent-graft in the treatment of type B aortic dissection or intramural hematoma. *Ann Thorac Cardiovasc Surg*. (2021) 27 (4):251–9. doi: 10.5761/atcs.oa.20-00166

10. Zhu JM, Qi RD, Liu YM, Zheng J, Xing XY, Sun LZ. Repair of complicated type B dissection with an isolated left vertebral artery using the stented elephant trunk technique. *Eur J Cardiothorac Surg*. (2016) 49(3):778–82. doi: 10.1093/ejcts/ezv242

11. Piffaretti G, Gelpi G, Tadiello M, Ferrarese S, Socrate AM, Tozzi M, et al. Transposition of the left vertebral artery during endovascular stent-graft repair of the aortic arch. *J Thorac Cardiovasc Surg*. (2020) 159(6):2189–2198.e1. doi: 10.1016/ j.jtcvs.2019.06.011

12. Yang G, Chen H, Sun G, Lou W, Chen X, Zhang L. Transposition of isolated left vertebral artery in hybrid thoracic endovascular aortic repair. *Front Cardiovasc Med*. (2021) 8:783656. doi: 10.3389/fcvm.2021.783656

13. Ding H, Zhu Y, Wang H, Luo S, Liu Y, Huang W, et al. Management of type B aortic dissection with an isolated left vertebral artery. *J Vasc Surg*. (2019) 70 (4):1065–71. doi: 10.1016/j.jvs.2018.11.052

14. Ad N, Lee P, Cox JL. Type A aortic dissection with associated anomaly of the carotid and vertebral vessels. *J Thorac Cardiovasc Surg*. (2002) 123(3):570–1. doi: 10.1067/mtc.2002.121673

15. Qi R, Sun L, Zhu J, Liu Y, Zheng J, Li C, et al. Total arch replacement in patients with aortic dissection with an isolated left vertebral artery. *Ann Thorac Surg*. (2013) 95 (1):36–40. doi: 10.1016/j.athoracsur.2012.07.078

16. Woo EY, Bavaria JE, Pochettino A, Gleason TG, Woo YJ, Velazquez OC, et al. Techniques for preserving vertebral artery perfusion during thoracic aortic stent grafting requiring aortic arch landing. *Vasc Endovascular Surg*. (2006) 40(5):367–73. doi: 10.1177/1538574406293735

17. Li Q, Li J, Lv F, Li K, Luo T, Xie P. A multidetector CT angiography study of variations in the circle of willis in a Chinese population. *J Clin Neurosci*. (2011) 18 (3):379–83. doi: 10.1016/j.jocn.2010.07.137

18. Sun LZ, Qi RD, Chang Q, Zhu JM, Liu YM, Yu CT, et al. Istotal arch replacement combined with stented elephant trunk implantation justified for patients with chronic stanford type a aortic dissection? *J Thorac Cardiovasc Surg*. (2009) 138:892–6. doi: 10.1016/j.jtcvs.2009.02.041

19. Jing Z, Lu Q, Feng J, Zhou J, Feng R, Zhao Z, et al. Endovascular repair of aortic dissection involving the left subclavian artery by castor stent graft: a multicentre prospective trial. *Eur J Vasc Endovasc Surg*. (2020) 60(6):854–61. doi: 10.1016/j.ejvs. 2020.08.022

20. Huang B, Jia H, Lai H, Chen Z, Sun Y, Wang C. Outcomes of thoracic endovascular aortic repair for penetrating aortic ulcers involving the left subclavian artery with the castor single-branched stent graft. *Eur J Cardiothorac Surg*. (2022) 62(2):ezac102. doi: 10.1093/ejcts/ezac102

21. Chen BL, Zhuang XM, Wei MX. Short-term efficacy of unibody single-branched stent in the treatment of lesions involving the left subclavian artery: two-year follow-up outcomes. *J Geriatr Cardiol*. (2020) 17(2):120–3. doi: 10.11909/j.issn.1671-5411. 2020.02.006

22. McWilliams RG, Murphy M, Hartley D, Lawrence-Brown MM, Harris PL. In situ stent-graft fenestration to preserve the left subclavian artery. *J Endovasc Ther*. (2004) 11(2):170–4. doi: 10.1583/03-1180.1

23. Glorion M, Coscas R, McWilliams RG, Javerliat I, Goëau-Brissonniere O, Coggia M. A comprehensive review of in situ fenestration of aortic endografts. *Eur J Vasc Endovasc Surg*. (2016) 52(6):787–800. doi: 10.1016/j.ejvs.2016.10.001

24. Chang H, Wang Y, Liu B, Wang W, Li Y. Endovascular repair for acute type B aortic dissection with unfavorable proximal landing zone. *Ann Thorac Surg*. (2022) 113(2):545–53. doi: 10.1016/j.athoracsur.2021.02.092

25. Shu C, Fan B, Luo M, Li Q, Fang K, Li M, et al. Endovascular treatment for aortic arch pathologies: chimney, on-the-table fenestration, and in-situ fenestration techniques. *J Thorac Dis*. (2020) 12(4):1437–48. doi: 10.21037/jtd.2020.03.10

26. Luo M, Fang K, Fan B, Li Q, Li M, He H, et al. Midterm results of retrograde in situ needle fenestration during thoracic endovascular aortic repair of aortic arch pathologies. *J Endovasc Ther*. (2021) 28(1):36–43. doi: 10.1177/1526602820953406

27. Qiao Y, Mao L, Ding Y, Fan J, Zhu T, Luo K. Hemodynamic consequences of TEVAR with in situ double fenestrations of left carotid artery and left subclavian artery. *Med Eng Phys*. (2020) 76:32–9. doi: 10.1016/j.medengphy.2019.10.016

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Analysis of clinical characteristics and imagological features of the aortic dissection patients with negative D-dimer results

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Background: D-dimer (DD) is a vital biomarker to rule out the diagnosis of aortic dissection (AD). However, the DD level in some patients with AD is not high in clinical practice, which often leads to missed diagnosis; therefore, understanding the characteristics of patients with AD and negative DD is of great clinical value.
Methods: From May 2015 to October 2020, 286 patients with AD who visited the first medical contact (FMC) within 24 h of symptom onset and were hospitalized in the Xiamen Cardiovascular Hospital of Xiamen University were enrolled in this study. Clinical characteristics and outcomes of patients were assessed.
Results: Among them, 13 cases (approximately 4.5%) had negative DD results. Compared to patients with positive DD results, patients with negative DD results had significantly higher platelet counts and lower aortic dissection detection risk scores (ADD-RS). The imagological analysis showed that patients with AD and negative DD had lower extension scores and milder damage to the mesenteric artery and three branches of the aortic arch. Furthermore, the results of the multivariable analysis showed that white blood cell count (WBC) [odds ratio (OR): 1.379, $P = 0.028$], FMC (OR: 0.904, $P = 0.028$), and extension score (OR: 1.623, $P = 0.046$) were associated with negative DD result.
Conclusions: Patients with AD and negative DD results had longer FMC and lower WBC. Imaging showed a smaller tear extension range and less damage to the mesenteric artery and three branches of the aortic arch. A negative DD result could not completely rule out AD even if the ADD-RS was zero.

KEYWORDS

aortic dissection, D-dimer, clinical characteristics, imagological features, diagnosis

1. Introduction

As shown previously, aortic dissection (AD) is one of the most life-threatening conditions caused by tears in the intimal layer of the aorta or bleeding into the aortic wall, resulting in severe aortic rupture or peripheral hypoperfusion (1). Recent epidemiological studies reported that the annual prevalence of AD is approximately 40 cases per 100,000 among people aged between 65 and 75 worldwide (2). Moreover, AD is a common fatal macrovascular disease with different clinical manifestations, which is likely to be misdiagnosed (3). Therefore, effective, rapid, and accurate diagnosis and confirmation are crucial for managing patients with suspected AD.

DD, a serum biomarker for early diagnosis of AD, can be easily detected in the emergency department (4). Previous studies demonstrated that higher serum concentrations of DD show higher sensitivity for diagnosing AD, whereas negative DD can rule out AD (5). Recent findings from different studies have confirmed that approximately 7.5% of patients with AD have negative DD results (6–8). These findings suggest that a negative DD result cannot simply rule out AD. Our study aimed to analyze the clinical characteristics and the imagological features of patients with AD and negative DD results, which may help the early diagnosis of AD in the emergency department.

2. Methods

2.1. Selection of participants

From May 2015 to October 2020, this single-center, retrospective observational study enrolled 286 consecutive patients with AD visiting the first medical contact (FMC) within 24 h of symptom onset who were admitted to Xiamen Cardiovascular Hospital of Xiamen University. AD was classified according to the Stanford standard. Type A dissection was defined as any dissection involving the ascending aorta or the arch (proximal to the left subclavian artery), and type B dissection was defined as dissection limited to the descending aorta. For patients with several episodes of AD, only the first registered episode was included in the analysis. Definite diagnosis of AD was made using thoracic and abdominal contrast-enhanced computed tomography (CT).

The exclusion criteria were as follows: (1) patients without on-admission DD result; (2) patients who were also diagnosed with intramural hematoma; (3) patients with treated AD who were hospitalized for other reasons; (4) original imaging data could not be obtained; (5) symptoms persisting for more than 24 h; (6) having a history of malignant tumors; and (7) pregnancy. A flowchart of the patients' enrollment is shown in **Figure 1**.

2.2. Study protocol

The study was approved by the Ethics Committee of Xiamen Cardiovascular Hospital of Xiamen University. The study was conducted in accordance with the revised Declaration of Helsinki. We retrospectively reviewed the medical records of patients. On admission, blood samples were obtained for routine laboratory tests.

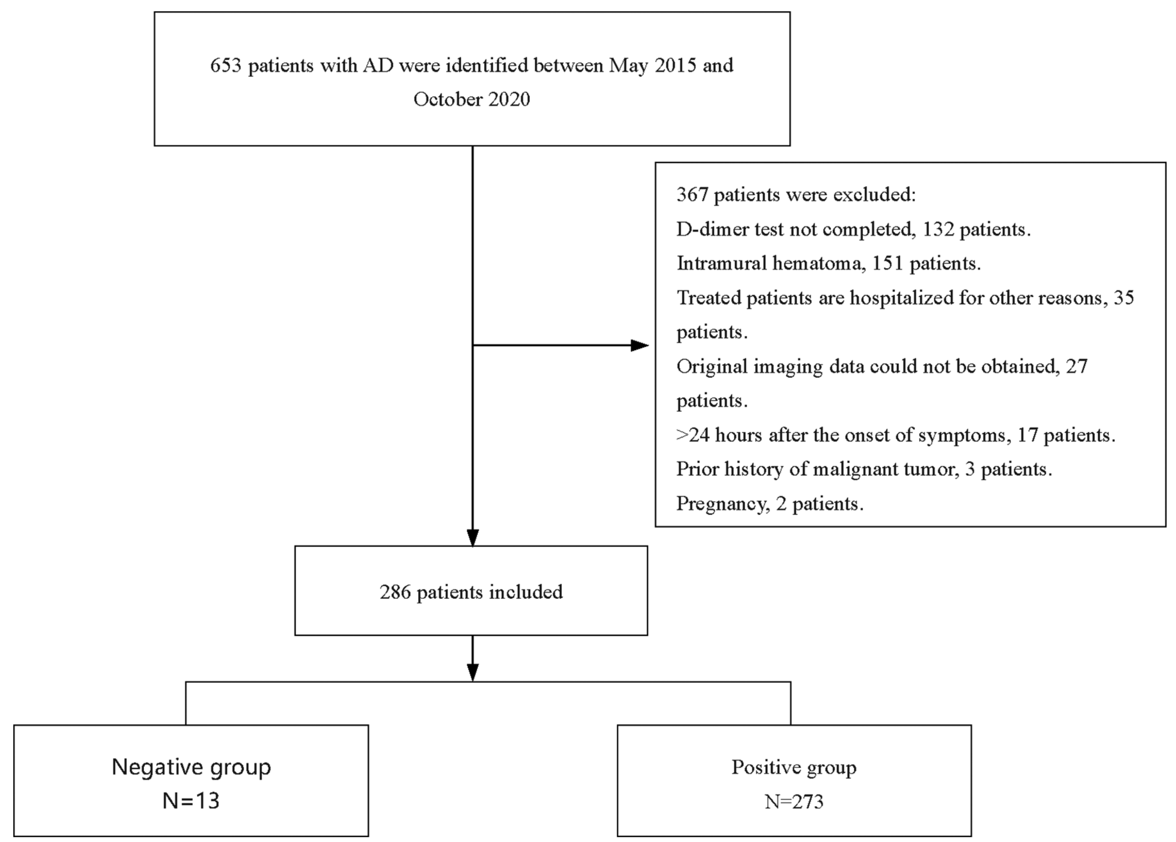

FIGURE 1
Flow chart of patient enrollment.

The following factors were compared between patients with negative DD results (negative group) and those with positive DD results (positive group): age, gender, Stanford classification, FMC, past medical history, presenting symptoms, aortic dissection detection risk score (AAD-RS), laboratory results, extension score, physical and CT findings.

True lumen and false lumen diameters were measured on the same slice in the thickest part of the arterial false lumen in CT angiography. Significant involvement of aortic branches was defined as branch stenosis >50% or blood supply from false lumen. The extension score of AD in each patient was determined by considering the location of dissection in the following segments: ascending aorta, aortic arch, thoracic descending aorta, suprarenal abdominal aorta, infra-renal abdominal aorta, and iliac arteries. Scores (1–7) were calculated according to the segment involved, with the thoracic descending aorta receiving 2 scores due to its length and the remaining segments, each one receiving 1 score. ADD-RS was calculated retrospectively based on 12 clinical risk factors classified into three categories (predisposing conditions, pain features, and physical findings). The score was calculated based on the number of categories where at least one risk factor was present (9).

The results of the imaging study were interpreted by experienced radiologists and cardiologists. All patients underwent urgent CT scans for final diagnosis.

2.3. DD level measurement

All blood samples collected during the routine clinical evaluation were immediately sent to the laboratory for measuring DD level using the immunoturbidimetry method. Sysmex CS-5100 Automated Coagulation Analyzer from Japan and INNOVANCE reagents from Germany were used for the assay. The reference range of DD was 0–0.55 µg/mL, and patients with DD level <0.55 µg/ml were classified into the negative group, and patients with DD level ≥0.55 µg/ml were classified into the positive group.

2.4. Data analysis

SPSS 25.0 (IBM, Armonk, NY, USA) and GraphPad Prism 9.0 were used for statistical analysis. Continuous variables with normal distribution are described as mean ± standard deviation, and continuous variables without normal distribution are described as median and quartile. Categorical data are expressed as frequency and percentages. Independent t-test or nonparametric Mann-Whitney U test was used to compare continuous variables, whereas chi-square or Fisher exact test was applied for categorical variables. Laboratory results, CT findings, and clinical characteristics (excluding AAD-RS) with $p < 0.05$ in the univariate analysis were used in the multivariate analysis model. Odds ratio (OR) and 95% confidence interval (CI) were calculated. A p-value of <0.05 was considered statistically.

3. Results

3.1. Baseline characteristics of patients

Based on the inclusion and exclusion criteria, 286 participants, with a median age of 53 years, were included in the final analysis (see **Figure 1**), most of whom were men (82.5%). The baseline characteristics of the 286 participants are shown in **Table 1**. In general, 13 (4.5%) and 273 (95.5%) patients showed negative and positive DD results, respectively. The median age of the negative group was 53 years, and 11 (84.6%) of them were male (as shown in **Table 1**). Compared with the positive group, patients in the negative group showed a significantly longer FMC period (24 vs. 6, $P < 0.001$), higher platelet count (218 vs. 167, $P = 0.007$), and relatively lower WBC (8.29 vs. 13.22, $P < 0.001$). Meanwhile, pain was milder in the negative group (46.15% vs. 97.07%, $P < 0.001$). Additionally, the ADD-RS was significantly lower in the negative group compared to the positive group (1 vs. 2, $P < 0.001$). Imaging results showed the extension score of dissection was lower in the negative group than in the positive group (3 vs. 5, $P = 0.002$). The extension scores were mainly 1–2 points in the negative group (**Figure 2**), while 7 points in the positive group. Moreover, the involvement of the mesenteric artery and the three branches of the aortic arch was less likely in the negative group than in the positive group.

3.2. Multivariable logistic regression analysis

WBC [odds ratio (OR): 1.379, $P = 0.028$], FMC (OR: 0.904, $P = 0.028$), and the extension score (OR: 1.623, $P = 0.046$) were associated with negative DD result (**Table 2**).

4. Discussion

4.1. Negative DD results combined with ADD-RS zero score could not completely rule out suspected aortic dissection

DD, a small fragment that can be detected after coagulation, is currently used in clinical practice for its high sensitivity; however, it has low specificity for diagnosing AD. Notably, the negative value of DD has recently been confirmed to have a high predictive power (10). Since 2007, It has been accepted that a DD value less than 0.1 mg/ml can rule out AD (11), which has been confirmed by many clinical observations from different countries (12). More recently, Yin et al. conducted a comprehensive systemic meta-analysis and found that the pooled sensitivity of DD for AD was approximately 94.5% and 69.1%, respectively, indicating that DD is the best biomarker for ruling out AD (13).

Nevertheless, recent reports have demonstrated that patients with AD can have negative DD results. Morita et al. found that among 113 consecutive patients with AD who came within 24 h of symptom onset, nine patients (8%) exhibited negative DD

TABLE 1 Baseline characteristics of all patients ($N = 286$).

	Negative group ($n = 13$)	Positive group ($n = 273$)	P-value
Gender (male)	11 (84.61%)	225 (82.42%)	>0.999
Age (year)	53 (48.00–55.00)	53 (45.00–64.00)	0.948
FMC (h)	24.00 (8.50–24.00)	6.00 (5.00–9.00)	<0.001
Temperature (°C)	36.5 (36.25–36.75)	36.5 (36.30–36.75)	0.875
Heart rate (beat/min)	80 (66.00–88.50)	79 (67.00–89.00)	0.829
Systolic blood pressure (mmHg)	156 (133.5–169.5)	148 (120.5–169.5)	0.318
Diastole blood pressure (mmHg)	90 (65.50–102.5)	81 (66.00–94.00)	0.343
Syncope or unconsciousness	0 (0%)	18 (6.59%)	>0.999
Cerebrovascular disease	1 (7.69%)	12 (4.40%)	0.461
Diabetes	1 (7.69%)	4 (1.47%)	0.209
Hypertension	12 (92.31%)	225 (82.42%)	0.704
Pain*	6 (46.15%)	265 (97.07%)	<0.001
AAD-RS	1 (1–1)	2 (1–2)	<0.001
Laboratory results			
White blood cell (10^9/L)	8.29 (6.16–11.96)	13.22 (10.95–16.05)	<0.001
Platelet (10^9/L)	218 (171–248.5)	167 (138–204)	0.007
Calcitoninogen (ng/ml)	0.09 (0.04–0.44)	0.15 (0.06–0.44)	0.311
Hs-cTnT (ng/L)	9.40 (7.26–23.28)	13.99 (8.19–45.90)	0.134
NT-proBNP (ng/L)	105.00 (45.75–729.57)	214.10 (95.47–729.57)	0.284
CT findings			
Extension score	3.00 (1.50–5.00)	5.00 (4.00–7.00)	0.002
True lumen diameter (cm)	1.50 (1.12–2.76)	1.43 (0.94–1.83)	0.252
False lumen diameter (cm)	2.32 (1.18–2.69)	2.36 (1.68–3.25)	0.352
Stanford type A dissection	4 (30.77%)	158 (57.88%)	0.054
False lumen with partial thrombosis	8 (61.54%)	173 (63.40%)	>0.999
Coronary artery involvement	0 (0%)	16 (5.86%)	>0.999
Three bifurcated vessels of the aortic arch involvement	2 (15.38%)	123 (45.05%)	0.035
The mesenteric artery involvement	0 (0%)	77 (28.20%)	0.023
Coeliac trunk artery involvement	3 (23.08%)	102 (37.36%)	0.385
Renal artery involvement	5 (38.46%)	161 (58.97%)	0.143
Iliac artery involvement	6 (46.15%)	170 (62.27%)	0.243

AAD-RS, the aortic dissection detection risk score; FMC, symptom onset to the first medical contact; Pain*, Contains chest pain, back pain, abdominal pain, low back pain.

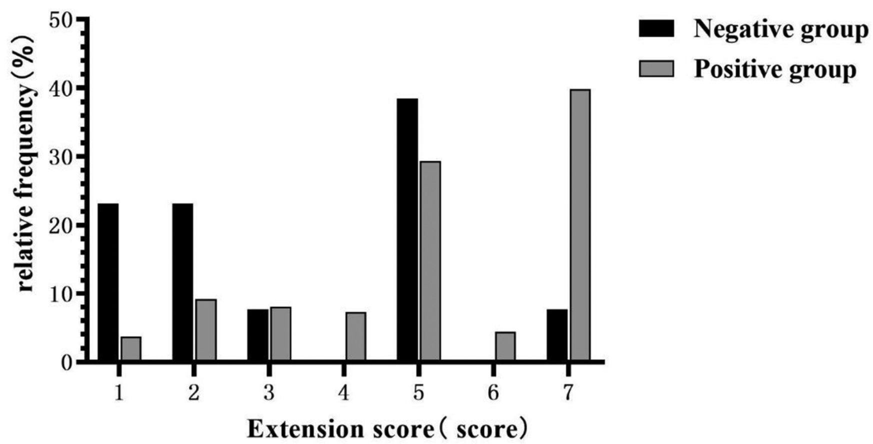

FIGURE 2
Comparison of extension scores between negative D-dimer (DD) group and positive DD group.

results (14). Additionally, approximately 45% of patients in the negative group were diagnosed with type A dissection, and 33% underwent emergency surgery due to cardiac tamponade (15), implying fatal conditions even in patients with negative DD. Therefore, we analyzed the characteristics of patients with AD and negative DD to provide a reference for the accurate and effective diagnosis of AD in patients with suspected AD. We enrolled patients admitted within 24 h of symptom onset and figured out

TABLE 2 Multivariable logistic regression models for risk factors related to negative results of D-dimer testing on the diagnosis of AD.

	OR	95% CI	*P*-value
FMC (h)	0.904	0.826–0.989	0.028
Non-pain	0.130	0.017–0.996	0.050
White blood cell (10^9/L)	1.379	1.034–1.839	0.028
Platelet (10^9/L)	0.988	0.974–1.002	0.087
Stanford type A dissection	0.469	0.055–4.004	0.489
Extension score	1.623	1.008–2.613	0.046
Three bifurcated vessels of the aortic arch involvement	1.098	0.112–10.733	0.936
The mesenteric artery involvement	0.000	0.000–0.000	0.997
False lumen with partial thrombosis	1.861	0.314–11.032	0.494

OR, odds ratio; 95% CI, 95% confidence interval; FMC, symptom onset to the first medical contact.

that approximately 4.5% of patients with AD had a negative DD result. Additionally, we found that low ADD-RS was significantly associated with negative DD. Takayama et al. reported that none of the DD-negative patients had an AAD-RS score of zero (15). Stefano et al. reported that ADD-RS 0 or ≤1 combined with a negative DD can accurately rule out AD (16), whereas Ruth et al. reported two patients with acute AD who had zero AAD-RS and negative DD (17). We found 2 (15.4%) patients with a zero score in the negative group, suggesting a negative DD result can not completely rule out AD even if the ADD-RS is zero.

4.2. Extension score, false lumen diameter, and affected vessels in patients with negative DD result

The exposed area of the intimal layer was decided based on the length of the dissection tear and false lumen diameter. Smaller exposed area was associated with weaker activation of exogenous coagulation factors. Therefore, patients with a smaller dissection tear range and smaller false lumen diameter were more likely to have negative DD results. We divided the aorta into several segments in a relatively average way, and the extension score was calculated based on the number of these segments, which could indirectly indicate the length of the dissection tear. Our imagological analysis showed that there were lower extension scores, smaller false lumen diameters, and milder involvement of the mesenteric artery and branches of the aortic arch in the negative group than in the positive group.

Damages to peripheral organs supplied by the three branches of the aortic arch and the mesenteric artery were associated with large dissection areas in patients with AD. Thus, the involvement of these vessels caused a large area of hypoperfusion, damaging vascular endothelial cells and activating endogenous coagulatory pathways (18). Thus, severe dissection can present with increased serum concentrations of DD. Consistently, we found a lower extension score in AD patients with negative DD results, suggesting milder organ ischemia. Additionally, our imagological analysis might provide a possible explanation for Chai X et al.' outcome that increased DD concentrations can predict a higher risk of in-hospital mortality in patients with AD (19).

4.3. Inflammatory response in patients with AD and negative DD results

During the development of AD, the inflammatory response is involved in several pathological processes in the affected artery, including medial degradation of the aortic artery and arterial wall remodeling, which subsequently weaken the aortic wall and increase mortality (20). On the other hand, the imbalance between pro-inflammatory and anti-inflammatory signals can contribute to AD (21). Takayama et al. demonstrated that WBC significantly increases in patients with AD owing to the inflammatory response in the acute phase reaction (15). Recently, some studies have shown a wide range of interactions between inflammatory response systems and vascular systems. The inflammatory response not only stimulates coagulation but also accelerates the progression of coagulation (22, 23). Previous clinical trials on patients with AD demonstrated that increased concentrations of DD can reflect the severity of systemic inflammatory response (24). Besides, it was shown that patients with AD and increased WBC possess higher levels of DD (25). Similarly, another clinical trial reported that WBC is increased in patients with positive DD (19). We have shown that patients with negative DD results have a lower WBC and a higher platelet count compared with those with positive DD, possibly due to lower tear extension scores in the negative group. Because of the smaller tear extension score, the exposure area of the intima of the artery is relatively smaller, and the elevating count of WBC caused by both the acute phase reaction as well as the underlying inflammatory process is smaller (26), resulting in a lower WBC count in the negative group. Additionally, as the exposed area of the intimal layer was smaller in the negative group, coagulation and platelet aggregation were less likely in this group, resulting in a higher platelet count.

Multivariable logistic regression also showed that a low WBC is associated with a negative DD result. These findings also shed light on the underlying processes of the inflammatory response is inclined to become the targets for treating AD in the future.

4.4. Painless AD in the negative DD group

Typically, AD presents with acute or severe chest, back, and tearing abdominal pain. It has also been suggested that AD can be rarely painless (27). Imamura et al. demonstrated that AD can be painless due to neurologic deficit, syncope, or disturbance of consciousness (28). Besides, slow or gradual dissection with less wall stretching can be painless. Though there are several potential explanations for the absence of pain, none are convincing (25). Since the negative group presented a smaller extension range with less wall stretching, asymptomatic AD is expected to be more common in this group.

4.5. Others

We found that among patients with negative DD results, the FMC of nine patients (approximately 69.2%) was between 20 and

24 h, which was slightly longer than that in patients with positive DD results. In addition, the results of the multivariable analysis showed that FMC (OR: 0.904, $P = 0.028$) was associated with negative DD results. Eggebrecht et al. reported that FMC is inversely associated with the serum concentrations of DD in patients with AD (29). However, they did not provide a reasonable explanation for the underlying mechanism. Thus, it is still needed to conduct in-depth investigations.

Cai Y et al. showed a statistically significant association between relatively low blood pressure and negative DD results (19), but our study did not find a similar association. Murai M et al. reported that age is an independent risk factor for positive DD, and none of the patients with negative DD were older than 70 years in their study (14). However, in our study, two patients with negative DD were 73 years old and 81 years old, and age did not significantly differ between the positive and negative groups.

5. Conclusions

Patients with AD and negative DD had longer FMC and slighter chest pain. Imaging showed a smaller tear extension range and less involvement of the mesenteric artery and three branches of the aortic arch. In clinical practice, physicians should be aware that a negative DD result cannot completely rule out AD even if the ADD-RS is zero. Therefore, imaging should be conducted as early as possible for patients with suspected AD.

6. Study limitations

There are some limitations to this study. First, it was a single-center retrospective study with a relatively small number of AD patients in the negative group. Second, participants with both Stanford type A and type B AD were included. Given the small number of participants, we did not conduct an independent analysis on patients with type A or B dissection. Nevertheless, our findings are important since the molecular mechanisms through which D-dimer is produced are similar between Stanford type A and type B aortic dissection. Finally, as we focused on Chinese patients, similar studies on other nationalities are needed.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Xiamen Cardiovascular Hospital of Xiamen University. The studies were conducted in accordance with the local legislation and institutional requirements. The informed consent was waived due to its retrospective nature.

Author contributions

ZZ: Writing – original draft, Supervision. LW: Writing – original draft. XS: Writing – review & editing. YZ: Writing – review & editing, Formal Analysis. KW: Writing – review & editing. GS: Writing – review & editing, Formal Analysis. WO: Writing – review & editing, Data curation. LY: Writing – review & editing, Data curation. WC: Writing – review & editing, Data curation. BW: Writing – review & editing, Conceptualization, Supervision, Validation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Sayed A, Munir M, Bahbah EI. Aortic dissection: a review of the pathophysiology, management and prospective advances. *Curr Cardiol Rev.* (2021) 17(4):e230421186875. doi: 10.2174/1573403X16666201014142930

2. Deleeuw V, De Clercq A, De Backer J, Sips P. An overview of investigational and experimental drug treatment strategies for Marfan syndrome. *J Exp Pharmacol.* (2021) 13:755–79. doi: 10.2147/JEP.S265271

3. Juraszek A, Czerny M, Rylski B. Update in aortic dissection. *Trends Cardiovasc Med*. (2022) 32(7):456–61. doi: 10.1016/j.tcm.2021.08.008

4. Long DA, Keim SM, April MD, Koyfman A, Long B, Ankel F. Can D-dimer in low-risk patients exclude aortic dissection in the emergency department? *J Emerg Med*. (2021) 61(5):627–34. doi: 10.1016/j.jemermed.2021.07.028

5. Tsutsumi Y, Tsujimoto Y, Takahashi S, Tsuchiya A, Fukuma S, Yamamoto Y, et al. Accuracy of aortic dissection detection risk score alone or with D-dimer: a systematic review and meta-analysis. *Eur Heart J Acute Cardiovasc Care*. (2020) 9 (3_suppl):S32–39. doi: 10.1177/2048872620901831

6. Li W, Huang B, Tian L, Yang Y, Zhang W, Wang X, et al. Admission D-dimer testing for differentiating acute aortic dissection from other causes of acute chest pain. *Arch Med Sci*. (2017) 13(3):591–6. doi: 10.5114/aoms.2017.67280

7. Paparella D, Malvindi PG, Scrascia G, de Ceglia D, Rotunno C, Tunzi F, et al. D-dimers are not always elevated in patients with acute aortic dissection. *J Cardiovasc Med (Hagerstown)*. (2009) 10(2):212–4. doi: 10.2459/JCM.0b013e32831c849e

8. Wiegand J, Koller M, Bingisser R. Does a negative D-dimer test rule out aortic dissection? *Swiss Med Wkly*. (2007) 137(31–32):462. doi: 10.4414/smw.2007.11731

9. Rogers AM, Hermann LK, Booher AM, Nienaber CA, Williams DM, Kazerooni EA, et al. Sensitivity of the aortic dissection detection risk score, a novel guideline-based tool for identification of acute aortic dissection at initial presentation: results from the international registry of acute aortic dissection. *Circulation*. (2011) 123 (20):2213–8. doi: 10.1161/CIRCULATIONAHA.110.988568

10. Shimony A, Filion KB, Mottillo S, Dourian T, Eisenberg MJ. Meta-analysis of usefulness of D-dimer to diagnose acute aortic dissection. *Am J Cardiol*. (2011) 107 (8):1227–34. doi: 10.1016/j.amjcard.2010.12.027

11. Sodeck G, Domanovits H, Schillinger M, Ehrlich MP, Endler G, Herkner H, et al. D-dimer in ruling out acute aortic dissection: a systematic review and prospective cohort study. *Eur Heart J*. (2007) 28(24):3067–75. doi: 10.1093/eurheartj/ehm484

12. Sutherland A, Escano J, Coon TP. D-dimer as the sole screening test for acute aortic dissection: a review of the literature. *Ann Emerg Med*. (2008) 52(4):339–43. doi: 10.1016/j.annemergmed.2007.12.026

13. Cui JS, Jing ZP, Zhuang SJ, Qi SH, Li L, Zhou JW, et al. D-dimer as a biomarker for acute aortic dissection: a systematic review and meta-analysis. *Medicine (Baltimore)*. (2015) 94(4):e471. doi: 10.1097/MD.0000000000000471

14. Hazui H, Nishimoto M, Hoshiga M, Negoro N, Muraoka H, Murai M, et al. Young adult patients with short dissection length and thrombosed false lumen without ulcer-like projections are liable to have false-negative results of D-dimer testing for acute aortic dissection based on a study of 113 cases. *Circ J*. (2006) 70 (12):1598–601. doi: 10.1253/circj.70.1598

15. Nitta K, Imamura H, Kashima Y, Kamijo H, Ichikawa M, Okada M, et al. Impact of a negative D-dimer result on the initial assessment of acute aortic dissection. *Int J Cardiol*. (2018) 258:232–6. doi: 10.1016/j.ijcard.2018.01.104

16. Nazerian P, Morello F, Vanni S, Bono A, Castelli M, Forno D, et al. Combined use of aortic dissection detection risk score and D-dimer in the diagnostic workup of suspected acute aortic dissection. *Int J Cardiol*. (2014) 175(1):78–82. doi: 10.1016/j.ijcard.2014.04.257

17. Ruf TF, Pfluecke C, Mues C, Strasser RH. Aortic dissection albeit negative D-dimers and zero clinical probability—another facet of medicine's deadly chameleon. *J Cardiol Cases*. (2017) 15(2):53–5. doi: 10.1016/j.jccase.2016.10.008

18. Logghe G, Trachet B, Segers P, De Backer J, Mulorz J, Dueppers P, et al. Outflow through aortic side branches drives false lumen patency in type B aortic dissection. *Front Cardiovasc Med*. (2021) 8:710603. doi: 10.3389/fcvm.2021.710603

19. Yang G, Peng W, Zhou Y, He H, Pan X, Cai Y, et al. Characteristics and prognosis of acute type A aortic dissection with negative D-dimer result. *Am J Emerg Med*. (2020) 38(9):1820–4. doi: 10.1016/j.ajem.2020.05.055

20. Cifani N, Proietta M, Tritapepe L, Di Gioia C, Ferri L, Taurino M, et al. Stanford-A acute aortic dissection, inflammation, and metalloproteinases: a review. *Ann Med*. (2015) 47(6):441–6. doi: 10.3109/07853890.2015.1073346

21. Zeng T, Yuan J, Gan J, Liu Y, Shi L, Lu Z, et al. Thrombospondin 1 is increased in the aorta and plasma of patients with acute aortic dissection. *Can J Cardiol*. (2019) 35(1):42–50. doi: 10.1016/j.cjca.2018.11.008

22. Ito S, Hashimoto Y, Majima R, Nakao E, Aoki H, Nishihara M, et al. MRTF-A promotes angiotensin II-induced inflammatory response and aortic dissection in mice. *PLoS One*. (2020) 15(3):e0229888. doi: 10.1371/journal.pone.0229888

23. Wu Z, Wang Z, Wu H, Hu R, Ren W, Hu Z, et al. Obesity is a risk factor for preoperative hypoxemia in Stanford A acute aortic dissection. *Medicine (Baltimore)*. (2020) 99(11):e19186. doi: 10.1097/MD.0000000000019186

24. Shinohara T, Suzuki K, Okada M, Shiigai M, Shimizu M, Maehara T, et al. Soluble elastin fragments in serum are elevated in acute aortic dissection. *Arterioscler Thromb Vasc Biol*. (2003) 23(10):1839–44. doi: 10.1161/01.ATV.0000085016.02363.80

25. Park SW, Hutchison S, Mehta RH, Isselbacher EM, Cooper JV, Fang J, et al. Association of painless acute aortic dissection with increased mortality. *Mayo Clin Proc*. (2004) 79(10):1252–7. doi: 10.4065/79.10.1252

26. Peng W, Zhu QY, Zhou XH, Chai XP. A simple emergency prediction tool for acute aortic dissection. *Iran J Public Health*. (2013) 42(10):1085–91.

27. Bossone E, LaBounty TM, Eagle KA. Acute aortic syndromes: diagnosis and management, an update. *Eur Heart J*. (2018) 39(9):739–749d. doi: 10.1093/eurheartj/ehx319

28. Imamura H, Sekiguchi Y, Iwashita T, Dohgomori H, Mochizuki K, Aizawa K, et al. Painless acute aortic dissection. Diagnostic, prognostic and clinical implications. *Circ J*. (2011) 75(1):59–66. doi: 10.1253/circj.CJ-10-0183

29. Eggebrecht H, Naber CK, Bruch C, Kröger K, von Birgelen C, Schmermund A, et al. Value of plasma fibrin D-dimers for detection of acute aortic dissection. *J Am Coll Cardiol*. (2004) 44(4):804–9. doi: 10.1016/j.jacc.2004.04.053

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