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Risk factors of distal segment aortic enlargement after complicated type B aortic dissection

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ABSTRACT

Objectives: Distal segment aortic enlargement (DSAE) is a common complication that influences the long-term prognosis of type B aortic dissection (TBAD) after thoracic endovascular aortic repair (TEVAR). In this study, a multivariate analysis was performed to find potential factors predictive of DSAE.
Methods: A single-center retrospective study was performed from 1999 to 2016. Included in the study were complicated TBAD patients who underwent TEVAR with uncovered residual tears. Based on the diameter of the distal segment of the uncovered aorta, we assigned patients to an enlargement group and a non-enlargement group. Data extracted from the medical records included demographic and clinical characteristics and follow-up computed tomography angiography data. The primary endpoints were the all-cause mortality and the presumably aortic-related events that required reintervention during the follow-up period.
Results: For the 333 patients, all-cause mortality was 38 (11.41%), and 76 (22.82%) patients underwent reintervention. A total of 70 (21.02%) patients experienced DSAE, among them were 2 patients who died of aortic rupture and 58 patients who accepted reintervention. Multivariate analysis reviewed independent risk factors of postoperative DSAE, including current smoking, the residual length of the patent false lumen, the postoperative number of dissection tears in the thoracic aorta and type III aortic arch; as well as protective factors, including the application of a restrictive bare stent (RBS), the length of covered stent in the descending thoracic aorta, and the distance from the residual first tear to the left subclavian artery (LSA).
Conclusion: DSAE after TEVAR for patients with a complicated TBAD can be influenced by their current smoking habit, the residual length of patent false lumen, the postoperative number of dissection tears in the thoracic aorta and the aortic arch type. Meanwhile, RBS usage, the length of the covered stent in the descending thoracic aorta and the distance from the residual first tear to the LSA could have positive effect on the prognosis.

Introduction

Thoracic endovascular aortic repair (TEVAR) has become the primary management for complicated type B aortic dissections (TBADs). However, a ruptured dissection is a surgical indication for emergent TEVAR. In addition, a ruptured dissection usually involves a longer section of dissected aorta and the early survival rate may be poorer than that of patients with a complicated TBAD.[1] The aim of TEVAR is to cover the proximal entry tear, stop the inflow of blood into the false lumen and permit re-expansion of the true lumen, therefore most patients have a residual downstream dissection with a patent false lumen, which increases the occurrence of a distal segment aortic enlargement (DSAE). Recent studies have shown that DSAE occurs in 10%–50% of TEVAR-treated patients and has a mortality rate of 30%.[2,3] DSAE is mainly caused by the persistent perfusion from residual entry tears. In addition, some related factors will further increase the occurrence of DSAE, but have not been fully explored.[2,4–7] The purpose of this retrospective study is to assess the risk factors that may affect distal aortic

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remodeling of complicated TBAD after TEVAR.

Materials and methods

Selection of patients with complicated TBAD

Study population

From April 1999 to October 2016, first-episode complicated TBAD patients treated with endovascular repair or a hybrid technique for proximal entry tears at this center were included.

Patients that were excluded included those without residual dissection; with preoperative DSAE; with isolated abdominal aortic dissection; with penetrating aortic ulcer; with intramural hematomas; and those needing simultaneous abdominal aortic dissection treatment. In-hospital death or death due to non-aortic events within one year; type I endoleaks, new entry, or aortic complications other than DSAE that needed reintervention within one year; and patients who had less than one-year of follow-up among the non-expansion group were also excluded (Fig. 1).

Distal aorta refers to the untreated aortic segment from the distal end of the aortic stents to the common iliac arteries. DSAE is defined as the maximum diameter of the aorta 1.5 times greater than normal aorta[8] or a growth rate of over 10 mm per year. Patients were categorized into two groups (a DSAE group and a non-DSAE group). The potential risk factors include demographics, clinical characteristics, features of the procedure, and early postoperative computed tomography angiography (CTA) findings.

This study was approved by the institutional review board of the Second Military Medical University, and all patients gave their permission to publish.

Data collection and imaging measurement

Patient-level variables were extracted from the medical records database, including information on baseline characteristics, patient demographics, and comorbidity profiles. Treatment-level variables, including therapeutic strategy and imaging results before and after the treatment, were analyzed.

All patients underwent CTA for preoperative and postoperative examination. Imaging data were stored in the DICOM (Digital Imaging and Communications in Medicine) format and were transferred to a TeraRecon Vascular workstation (version 4.4.6, Aquarius iNtuition Edition; TeraRecon Inc., Foster City, CA USA), and 3-dimensional images were reconstructed. The stages of the dissection were divided into acute (14 days from the first dissection), sub-acute (2 weeks–2 months) and chronic dissection (>2 months).[9] The length and diameter were measured based on the centerline of flow. Aortic diameter including both diameters of the true and false lumina were measured before treatment. The length of the covered stent refers to the length covered by the stent from the left subclavian artery (LSA). The length of the dissection refers to the extent of preoperative aortic dissection. The number of tears was recorded. The location of the residual tear was measured from the LSA.

All measurements were performed by two experienced researchers from the same vascular center and were cross-checked by the corresponding author.

Surgical technique

In this retrospective study, a standard TEVAR was performed.[10,11] In addition, fenestration of the intimal flap and chimney grafts were used when needed. For a more challenging aortic dissection involving the aortic arch, a hybrid technique that combines the intervention procedure and open surgery was chosen.

Follow-up

All patients were treated with antihypertensive agents, and their systolic blood pressure (SBP) was controlled to $\leq$120 mmHg. Patients were scheduled for outpatient clinical assessment on the 3rd, 6th, and 12th postoperative month and then annually thereafter; symptoms, physical signs, and the results of a CTA were evaluated at each assessment. The distal aortic diameter was recorded with each follow-up CTA result. Early postoperative CTA findings were obtained from CTA scans within 3 months after the procedure.

Statistical analysis

Summary statistics of the DSAE group and the non-DSAE group were presented as frequencies and percentages for categorical variables or as means $\pm$ standard deviation (SD) for normal distribution variables.

The Box-Cox power-normal family of scaled power transformations (with negatives allowed) was applied to the non-normalized covariant to adjust the distribution (Table 1). The transformation function can be expressed as following:

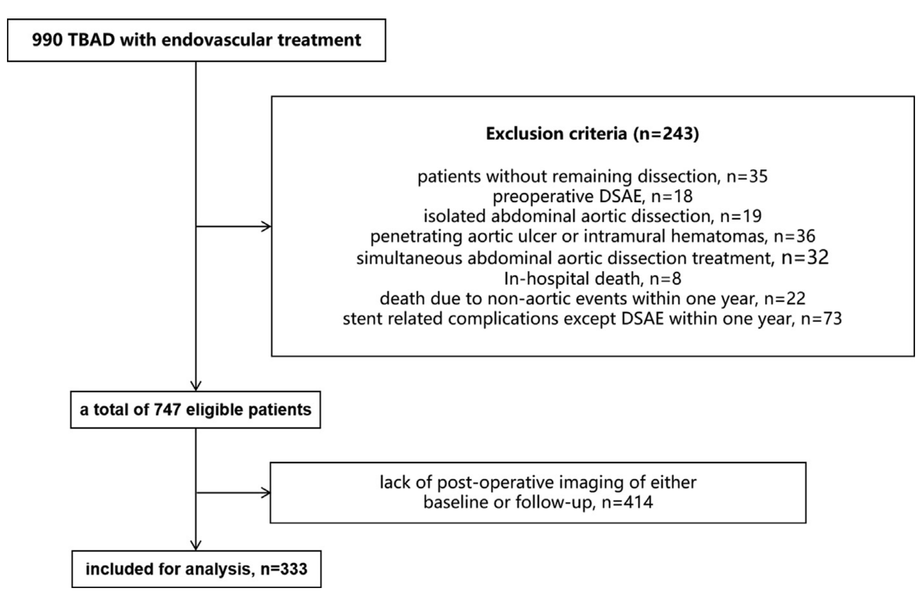

Fig. 1. Study population.

Table 1
Information of non-distributed variables with Box-Cox transformation.

	Original data		Transformed data		Transform parameter	
	$\bar{x} \pm s$	*M [Q1,Q3]*	$\bar{x} \pm s$	*M [Q1,Q3]*	λ	γ
length of covered stent	154.45 ± 35.13	153.00 [133.00,190.00]	191.72 ± 46.04	189.53 [163.38,238.38]	1.054	0.100
length of non-thrombus	264.54 ± 98.18	245.00 [208.00,330.00]	20.98 ± 3.31	20.61 [19.25,23.38]	0.402	96.684
length of complete thrombus	102.40 ± 71.86	88.00 [50.00,137.00]	8.92 + 2.06	8.94 [7.53,10.28]	0.247	15.339
length of partial thrombus	110.78 ± 53.09	102.00 [87.00,153.00]	46.70 + 18.75	44.38 [39.41,61.62]	0.774	0.100
distance from the first tear to LSA	281.29 ± 63.02	269.00 [238.00,315.70]	6.13 ± 0.25	6.11 [5.97,6.29]	0.029	79.710
diastolic pressure	81.50 + 12.80	80.00 [73.00, 90.00]	13.76 + 0.90	13.69 [13.19,14.38]	0.573	12.726
systolic pressure	134.89 + 16.76	135.00 [120.00,145.00]	3.49 + 0.06	3.49 [3.44,3.53]	−0.163	0.100

LSA, left subclavian artery.

$$f(z) = \begin{cases} \log(z) & (\lambda = 0) \\ (z^{\lambda} - 1)/\lambda & (\lambda \neq 0) \end{cases}$$

$$z = 0.5 \times \left(U + \sqrt{U^2 + \gamma^2} \right)$$

where U represents the original data; γ is the transform parameter to ensure that z is always positive; λ is the transform parameter to adjust the shape of distribution. Both transform parameters were optimized for each variable in the companion to applied regression ("car") package (vision 3.0–3). Comparisons of continuous variables after transformation between the two groups were conducted by independent *t*-tests and the differences of categorical variables between the groups were compared by χ^2 test. A Wilcoxon rank-sum test was also used for ordinal data.

The variables which showed statistical significance were taken into multivariate logistic regression models. Multivariate logistic regression models were performed to identify independent risk factors for the occurrence of DSAE. The stepwise method was applied to select suitable variables for each multivariate model. The level of significance for most of the tests was set as α = 0.05 for 2 sides. The level of Significance was set as α = 0.10 when a normality test was applied. All analyses were performed with R software (vision 3.5.1; The R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org).

Results

Follow up information

From 1999 to 2016, a total of 990 patients with first-episode complicated TBAD were treated with TEVAR in our center. Among them, 243 patients were excluded for the following reasons: 35 without residual dissection, 18 with preoperative DSAE, 19 with isolated abdominal aortic dissection, 36 with penetrating aortic ulcer and intramural hematomas, 32 with simultaneous abdominal aortic dissection treatment, 8 in-hospital deaths and 22 deaths due to non-aortic events within one year, 73 with stent-related complications that required reintervention within one year (type I endoleak, new entry, or aortic complications other than DSAE). An additional 414 patients were excluded because of the lack of imaging either at postoperative baseline (within three months) or at follow-up (of more than one year), resulting in the inclusion of total 333 cases in this retrospective study. Of these 333 patients, 281 (84.38%) were males and 52 (15.62%) were females. The mean (±SD) age was 54.42 (±12.59) years (range: 25–86 years). A total of 311 (93.39%) patients received TEVAR, and hybrid techniques were applied to the remaining 22 (6.61%) patients. During the mean follow-up period of 48.07 ± 32.20 months, all-cause mortality was 38 (11.41%), and 76 (22.82%) patients required reintervention. DSAE occurred in 70 (21.02%) patients with an average postoperative time to occurrence of 51.18 (±15.05) months. (Fig. 1). Among the DSAE patients, 2 patients died of aortic rupture and 58 patients accepted reintervention.

Clinical features

The cardiovascular risk factors for the patients and their clinical presentation are presented in Table 2. Patients who developed DSAE during the follow-up period were more likely to have lower systolic blood pressure (p = 0.043) and diastolic blood pressure (p = 0.022) after their onset, have a comorbidity of Marfan syndrome (p = 0.024) and have a history of surgery (p = 0.009).

Preoperative aortic condition and anatomies

The details of the preoperative aortic condition and anatomies are summarized in Table 3. In patients with DSAE, the maximum diameter of the dissected aorta was much larger than that of the non-DSAE patients (p = 0.002), and the length of the dissected aorta was also significantly longer (p = 0.001). Moreover, different arch types showed a significant difference between the two groups (p = 0.023). The phase of the dissection and aortic distortion did not have a significant relationship with an increased occurrence of DSAE.

Characteristics of the TEVAR procedure

A summary of the technical features of all procedures is shown in Table 4. The mean length of the covered stent in the descending thoracic aorta was 172.60 ± 45.29 mm in the DSAE group and

Table 2
Demographic information.

	Non-DSAE (n = 263)	DSAE (n = 70)	*P*
Age (year)	54.89 ± 12.65	52.69 ± 12.31	P = 0.189
Gender (female)	43 (16.35)	9 (12.86)	P = 0.474
Hypertension[a]	250 (95.06)	67 (95.71)	P = 1.000
Systolic blood pressure (mmHg)	135.70 ± 16.20	130.76 ± 18.36	P = 0.043
Diastolic blood pressure (mmHg)	82.47 ± 12.88	78.21 ± 13.72	P = 0.022
Cerebral infarction[a]	1 (0.38)	1 (1.43)	P = 0.890
Diabetes[a]	14 (5.32)	6 (8.57)	P = 0.463
Chronic renal insufficient[a]	11 (4.18)	4 (5.71)	P = 0.822
Marfan syndrome[a]	2 (0.76)	4 (5.71)	P = 0.024*
Autoimmune disease[a]	3 (1.14)	1 (1.43)	P = 1.000
Atherosclerosis[a]	14 (5.32)	3 (4.29)	P = 0.964
Interventional surgery[a]	1 (0.38)	2 (2.86)	P = 0.210
History of surgery[a]	8 (3.04)	8 (11.43)	P = 0.009*

DSAE, distal segment aortic enlargement.
Data are presented as mean ± standard deviation or as number (%).
*P < 0.05 indicates significant difference between patients with and without DSAE occurrence.
[a] Pearson's Chi-squared test with Yates' continuity correction were applied when theoretical frequency was between 1 and 5.

Table 3
Preoperative aortic condition and anatomies.

	Non-DSAE (n = 263)	DSAE (n = 70)	P
Maximal diameter of dissected aorta (mm)	39.39 ± 6.06	43.43 ± 9.92	P = 0.002*
Length of dissection (mm)	461.20 ± 67.10	484.57 ± 50.57	P = 0.001*
Phase of dissection			
acute	127 (48.29)	33 (47.14)	P = 0.399
sub-acute	49 (18.63)	9 (12.86)	
chronic	87 (33.08)	28 (40.0)	
Aortic arch type			
type I	78 (29.66)	10 (14.29)	P = 0.023*
type II	82 (31.18)	18 (25.71)	
type III	103 (39.16)	42 (60.0)	
Aorta distortion	99 (37.64)	31 (44.29)	P = 0.465

DSAE, distal segment aortic enlargement.
Data are presented as mean ± standard deviation or as number (%).
*P < 0.05 indicates significant difference between patients with and without DSAE occurrence.

196.81 ± 44.97 mm in the non-DSAE group, with a significant difference between the two groups (p < 0.001). To reduce the distal oversizing, a restrictive bare stent (RBS) was used in 130 patients, 15 (21.43%) cases in the DSAE group and 115 (43.73%) cases in the non-DSAE group and was more likely to reduce the occurrence of DSAE (p = 0.001).

Early follow-up results and CTA findings

During the follow-up period, the incidence of DSAE in patients with current smoking was significantly higher than that in patients who did not develop DSAE (p = 0.013). Patients who developed DSAE had a longer length of patent false lumen (p < 0.001) and a shorter length of complete thrombosis (p < 0.001). Moreover, the distance from the first residual tear to the LSA was significantly shorter (p = 0.014) for DSAE patients. DSAE patients were likely to have more residual tears in the thoracic descending aorta (p = 0.007) and fewer tears in the infrarenal abdominal aorta (p < 0.001) (Table 5).

Multi-factor logistic regression analysis

According to the multivariate analysis, patients who developed DSAE during the follow-up period were more likely to have a type III aortic arch (odds ratio [OR]: 4.63; 95% confidence interval [CI]: 1.97–11.77; p = 0.001), a longer length of patent false lumen (OR: 1.37; 95% CI: 1.22–1.55; p < 0.001), currently smoke (OR: 3.70; 95% CI: 1.40–9.70; p = 0.008), and have a greater number of residual tears in the thoracic descending aorta (OR: 1.43; 95% CI: 1.01–2.00; p = 0.040). On the contrary, the use of a RBS (OR: 0.16; 95% CI: 0.06–0.45; p < 0.001), the length of the covered stent (OR: 0.99; 95% CI: 0.98–0.99; p < 0.001), and the distance from the first residual tear to the LSA (OR: 0.16; 95% CI: 0.04–0.69; p = 0.014) appeared to reduce the occurrence of DSAE significantly. (Table 6).

Table 4
Procedure related factors.

	Non-DSAE (n = 263)	DSAE (n = 70)	P
Length of covered stent (transformed)	196.81 ± 44.97	172.60 ± 45.29	P < 0.001*
RBS	115 (43.73)	15 (21.43)	P = 0.001*
aortic stent			
Straight stent-grafts	176 (66.92)	46 (65.71)	P = 0.923
Tapered stent-grafts	87 (33.08)	24 (34.29)	

DSAE, distal segment aortic enlargement; RBS, restrictive bare stent.
Data are presented as mean ± standard deviation or as number (%).
*P < 0.05 indicates significant difference between patients with and without DSAE occurrence.

Table 5
Early follow-up results and CT findings.

	Non-DSAE (n = 263)	DSAE (n = 70)	P
Current Smoking	22 (8.37)	13 (18.57)	P = 0.013*
Alcohol	12 (4.56)	5 (7.14)	P = 0.571
Length of non-thrombus (transformed)	20.54 ± 3.16	22.64 ± 3.34	P < 0.001*
Length of complete thrombus (transformed)	8.48 ± 2.08	6.75 ± 2.08	P < 0.001*
Length of partial thrombus (transformed)	46.80 ± 18.65	47.19 ± 20.04	P = 0.927
Distance from the first tear to LSA (transformed)	6.15 ± 0.26	6.07 ± 0.22	P = 0.014*
Number of visceral branches arising from the false lumen			
0	21 (7.98)	3 (4.29)	P = 0.074
1	82 (31.18)	37 (52.86)	
2	136 (51.71)	23 (32.86)	
≥3	24 (9.13)	7 (10.0)	
Number of tears in the thoracic descending aorta			
0	160 (60.84)	29 (41.43)	P = 0.007*
1	54 (20.53)	23 (32.86)	
2	37 (14.07)	13 (18.57)	
≥3	12 (4.56)	5 (7.14)	
Number of tears in the branched area of abdominal aorta			
0	61 (23.19)	15 (21.43)	P = 0.754
1	143 (54.37)	41 (58.57)	
2	24 (9.13)	11 (15.71)	
≥3	35 (13.31)	3 (4.29)	
Number of tears in the infrarenal abdominal aorta			
0	8 (3.04)	17 (24.29)	P < 0.001*
1	60 (22.81)	21 (30.0)	
2	64 (24.33)	17 (24.29)	
≥3	131 (49.81)	15 (21.43)	
Number of tears in the iliac artery			
0	57 (21.67)	7 (10.0)	P = 0.205
1	103 (39.16)	50 (71.43)	
2	93 (35.36)	12 (17.14)	
≥3	10 (3.80)	1 (1.43)	
Endoleak[a]	5 (1.90)	5 (7.14)	P = 0.060

DSAE, distal segment aortic enlargement; LSA, left subclavian artery.
*P < 0.05 indicates significant difference between patients with and without DSAE occurrence.
[a] Pearson's Chi-squared test with Yates' continuity correction were applied when theoretical frequency was between 1 and 5.

Discussion

The strategy of merely treating the proximal entry tear for acute complicated TBAD is not enough for a significant amount of patients. A stepwise approach and adjunctive endovascular techniques are essential for those patients. In our center, an additional aortic covered stent is needed when the residual tear located 20 mm proximal to the supraceliac abdominal aorta is expected to be the re-entry point. To avoid paraplegia, simultaneous interventional treatment for the branched area of the

Table 6
Independent influential factors for DSAE.

	OR	*95%CI*	*P*
RBS	0.26	(0.12, 0.52)	<0.001
Aortic arch type (ref = type I)			
type II	1.32	(0.48, 3.77)	0.595
type III	4.63	(1.97,11.77)	0.001
Length of non-thrombus	1.37	(1.22, 1.55)	<0.001
Current Smoking	3.70	(1.40, 9.70)	0.008
Number of tears in the thoracic descending aorta	1.43	(1.01, 2.00)	0.040
Length of covered stent	0.99	(0.98, 0.99)	<0.001
Distance from the first tear to LSA	0.16	(0.04, 0.69)	0.014

DSAE, distal segment aortic enlargement; OR, odds ratio; CI, Confidence interval; LSA, left subclavian artery; RBS, restrictive bare stent.
**P* < 0.05 indicates significant difference between patients with and without DSAE occurrence.

abdominal aorta is avoided most of the time. Further treatment is needed when DSAE or visceral ischemia occurs during the follow-up period.

In this study, among patients with complicated TBAD, DSAE occurred in 70 patients (21.02%) after the TEVAR treatment, with an average onset 51.18 (±15.05) months after the procedure. According to the follow-up results, current smoking, the residual length of the patent false lumen, the postoperative number of dissection tears in thoracic aorta, a type III aortic arch, RBS usage, the length of the covered stent in the descending thoracic aorta, and the distance from the residual first tear to the LSA have impacts on the prognosis.

Studies have reported that people who smoke are at a higher risk for aortic dissection.[12,13] In the current study, we found that the occurrence of DSAE had an apparent increase in currently smoking patients versus non-smoking patients (OR: 3.70; 95% CI: 1.40–9.70; $p = 0.008$). Researchers have suggested that smoking can enhance oxidation and inflammation, which can accelerate the process of atherosclerosis.[14] Moreover, smoking can mediate the elastin degradation in the vascular wall by enhancing the proteolytic systems.[13,15] These findings suggest that smoking may have an impact on the distal aortic reconstruction after TEVAR. However, the effect of the smoking habit on the distal aortic remodeling after TEVAR requires further study.

Some studies have reported that advanced age and atherosclerotic degenerative processes would prolong the aortic arch, thus the ostia of the aortic arch branches were changed accordingly, turning to a type III aortic arch.[16,17] In this study, a type III arch was found to be an independent risk factor of DSAE. Coady et al.[18] reported that the pathological changes of a penetrating ulcer and an intramural hematoma were higher in patients with severe aortic degeneration when compared to healthy people, which raised the occurrence of aortic dissection. In addition, many researchers suggest that the aortic arch type is an important factor associated with late complications after TEVAR.[19,20] Even in the same lesion segment, the angulation of the proximal aortic neck is different. When the angle is sharp, the stent is difficult to attach to the artery wall, and the stent often cannot be completely open at the corner of the aortic arch, which may lead to collapse of the stent and be associated with a type III endoleak. We propose that the aortic arch type is potentially related to the prognosis after TEVAR; however, research on the correlation of aortic arch type and dissection prognosis is so far insufficient.

Consistent with previous research,[2] the current study identified that the maximal diameter of the dissected aorta was an independent risk factor for late residual downstream aortic expansion. A similar report was supported by Marui and colleagues.[5] In their research, the authors noted that the maximal diameter of the descending aorta was a significant predictor for late aortic events, and the hazard ratio for a maximum aortic diameter of 40 mm or more was 3.18 times higher than that for a maximum aortic diameter of less than 40 mm (95% CI: 2.12–5.05).

In this study, we found that the length of patent false lumen, the number of residual tears in the thoracic descending aorta, the distance from the first tear to the LSA, and the length of the covered stent were independent influencing factors of DSAE. Theoretically, the pressure at the distal aortic segment is lower than that at the proximal aortic segment. From these results, we might suggest that the closer the main entry tear is, the higher the relative risk is. Meanwhile, Conrad et al.[21] reported that the longer stent graft coverage was beneficial to thrombosis of the false lumen. Moreover, researchers[22–24] proposed that the longer stent graft coverage mainly affected the descending thoracic aortic remodeling and increased the coverage of the minor entry tears, which is consistent with our conclusion. It has been suggested that the length of the covered stent graft promotes the formation of thrombosis adjacent to the stent graft, which can reduce the number of tears in thoracic descending aorta and increase the distance from the first residual tear to the LSA, thus reducing the pressure in the false lumen and reducing the risk of DSAE.

The strong radial force helps to strengthen the stent fixation, and entails a higher risk of injury to the aortic wall. The selection of thoracic aorta stent is usually based on the proximal landing zone, and the distal end of the graft will oversize the true lumen of the descending aorta by more than 60%,[25] which could cause a stent graft-induced new entry and, ultimately, aneurysmal expansion.[26] In this study, tapered stent grafts and RBS were used to reduce the distal oversizing. Although no significant differences were found between the use of the tapered stent graft and the straight stent graft, multivariate analysis showed that the use of RBS can significantly reduce the incidence of DSAE. The result suggested that the use of RBS could better reduce the stent graft oversizing in the distal landing zone. However, commercially available tapered stent grafts have limited taper ratios.

This study is a single-center retrospective analysis, and is limited in the number of patients, the comprehensiveness of the data, and the time span of the follow-up. Further investigations are still needed.

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Declaration of competing interest

None.

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