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Unpredictable Aortic Behavior in Identifying Risk Factors for Reintervention: A Prospective Cohort Study

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Abstract

Background Although advancements in the management of thoracic aortic disease have led to a reduction in acute mortality, individuals requiring postoperative reintervention experience substantially worse long-term clinical outcomes and increased mortality. We aimed to identify the risk factors for postoperative reintervention in this high-risk population.

Patients and Methods This prospective observational cohort study included patients who survived endovascular or open surgical treatment for thoracic aortic disease between January 2009 and June 2020. We excluded those with inflammatory or traumatic thoracic aortic diseases. The risk factors were identified using multivariate logistic regression and Cox proportional hazards regression models.

Results The study included 95 genetically tested patients aged 54.13 ± 12.13 years, comprising 67 men (70.53%) and 28 women (29.47%). Primary open surgery was performed in 74.7% and endovascular repair in 25.3% of the patients. Of these, 35.8% required one or more reinterventions at the time of follow-up (3 ± 2.5 years, mean $\pm$ standard deviation). The reintervention rate was higher in the endovascular repair group than in the open repair group. Among the potential risk factors, only residual aortic dissection emerged as an independent predictor of reintervention (odds ratio: 3.29, 95% confidence interval: 1.25–8.64).

Conclusion Reintervention after primary thoracic aortic repair remains a significant clinical issue, even in high-volume tertiary centers. Close follow-up and personalized care at aortic centers are imperative. In our cohort of patients with thoracic aortic

Keywords
- thoracic aorta
- endovascular repair
- reintervention
- aortic dissection

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disease undergoing open or endovascular surgery, postoperative residual dissection was independently associated with the necessity of reintervention, emphasizing the importance of intensified clinical monitoring in these patients.

Introduction

Reintervention after thoracic open or endovascular aortic repair poses a considerable challenge compared with the primary intervention. The etiology of aortic reinterventions is multifactorial, with varying long-term treatment success rates. Currently, the specific independent predictors of aortic reinterventions remain unknown. Reintervention aims to achieve favorable aortic remodeling, prompt false lumen thrombosis, and decrease perioperative mortality.[1]

Dr. Crawford, one of the pioneers of aortic surgery, emphasized, "No patients should be considered cured of the disease." Patients with persistent distal aortic pathology and even those with an anatomically normal, nondissected aorta after the initial emergency surgery still have an increased risk of subsequent aortic events due to abnormal structural and functional properties of the aorta.[2]

Therefore, close follow-up of all patients undergoing aortic procedures in an expert tertiary center with multidisciplinary management (aortic board) and case-by-case discussions are essential.[3] Risk factors play a pivotal role in informed decision-making, tailored management to individual patients, optimized perioperative care, and customized surveillance to mitigate the risk of complications.[4]

Recent advances in DNA sequencing technology have identified several genes for hereditary thoracic aortic aneurysms (TAAs) and dissections.[5,6] Syndromic thoracic aortic aneurysm dissections (TAADs) are typically caused by pathogenic variants in the transforming growth factor beta signal and extracellular matrix-related genes (e.g., *FBN1*, *TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, and *COL3A1*). The nonsyndromic hereditary TAADs result from altered components of the contractile apparatus of vascular smooth muscle cells, which are encoded by *ACTA2*, *MYH11*, *MYLK*, and *PRKG1* genes (►**Fig. 1**). With the progress in next-generation sequencing (NGS), targeted NGS of disease-specific genes can be reliably implemented as a diagnostic test with high accuracy and cost-effectiveness.[6]

Nowadays, clinical genetic testing has become an integral part of the clinical evaluation for patients with thoracic aortic disease. However, the role of the predisposing genetic variations as an independent risk factor for reintervention is debatable.[7]

Previous studies have predominantly focused on reinterventions in a homogenous cohort; specific procedures such as thoracic endovascular aortic repair (TEVAR) or open repair; specific pathologies such as aortic dissection or aortic aneurysm; and localized anatomical pathologies either ascending, descending thoracic, or abdominal aorta. Moreover, most of these studies are retrospective.

We aimed to identify the independent predictors of aortic reinterventions after thoracic open or endovascular aortic repair in a prospective study (►**Fig. 1**).

Patients and Methods

This prospective study included all surviving patients with thoracic aortic pathology who received open surgery or endovascular procedures and provided written informed consent according to the revised Declaration of Helsinki[8] between January 2009 and June 2020. This study was approved by the ethics committee for clinical research of the hospital (13.08.2014, EK317082014).

Thoracic aortic pathologies included aortic dissection of thoracic origin, TAA, intramural hematoma, and penetrating aortic ulcer. All procedures in the thoracic aorta were included in the study. Patients without postoperative computed tomography scan follow-up at our center and those with traumatic, iatrogenic, or inflammatory thoracic aortic pathology were excluded.

The study enrolled patients aged 18 to 80 years, who provided consent to undergo human genetic testing to clarify the pathogenesis of the underlying aortic disease.

During the defined time, 1,334 patients with an International Classification of Diseases–coded primary diagnosis of thoracic aortic disease underwent surgical or endovascular treatment (TEVAR). Overall, 716 patients met the inclusion criteria of the present study. After contacting all surviving patients by telephone, 118 patients consented to participate in human genetic examinations. At the end of data collection, the findings of the human genetic examination and complete follow-up data of 95 patients were available (►**Fig. 2**). Data on demographic characteristics and pre- and intraoperative

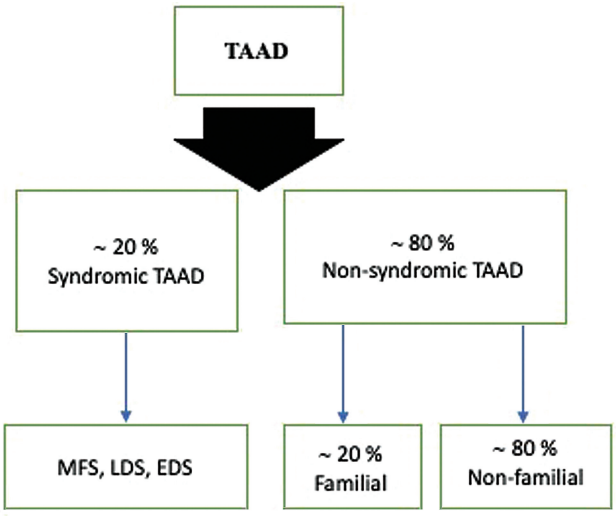

Fig. 1 Classification of thoracic aortic aneurysm and dissection (TAAD). EDS, Ehlers–Danlos' syndrome; LOS, Loeys–Dietz's syndrome; MFS, Marfan's syndrome; TAAD, thoracic aortic aneurysm dissection.[5]

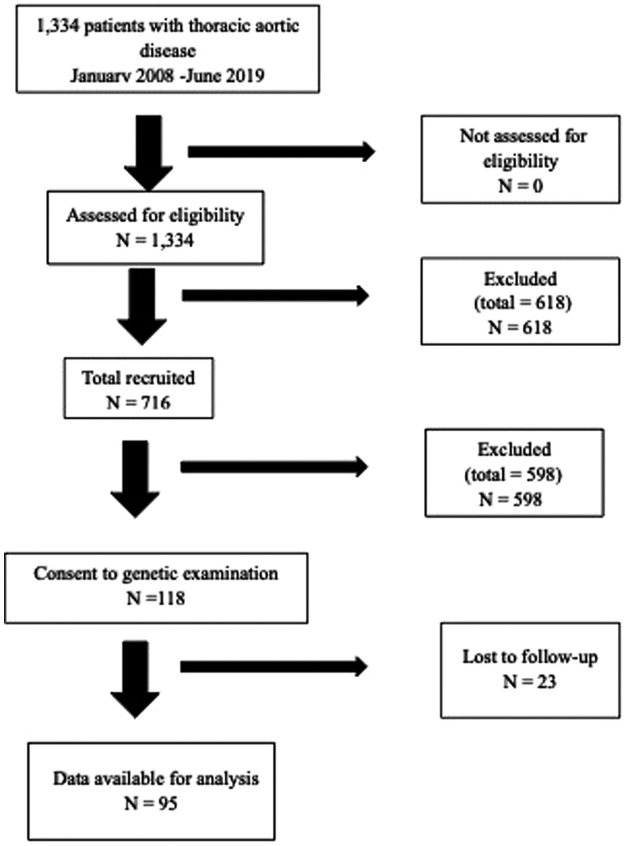

Fig. 2 Flow chart for patients included in the study.

variables were also collected. All patients who underwent reintervention were identified. Patients were grouped into those with and without reintervention.

Structured Follow-up after Surgically or Endovascular-Treated Aortic Pathology

Computed tomography angiography (CTA) scans were performed in all patients preoperatively, before discharge, on the third and ninth months after the primary intervention, and then at annual intervals or unscheduled when clinically warranted. A weekly interdisciplinary aortic board meeting was held, involving specialties such as cardiac surgery, vascular surgery, interventional radiology, angiology, and cardiology. CTA was the preferred radiological examination in the absence of contraindications, such as severely impaired renal function, hyperthyroidism, or iodine allergy. In patients with a stable course of aortic disease without findings requiring prompt intervention, magnetic resonance angiography was performed annually, alternating with transesophageal echocardiography in combination with sonography of the abdominal aorta.

All clinical information and imaging procedures were presented and reviewed at an interdisciplinary vascular conference. Aortic remodeling was assessed after each CTA, and the findings were compared with those of previous studies.

The following key aspects were primarily evaluated: the outcomes of the primary aortic procedure, the presence of persistent aortic pathology in the native untreated aorta, further aortic dynamics associated with persistent or de novo aortic dissection or secondary aortic expansion/development of an aortic aneurysm, and any complications related to the prosthetic graft or implanted stent.

The following potential risk factors for reintervention were considered as covariates in the multivariate logistic regression model. The nonmodifiable risk factors were age, sex, genetic predisposition, and aortic disease progression. The modifiable risk factors were smoking, arterial hypertension, diabetes mellitus (DM), and type of intervention.[1–4]

Human Genetic Analysis to Clarify the Pathogenesis of Aortic Disease

After extraction of the DNA from the collected blood sample, an NGS procedure was applied. First, capture-based enrichment was performed, followed by MiSeq Desktop Sequencer analysis (Illumina Company) (►**Table 1**).

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies.[9]

Statistical Analysis

Data from 95 patients were analyzed. The normality of continuous data was assessed using the Shapiro–Wilk's test. If the data followed a normal distribution, two-sample *t*-tests were used to compare the means between the groups. Otherwise, the Mann–Whitney's *U* test was used to compare the study groups. The normally distributed data were expressed as the means ± standard deviations, while the nonnormally distributed data were expressed as the medians (interquartile ranges). Chi-square and Fisher's exact tests were used to investigate the relationships between categorical characteristics in the nonreintervention and reintervention groups. Multivariate logistic regression was employed for reintervention analysis. Time-to-event analysis was performed using Cox proportional hazard models to obtain the hazard ratios (HRs) and the Kaplan–Meier's method (►**Fig. 3**). For survival time, the odds ratios (ORs), HRs, and 95% confidence intervals (CIs) were reported. A p-value of <0.05 was considered significant. Statistical analyses were performed using STATA BE (version 17.0, Stata Corp, College Station, Texas, United States) (►**Fig. 3**).

Results

A total of 95 patients who underwent endovascular or open surgical repair for thoracic aortic disease and fulfilled the inclusion criteria of the current study were included (67 men [70.53%] and 28 women [29.47%]). No significant difference was observed in age between sexes at the time of initial diagnosis (men, 51.3 ± 12.2 vs. women, 52.4 ± 12.4; $p = 0.696$).

Patients treated with primary TEVAR were significantly older than those treated with open surgical repair (mean age: 59.4 ± 12.0 vs. 48.0 ± 10.5 years, $p < 0.001$). ►**Table 2** shows the preexisting cardiovascular risk factors in the study cohort.

Table 1 Investigated gene loci associated with syndromic or nonsyndromic thoracic aortic diseases with aneurysm and/or dissection

	Protein	Associated aortic disease/syndrome
ACTA2 (NM_001613.2)	Smooth muscle α-ac-tin	TAAD, AAT6 multisystem smooth muscle dysfunction, MYMY5
AEBP1 (NM_001129.4)	AE binding protein 1	BAA, EDS
BGN (NM_01711.5)	Biglycan	TAAD, Meester-Loeys syndrome
COL1A1 (NM_000088.3)	Collagen type I α1 chain	TAAD, EDS
COL3A1 (NM_000090.3)	Collagen type III α1 chain	TAAD, EDS vascular type (IV)
COL4A5 (NM_000495.3)	Collagen type IV α5 chain	TAAD, Alport's syndrome (collagen type IV deficiency)
COL5A1 (NM_000093.4)	Collagen type V α1 chain	TAAD, EDS classical type I
COL5A2 (NM_000393.4)	Collagen type V α2 chain	TAAD, EDS classical type II
EFEMP2 (FBLN4) (NM_016938.4)	Fibulin-4	TAAD, other arterial aneurysms, cutis laxa (autosomal recessive) type Ib
ELN (NM_000501.3, NM_001278939.1)	Elastin	TAAD, cutis laxa (autosomal dominant)
FBLN5 (NM_006329.3)	Fibulin 5	TAAD, cutis laxa, macular degeneration
FBN1 (NM_000138.4)	Fibrillin-1	TAAD, AAA, other arterial aneurysms, Marfan's syndrome
FBN2 (NM_001999.3)	Fibrillin-2	TAAD, congenital contractural arachnodactyly
FLNA (NM_001110556.2)	Filamin A	TAAD, periventricular nodular heterotopia, otopalatodigital syndromes
FOXE3 (NM_012186.2)	Forkhead box E3	TAAD, AAT11
GATA5 (NM_080473.4)	GATA-binding protein 5	TAAD
LOX (NM_002317.6)	Lysyl oxidase	AAD, AAA, AAT10
MAT2A (NM_005911.5)	Methionine adenosyltransferase II α	TAA, FTAA
MFAP5 (NM_003480.3)	Microfibril-associated glycoprotein 2	TAAD, AAT9
MYH11 (NM_002474.2)	Smooth muscle myosin heavy chain	TAAD, AAT4
MYLK (NM_053025.3)	Myosin light chain kinase	TAAD, AAT7
NOTCH1 (NM_017617.4)	Notch receptor 1	TAAD, AOVD
NOTCH3 (NM_000435)	Notch receptor 3	TAAD
PLOD1 (NM_000302.3)	Procollagen-lysine, 2 oxoglutarate 5-dioxygenase 1	TAAD, EDS
PRKG1 (NM_006258.3)	Type I cGMP-dependent protein kinase	TAAD, AAA, AAT8
RLP26 (NM_000987.4)	Receptor-like protein 26	TAAD
SKI (NM_003036.3)	Sloan Kettering proto-oncoprotein	TAA, Shprintzen–Goldberg's syndrome
SLC2A10 (NM_030777.3)	Glucose transporter 10	TAA, other arterial aneurysms

Abbreviations: AAT (n), familial thoracic aortic aneurysms (1–11); AOVD, aortic valve disease; BAA, abdominal artery aneurysm; EDS, Ehlers–Danlos' syndrome; TAA, thoracic aortic aneurysm; TAAD, thoracic aortic aneurysm dissection.

Regarding preoperative medications, 95 and 83% of the patients used beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin II type 1–receptor antagonists, respectively. Antiplatelet therapy was prescribed in 42% and oral anticoagulation in 37% of the studied cohort (►**Table 3**).

Thoracic aortic dissection (TAD) and TAA were diagnosed in 57 and 41% of the study population, respectively. In 2% of the patients, both clinical pictures were recognized at the time of initial diagnosis. Covered aortic rupture, intramural hematoma, and penetrating aortic ulcer were diagnosed in 6.3, 8.4, and 2.1% of the patients, respectively. Of the total

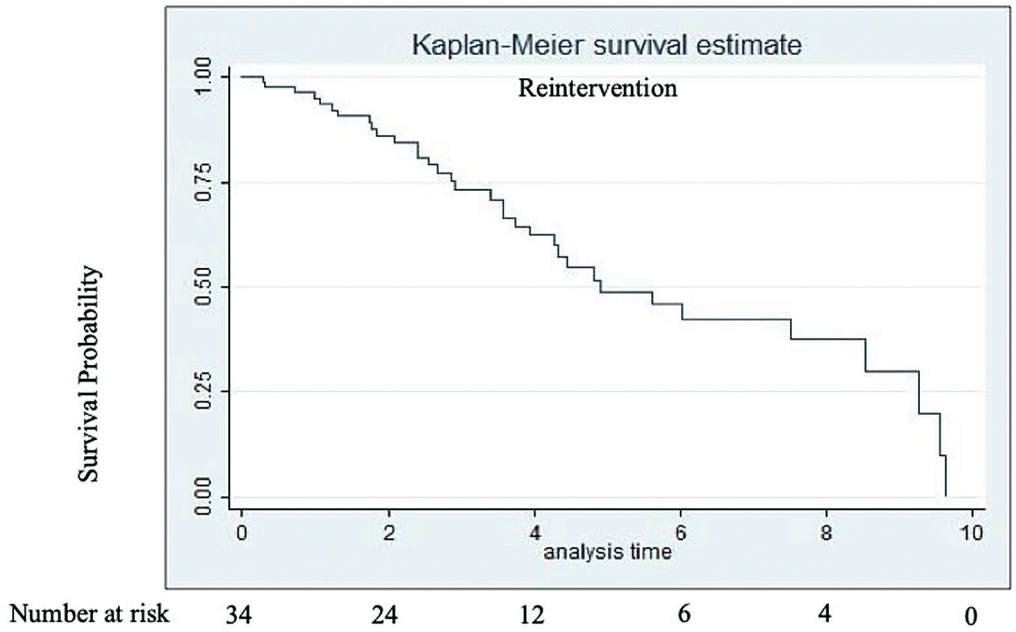

Fig. 3 Kaplan–Meier survival curve for reintervention (years). The median survival curve showed that 50% of the study cohort might undergo reintervention after 5 years (median survival time).

study patients, 45.3% had Stanford type A, while 23.2% had Stanford type B TAD. Surgery was the primary management of thoracic aortic pathologies in 74.7% of the patients. An endovascular interventional approach was adopted in 25.3% of the patients. The mean follow-up period was approximately 3 ± 2.5 years.

Follow-up surveillance revealed that complete repair of existing aortic pathology could be achieved by primary intervention in only 31% of patients, whereas 69% of patients had persistent aortic pathology, which was mainly residual aortic dissection in 60% of the cases, in addition to 9% having residual aortic ectasia or aortic aneurysm without indication for repair at the time of primary intervention. Secondary expansion of the aortic diameter or de novo development of aortic ectasia/aneurysm was observed in 24.2% of those treated. In cases of residual aortic dissection after primary intervention, 83.1% demonstrated a stable course during further follow-up, and 15% progression with expansion into primarily unaffected vessel segments could be detected by follow-up imaging.

A total of 35.8% of the patients required one or more reinterventions during the follow-up, with a maximum of four reinterventions. The number of required reinterventions increased with age (►**Table 4**).

Genetic mutations were confirmed in 40% ($n = 38$) of the study population, including both the classic and variant types (►**Table 5**).

►**Table 6** demonstrates that the age at genetic testing was significantly higher in the reintervention group than in the nonreintervention group ($p = 0.01$). The age at initial

Table 2 Comorbidities and cardiovascular risk factors of the study group

	N	Percentage of the study group
Cardiovascular risk factors		
Arterial hypertension	79	83%
Smoking	32	34%
Hypercholesterolemia	31	33%
Diabetes mellitus	8	8%
Comorbidities		
Ischemic heart disease	13	14%
Renal insufficiency	9	9%
Carotid stenosis/stroke	5	5%
Peripheral vascular disease	4	4%
COPD	2	2%

Abbreviation: COPD, chronic obstructive pulmonary disease.

Table 3 Preoperative medications

Medication	*N*	Percentage of the study group
Beta-blocker	90	95%
ACEI/AT_1-receptor antagonist	79	83%
Antiplatelet therapy	40	42%
Calcium channel blocker	39	41%
Oral anticoagulation	35	37%
Statins	31	33%
Other antihypertensive	20	21%

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AT_1, angiotensin II type 1.

Table 4 Reintervention during follow-up

No. of reintervention	No. of patients	Percentage of patients with reintervention	Mean age (y)	Follow-up until reintervention	SD
1	20	21.1%	49.2	0.8 y	± 1.1 y
2	10	10.5%	66.6	1.9 y	± 2.1 y
3	2	2.1%	72.6	2.1 y	± 1.1 y
4	2	2.1%	76.4	2.1 y	± 1.8 y

Abbreviation: SD, standard deviation.

Table 5 Mutation analysis results

Affected gene	Type of mutation	*n*	%
FBN1	Classic	3	7.5
	Variant	10	25
COL3A1	Classic	1	2.5
SMAD3	Variant	1	2.5
TGFB2	Classic	1	2.5
	Variant	3	7.5
TGFBR1	Variant	2	5.0
MYLK	Variant	2	5.0
MYH11	Variant	8	20
PRKG1	Variant	1	2.5
NOTCH1	Variant	3	7.5
NOTCH3	Classic	1	2.5
TGRBR2	Variant	1	2.5
ACTA2	Variant	2	5.0
SMAD6	Variant	1	2.5

diagnosis was significantly higher in the reintervention group than in the nonreintervention group ($p = 0.03$). The mean follow-up time was significantly longer in the reintervention group than in the nonreintervention group ($p = 0.02$).

The multivariate logistic regression analysis identified antiplatelet drugs as a significant risk factor for reintervention. The odds of reintervention were 8.6293 (95% CI: 1.9996–37.2399) times higher in patients who used antiplatelet drugs than in those who did not use them (►**Table 7**).

In the Cox proportional hazards model, only aortic dissection was a significant predictor for reintervention. The HR was 3.287465 (95% CI: 1.250428–8.642979) times higher in patients who had progressive aortic dissection than in those who did not have aortic dissection (►**Tables 8** and **9**).

Discussion

The most essential findings of this study can be summarized as follows. First, aortic reinterventions were notably

Table 6 Comparison of different variables between the nonreintervention and reintervention groups

Variables	Subcategory	Reintervention		*p*-Value
		No	Yes	
Age at genetic testing	Mean ± SD	52.43 ± 10.98	58.65 ± 14.21	0.01
Sex	Male	45 (73.77%)	22 (64.71%)	0.35
	Female	16 (26.23%)	12 (35.29%)	
Evidence of mutation	No	37 (60.66%)	20 (58.82%)	0.86
	Yes	24 (39.34%)	14 (41.18%)	
Associated syndrome	No	54 (88.52%)	31 (91.18%)	0.52
	Marfan's syndrome	1 (1.64%)	1 (2.94%)	
	Ehlers–Danlos' syndrome	1 (1.64%)	0 (0%)	
	Loeys–Dietz's syndrome	2 (3.28%)	0 (0%)	
	Others	3 (4.92%)	2 (5.88%)	
Arterial hypertension	No	11 (18.03%)	5 (14.71%)	0.68
	Yes	50 (81.97%)	29 (85.29%)	
Hypercholesterolemia	No	46 (75.41%)	18 (52.94%)	0.03
	Yes	15 (24.59%)	16 (47.06%)	
Diabetes mellitus	No	56 (91.8%)	31 (91.18%)	0.92
	Yes	5 (8.2%)	3 (8.82%)	
Smoking history	No	40 (66.67%)	22 (64.71%)	0.85
	Yes	20 (33.33%)	12 (35.29%)	
Beta-blocker	No	2 (3.28%)	3 (8.82%)	0.25
	Yes	59 (96.72%)	31 (91.18%)	
ACE-inhibitor/AT_1-receptor antagonist	No	9 (14.75%)	7 (20.59%)	0.47
	Yes	52 (85.25%)	27 (79.41%)	
Diuretics	No	38 (62.3%)	19 (55.88%)	0.54
	Yes	23 (37.7%)	15 (44.12%)	
Calcium channel blockers	No	40 (65.57%)	16 (47.06%)	0.08
	Yes	21 (34.43%)	18 (52.94%)	
Antiplatelet	No	44 (72.13%)	11 (32.35%)	< 0.001
	Yes	17 (27.87%)	23 (67.65%)	
Oral anticoagulation	No	37 (60.66%)	23 (67.65%)	0.5
	Yes	24 (39.34%)	11 (32.35%)	
Ischemic heart disease	No	53 (86.89%)	29 (85.29%)	0.83
	Yes	8 (13.11%)	5 (14.71%)	
Peripheral vascular disease	No	61 (100%)	30 (88.24%)	0.006
	Yes	0 (0%)	4 (11.76%)	
Carotid stenosis/stroke	No	57 (93.44%)	33 (97.06%)	0.45
	Yes	4 (6.56%)	1 (2.94%)	
COPD	No	61 (100%)	32 (94.12%)	0.06
	Yes	0 (0%)	2 (5.88%)	
Ischemic heart disease	No	53 (86.89%)	29 (85.29%)	0.83
	Yes	8 (13.11%)	5 (14.71%)	
Renal function (GFR < 60 mL/min)	No	55 (90.16%)	31 (91.18%)	0.87
	Yes	6 (9.84%)	3 (8.82%)	

(*Continued*)

Table 6 (*Continued*)

Variables	Subcategory	Reintervention		*p*-Value
		No	Yes	
Age at initial diagnosis	Mean ± SD	50.28 ± 10.81	55.24 ± 14.17	0.03
Aortic pathology diagnosis	Aortic aneurysm (TAA)	24 (39.34%)	15 (44.12%)	0.14
	Aortic dissection (TAD)	37 (60.66%)	17 (50%)	
	Both	0 (0%)	2 (5.88%)	
Aortic pathology (TAA—detailed)	No	48 (78.69%)	22 (64.71%)	0.27
	TAA and aortic dissection (no rupture)	11 (18.03%)	8 (23.53%)	
	TAA with covered Aortic rupture /Perforation	1 (1.64%)	1 (2.94%)	
	TAD with covered rupture	1 (1.64%)	2 (5.88%)	
	TAA and TAD with covered rupture	0 (0%)	1 (2.94%)	
Aortic pathology (TAD—detailed)	No	19 (31.15%)	11 (32.35%)	0.003
	Stanford type A aortic dissection	34 (55.74%)	9 (26.47%)	
	Stanford type B aortic dissection	8 (13.11%)	14 (41.18%)	
Aortic pathology (others)	No	55 (90.16%)	30 (88.24%)	0.13
	Intramural hematoma	6 (9.84%)	2 (5.88%)	
	Penetrating aortic ulcer	0 (0%)	2 (5.88%)	
Localization of aortic pathology/aneurysm (TAA)	No	28 (45.9%)	10 (29.41%)	<0.001
	Ascending aorta	25 (40.98%)	6 (17.65%)	
	Aortic arch	2 (3.28%)	0 (0%)	
	Descending thoracic aorta	5 (8.2%)	9 (26.47%)	
	Complete thoracic aorta	0 (0%)	7 (20.59%)	
	Sinus of Valsalva aneurysm	1 (1.64%)	0 (0%)	
	Ascending and descending aorta	0 (0%)	2 (5.88%)	
Type of intervention	Operative	54 (88.52%)	17 (50%)	<0.001
	Endovascular	7 (11.48%)	17 (50%)	
Type of intervention (detailed)	Replacement of ascending aorta and supracoronary (without aortic valve valve)	15 (24.59%)	6 (17.65%)	0.005
	Bentall and David (with aortic valve)/valved conduit	25 (40.98%)	5 (14.71%)	
	Plus replacement of a part of the aortic arch	6 (9.84%)	1 (2.94%)	
	Plus complete replacement of the aortic arch	0 (0%)	1 (2.94%)	
	Aortic arch replacement	3 (4.92%)	0 (0%)	
	Frozen elephant trunk procedure	4 (6.56%)	2 (5.88%)	
	TEVAR (without overstenting the left subclavian artery)	3 (4.92%)	7 (20.59%)	
	TEVAR (with complete overstenting of the left subclavian artery)	3 (4.92%)	5 (14.71%)	

Table 6 (*Continued*)

Variables	Subcategory	Reintervention		*p*-Value
		No	Yes	
	Performing carotidosubclavian bypass	1 (1.64%)	3 (8.82%)	
	TEVAR (with partial overstenting of the left subclavian artery)	0 (0%)	2 (5.88%)	
	Valved conduit and prothesis elongation	1 (1.64%)	0 (0%)	
	Elephant trunk procedure und TEVAR	0 (0%)	1 (2.94%)	
Persistent aortic pathology	No	22 (36.07%)	7 (20.59%)	0.12
	Yes	39 (63.93%)	27 (79.41%)	
Art of persistent aortic pathology	No	22 (36.07%)	7 (20.59%)	0.01
	Ectasia/aneurysm	2 (3.28%)	7 (20.59%)	
	Residual aortic dissection	37 (60.66%)	20 (58.82%)	
Progression of aortic aneurysm	No	54 (88.52%)	16 (47.06%)	<0.001
	Yes	5 (8.2%)	18 (52.94%)	
	NA	2 (3.28%)	0 (0%)	
Progression of aortic dissection	No	58 (95.08%)	21 (61.76%)	<0.001
	Yes	1 (1.64%)	13 (38.24%)	
	NA	2 (3.28%)	0 (0%)	
Mean follow-up time	Median (IQR)	1.72 (1.14, 2.63)	3.16 (2.35, 4.29)	0.02

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AT_1, angiotensin II type 1; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NA, not available; SD, standard deviation; TAA, thoracic aortic aneurysm; TAD, thoracic aortic dissection; TEVAR, thoracic endovascular aortic repair.

prevalent even at tertiary, high-volume centers, with an incidence of 35.8%. Second, after adjusting for covariates using a Cox regression model, residual aortic dissection emerged as the sole predictor of reintervention (HR: 3.28; 95% CI: 1.25–8.64; $p = 0.016$). Third, the multivariate logistic regression revealed antiplatelets as a significant risk factor of reintervention (OR: 8.6293; 95% CI: 1.99–37.23; $p = 0.004$). However, this result was in contrast with that of the Cox proportional hazards regression analysis, in which neither antiplatelets nor oral anticoagulation was an independent risk factor for reintervention (HR: 3.0, 95% CI: 0.94–9.5; $p = 0.06$ and HR: 1.17, 95% CI, 0.40–3.43; $p = 0.76$,

Table 7 Multivariate logistic regression analysis with reintervention as the dependent variable

Variables	OR	SE	*z*	$p > \|z\|$	95% lower CI	95% upper CI
Age at initial diagnosis	1.024151	0.0249911	0.98	0.328	0.9763224	1.074323
Sex	1.901746	1.108817	1.1	0.27	0.6065372	5.962761
Evidence of genetic mutation	1.793171	0.9584445	1.09	0.275	0.629009	5.111947
Arterial hypertension	0.7891829	0.5883407	−0.32	0.751	0.1830634	3.402152
Hypercholesterolemia	1.421847	0.8276822	0.6	0.545	0.454311	4.449921
Diabetes mellitus	0.5437789	0.5282385	−0.63	0.531	0.0810115	3.650042
Nicotine use	1.279178	0.6807071	0.46	0.644	0.4507845	3.629886
Antiplatelet	8.629319	6.437827	2.89	0.004	1.999609	37.23985
Oral anticoagulation	3.625626	2.747243	1.7	0.089	0.8211127	16.00897
Aortic aneurysm progression	1.481182	0.9304347	0.63	0.532	0.4324227	5.073505
Aortic dissection progression	0.7598545	0.478684	−0.44	0.663	0.2210552	2.611922
Constant	0.0119832	0.0214087	−2.48	0.013	0.0003613	0.3974636

Abbreviations: CI, confidence interval; OR, odds ratio; SE, standard error.

Table 8 Cox proportional hazards regression with reintervention as the dependent variable

Variables	HR	SE	*z*	$p > \|z\|$	95% lower CI	95% upper CI
Age at initial diagnosis	1.026668	0.021528	1.26	0.209	0.9853289	1.069741
Sex	1.186074	0.603913	0.34	0.738	0.4372259	3.217495
Evidence of genetic mutation	1.061482	0.4542917	0.14	0.889	0.4587931	2.455889
Arterial hypertension	0.6742314	0.4702377	−0.57	0.572	0.1718481	2.645289
Hypercholesterolemia	0.8730389	0.4011629	−0.3	0.768	0.3547358	2.148633
Diabetes mellitus	0.5809916	0.4209136	−0.75	0.454	0.1404417	2.403497
Nicotine use	1.241701	0.5281353	0.51	0.611	0.5394777	2.857988
Antiplatelet	3.008961	1.777932	1.86	0.062	0.9450597	9.580183
Oral anticoagulation	1.176889	0.6439599	0.3	0.766	0.4027011	3.439447
Aortic aneurysm progression	0.8823175	0.4778883	−0.23	0.817	0.3052037	2.550703
Aortic dissection progression	3.287465	1.621338	2.41	0.016	1.250428	8.642979

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; SE, standard error.

Table 9 Kaplan–Meier survival analysis

Time at risk	Incidence rate	No. of patients	Survival time		
			25%	50%	75%
279.5865845	0.1216081	95	2.913073	4.900753	9.273101

respectively). Fourth, a considerable proportion of patients exhibited genetic alterations, with 40% (38 out of 95 patients) showing evidence of mutations in the genes associated with hereditary TAADs. However, genetic mutations were not identified as independent risk factors for reintervention (OR: 1.79; 95% CI: 0.62–5.11; $p = 0.27$). Fifth, age at initial diagnosis (a nonmodifiable risk factor) was significantly higher in the reintervention group than in the nonreintervention group ($p = 0.03$). Finally, the incidence of reintervention was higher in the endovascular repair group than in the open repair group ($p < 0.001$). Furthermore, the mean follow-up period varied significantly between the two groups. Patients in the open surgical repair group (mean follow-up: 2.48 years) had a shorter average follow-up duration than those in the endovascular group (mean follow-up: 4.02 years) ($p = 0.005$).

The risk of reintervention was inherently heterogeneous and inconsistent, owing to the dynamic nature of aortic disease and its unpredictable behavior. Kreibich et al (2020) noted the multifactorial etiology of aortic reinterventions and were unable to identify any risk factors for aortic reinterventions in their competing risk analysis.[10]

In accordance with our results, Konertz et al (2021) identified postoperative residual dissection as an independent risk factor for reinterventions after surgical repair of TAD.[11] This finding has sparked a significant debate in aortic surgery. Some surgeons advocate for curative surgical repair involving the removal and grafting of the entire dissected aortic segments to achieve better mid- and long-term results. Conversely, others believe that acute intervention should be restricted to a life-saving procedure targeting the entry tear only to minimize operative and mortality risks.[12,13] The remaining dissection could be addressed in a more controlled setting later on following the "live to fight another day" philosophy.[14] Wang et al (2017) resolved this debate and advocated for limited index (first) repair of acute type A dissection, especially for patients undergoing index repair in lower-volume centers without expertise in extensive repair.[15] They preferred extensive repair in selected patients, particularly those who are stable and young, and recommended it specifically in the aortic center of excellence. Most importantly, they emphasized the necessity for such extensive repair to be conducted by an experienced surgeon.[15,16]

Data from several studies in agreement with our results have confirmed that advanced age is a potential risk factor for reintervention.[1,17]

Although genetics plays a complex role in the development of thoracic aortic pathologies, the present study found that genetic aortic syndrome did not influence the need for reintervention ($p = 0.27$). Hence, our results contribute to the robustness of the findings reported in other studies.[11]

Recent evidence suggests that DM may exert a protective effect against aortic disease progression.[18,19] This research direction has significantly expanded over the past decade. It is well established that diabetes increases the thickness of the aortic wall. The wall thickness is a critical component of Laplace's law ($T = P \times r/2 \times t$), where T represents wall tension, P is the intraluminal pressure, r is the radius, and t is the thickness, and the wall tension decreases. Decreased wall tension is beneficial for the aneurysmal wall. Paradoxically, diabetes, which is detrimental to arteriosclerosis, has been indicated to be markedly beneficial from a purely aneurysm

standpoint; the diabetic aorta, which is dense, thickened, and stiff, has been reported to be less prone to aortic dissection. Metformin, a common medication for diabetes, has also been reported to be beneficial, which might be another reason for a lower prevalence of aortic dissections in diabetic patients.[20] Our study did not reveal any protective effect of DM on reintervention in the multivariate regression analysis and Cox regression models ($p = 0.53$ and 0.45, respectively).

The various repair strategies used in this study reflect the complexity of the disease. Open surgical repair is the gold standard for ascending aortic diseases such as acute aortic syndrome, although some cases of successful ascending aorta stenting have been reported.[21,22] Regarding the descending thoracic aorta, the development of TEVAR has altered the approach and reduced the risk associated with treating most of the descending thoracic aortic conditions.[23] Our study demonstrated a higher reintervention rate in the endovascular repair group than in the open repair group ($p < 0.001$). This significant difference in the reintervention rate supports the notion that "TEVAR is not a one-size-fits-all solution."[24] However, evaluating the two different approaches (open surgical repair vs. endovascular repair) without randomization to obtain two balanced homogenous groups of patients in terms of covariates is challenging. Moreover, the goals of endovascular and open surgery differ.[2]

These findings highlight the dynamic nature and complexities of addressing aortic diseases, as well as the necessity for personalized, long-term care strategies to meet the different needs of patients in this setting.

Limitations

The analysis included only 95 patients, representing a relatively small sample of real-world data. This can be attributed to two factors. First, the long follow-up period, inherent to observational cohort studies, resulted in attrition bias by excluding patients without a CT scan follow-up at our center. Second, due to the belief that genetic aortopathies are more aggressive and genetic mutations play a vital role in the pathological progression of thoracic aortic disease, patients who did not provide consent for genetic testing were excluded, challenging adherence and increasing the dropout rate. To obtain real-world data, our cohort was extremely heterogeneous, including a broad range of patients presenting with different pathologies and undergoing various surgical and interventional procedures for the thoracic aorta. However, this could also be considered a limitation, and identifying perioperative risk factors in a more homogeneous group would be ideal (tradeoff between internal and external validity). However, the magnitude of bias in the current study is unlikely to seriously affect results. Although our patients underwent detailed cardiovascular phenotyping, we were not able to study aspects of cardiovascular autonomic functions that might have impacted the clinical course after aortic repair since these data were not available.[25]

Our study prospectively collected data over a significant period of 10.5 years, mitigating the potential confounding effects of selection bias. Nevertheless, surgical techniques and TEVAR have rapidly evolved, with continuous improvements in clinical practice, perioperative care, and devices in the past decade. Although our study was conducted in a high-volume tertiary center, it was a single-center study, emphasizing the need for multicenter analyses.

Conclusion

Reintervention after primary thoracic aortic repair still represents an important clinical challenge, even in high-volume tertiary centers. Close follow-up and personalized care at aortic centers are mandatory. Postoperative residual dissection was the only independent risk factor for reinterventions. Predicting the risk of reintervention is difficult owing to the dynamic nature of aortic diseases and their unexpected behavior. Adequately powered multicenter studies or the use of artificial intelligence to improve patient-centered outcomes in the era of predictive medicine are desirable.

Authors' Contribution

M.E. and T.G. contributed to the conceptualization; M.E., T.C., and T.S. to methodology ; M.E. and J. L. L. to software; A.M, T.C., and T.S. to validation; M.E. and J.L.L. to formal analysis; T.G., A.M., and T.S. to investigation; T.G., J.L.L., and A.M. to resources; T.G., J.L.L., and A.M. to data curation; M.E. to writing—original draft preparation; T.C., T.S., J.L.L., and A.M. to writing—review and editing; A.M., T.C., and T. S. to supervision; and none to funding acquisition.

Conflict of Interest

None declared.

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