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The Value of NOX3 Gene Polymorphism (Rs3749930) To Predict Lower Overall Survival of Patients with Abdominal Aortic Aneurysm Undergoing Endovascular Aneurysm Repairing Surgery

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Abstract

BACKGROUND: Due to the relationship between changes in NOX3 gene expression and production of reactive oxygen species (ROS) activity, as well as the correlation between ROS activity and the occurrence of abdominal aortic aneurysm (AAA), this study proposed the hypothesis for the first time that the occurrence of rs3749930 polymorphism in the NOX3 gene may predict adverse outcomes in patients with AAA undergoing endovascular aneurysm repairing (EVAR) surgery.

METHODS: The study participants included 1092 patients aged higher than 18 years suffered from AAA and candidate for EVAR. The Kompetitive Allele Specific polymerase chain reaction (KASP) method was used to genotyping the rs3749930 polymorphism in the NOX3 gene. The mean follow-up time of the patients was 6.6 years to assess post-procedural long-term outcome.

RESULTS: The prevalence of G and T alleles in the study population was found to be 86.3% and 13.7% respectively. The prevalence of G and T alleles in died patients 93.0% and 7.0% and in survived patients was 83.2% and 16.8% respectively indicating a significant difference (P = 0.012). The 5-year overall survival in patients with the GG variant of rs3749930 polymorphism 58.6% and in those with GT+TT genotype was 73.4%. According to Cox proportional hazard modeling, the presence of GG variant along with older age, female gender, history of renal dysfunction, and higher aneurysm diameter were the correlates of long-term death.

CONCLUSION: Tracking the presence of G dominant allele of NOX3 gene polymorphism (rs3749930) can predict lower overall survival following EVAR surgery.

Keywords: Arterial aneurysm; Endovascular surgery; Nadph oxidase; Gene; Reactive oxygen species

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Introduction

An abdominal aortic aneurysm (AAA) is a focal enlargement of the abdominal aorta that is typically identified by imaging with a maximum aortic diameter of ≥30 mm[1]. Until it ruptures, which is lethal if surgery is not performed, abdominal aortic aneurysms are typically asymptomatic[2]. According to reports, AAA was responsible for 167,200 deaths and 3 million disability-adjusted life years globally in 2017[3]. However, these figures are probably erroneous because post-mortem rates are so low. Early detection and better surgical care have been the main focuses of efforts to lessen the burden associated with AAA. Despite developing advanced open and endovascular procedures for repairing AAA, the morbidity and even mortality of this event has remained considerable[4]. In addition, the pathophysiological basis of AAA has been also uncertain. In this regard, it has been revealed that vascular wall remodeling linked to a high production of reactive oxygen species (ROS) is one of the hallmarks of AAA, and it has been recently established a causal role of eNOS uncoupling in its formation[5]. In studies on animal models, the infusion of Ang II into mice with hyperphenylalaninemia (hph)-1 caused a three-fold increase in eNOS uncoupling activity, which led to 79% of AAA development within two weeks[6]. In Ang II-infused apoE null mice, AAA formation is also caused by eNOS uncoupling[7].

It has been demonstrated that in endothelial cells, diabetic mice, and the heart after ischemia/reperfusion injury, NADPH oxidase (NOX) activation occurs upstream of eNOS uncoupling[8,9]. The cardiovascular system expresses different isoforms of NOX including NOX 1 to 5[10]. It appears that the pathophysiology of various cardiovascular disorders involves distinct NOX isoforms. For instance, endothelial dysfunction in streptozotocin-induced type 1 diabetes mellitus is caused by NOX1, but not NOX2 or NOX4[11]. Atherogenic oscillatory shear stress activates the NOX1-NOXO1 complex to uncouple eNOS and maintain oxidative stress, whereas protective laminar shear stress assembles NOX2-p47phox at basal levels to increase eNOS phosphorylation and nitric oxide (NO) production[12]. Moreover, in ischemia/reperfusion (I/R)-injured hearts, NOX4—but not NOX1/2—is activated to mediate eNOS uncoupling and is implicated in cardiac remodeling and damage[13]. In a zebrafish model, NOX4 upregulation also promotes cardiac arrhythmic phenotype and is associated with atrial fibrillation in patients[14]. Furthermore, in young apoE null mice, it has been demonstrated that NOX1/2 inhibition via p47phox genetic deletion reduced atherogenesis[15].

Among different isoforms of NOX, the role of NOX3 and its-related some polymorphisms in the pathogenesis of vascular pathologies has received a lot of attention. Some studies revealed the detection and expression of Nox3 in endocardial endothelial cells (hEECs) and vascular smooth muscle cells (hVSMCs)[16]. Some comparative studies could show significantly higher risk of AAA related to the Nox3-related polymorphism (rs3749930) that men with dominant allele of this polymorphism had a 2.5-fold increased risk of AAA compared to the general population[17]. However, it is unclear whether the presence of this gene variant could affect the outcomes of abdominal aortic aneurysm repair procedures. The present study evaluated the role of Nox3 gene polymorphism (rs3749930) in predicting adverse outcomes after endovascular repair of AAA.

Materials And Methods

Study population

In this retrospective cohort study, the study participants included 1092 patients aged higher than 18 years suffering from abdominal aortic aneurysm and candidate for endovascular aortic aneurysm repair (EVAR) that were finally scheduled for bifurcated stent graft insertion. Samples were selected from available patients who were entered and analyzed in a non-random and sequential manner. Those with solitary iliac aneurysm and ruptured aneurysm candidate for emergency surgery were excluded from the study. Patients with aneurysm diameter less

than 40mm, neck diameter higher than 40mm or less than 10mm and proximal landing zone higher than 100mm were excluded from the study.

Since 2017, our center has been collecting information on all patients undergoing EVAR surgery, including all demographic information, clinical and medication history, laboratory findings, and information related to the patients' hospital outcomes. In addition to collecting patients' clinical information in the form of a data registry, our center also collects patients' serum samples in a biobank for the purpose of extracting and storing DNA. To evaluate polymorphism, DNA samples stored in this biobank were utilized.

In addition to collecting clinical information, patients' serum samples are also extracted immediately before the procedure and transferred to the hospital laboratory according to standard protocol and stored at a temperature of minus 70 degrees to be used if needed for genomic studies of the patients.

DNA extraction and genotyping

Tiangen Oral Mucosa Genomic DNA extraction kits (Tiangen Biotech, Beijing, China) were used to extract the DNA. The genes, alleles and primers characteristics are shown in Table 1. Hangzhou Hechuan Biological Technology Co., Ltd. uses the Kompetitive Allele Specific polymerase chain reaction (KASP) method (Laboratory of the Government Chemist, England) to genotype the DNA[18]. The entire reaction mixture was made up of the following ingredients: Two allele forward primers with distinct 3' sequences, a reverse primer, and detection primers with two forward primers with distinct 5' sequences make up the primer mix; two detection primers with distinct fluorophores make up the master mix; and three is the DNA template. The following is how the assay was carried out: The PCR reaction 1. The denatured template joins the primer mix's corresponding primers and anneals. Following the extension step, the detection primer was added to the PCR mixture. Allele-specific end sequences were synthesized by complementary strand synthesis in PCR reaction II. The Fluor-labeled portion of the FRET cassette, which was complementary to the tail sequences, bonded to them, released the Fluor, and produced a fluorescent signal in PCR reaction III-Signal generation, where the levels of allele-specific tails raised exponentially. We randomly choose 10% of the samples to reclassify the genes in order to control the quality, and the concordance was 99.5% for rs3749930.

Procedure-related outcome

In-hospital mortality, overall survival, event-free survival, dilatation rate, and re-intervention-free survival were among the outcomes that were

Table 1. Gene and primers information (NOX3)

Single nucleotide polymorphism (SNP)	rs3749930
Gene Chromosomal location	6q25.3
Gene Chromosomal zone	155440112
Functional consequence of SNP	Missense Variant
SNP allele	G>T
Minor allele frequency	0.477
Hardy–Weinberg equilibrium	0.662
Primer information	
Primer Allele FAM	ACACAACCACTGAATTGCTAAGGAC
Primer Allele HEX	AACACAACCACTGAATTGCTAAGGAA
Primer Common	CAGACCGGTGACGCCTGCTATT
SNP Allele FAM	G
SNP Allele HEX	T
SNP Sequence	GACCGGTGACGCCTGCTATT[G/T]TCCTTAGCAATTCAGTGGTT
CG%_FAM	44.0
CG%_HEX	38.5
CG% Common	59.1

assessed. Survival without stent graft migration, stenosis or occlusion of the stent graft, stent graft infection, acute arterial thrombus or embolus of the lower legs, or rupture of the aortic aneurysm was referred to as event-free survival. Survival without re-intervention for any reason was known as re-intervention-free survival. Dilatation was defined as an increase in the aneurysmal diameter of at least 5 mm over any previously recorded and measured diameter. Data were censored on the date of the patient's deregistration, the end of follow-up, or the first recording of the outcome of interest. The mean follow-up time of the patients was 6.6 years to assess post-procedural long-term outcome.

Statistical analysis

Continuous variables are shown as mean ± standard deviation, while categorical variables are shown as numbers and percentages. Chi-square tests were used to compare categorical variables. Hazard ratios (HRs) and 95% CIs for long-term death estimated using multivariable Cox regression analyses. Overall survivals were analyzed using the Kaplan-Meier method with the log-rank test. Version 23 of the SPSS software (IBM Corp., Armonk, NY) was used for all statistical analyses.

Ethical consideration

The study protocol was ethically approved by Istanbul University ethical committee with the ethical code of TR.OK.REC.2025.124.

Results

Baseline characteristics of study population

A total of 1220 cases scheduled for endovascular repair of AAA were registered between 2016 and 2022 that 1092 cases were finally analyzed after applying the exclusion criteria. The baseline parameters of the study population are summarized in Table 2. The mean age of the subjects was 52.2±9.8 years and 725 (66.4%) were female. Overall, 426 (39.0%) were hypertensive, 329 (30.1%) were diabetics, and 288 (26.3%) were current smoker. The mean aneurysm diameter was 48.8±2.2mm ranged 46 to 59mm and mean proximal neck diameter was 22.6±3.6mm ranged 19.6 to 24.1mm.

In-hospital and long-term outcome

Regarding the in-hospital postoperative outcome, the rate of in-hospital mortality was reported to be 35 (3.2%). Intraoperative blood transfusion was planned for 4.9%. The most frequent early postoperative complications included vascular injury in 3.3%, renal dysfunction in 1.4%, wound complications in 1.4%, cerebrovascular events in 1.0%, thromboembolism in 1.0%, stent graft migration in 0.7%, and rupture in 0.4%. Endoleaks were reported intraoperatively in 224 patients (20.5%). The mean follow-up time of the patients was 6.6 years. During this period, 926 patients were eligible for follow-up (with a final follow-up rate of 84.8%). Regarding long-term outcome, the overall survival rates were 92.2% at 1 year, 79.9% at 3 years, and 68.6% at 5 years. The 1-, 3- and 5-year event-free survival was also 91.6%, 77.9%, and 64.4% and the re-intervention-free survival was also 91.6%, 78.7%, and 66.4% respectively.

Comparing baseline parameters between survived and died cases (Table 1) showed high mean age, higher female to male ratio, higher prevalence rates of diabetes mellitus and renal dysfunction, as well as higher mean aneurysm diameter in died subgroup.

The association of Nox3 polymorphism and lone-term outcome

The SNP of rs3749930 in the study subjects were in Hardy–Weinberg equilibrium (P > 0.05). Overall, considering the genotype of GG of the pointed SNP as the reference, the prevalence of G and T alleles in the study population was found to be 86.3% and 13.7% respectively. Regarding the association of rs3749930 genotypes and postoperative long-term outcome, the prevalence of G and T alleles in died patients 93.0% and 7.0% and in survived patients was 83.2% and 16.8% respectively indicating a significant difference (p = 0.012). In the patients with long-term postoperative events, the prevalence rate of G and T alleles was 79.9% and

Table 2. Baseline parameters of study population (n = 1092)

Characteristics	Total (n=1092)	Survival (n=750)	Non-survival (n=342)	P-value
Mean age, year	52.2±9.8	55.6±8.7	59.00±10.1	<0.001
Mean body mass index, kg/m²	27.7±3.6	26.8±3.2	28.1±3.6	0.556
Male gender, %	725 (66.4%)	466 (62.1)	259 (75.7)	<0.001
Marital status, %				0.879
Single	326 (29.8)	225 (30.0)	101 (29.5)	
Married	675 (61.8)	464 (61.8)	211 (61.7)	
Divorced	62 (5.8)	40 (5.3)	21 (6.1)	
Widow	29 (2.6)	21 (2.8)	9 (2.6)	
Education level, %				0.192
Illiterate	22 (2.0)	14 (1.8)	8 (2.3)	
Primary level	198 (18.1)	161 (21.5)	37 (10.8)	
Secondary level and diploma	625 (57.2)	386 (51.4)	239 (69.9)	
Academic degree	247 (22.7)	189 (25.3)	58 (17.0)	
History of hypertension, %	426 (39.0%)	272 (36.2)	154 (45.0)	0.127
History of hyperlipidemia, %	198 (18.1%)	125 (16.7)	73 (21.3)	0.656
History of diabetes mellitus, %	329 (30.1%)	189 (25.2)	140 (40.9)	0.036
Current smoking, %	288 (26.3%)	166 (22.1)	122 (35.7)	0.123
Family history of cardiovascular disorder	56 (5.1%)	43 (5.7)	13 (3.8)	0.756
History of renal dysfunction, %	55 (5.0%)	19 (2.5)	36 (10.5)	0.032
History of brain stroke, %	88 (8.1%)	44 (5.9)	44 (12.8)	0.082
History of statin use, %	187 (17.1%)	122 (16.3)	65 (19.0)	0.826
Functional class (NYHA)				0.224
I	129 (11.8)	76 (10.1)	36 (10.5)	
II	279 (25.5)	202 (26.9)	101 (29.5)	
III	302 (27.6)	192 (25.6)	126 (36.8)	
IV	382 (35.1)	280 (37.3)	79 (23.1)	
Mean aneurysm diameter, mm	48.8±2.2	45.2±1.8	52.4±2.7	<0.001
Mean proximal neck diameter, mm	22.6±3.6	21.8±3.2	23.5±3.3	0.097
Allele frequency (rs3749930)				0.036
G allele	942 (86.3)	624 (83.2)	318 (93.0)	
T allele	150 (13.7)	126 (16.8)	24 (7.0)	
Genotype frequency (rs3749930)				0.012
GG	817 (74.8)	519 (69.2)	298 (87.2)	
GT	251 (23.0)	210 (28.0)	41 (12.0)	
TT	24 (2.2)	21 (2.8)	3 (0.8)	

20.1% and in those without events was 76.9% and 23.1% respectively indicating no difference (p = 0.224). Also, in the subgroup underwent re-intervention, the prevalence of G and T alleles was 78.9% and 21.1% and in patients without requiring re-intervention was 77.9% and 22.1% indicating no difference (p = 0.756) (Table 3). In this regard, using the Cox proportional hazard modeling adjusting baseline parameters (Table 4), the presence of GG variant in NOX3 (rs3749930) was associated with higher risk for long-term death (HR: 1.729, 95%CI: 1.112 to 2.425, p = 0.036). The 5-year overall survival in patients with the GG variant of rs3749930 polymorphism 58.6% and in those with GT+TT genotype was 73.4% (Figure 1). Along with GG variant as the risk profile for long-term death, other main determinants for long-term death were older age, female gender, history of renal dysfunction, and an aneurysm diameter ≥55 mm (Table 3).

Discussion

One of the main causes of oxidative stress in the blood vessels is NOXs. Numerous vascular diseases, such as endothelial dysfunction, inflammation, and vascular remodeling, are influenced by Nox isoforms. Separately or in combination, various isoforms exhibit distinct functions. Endothelial cell response to atherogenic oscillatory shear stress and diabetic endothelial dysfunction have both been linked to NOX1[15,16]. Conversely, NOX4 is essential for cardiac I/R damage. Consequently, there is no

Table 3. The association of Nox3 polymorphism and postoperative outcome

Event	Genotypes			P-value	Alleles		P-value
	GG	GT	TT		G	T	
In-hospital death				0.097			0.087
Died (n = 35)	28 (80.0)	5 (14.4)	2 (5.6)		31 (87.1)	4 (12.9)	
Survived (n = 1057)	831 (78.7)	212 (20.0)	14 (1.3)		937 (88.6)	120 (11.4)	
In-hospital complications				0.212			0.126
With complication (n = 42)	32 (78.2)	9 (20.4)	1 (1.4)		36 (86.9)	6 (13.1)	
Without complication (n = 1050)	813 (77.4)	222 (21.1)	15 (1.5)		924 (88.0)	126 (12.0)	
Long-term death				0.012			0.036
Died (n = 342)	298 (87.2)	41 (12.0)	3 (0.8)		318 (93.0)	24 (7.0)	
Survived (n = 750)	519 (69.2)	210 (28.0)	21 (2.8)		624 (83.2)	126 (16.8)	
Long-term complications				0.245			0.224
With complication (n = 448)	358 (79.9)	84 (18.9)	6 (1.2)		400 (89.3)	48 (10.7)	
Without complication (n = 644)	495 (76.9)	139 (21.6)	10 (1.5)		565 (87.7)	79 (12.3)	
Lon-term re-intervention				0.884			0.756
With re-intervention (n = 367)	289 (78.9)	73 (19.8)	5 (1.3)		325 (88.7)	42 (11.3)	
Without re-intervention (n = 725)	565 (77.9)	148 (20.5)	12 (1.6)		638 (88.1)	87 (11.9)	

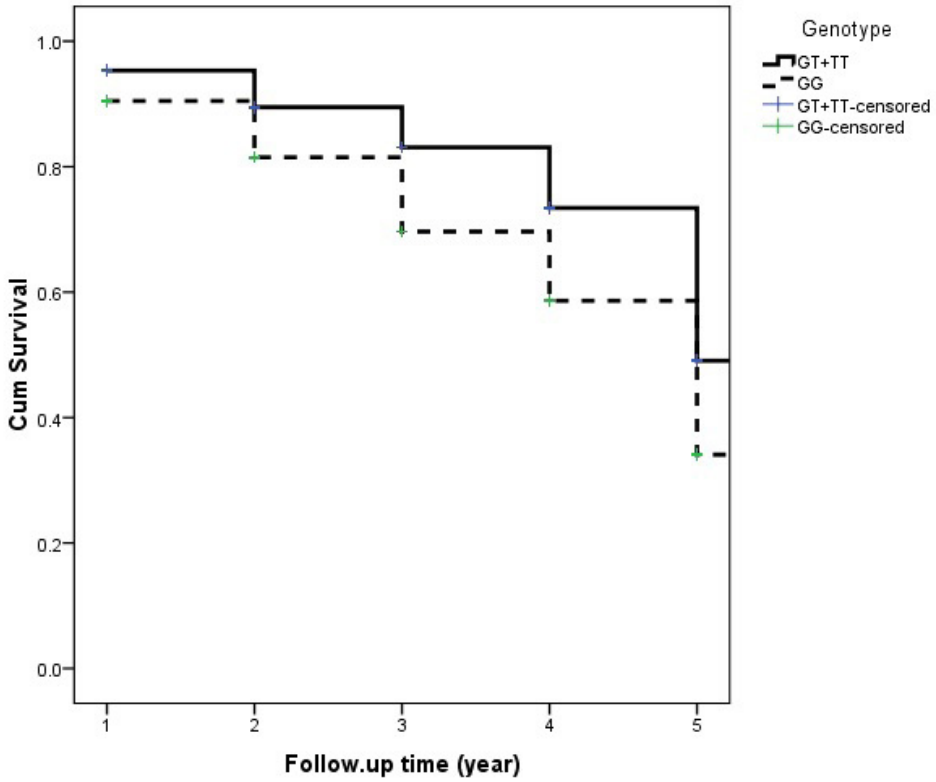


Figure 1. The Kaplan-Mayer survival analysis to determine the overall survival in the subgroups with GG and GT+TT genotypes of rs3749930 polymorphism

Table 4. Cox proportional hazard analysis to determine the correlates of long-term death

Index	p-value	Hazard Ratio (HR)	95% Confidence Interval for HR	
			Lower limit	Upper limit
Female gender	0.012	2.226	1.426	3.742
Higher age	0.008	2.779	1.485	3.728
Hypertension	0.226	0.456	0.223	1.478
Hyperlipidemia	0.178	0.429	0.226	1.786
Diabetes	0.079	0.779	0.246	1.478
Smoking	0.122	0.112	0.079	1.472
Family history of CVD	0.658	0.224	0.147	1.089
Renal dysfunction	0.024	1.226	1.012	1.779
Brain stroke	0.779	1.779	0.756	2.012
Functional class	0.226	1.246	0.789	1.476
Aneurysm diameter≥55mm	0.002	2.179	1.478	3.483
Proximal neck diameter≥20mm	0.123	1.213	0.742	1.746
GT+TT genotype of SNP	0.036	1.729	1.112	2.425

functional duplication among these isoforms. NOX2 is a key mediator of Ang II-induced cerebral endothelial dysfunction in the Ang II infusion condition[19]. However, it was discovered that Ang II-induced hypertension involved both NOX1 and NOX2[20–22]. Despite the strong correlation between Nox3 and reactive oxygen species (ROS) production, studies on the relationship between this isoform and vascular pathologies, especially AAA, have been very few.

In this study, we evaluated for the first time the value of a SNP on NOX3 (rs3749930) in predicting outcomes after endovascular AAA repair. Given the limited evidence for the association between NOX polymorphisms and aortic aneurysm pathologies, we hypothesized that expression of the dominant variant of rs3749930 polymorphism may predispose to adverse outcomes after this procedure, such as mortality, postoperative vascular complications, and the need for re-intervention. Accordingly, we showed that the presence of the GT+TT genotype could predict an increased risk of long-term death in patients with AAA undergoing the EVAR procedure. This conclusion was reached even after adjusting the Cox predictive model for other background variables. However, the presence of this variant could not predict other outcomes such as long-term complications after surgery or the need for re-intervention. In a recent experience by Sakshi Vats et al[17], the presence of rs3749930 variant in NOX3 was strongly associated with higher risk for ruptured AAA.

It has been claimed so far that the NADPH oxidase family member NOX3 is not usually linked to vascular pathology or function. However, it has been clearly demonstrated that NOX3 contributes to the generation of reactive oxygen species (ROS)[23]. Additionally, the development and progression of AAAs are significantly influenced by ROS the elevated ROS levels, which are frequently linked to inflammation, weaken the aorta and cause dilatation by promoting smooth muscle cell death and degrading the extracellular matrix of the aortic wall[24]. Overall, progressive dilatation of the abdominal aorta, frequently coupled with inflammation and the disintegration of the structural elements of the aortic wall, is the hallmark of AAAs. This process involves ROS, which are generated by a variety of cellular sources, such as inflammatory cells and NADPH oxidases. Also, oxidative stress, which harms cells and tissues, results when the body's production of ROS surpasses its antioxidant defenses[25]. Oxidative stress plays a role in the breakdown of collagen and elastin, two essential aortic wall constituents, in the setting of AAA[26]. Moreover, enzymes called matrix metalloproteinases (MMPs), which degrade the extracellular matrix (ECM), can be activated by ROS. The aortic wall becomes weaker due to this ECM degradation, increasing its vulnerability to dilatation and aneurysm formation[27]. Given the strong relationship between NOX3 activity and ROS activity on the

one hand, and the prominent role of the ROS production in aortic wall degradation in the context of aneurysm on the other hand, the prominent role of NOX3 polymorphisms in the pathological defects of aortic aneurysms and therefore their relationship with outcomes after AAA repair can also be considered.

The present study demonstrated the value of rs3749930 polymorphism detection in predicting adverse outcomes after the procedure, especially mortality. However, post-surgical predictive systems will be valuable when, in addition to molecular and biological indicators, they also consider other contextual indicators such as demographic characteristics and clinical risk indicators. According to the present study, the most important of these indicators included older age, female gender, impaired renal function, and also higher initial aneurysm size. In fact, to more accurately predict long-term mortality after AAA repairing surgery, one should focus on designing a system that, in addition to these indicators, also considers the examination of genomic polymorphisms such as the polymorphism under study.

This study however has several limitations that should be acknowledged. First, its retrospective design may introduce selection and information biases, which could affect the accuracy of data collection and the interpretation of results. Second, the study did not extensively explore the mechanistic pathways linking NOX3 polymorphism to abdominal aortic aneurysm (AAA) outcomes, limiting the ability to draw conclusions about causality. Finally, the generalizability of our findings may be restricted by the single-center design, as the patient population may not fully represent broader or more diverse populations. Future prospective, multicenter studies with mechanistic investigations are warranted to validate and extend these findings.

Conclusion

As a final conclusion, in patients who are candidates for AAA reconstructive surgery, detection of polymorphisms related to the NOX3 gene can predict long-term mortality after this surgery. In addition to detection of the relevant polymorphism, indicators such as older age, female gender, postoperative renal dysfunction, and larger aneurysm size can also predict adverse outcomes after this repairing surgery. Based on the discovery of the relationship between polymorphism expression and adverse outcomes after surgery, it can be expected that the occurrence of such polymorphisms can be related to the pathophysiology of aortic wall destruction and therefore the occurrence of dissection.

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Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: MAT
Data Acquisition: HD, MS
Data Analysis or Interpretation: SMA
Manuscript Drafting: SMA
Critical Manuscript Revision: MAT
All authors have approved the final manuscript and are responsible for all aspects of the work.

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