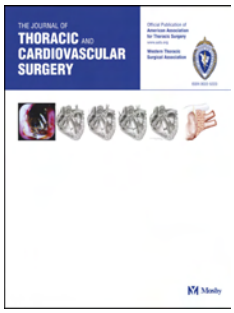

"THE COMPLEX INTERPLAY BETWEEN ATHEROSCLEROSIS, INFLAMMATION AND DEGENERATION IN ASCENDING THORACIC AORTIC ANEURYSMS"

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Title: "THE COMPLEX INTERPLAY BETWEEN ATHEROSCLEROSIS, INFLAMMATION AND DEGENERATION IN ASCENDING THORACIC AORTIC ANEURYSMS"

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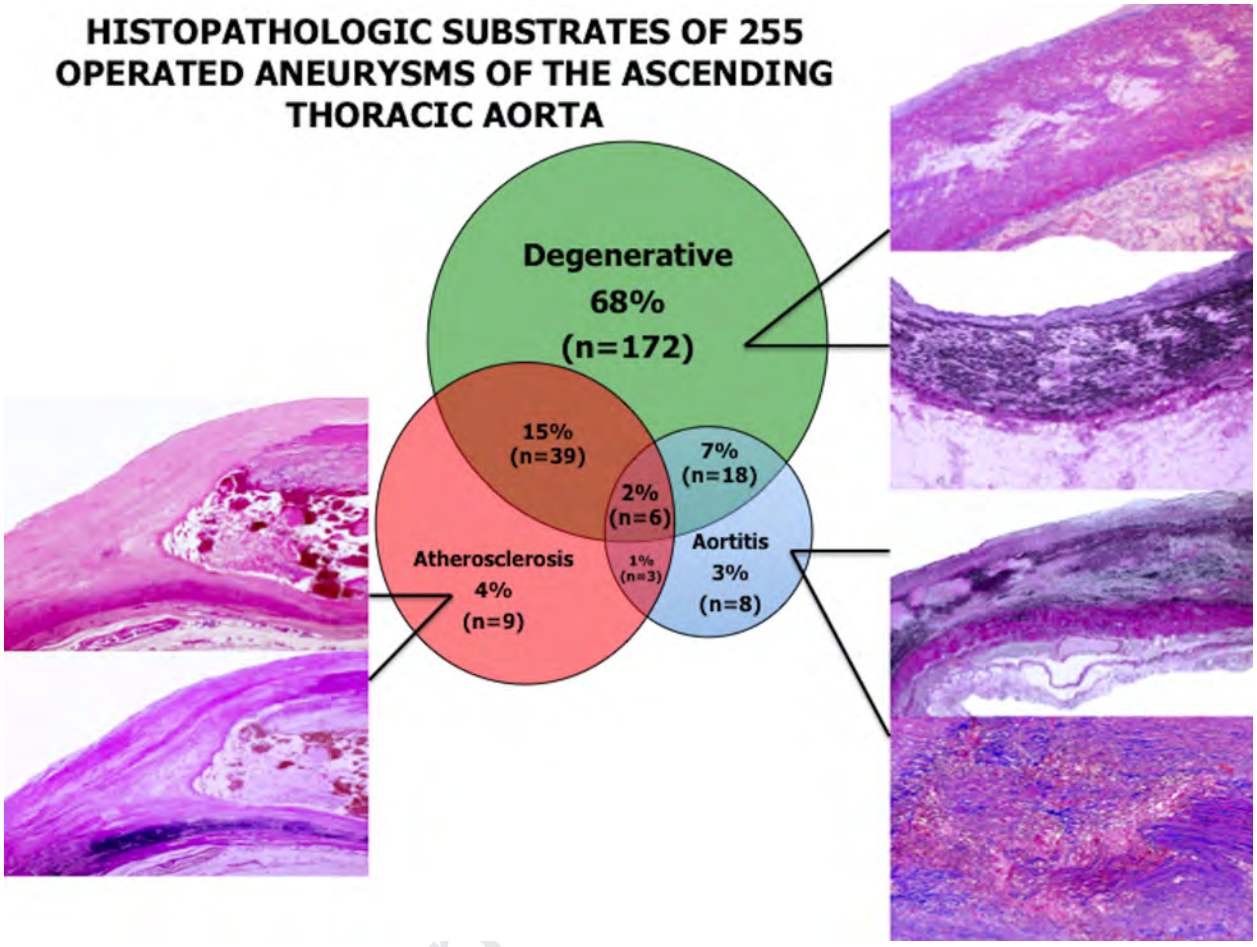
Central message: Degenerative histopathology is the most frequent substrate in ascending TAA, but atherosclerosis and inflammation significantly contribute to the development of chronic aortic thoracic disease.

Perspective statement: Awareness of the significant burden of aortitis and atherosclerosis related inflammation might guide future research and therapies in the field of ascending thoracic aortic aneurysms.

Central picture legend: Clinical characteristics and histopathologic substrates of 255 operated aneurysms of the ascending thoracic aorta.

Word count: 3090


HISTOPATHOLOGIC SUBSTRATES OF 255 OPERATED ANEURYSMS OF THE ASCENDING THORACIC AORTA
Degenerative
68%
(n=172)
15%
(n=39)
7%
(n=18)
2%
(n=6)
Atherosclerosis
4%
(n=9)
1%
(n=3)
Aortitis
3%
(n=8)

ABSTRACT

Objectives: we assessed the histopathologic findings of a large series of ascending thoracic aortic aneurysms (TAAs) surgical specimens applying the updated classification on non-inflammatory-degenerative and inflammatory aortic diseases proposed by the Association for European Cardiovascular Pathology (AECVP) and the Society for Cardiovascular Pathology (SCVP) and looked for clinico-pathological correlations.

Methods: 255 patients surgically treated for ascending TAA were enrolled. Surgical ascending aorta specimens were examined.

Results: histopathologic substrate of ascending TAAs is mainly degenerative (67.5%), but with a remarkable prevalence of atherosclerotic lesions (18.8%) and aortitis (13.7%). Degenerative patients more frequently had bicuspid aortic valve (37.2%, p=0.002). Patients in the atherosclerotic group were older (median 69 years, p<0.001), more often with a history of hypertension (87.5%, p=0.059), hypercholesterolemia (75%, p=0.019), diabetes (16.6%, p=0.054), current smoking (22.9%, p=0.066), and a history of coronary artery disease (18.7%, p=0.063). Patients with aortitis represented the older group (median 75 years, p<0.001), were mostly females (68.6%, p<0.001), and had a larger ascending aorta diameter (median 56 mm, p<0.001). Both patients with atherosclerosis and aortitis presented a higher incidence of concomitant abdominal aortic aneurysm (20.8% and 22.8% respectively, p<0.001).

Conclusions: although degenerative histopathology is the most frequent substrate in ascending TAA, atherosclerosis and inflammation significantly contribute to the development of chronic aortic thoracic disease.

INTRODUCTION

From a clinical point of view, thoracic aortic diseases mainly include thoracic aortic aneurysms (TAA) and type A acute aortic syndromes (AAS) that include aortic dissection (AD), intramural haematoma (IMH), and penetrating aortic ulcer (PAU). Previous histopathologic studies in chronic thoracic aortic diseases have mainly focused on the role of degenerative lesions of the medial aortic layer, first identified by Erdheim in 1930 as ‘‘aortic idiopathic (cystic) medial necrosis’’ (1) leading to the common perception of TAA as mainly genetic-based diseases associated with degenerative substrate. This conception could be challenged by recent histopathologic advances. In particular the Association for European Cardiovascular Pathology (AECVP) and the Society for Cardiovascular Pathology (SCVP) have proposed a revised and updated classification of the histopathologic diagnostic criteria for aortic diseases in 2 consensus statements on non-inflammatory-degenerative (2) and inflammatory (3) aortic diseases. These criteria have not been applied to a large ascending TAA series yet.

In our study we assessed the histopathologic findings of a large series of ascending TAA surgical specimens and searching for clinico-pathological correlations.

METHODS

Clinical setting and study design

The study population consisted of 255 patients who underwent surgery in our centre for ascending TAA between January 1st 2015 and December 31st 2016. Patients aged <18 years were excluded.

Moreover, we could compare histopathologic profile of patients with chronic ascending TAA with that of patients with a final diagnosis of spontaneous type A

acute aortic syndrome (AAS) treated surgically in our centre between January 1st 2000 and December 31st 2013, whose data have been previously reported by our group (4). The study conforms to the principles outlined in the Declaration of Helsinki and has been approved by our institutional Ethics Committee.

Clinical definitions

The population's main characteristics and clinical features at presentation were evaluated. Cardiovascular risk factors included history of hypertension and ongoing anti-hypertensive therapy, hypercholesterolemia (total cholesterol >200 mg/dl) and ongoing lipid-lowering therapy, diabetes (type 1 or type 2), current smoking, familial history of premature coronary artery disease (CAD - i.e. history of myocardial infarction affecting a first-degree relative younger than 55 years if men and 65 years if women).

Known thoracic aortic aneurysm in patients operated for ascending TAA was defined as the presence of aneurysm in another thoracic vascular segment.

Baseline Glomerular Filtration Rate (GFR) was calculated with the modified MDRD equation (5).

Histopathology

Ascending aorta specimens ranging from 2.5 to 4.5 cm in length were examined for patients undergoing surgery for ascending TAA. An average of six samples were taken from each formalin-fixed specimen, routinely processed and embedded in paraffin. The histologic sections were stained with standard Hematoxylin-Eosin and histo-morphological staining for collagen (Azan-Mallory trichrome) and elastic fibers (Weigert-Van Gieson staining).

Histological samples were all evaluated *de novo* according to the diagnostic criteria from the two AECVP/SCVP documents (2,3) by personnel blinded to the clinical data. Specifically, the following abnormalities were evaluated:

1. **Non-inflammatory/degenerative substrates**

   Overall degeneration of aortic media was assessed as the sum of 6 major individual lesions involving various cellular and extracellular components of the medial layer:

   - Mucoid extracellular matrix accumulation, an increase of mucopolysaccharides, both intralamellar (I-MEMA) - preserving the arrangement of lamellar unit - and translamellar (T-MEMA) - altering the structural architecture of the tunica media due to large pool formation;
   - Elastic fiber fragmentation/loss (EFFL);
   - Elastic fiber thinning out (EFTO);
   - Laminar medial collapse (LMC), a thin/dense band-like smooth muscle cell loss generating architectural compaction of elastic fibers;
   - Collagen increase, intralamellar (ICI) - in absence of significant alterations of the lamellar unit - and translamellar (TCI) - i.e. replacement fibrosis.

Overall medial degeneration (MD) was graded as mild, moderate or severe, based on severity and distribution of each individual abnormality.

2. **Inflammatory substrates**

   - Atherosclerosis: after assessing single atherosclerotic plaques using the American Heart Association (AHA) schemes (6,7), atherosclerosis was

classified and graded as not significant, mild, moderate or severe using the simplified AECVP/SCVP classification, according to which only moderate or severe disease leads to significant medial damage;

- Atherosclerosis with excessive inflammation - i.e. with intense inflammatory reaction;
- Inflammatory atherosclerotic aneurysm;
- Aortitis and periaortitis, classified according to histopathologic inflammatory patterns (granulomatous/giant cells, lymphoplasmacytic, mixed inflammatory and suppurative).

Only patients with moderate to severe atherosclerotic disease (AHA's plaques V-VII) were classed as atherosclerotic.

Clinico-pathological correlations

To investigate clinico-pathological correlations patients were classified according to three histopathological patterns: isolated degeneration (pure degenerative lesions or associated with mild atherosclerosis - i.e. AHA's plaques I-IV), mainly atherosclerosis in presence of moderate to severe atherosclerosis (isolated or associated with various degrees of degeneration), and aortitis (isolated or associated with various degrees of medial degeneration or atherosclerosis).

Statistical analysis

Categorical variables are expressed as number and percentage; continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) for normal or non-normal distribution, respectively.

Comparisons between categorical variables were performed with the chi-squared test.

Comparisons between two continuous variables were performed with student's t test or Wilcoxon test as appropriate. Comparisons between three groups were performed with ANOVA for height values and with Kruskal Wallis test when the assumptions for ANOVA application were not met (age, body mass index, glomerular filtration rate, systolic and diastolic blood pressure values, and ascending aorta diameters). Variables with P-value < 0.1 in table 3 where included in the multivariable analysis (multinomial logit model) which is shown in table 4. All statistical analyses were performed using STATA/SE 14.2 (StataCorp LP, College Station, Tex).

RESULTS

Clinical findings in patients with ascending TAA

Severe aortic stenosis was present in 26/255 patients; severe aortic regurgitation in 77/255 patients; concomitant severe stenosis and regurgitation was present in 4/255 patients. Concomitant aortic valve replacement was performed in 196/255 cases. Indications for surgery were as follows: maximal ascending aorta diameter ≥ 55 mm in 117 patients; maximal ascending aorta diameter ≥ 50 mm in the presence of a bicuspid aortic valve with additional risk factors in 29 patients; maximal ascending aorta diameter ≥ 45 mm in the presence of Marfan syndrome in 5 patients and Loeys-Dietz syndrome in 1 patient; severe aortic stenosis or regurgitation with maximal ascending aorta diameter ≥ 45 mm in 103 patients.

Table 1 reports the baseline characteristics and clinical features of the 255 patients with ascending TAA.

Median age was 66 years. A history of hypertension and antihypertensive therapy was common (211, 82.7%), as well as hypercholesterolemia (134, 52.5%) and lipid-lowering therapy (81, 31.7%). A high percentage of patients with ascending TAA

were ex-smokers rather than current smokers (84, 32.9% and 35, 13.7%, respectively).

Bicuspid aortic valve (BAV) was common in patients with ascending TAA (77, 30.1%), while Marfan syndrome (MFS) was rare (5, 1.9%); patients with BAV were younger (58 vs 69 years, p<0.001, **supplementary table 1**) and less frequently had a history of hypertension (154, 86.5% vs 57, 74%, p=0.015). The incidence of concomitant abdominal aortic aneurysm was 10.5% (27 patients).

Histopathologic findings in patients with ascending TAA

Table 2, **supplementary table 2**, **figure 1** and **figure 3** show the histopathologic findings. In about 75% of ascending TAA patients histopathology revealed a single pattern (degenerative in 67.5% of cases, atherosclerosis in 3.5%, and aortitis in 3.1%) while in approximately 25% the pattern was mixed (degenerative-atherosclerosis in 15.2%, degenerative-aortitis in 7.1%, atherosclerosis-aortitis in 1.1%, degenerative-atherosclerosis-aortitis in 2.3%).

When ascending TAA patients were classified according to the three main histopathologic patterns, medial degeneration was present in 67.5% (172 patients), mainly atherosclerosis in 18.8% (48 patients), and aortitis in 13.7% of patients (35 patients).

Medial degeneration was the most frequent histopathologic substrate found in ascending TAA (235, 92.2%), with isolated (172, 67.5%) or mixed patterns (63, 24.6%) and was most frequently moderate (130, 50.9%). As to individual degenerative lesions found in ascending TAA patients, MEMA was the most frequent (244, 95.6%), more translamellar (234, 91.7%) than intralamellar (201, 78.8%), followed by EFFL (243, 95.2%), ICI (219, 85.8%), and EFTO (201, 78.8%). TCI and

LMC were relatively rare (92, 36% and 68, 26.6% respectively), the latter being more frequently associated with atherosclerosis rather than with a degenerative substrate. In particular, LMC associated with atherosclerosis was represented by a thick compaction band bordering the medial side of the plaques (**figure 1**). Mucoid extracellular matrix and elastic fiber lesions as well as ICI were more frequently moderate and multifocal.

Atherosclerosis was present in a significant number of ascending TAA patients (57, 22.3%), prevalently as a mixed pattern (degenerative-atherosclerosis: 39, 15.2%; atherosclerosis-aortitis: 3, 1.1%; degenerative-atherosclerosis-aortitis: 6, 2.3%). Atherosclerosis was graded moderate in 10.9% (28 patients) and severe in 11.3% (29 patients). In 31.7% (81 patients) of cases atherosclerotic lesions were mild and associated to other histopathologic patterns. Atherosclerosis with excessive inflammation and inflammatory atherosclerotic aneurysm were very rare (both found in one patient with ascending TAA) (**figure 1**).

Aortitis was found in 13.7% (35 patients) of ascending TAA, prevalently with a granulomatous-giant cell pattern (20, 7.8%) followed by lymphoplasmacytic (2, 0.7%). In 5.1% of cases (13 patients) the inflammatory process was in a chronic/healing phase and the aortitis pattern was difficult to classify and aortitis was considered unclassified, the inflammatory cell types were described as was the presence of necrosis and scarring (**figure 1**). All aortic specimens with aortitis had severely damaged vessel walls.

Periaortitis was present in 28/35 ascending TAA aortitis cases (80%) and was also found in other 17 ascending TAA cases, where the histopathologic substrate was atherosclerotic or degenerative (**figure 1**). The periaortic inflammatory infiltrate

grading was more frequently moderate (26, 10.1%) than mild (10, 3.9%) ore severe (9, 3.5%).

Clinico-pathological correlations in patients with ascending TAA

As shown in **table 3** and **figure 2**, the clinico-pathological correlations were assessed according to the three main categories: isolated degeneration (172, 67.5%), mainly atherosclerosis (48, 18.8%) and aortitis (35, 13.7%).

Degenerative patients had bicuspid aortic valve more frequently. Patients in the atherosclerotic group were older, more often with a history of hypertension, hypercholesterolemia, diabetes, current smoking, and a history of coronary artery disease particularly when compared with degenerative patients. Patients with aortitis were the oldest group, had a female predominance, and presented a high prevalence of classic cardiovascular risk factors such as hypertension, hypercholesterolemia, and diabetes. Moreover, patients in the atherosclerotic group and even more in the aortitis group had a larger ascending aorta. Patients with atherosclerosis and aortitis had a higher prevalence of concomitant abdominal aortic aneurysm compared to those with isolated degeneration. After multivariable analysis (**table 4**) variables independently associated with atherosclerotic patterns were found to be older age, increased BMI values, hypercholesterolemia, smoking and lager ascending aorta diameters; variables independently associated with aortitis pattern were found to be older age, female gender, increased BMI values and larger ascending aorta diameters.

The distribution of histopatological lesions according to age in ascending TAA patients is reported in **supplementary table 3**. Younger patients (aged ≤65: 118, 46.3%) had degenerative lesions more frequently (99, 83.8% vs 73, 53.2%, P<0.001) than those aged >65 (137, 53.7%). By contrast, older patients more frequently had

mixed degenerative-atherosclerotic lesions than younger ones (29, 21.1% vs 10, 8.4%, P=0.008). Overall medial degeneration grading was similar in the two age groups. As to individual degenerative lesions, younger patients showed more intralamellar MEMA, EFTO and ICI, while older ones showed more TCI. No differences were found with respect to EFFL and translamellar MEMA. The grading of atherosclerosis was more frequently severe in the older patients (24, 17.5% vs 5, 4.2%, P=0.001). Aortitis were more frequent in older patients (29, 21.1% vs 6, 5.1%, P<0.001), with a pattern that was predominantly granulomatous-giant cell and healed.

DISCUSSION

Our paper describes the histopathologic findings of a large TAA series using the recent and not yet widely validated AECVP and SCVP classification systems (2,3). This new system is receiving an increasing attention for many reasons including the nomenclature's standardization, a clear definition of diagnostic categories and the standardization of histopathologic diagnostic criteria for inflammatory and degenerative lesions, still a poorly defined topic. Our study documents the applicability and usefulness of such a system in the setting of ascending aorta lesions necessitating surgical therapy.

Although MD is confirmed as the most common finding in ascending TAA (8), atherosclerosis and aortitis are the main histopathologic substrate in a significant number of cases (one in three). Across these main patterns, mixed forms (with two or more types of lesions) are quite common (around 25%).

Comparing the histopathologic profile of ascending TAA patients with that found in a series of patients operated on for type A AAS previously described by our group (4), we can observe first of all that acute and chronic forms have a similar

prevalence of degenerative and atherosclerotic lesions (in AAS isolated MD was found in 77.2% and mainly atherosclerosis in 22.8%). In both ascending TAA and AAS, the coexistence of two or more patterns (mixed forms) is also quite common (about 25%). Notably the presence of LMC is not confined to the degenerative pattern but can also be associated with atherosclerosis and is probably the common final result of different pathogenetic mechanisms; LMC is much more frequent and extensive in the acute setting. AAS patients showed more frequently a greater severity of overall MD lesions when compared to ascending TAA setting (24.1% vs 14.9%) and, finally, aortitis, found in 13.7% of ascending TAA, was not described in the AAS setting.

Our study also provides some interesting clinico-pathologic correlations by comparing clinical profiles across the three main histological patterns (**table 3**) and considering five pre-specified subgroups (**figure 2**). Compared to degenerative patients, atherosclerotic patients with ascending TAA were older and more frequently had a history of hypertension, hypercholesterolemia, diabetes, current smoking, and a history of coronary artery disease. Patients with aortitis were older, mostly female, and with a significantly larger ascending aorta. A similar correlation between sex, age and histological substrate of aortic lesions had been previously underlined by Nesi et al in a cohort of 171 surgically treated TAA (8). In aortitis patients the most common histopathological pattern was granulomatous-giant cell, as in other series (9,10). Approximately 40% of all cases with aortitis showed a healing phase, with massive fibrosis probably protecting the wall from dissection. Chronic periaortitis was associated in 80% of cases and probably contributed to the overall remodelling process. In most cases the diagnosis of aortitis had not been suspected prior to surgery. Aortic and periaortic inflammation can be investigated with non-invasive

imaging techniques, but the therapeutic implications have yet to be been fully established (11).

Ascending TAA patients with atherosclerosis and aortitis frequently had a concomitant abdominal aortic aneurysm. The pathogenetic role of inflammation in aortic aneurysms has been addressed mainly in the context of abdominal aneurysms (12, 13, 14, 15, 16, 17) whereas the implications of inflammatory substrates for thoracic aortic remodelling have yet to be fully established (12, 18, 19). Medial inflammatory response to atherosclerosis is known to concur to a negative histological remodelling of the aortic media (20).

Overall, age was a strong determinant of the histopathologic substrate, with a higher prevalence of atherosclerosis and aortitis in subjects older than 65 (**figure 2**). Age also influences the type of degenerative lesion. Age-related aortic changes include the loss of elastin content with elastic fiber fragmentation and loss and increase of other matrix components, primarily collagen. Fragmentation of elastic fibres creates gaps in the lamellar structure of the aorta, which are partially filled with proteoglycans (T-MEMA). In our cohort, younger patients were found to have I-MEMA and EFTO more frequently, while prevalence of EFFL and T-MEMA were similar in the two age groups. Increased collagen was more frequently intralamellar in young patients and translamellar in older ones, where the scar-like morphology suggests a repair process.

In our cohort it was difficult to assess the effect of genetics on the histological substrate due to the low prevalence of patients with genetic syndromes and the unavailability of systematic genotyping. It is however known that genetic syndromes lead to degenerative changes that are mainly mucoid and that elastic fiber lesions are more extensive and occur at an earlier age (21). A recent study by Waters et al (22)

which analysed 148 surgical ascending aorta specimens (including both aneurysms and dissections) found that MFS cases had more overall MD and MEMA compared to patients with other hereditary syndromes and those with non-syndromic aortopathies. In our study population, the 5 patients with MFS were younger (mean age 37) with a purely degenerative substrate and overall moderate MD in 3 cases and severe in 2. BAV patients showed medial degenerative lesions in about 83% of cases. BAV was frequent in ascending TAA and relatively rare in our previously described series of AAS, but this is at least partially due to a policy of prophylactic surgery in BAV patients with aortic dilatation in our Centre.

STUDY LIMITATIONS

We analysed a single centre cohort with a limited number of patients and without systematic genetic assessment. The possible prognostic implications of histological findings in this setting were not assessed. The exclusion of patients aged <18 necessarily restricted the spectrum of histopathological findings and the contribution of genetic based mechanisms.

CONCLUSIONS

Although degenerative histopathology is the most frequent substrate in ascending TAA, atherosclerosis and inflammation significantly contribute to the development of chronic aortic thoracic disease, in isolation or in mixed patterns. Awareness of the significant burden of aortitis and atherosclerosis-related inflammation could potentially guide future research an innovative therapies in this field.

TABLES AND FIGURES

TABLE 1. STUDY POPULATION CHARACTERISTICS AT PRESENTATION

	ASCENDING TAA N=255
Age (years), median (Q1-Q3)	66 (58-74)
Male gender	189 (74.1%)
BMI (kg/m^2), median (Q1-Q3)	26 (24-28)
Height (cm), mean ± SD	171 ± 10
Hypertension (history)	211 (82.7%)
Antihypertensive therapy	211 (82.7%)
Hypercholesterolemia *	134 (52.5%)
Lipid-lowering therapy	81 (31.7%)
Diabetes	21 (8.2%)
Insulin-dependent diabetes	16 (6.2%)
Non insulin-dependent diabetes	5 (1.9%)
Current smoker	35 (13.7%)
Ex-smoker	84 (32.9%)
Familial history of CAD	48 (18.8%)
Previous ACS/exertion-induced angina	25 (9.8%)
Previous PTCA O CABG	29 (11.3%)
PAOD	1 (0.3%)
Previous stroke/TIA	15 (5.8%)

Clinical diagnosis of aortitis	5 (1.9%)
Aortic coarctation	3 (1.1%)
Bicuspid aortic valve	77 (30.1%)
Turner syndrome	1 (0.3%)
Marfan syndrome °	5 (1.9%)
Loeys-Dietz syndrome °	1 (0.3%)
Ehlers-Danlos syndrome °	0 (0%)
Previous aortic surgery	20 (7.8%)
Previous AAS	7 (2.7%)
Known thoracic aortic aneurysm (surgically treated or not) **	13 (5.1%)
Known abdominal aortic aneurysm (surgically treated or not)	27 (10.5%)
Familial history of aortic disease	15 (5.8%)
GFR (ml/min/1.73m^2), median (Q1-Q3)	84 (66-102)
Systolic blood pressure (mmHg), median (Q1-Q3)	120 (120-135)
Diastolic blood pressure (mmHg), median (Q1-Q3)	80 (70-80)
Maximum ascending aorta diameter (mm), median (Q1-Q3) #	51 (47-55)

AAS: acute aortic syndrome; ACS: acute coronary syndrome; BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; GFR: glomerular filtration rate; PAOD: peripheral arterial occlusive disease; PTCA: percutaneous transluminal coronary angioplasty; SD: standard deviation; TIA: transient ischemic attack.

* When the total cholesterol value was >200 or when the patient took lipid-lowering therapy.

** Aneurysm in a thoracic aortic segment other than ascending.

Data available for 253/255 patients.

° A systematic genotyping was not available, so the effective prevalence of the different genetic syndromes could have been underestimated in our study population.

TABLE 2. HISTOPATHOLOGIC FINDINGS IN THE STUDY POPULATION

	ASCENDING TAA **N=255**
DIAGNOSTIC GROUPS	
Inflammatory-atherosclerosis	9 (3.5%)
Inflammatory-aortitis	8 (3.1%)
Degenerative	172 (67.5%)
Mixed: Degenerative-atherosclerosis	39 (15.2%)
Mixed: Degenerative-aortitis	18 (7.1%)
Mixed: Atherosclerosis-aortitis	3 (1.1%)
Mixed: Degenerative-atherosclerosis-aortitis	6 (2.3%)

TABLE 3. CLINICO-PATHOLOGICAL CORRELATIONS IN PATIENTS WITH THORACIC AORTIC ANEURYSM

	ISOLATED DEGENERATION N=172 (67.5%)	MAINLY ATHEROSCLEROSIS N=48 (18.8%)	AORTITIS +/- ATHEROSCLEROSIS N=35 (13.7%)	P-VALUE
Age (years), median (Q1-Q3)	63 (53-70)	69 (66-75)	75 (71-78)	<0.001
Male gender	141 (81.9%)	37 (77.1%)	11 (31.4%)	<0.001
BMI (kg/m^2), median (Q1-Q3)	26 (24-28)	27 (24-30)	27 (24-30)	0.12
Height (cm), mean ± SD	173 ± 9	171 ± 10	163 ± 10	0.808
Hypertension (history)	136 (79.1%)	42 (87.5%)	33 (94.2%)	0.059
Antihypertensive therapy	137 (79.6%)	41 (85.4%)	33 (94.2%)	0.097
Hypercholesterolemia *	90 (52.3%)	36 (75%)	20 (57.1%)	0.019
Lipid-lowering therapy	40 (23.2%)	30 (62.5%)	11 (31.4%)	<0.001
Diabetes	10 (5.8%)	8 (16.6%)	3 (8.5%)	0.054
Insulin-dependent diabetes	3 (1.7%)	2 (4.1%)	0 (0%)	0.376
Non insulin-dependent diabetes	7 (4%)	6 (12.5%)	3 (8.5%)	0.086
Current smoker	22 (12.7%)	11 (22.9%)	2 (5.7%)	0.066
Ex-smoker	49 (28.4%)	21 (43.7%)	14 (40%)	0.088
Familial history of CAD	32 (18.6%)	12 (25%)	3 (8.5%)	0.162
Previous ACS/exertion-induced angina	14 (8.1%)	9 (18.7%)	2 (5.7%)	0.063
Previous PTCA O CABG	18 (10.4%)	8 (16.6%)	3 (8.5%)	0.417
PAOD	1 (0.5%)	0 (0%)	0 (0%)	0.785

Previous stroke/TIA	9 (5.2%)	3 (6.2%)	3 (8.5%)	0.741
Clinical diagnosis of aortitis	0 (0%)	1 (2.1%)	4 (11.4%)	<0.001
Aortic coarctation	3 (1.7%)	0 (0%)	0 (0%)	0.481
Bicuspid aortic valve	64 (37.2%)	9 (18.7%)	4 (11.4%)	0.002
Turner syndrome	1 (0.5%)	0 (0%)	0 (0%)	0.785
Marfan syndrome	5 (2.9%)	0 (0%)	0 (0%)	0.292
Loeys-Dietz syndrome	1 (0.5%)	0 (0%)	0 (0%)	0.785
Ehlers-Danlos syndrome	0 (0%)	0 (0%)	0 (0%)	NA
Previous aortic surgery	13 (7.5%)	6 (12.5%)	1 (2.8%)	0.264
Previous AAS	6 (3.4%)	1 (2.1%)	0 (0%)	0.491
Known thoracic aortic aneurysm (surgically treated or not) **	6 (3.4%)	5 (10.4%)	2 (5.7%)	0.153
Known abdominal aortic aneurysm (surgically treated or not)	9 (5.2%)	10 (20.8%)	8 (22.8%)	<0.001
Familial history of aortic disease	11 (6.3%)	3 (6.2%)	0 (0%)	0.308
GFR (ml/min/1.73m^2), median (Q1-Q3)	88 (73-103)	79 (64-94)	66 (55-88)	0.471
Systolic blood pressure (mmHg), median (Q1-Q3)	120 (120-130)	120 (120-140)	120 (120-140)	0.219
Diastolic blood pressure (mmHg), median (Q1-Q3)	80 (70-80)	80 (75-80)	80 (70-80)	0.271
Maximum ascending aorta diameter (mm), median (Q1-Q3)	50 (46-53) #	52 (50-58)	56 (51-62)	<0.001

AAS: acute aortic syndrome; ACS: acute coronary syndrome; BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; GFR: glomerular filtration rate; NA: not applicable; PAOD: peripheral arterial occlusive disease; PTCA: percutaneous transluminal coronary angioplasty; SD: standard deviation; TIA: transient ischemic attack.

* When the total cholesterol value was >200 or when the patient took lipid-lowering therapy.

** Aneurysm in a thoracic aortic segment other than ascending.

Data available for 170/172 patients.

406 **TABLE 4. MULTIVARIABLE ANALYSIS FOR CLINICO-PATHOLOGICAL**

407 **CORRELATIONS IN PATIENTS WITH THORACIC AORTIC ANEURYSM:**

408 **ISOLATED DEGENERATION VS**

409

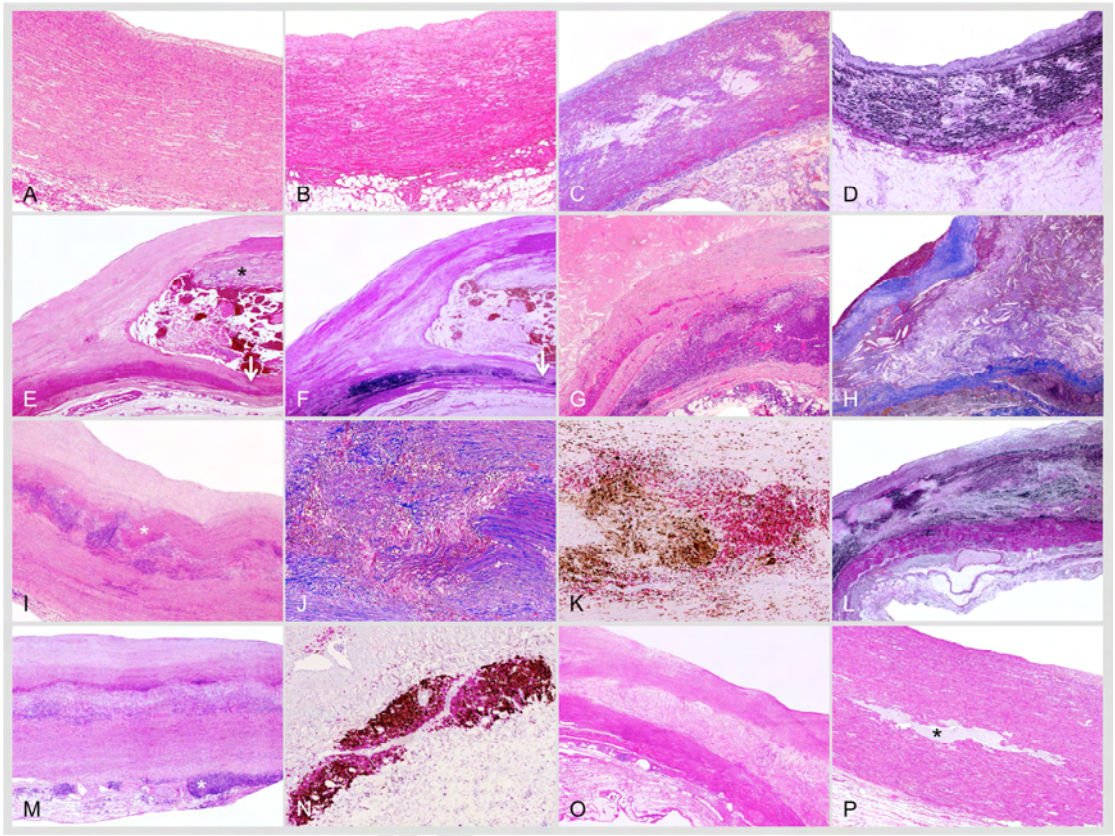
	MAINLY ATHEROSCLEROSIS VS ISOLATED DEGENERATION	**P-VALUE**	**AORTITIS +/- ATHEROSCLEROSIS VS ISOLATED DEGENERATION**	**P-VALUE**	**MAINLY ATHEROSCLEROSIS VS AORTITIS +/- ATHEROSCLEROSIS**	**P-VALUE**
	OR (95% CI)		**OR (95% CI)**		**OR (95% CI)**	
Age (for each 1 year increase)	1.08 (1.03-1.13)	0.002	1.09 (1.03-1.17)	0.004	1.01 (0.95-1.09)	0.676
Male gender	0.45 (0.17-1.23)	0.123	0.05 (0.01-0.15)	<0.001	0.11 (0.04-0.34)	<0.001
BMI (for each 1 kg/m^2 increase)	1.11 (1-1.23)	0.034	1.15 (1.01-1.3)	0.03	1.03 (0.91-1.17)	0.64
Hypertension (history)	0.61 (0.16-2.24)	0.461	2.83 (0.42-18.94)	0.282	4.61 (0.62-34.5)	0.136
Hypercholesterolemia *	2.92 (1.2-7.12)	0.018	1.36 (0.49-3.73)	0.544	0.47 (0.15-1.44)	0.184
Diabetes	2.35 (0.75-7.32)	0.139	1.31 (0.24-7.16)	0.75	0.56 (0.1-0.05)	0.502
Current smoker	3.95 (1.32-11.76)	0.014	0.71 (0.11-4.5)	0.717	0.17 (0.03-1.16)	0.072
Ex-smoker	3.18 (1.32-7.62)	0.009	2.23 (0.74-6.69)	0.151	0.7 (0.22-2.23)	0.55
Previous ACS/exertion-induced angina	1.23 (0.39-3.82)	0.715	0.48 (0.07-3.07)	0.446	0.39 (0.06-2.57)	0.333
Bicuspid aortic valve	0.94 (0.35-2.49)	0.904	0.66 (0.16-2.73)	0.576	0.71 (0.15-3.31)	0.664
Known abdominal aortic aneurysm	1.14 (0.34-3.73)	0.825	1.58 (0.38-6.51)	0.523	1.38 (0.34-5.68)	0.649

(surgically treated or not)						
Maximum ascending aorta diameter (for each 1 mm increase)	1.08 (1.03-1.14)	0.001	1.08 (1.02-1.15)	0.005	0.99 (0.95-1.04)	0.895

ACS: acute coronary syndrome; BMI: body mass index; CI: confidence interval; OR: odds ratio.

* When the total cholesterol value was >200 or when the patient took lipid-lowering therapy.

FIGURE 1. MAIN HISTOPATHOLOGIES OF ASCENDING THORACIC AORTIC ANEURYSM



A-D. Degenerative aneurysm cases. A: Mild medial degeneration prevalently characterized by EFTO and I-MEMA (Haematoxylin-Eosin, 50x). B: Moderate degenerative alterations with EFTO/EFFL and I-MEMA/T-MEMA (Haematoxylin-Eosin, 50x). C-D: Severe medial degeneration with large areas of accumulated extracellular matrix (C, Azan Mallory trichrome stain, 25x) and severe EFFL (D: Weigert-Van Gieson stain, 25x).

E-H. Mainly atherosclerosis pattern. E-F: Advanced fibroatheroma with calcification (asterisk): the underlying medial layer is very thinned and destroyed by replacement fibrosis (E, arrow; Haematoxylin-Eosin, 25x); only residual elastic lamellas are evident (F, arrow; Weigert-Van Gieson stain, 25x). G-H: Inflamed atherosclerosis with plaque rupture: under the plaque and in the periaortic tissue there are extensive

443 inflammatory infiltrates, partially with follicular-like structure (G, asterisk,
444 Haematoxylin-Eosin, 25x; H, Azan Mallory trichrome stain, 25x).
445 I-L. Giant cell aortitis, the most frequent type found. I: Severe and extensive
446 inflammation in the medial layer and at the intimo-medial junction associated with
447 acellular laminar necrosis areas (I, asterisk, Haematoxylin-Eosin, 25x). Inflammatory
448 infiltrates are composed of lymphocytes, macrophages and giant cells with or without
449 granulomas (J: Azan Mallory trichrome stain, 50x). K: Double CD68/CD3
450 immunostaining highlights macrophages and giant cells (brown) and T-lymphocytes
451 (red) (original magnification 100x). L: Elastic fibre staining clearly highlights the
452 severe, widespread alteration of the aortic wall due to the inflammatory disease
453 (Weigert-Van Gieson stain, 25x).
454 M-P. Case of severe aortitis with granulomatous/giant cell pattern and chronic
455 periaortitis (M, asterisk, Haematoxylin-Eosin, 25x). N: Double CD20/CD3
456 immunostaining shows that B lymphocytes (brown) prevail over T lymphocytes (red)
457 (original magnification, 100x). O-P: Aneurysm with mixed atherosclerosis-
458 degenerative pattern: Fibro-atheroma (AHA- grade V) (Haematoxylin-Eosin, 25x)
459 and, in another area, extracellular matrix accumulation (T-MEMA) within an EFFL
460 zone (Haematoxylin-Eosin, 25x).
461
462
463
464
465

FIGURE 2. HISTOPATHOLOGICAL FINDINGS ACCORDING TO PREDEFINED SUBGROUPS IN PATIENTS WITH ASCENDING THORACIC AORTIC ANEURYSM

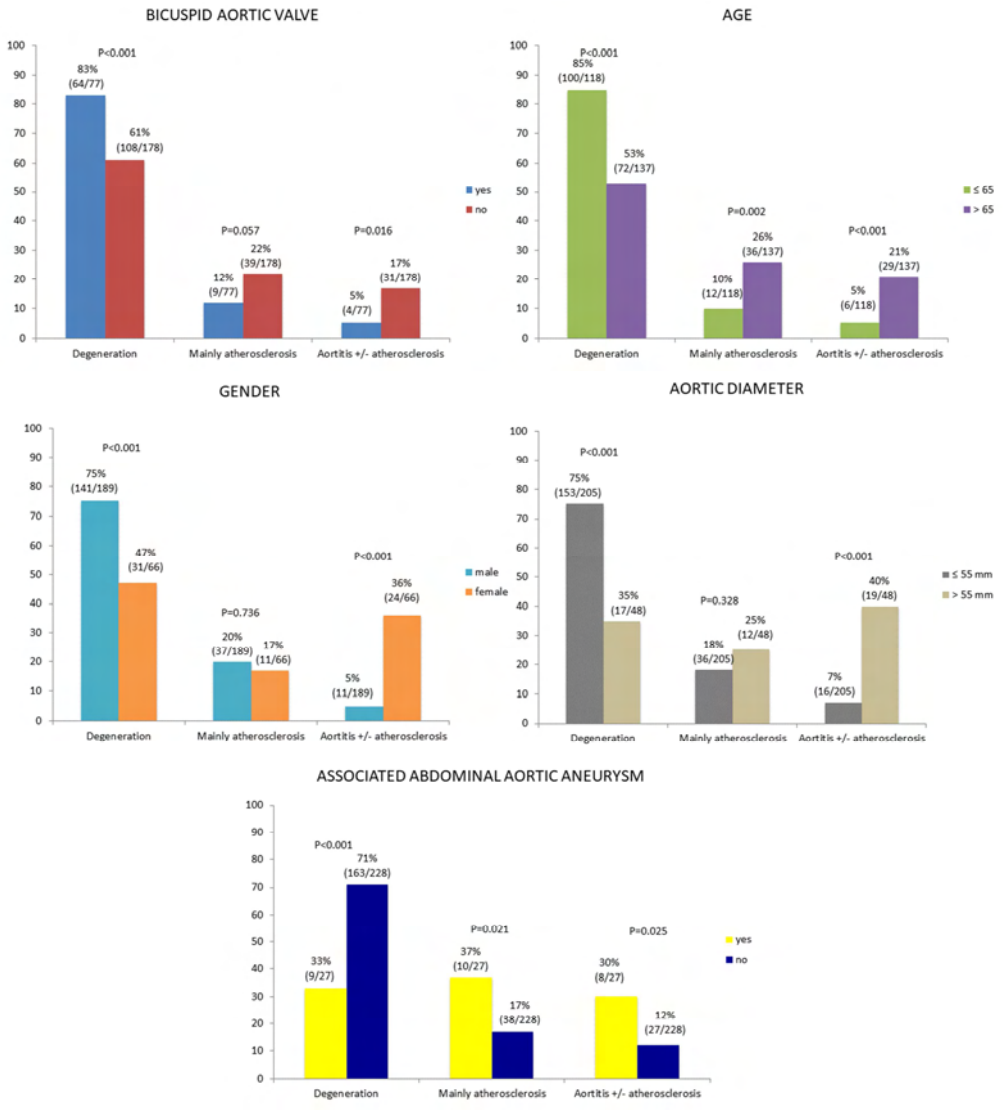
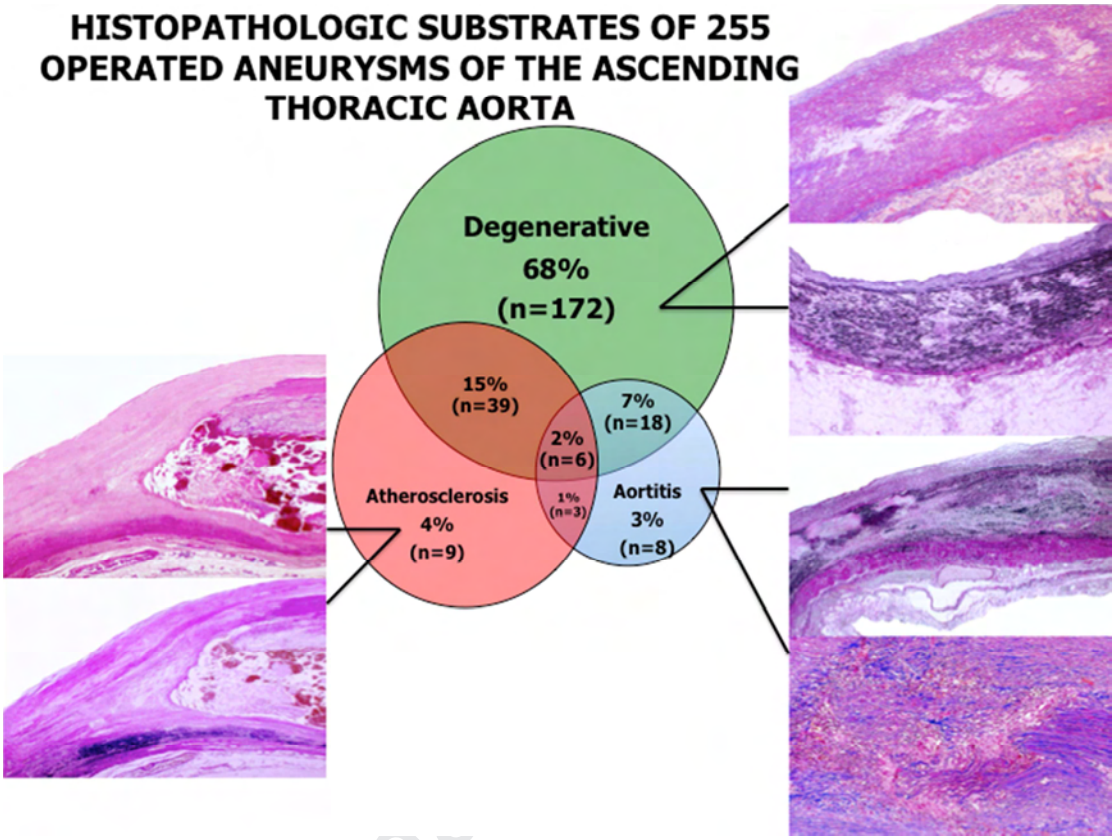


FIGURE 3. THE SPECTRUM OF HISTOPATHOLOGIC FINDINGS IN PATIENTS WITH ASCENDING THORACIC AORTIC ANEURYSM



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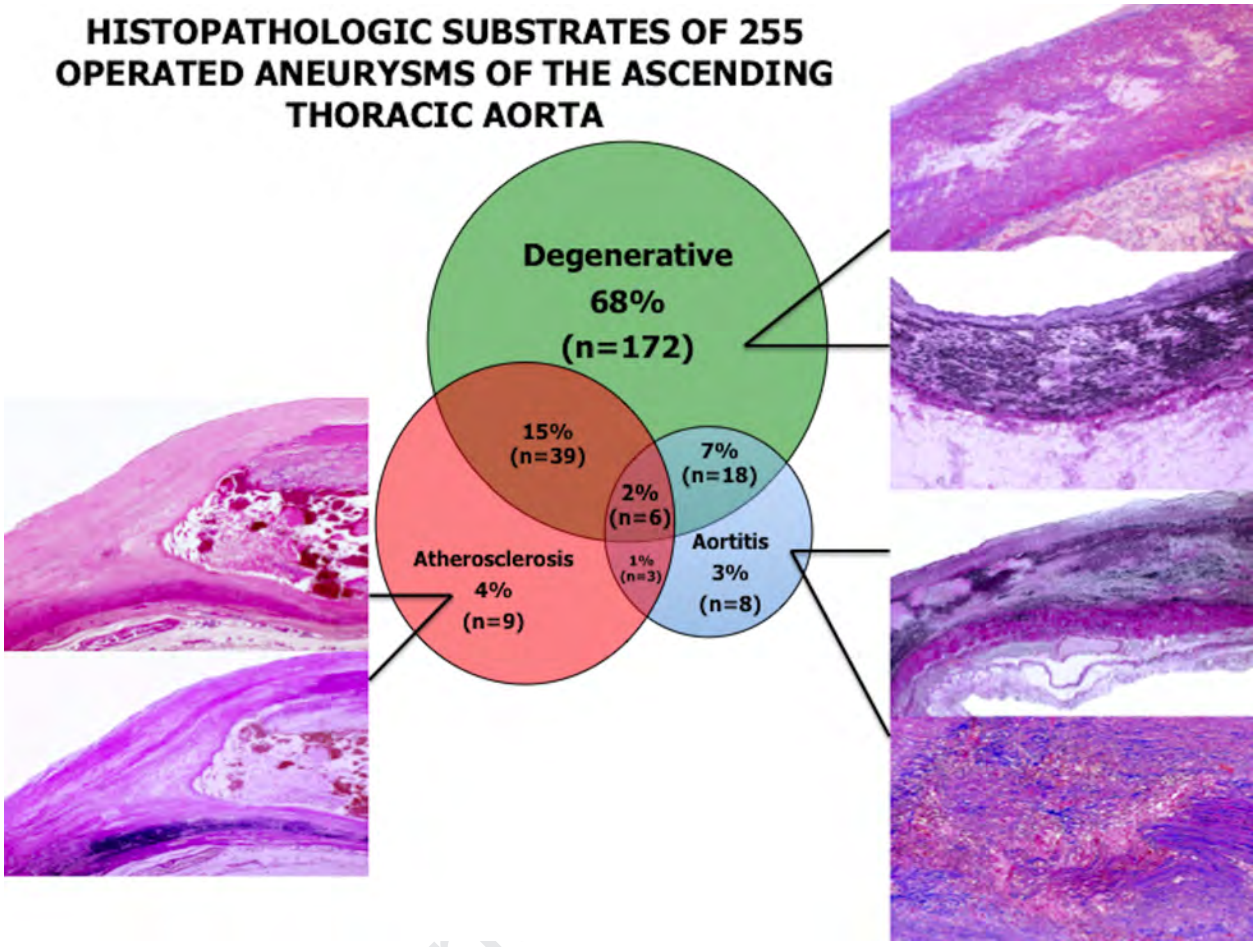
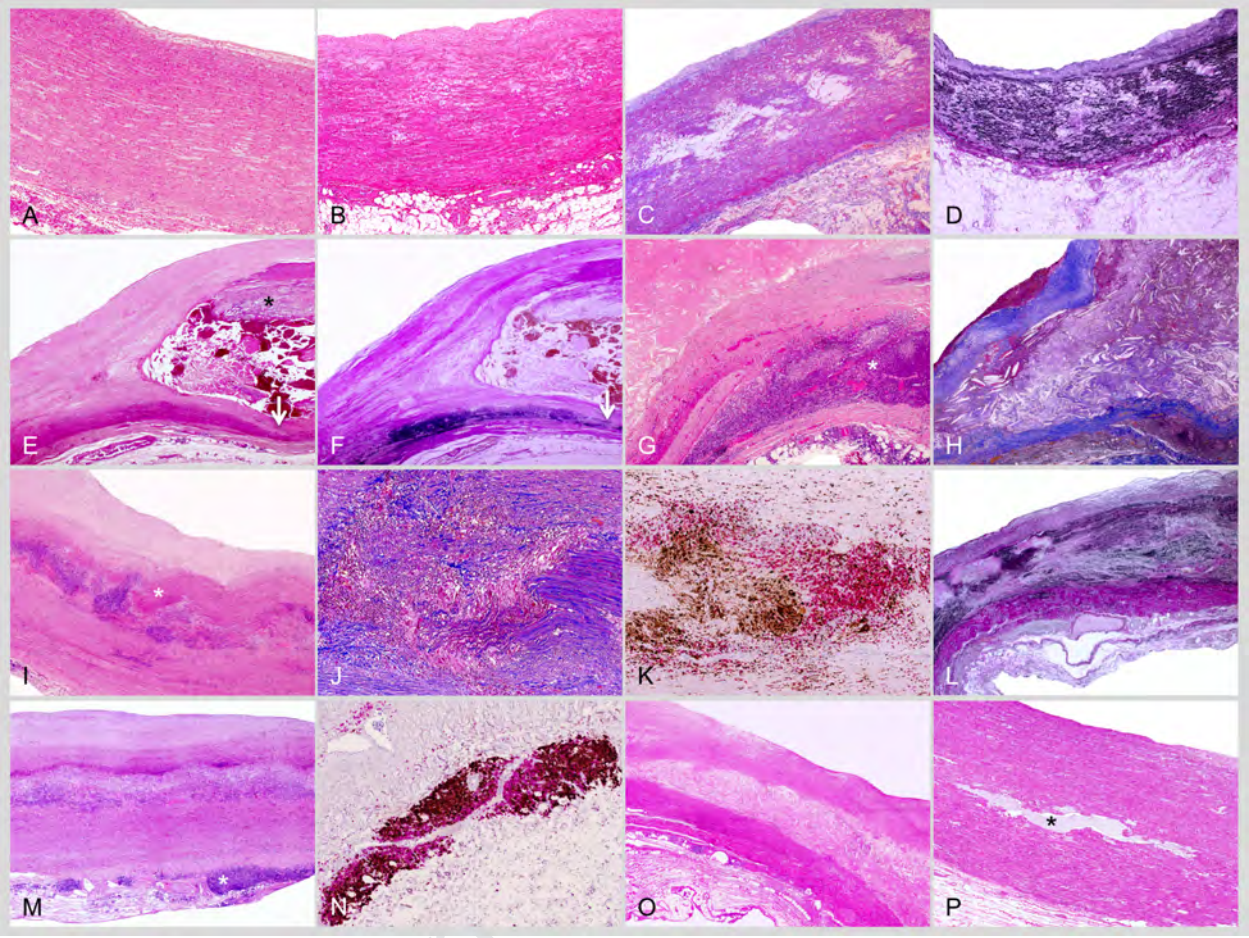
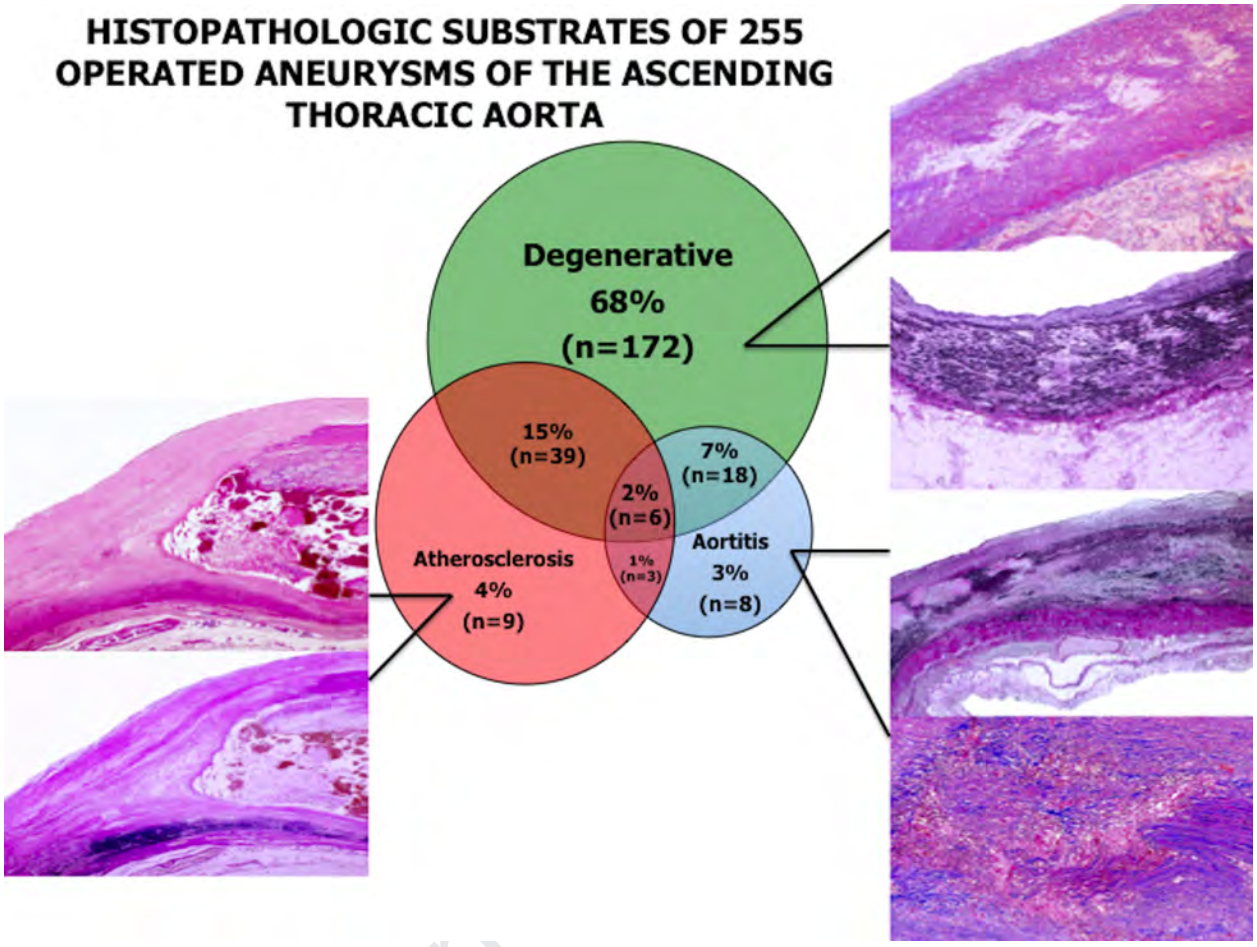

HISTOPATHOLOGIC SUBSTRATES OF 255 OPERATED ANEURYSMS OF THE ASCENDING THORACIC AORTA
Degenerative
68%
(n=172)
15%
(n=39)
7%
(n=18)
2%
(n=6)
Atherosclerosis
4%
(n=9)
1%
(n=3)
Aortitis
3%
(n=8)

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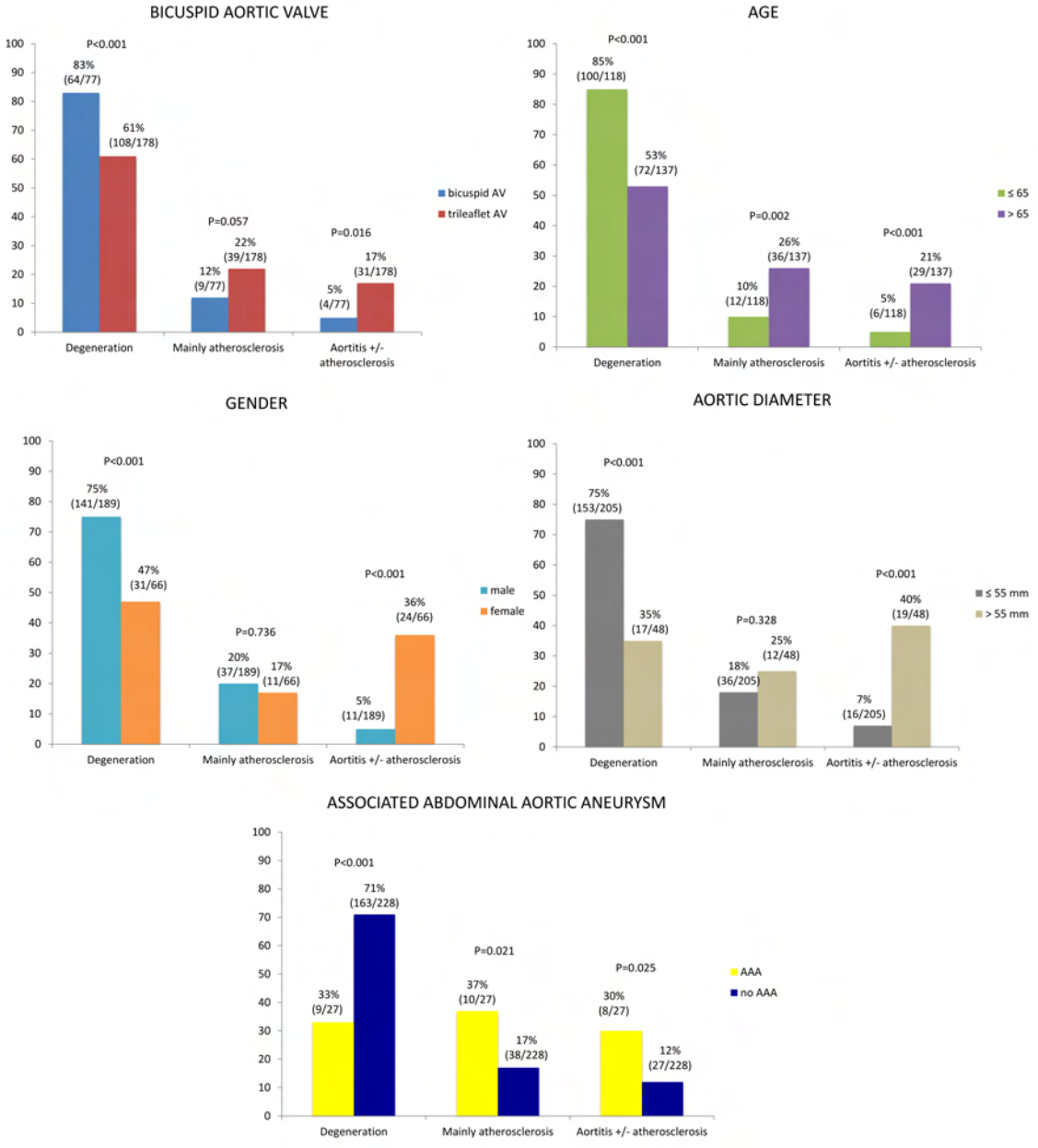
1%
(n=3)
Aortitis
3%
(n=8)


BICUSPID AORTIC VALVE
P<0.001
83% (64/77)
61% (108/178)
P=0.057
12% (9/77)
22% (39/178)
P=0.016
5% (4/77)
17% (31/178)
bicuspid AV
trileaflet AV
Degeneration
Mainly atherosclerosis
Aortitis +/- atherosclerosis
AGE
P<0.001
85% (100/118)
53% (72/137)
P=0.002
10% (12/118)
26% (36/137)
P<0.001
5% (6/118)
21% (29/137)
≤ 65
> 65
GENDER
P<0.001
75% (141/189)
47% (31/66)
P=0.736
20% (37/189)
17% (11/66)
P<0.001
5% (11/189)
36% (24/66)
male
female
AORTIC DIAMETER
P<0.001
75% (153/205)
35% (17/48)
P=0.328
18% (36/205)
25% (12/48)
P<0.001
7% (16/205)
40% (19/48)
≤ 55 mm
> 55 mm
ASSOCIATED ABDOMINAL AORTIC ANEURYSM
P<0.001
33% (9/27)
71% (163/228)
P=0.021
37% (10/27)
17% (38/228)
P=0.025
30% (8/27)
12% (27/228)
AAA
no AAA

SUPPLEMENTARY TABLE 1. CLINICAL FINDINGS IN PATIENTS WITH OR WITHOUT BICUSPID AORTIC VALVE

	BICUSPID AORTC VALVE N=77 (30.2%)	**TRICUSPID AORTIC VALVE N=178 (69.8%)**	**P-VALUE**
Age (years), median (Q1-Q3)	58 (49-67)	69 (62-75)	<0.001
Male gender	58 (75.3%)	131 (73.5%)	0.772
BMI (kg/m^2), median (Q1-Q3)	25 (23-29)	26 (24-28)	0.546
Height (cm), mean ± SD	174 ± 9	170 ± 10	0.997
Hypertension (history)	57 (74%)	154 (86.5%)	0.015
Antihypertensive therapy	56 (72.7%)	155 (87.1%)	0.005
Hypercholesterolemia *	29 (37.6%)	81 (45.5%)	0.217
Lipid-lowering therapy	20 (25.9%)	61 (34.2%)	0.191
Diabetes	8 (10.3%)	13 (7.3%)	0.458
Insulin-dependent diabetes	7 (9.1%)	9 (5.1%)	0.262
Non insulin-dependent diabetes	1 (1.2%)	4 (2.2%)	0.992
Current smoker	10 (12.9%)	25 (14%)	0.978
Ex-smoker	19 (24.6%)	65 (36.5%)	0.081
Familial history of CAD	12 (15.5%)	35 (19.6%)	0.441
Previous ACS/exertion-induced angina	8 (10.3%)	17 (9.6%)	0.836
Previous PTCA O CABG	5 (6.5%)	24 (13.4%)	0.161
PAOD	0 (0%)	1 (0.5%)	0.51
Previous stroke/TIA	2 (2.6%)	13 (7.3%)	0.143
Clinical diagnosis of aortitis	1 (1.3%)	4 (2.2%)	0.616

Aortic coarctation	2 (2.5%)	1 (0.5%)	0.166
Marfan syndrome	1 (1.3%)	4 (2.2%)	0.616
Turner syndrome	0 (0%)	1 (0.5%)	0.51
Loeys-Dietz syndrome	0 (0%)	1 (0.5%)	0.51
Ehlers-Danlos syndrome	0 (0%)	0 (0%)	NA
Previous aortic surgery	4 (5.2%)	16 (8.9%)	0.301
Previous AAS	0 (0%)	7 (3.9%)	0.078
Known thoracic aortic aneurysm (surgically treated or not) **	0 (0%)	13 (7.3%)	0.015
Known abdominal aortic aneurysm (surgically treated or not)	0 (0%)	27 (15.1%)	<0.001
Familial history of aortic disease	2 (2.5%)	13 (7.3%)	0.143
GFR (ml/min/1.73m^2), median (Q1-Q3)	90 (75-106)	83 (64-101)	0.379
Systolic blood pressure (mmHg), median (Q1-Q3)	120 (120-130)	120 (120-140)	0.064
Diastolic blood pressure (mmHg), median (Q1-Q3)	80 (70-80)	70 (70-80)	0.613
Maximum ascending aortic diameter (mm), median (Q1-Q3)	49 (45-51)	52 (48-56) #	<0.001

AAS: acute aortic syndrome; ACS: acute coronary syndrome; BMI: body mass index; CABG: coronary artery bypass graft; CAD: coronary artery disease; GFR: glomerular filtration rate; NA: not applicable; PAOD: peripheral arterial occlusive disease; PTCA: percutaneous transluminal coronary angioplasty; SD: standard deviation; TIA: transient ischemic attack.

* When the total cholesterol value was >200 or when the patient took lipid-lowering therapy.

** Aneurysm in a thoracic aortic segment other than ascending.

Data available for 176/178 patients.

SUPPLEMENTARY TABLE 2. HISTOPATHOLOGIC FINDINGS IN THE STUDY POPULATION

	ASCENDING TAA N=255
DIAGNOSTIC GROUPS	
Inflammatory-atherosclerosis	9 (3.5%)
Inflammatory-aortitis	8 (3.1%)
Degenerative	172 (67.5%)
Mixed: Degenerative-atherosclerosis	39 (15.2%)
Mixed: Degenerative-aortitis	18 (7.1%)
Mixed: Atherosclerosis-aortitis	3 (1.1%)
Mixed: Degenerative-atherosclerosis-aortitis	6 (2.3%)
Atherosclerosis grading Mild	81 (31.7%)
Moderate	28 (10.9%)
Severe	29 (11.3%)
AHA lesions classification AHA 1	5 (1.9%)
AHA 2	37 (14.5%)
AHA 3	62 (24.3%)
AHA 4	19 (7.4%)
AHA 5	35 (13.7%)
AHA 6	9 (3.5%)
AHA 7	13 (5.1%)
Atherosclerosis with excessive inflammation	1 (0.3%)

Inflammatory atherosclerotic aneurysm	1 (0.3%)
AORTITIS	35 (13.7%)
Aortitis patterns Granulomatous/giant cell	20 (7.8%)
Lymphoplasmacytic	2 (0.7%)
Mixed inflammatory	0 (0%)
Suppurative	0 (0%)
Unclassified	0 (0%)
Healing/Healed phase	13 (5.1%)
DEGENERATIVE	235 (92.2%)
Mucoid extracellular matrix accumulation	244 (95.6%)
I-MEMA	201 (78.8%)
I-MEMA grading Mild	72 (28.2%)
Moderate	101 (39.6%)
Severe	28 (10.9%)
I-MEMA extent Focal	17 (6.6%)
Multifocal	167 (65.4%)
Diffuse	17 (6.6%)
T-MEMA	234 (91.7%)
T-MEMA grading Mild	87 (34.1%)
Moderate	108 (42.3%)
Severe	39 (15.2%)

T-MEMA extent	
Focal	54 (21.1%)
Multifocal	174 (68.2%)
Diffuse	7 (2.7%)
Laminar medial collapse	68 (26.6%)
LMC grading	
Mild	16 (6.2%)
Moderate	51 (20%)
Severe	1 (0.3%)
LMC extent	
Focal	40 (15.6%)
Multifocal	26 (10.1%)
Diffuse	2 (0.7%)
Elastic fiber thinning out	201 (78.8%)
EFTO grading	
Mild	70 (27.4%)
Moderate	101 (39.6%)
Severe	30 (11.7%)
EFTO extent	
Focal	21 (8.2%)
Multifocal	163 (63.9%)
Diffuse	17 (6.6%)
Elastic fiber fragmentation and loss	243 (95.2%)
EFFL grading	
Mild	90 (35.2%)

Moderate	97 (38%)
Severe	56 (21.9%)
EFFL extent	
Focal	51 (20%)
Multifocal	179 (70.1%)
Diffuse	13 (5.1%)
Intralamellar collagen increase	219 (85.8%)
ICI grading	
Mild	103 (40.3%)
Moderate	100 (39.2%)
Severe	16 (6.2%)
ICI extent	
Focal	15 (5.8%)
Multifocal	167 (65.4%)
Diffuse	37 (14.5%)
Translamellar collagen increase	92 (36%)
TCI grading	
Mild	6 (2.3%)
Moderate	50 (19.6%)
Severe	36 (14.1%)
TCI extent	
Focal	32 (12.5%)
Multifocal	58 (22.7%)
Diffuse	2 (0.7%)
Overall MD grading	

Mild	66 (25.8%)
Moderate	130 (50.9%)
Severe	38 (14.9%)
Periaortitis	45 (17.6%)
Periaortitis grading Mild	10 (3.9%)
Moderate	26 (10.1%)
Severe	9 (3.5%)

SUPPLEMENTARY TABLE 3. HISTOPATOLOGICAL FINDINGS ACCORDING TO AGE AT PRESENTATION IN PATIENTS WITH THORACIC AORTIC ANEURYSM

	PATIENTS AGED ≤ 65 **N=118 (46.3%)**	**PATIENTS AGED > 65** **N=137 (53.7%)**	**P-VALUE**
DIAGNOSTIC GROUPS			
Inflammatory-atherosclerosis	3 (2.5%)	6 (4.3%)	0.650
Inflammatory-aortitis	1 (0.8%)	7 (5.1%)	0.112
Degenerative	99 (83.8%)	73 (53.2%)	<0.001
Mixed: Degenerative-atherosclerosis	10 (8.4%)	29 (21.1%)	0.008
Mixed: Degenerative-aortitis	5 (4.2%)	13 (9.4%)	0.165
Mixed: Atherosclerosis-aortitis	0 (0%)	3 (2.1%)	0.3
Mixed: Degenerative-atherosclerosis-aortitis	0 (0%)	6 (4.3%)	0.059
Atherosclerosis grading Mild	41 (34.7%)	40 (29.1%)	0.415
Moderate	8 (6.7%)	20 (14.5%)	0.073
Severe	5 (4.2%)	24 (17.5%)	0.001
AHA lesions classification AHA 1	3 (2.5%)	2 (1.4%)	0.866
AHA 2	17 (14.4%)	30 (21.8%)	0.168
AHA 3	32 (27.1%)	30 (21.8%)	0.410

AHA 4	9 (7.6%)	10 (7.2%)	0.920
AHA 5	9 (7.6%)	26 (18.9%)	0.014
AHA 6	3 (2.5%)	6 (4.3%)	0.651
AHA 7	1 (0.8%)	12 (8.7%)	0.009
Atherosclerosis with excessive inflammation	0 (0%)	1 (0.7%)	0.352
Inflammatory atherosclerotic aneurysm	0 (0%)	1 (0.7%)	0.352
AORTITIS	6 (5.1%)	29 (21.1%)	<0.001
Aortitis patterns Granulomatous/giant cell	4 (3.3%)	16 (11.6%)	0.026
Lymphoplasmacytic	0 (0%)	2 (1.4%)	0.544
Mixed inflammatory	0 (0%)	0 (0%)	1
Suppurative	0 (0%)	0 (0%)	1
Unclassified	0 (0%)	0 (0%)	1
Healing/Healed phase	2 (1.6%)	11 (8%)	0.044
DEGENERATIVE	114 (96.6%)	121 (88.3%)	0.026
Mucoid extracellular matrix accumulation	115 (97.4%)	129 (94.1%)	0.325
I-MEMA	102 (86.4%)	99 (72.2%)	<0.001
I-MEMA grading Mild	41 (34.7%)	31 (22.6%)	0.045
Moderate	46 (38.9%)	55 (40.1%)	0.951
Severe	15 (12.7%)	13 (9.4%)	0.535
I-MEMA extent	11 (9.3%)	6 (4.3%)	0.184

Focal			
Multifocal	83 (70.3%)	84 (61.3%)	0.167
Diffuse	8 (6.7%)	9 (6.5%)	0.946
T-MEMA	108 (91.5%)	126 (91.9%)	0.897
T-MEMA grading Mild	43 (36.4%)	44 (32.1%)	0.552
Moderate	49 (41.5%)	59 (43%)	0.903
Severe	16 (13.5%)	23 (16.7%)	0.589
T-MEMA extent Focal	26 (22%)	28 (20.4%)	0.875
Multifocal	79 (66.9%)	95 (69.3%)	0.783
Diffuse	3 (2.5%)	3 (2.1%)	0.853
Laminar medial collapse	31 (26.2%)	37 (27%)	0.894
LMC grading Mild	10 (8.4%)	6 (4.3%)	0.277
Moderate	20 (16.9%)	31 (22.6%)	0.330
Severe	1 (0.8%)	0 (0%)	0.940
LMC extent Focal	19 (16.1%)	21 (15.3%)	0.865
Multifocal	10 (8.4%)	16 (11.6%)	0.525
Diffuse	2 (1.6%)	0 (0%)	0.413
Elastic fiber thinning out	102 (86.4%)	99 (72.2%)	0.009
EFTO grading Mild	42 (35.5%)	28 (20.4%)	0.01
Moderate	45 (38.1%)	56 (40.8%)	0.750

Severe	15 (12.7%)	15 (10.9%)	0.809
EFTO extent Focal	12 (10.1%)	9 (6.5%)	0.415
Multifocal	82 (69.4%)	81 (59.1%)	0.112
Diffuse	8 (6.7%)	9 (6.5%)	0.946
Elastic fiber fragmentation and loss	109 (92.3%)	134 (97.8%)	0.08
EFFL grading Mild	46 (38.9%)	44 (32.1%)	0.311
Moderate	46 (38.9%)	51 (37.2%)	0.873
Severe	17 (14.4%)	39 (28.4%)	0.01
EFFL extent Focal	26 (22%)	25 (18.2%)	0.550
Multifocal	79 (66.9%)	100 (72.9%)	0.360
Diffuse	4 (3.3%)	9 (6.5%)	0.386
Intralamellar collagen increase	107 (90.6%)	112 (81.7%)	0.06
ICI grading Mild	59 (50%)	44 (32.1%)	0.005
Moderate	43 (36.4%)	57 (41.6%)	0.475
Severe	5 (4.2%)	11 (8%)	0.324
ICI extent Focal	8 (6.7%)	7 (5.1%)	0.765
Multifocal	80 (67.7%)	87 (63.5%)	0.557
Diffuse	19 (16.1%)	18 (13.1%)	0.623

Translamellar collagen increase	28 (23.7%)	64 (46.7%)	<0.001
TCI grading Mild	3 (2.5%)	3 (2.1%)	0.853
Moderate	17 (14.4%)	33 (24.1%)	0.07
Severe	8 (6.7%)	28 (20.4%)	0.003
TCI extent Focal	12 (10.1%)	20 (14.5%)	0.381
Multifocal	15 (12.7%)	43 (31.3%)	<0.001
Diffuse	1 (0.8%)	1 (0.7%)	0.915
Overall MD grading Mild	36 (30.5%)	30 (21.8%)	0.155
Moderate	57 (48.3%)	73 (53.2%)	0.504
Severe	21 (17.7%)	17 (12.4%)	0.303
Periaortitis	10 (8.4%)	35 (25.5%)	<0.001
Periaortitis grading Mild	2 (1.6%)	8 (5.8%)	0.168
Moderate	6 (5.1%)	20 (14.5%)	0.02
Severe	2 (1.6%)	7 (5.1%)	0.257