Marfan and Loeys-Dietz aortic phenotype: a potential tool for diagnosis and management

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A comparative retrospective CTI and MRI analysis of aortic morphology in three cohorts of LDS, MFS patients and controls.

Patients diagnosed at advanced disease stage or with less than optimal image quality were excluded.

- 19 LDS patients
- 20 controls
- 95 MFS patients

- Ao diameters
- Diameters/length ratios
- Arterial Vessel Analysis software
- Ao Lengths and Tortuosity

This morphologic comparative study:

- Found some aortic profiles and indexes as easy tools to differentiate LDS and MFS patients at early disease stages, especially when genetic analysis is lacking.

- Suggested further analysis and research to learn the different physiopathologic mechanisms and behavior of these two rare diseases.
TITLE: Marfan and Loeys-Dietz aortic phenotype: a potential tool for diagnosis and management

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Central Message:
Distinct aortic patterns identified by whole-body imaging help to differentiate Marfan from Loeys-Dietz patients, aiding early diagnosis, with potential impact on prognosis and management.

Perspective Statement:
Recognizing unique aortic patterns through CT and MRI in Marfan and Loeys-Dietz syndromes is pivotal, shedding light on genetic influences on aortic development. A
focused follow-up might be able to identify which subtype of anatomy is associated to a
high risk of dissection irrespective of aortic dilation

Central Picture:
CT/MR morphologic comparison identifies aortic phenotypes for early differentiation
STRUCTURED ABSTRACT

Objective

In heritable aortic diseases, different vascular involvement may occur with potential variable implications in aortic dilation/dissection risk. This study aimed to analyse the aortic anatomy of individuals with Marfan syndrome and Loeys-Dietz Syndrome, to identify possible morphological differences.

Methods

Computed Tomography and Magnetic Resonance imaging of the thoraco-abdominal aorta from the proximal supraortic vessels to the femoral bifurcation level of 114 Marfan and Loeys-Dietz patients and 20 matched control subjects were examined. Aortic diameters, areas, length, tortuosity were measured in different aortic segments using specific vessel analysis software.

Results

Marfan patients showed higher prevalence of ascending aorta and aortic root dilation \((p=0.005)\), larger and longer aortic root \((p=0.013)\) with pear-shaped phenotype, larger isthmus/descending aorta diameter ratio \((p=0.006)\), larger suprarenal aorta and iliac arteries. Loeys-Dietz patients showed longer indexed segments, significantly longer arch \((p=0.006)\) with type 2/3 arch prevalence \((p=0.097)\). Measurement ratios analysis provided cut-off values (aortic root-to-ascending aorta length/aortic root diameter, aortic root/sino-tubular junction, aortic root/ascending aorta diameter) differentiating Marfan from Loeys-Dietz patients, even in early stage of the disease.
Conclusions

Both syndromes show peculiar anatomical patterns at different aortic levels irrespective of aortic dilation and disease severity. These features may represent the expression of different genetic mutations on aortic development, with potential impact on prognosis and possibly contributing to better management of the diseases. The systematic adoption of whole body imaging with Magnetic Resonance or Computed Tomography should always be considered, as they allow a complete vascular assessment with practical indicators of differential diagnosis.

Word Count: 248

KEYWORDS:

Aortic anatomy; aortic root; Computed Tomography; Loeys-Dietz syndrome; Marfan syndrome; Magnetic Resonance Angiography
INTRODUCTION

The understanding of aortic disease has grown in the past decades. Among the young adult and adolescent population, hereditary aortic diseases represent a distinct yet clinically significant group of conditions (1–3). Identification of specific genes associated with hereditary thoracic aortic aneurysm and dissection has defined molecular mechanisms underlying aneurysm formation, highlighting the scientific and clinical attention to these entities (4,5). However, individuals with hereditary thoracic aortic diseases may remain undiagnosed, resulting in a substantial healthcare burden.

Marfan syndrome (MFS) and Loeys-Dietz syndrome (LDS) stand as the two more frequent forms of hereditary thoracic aortic disease (HTAD). MFS typically arises from heterozygous mutations in FBN1, a gene responsible for encoding the extracellular matrix protein fibrillin-1. Its predominant cardiovascular manifestation involves aortic aneurysms and dissections in the sinuses of Valsalva. On the other hand, LDS is associated with mutations in TGBR1/2, SMAD2/3, or TGFB2/3, genes that encode components of the TGFβ-signaling pathway. Both syndromes exhibit marked pleiotropism, displaying variable manifestations of skeletal, ocular, and cardiovascular defects, with the latter contributing most significantly to morbidity and mortality, impacting prognosis and life expectancy (6). Despite some characterizing features, phenotypical and clinical overlap between LDS and MFS patients can occur, as well as among young adults and especially tall stature athletes, causing unrecognition or delay in diagnosis and treatment (7). Compared to MFS, cardiovascular manifestations in LDS tend to be more severe and aggressive (8). Thus, timely and accurate diagnosis is paramount to enhance a patient's survival prospects and prevent severe complications.

For many years echocardiography was the only imaging technique used to evaluate
aortic involvement in HTAD. Recently, evolution of total body imaging techniques has led to a wider definition of vascular involvement in these disorders (9). Nevertheless, a systematic comparison of the aortic anatomy of LDS and MFS patients has never been considered. Aim of this study was to analyse segmental differences in aortic morphology between two cohorts of LDS and MFS patients, with the goal of identifying distinctive features of aortic involvement and specific aortic anatomical profiles.

METHODS

STUDY SUBJECTS AND DESIGN

A multicenter observational retrospective analysis of aortic morphology was conducted in patients with a confirmed diagnosis of LDS and MFS who underwent Magnetic Resonance Angiography (MRA) or Computed Tomography Angiography (CTA) of the aorta at the time of diagnosis or during initial clinical and imaging follow-up by two Nationwide Marfan and Heritable Rare Thoracic Aortic Diseases Hub centers (Bologna and Ancona, Italy) from July 2006 to August 2020. The study was approved by local ethics committee (EM624-2019_246/2016/O/Oss/AOUBo, July 17, 2019). Informed consent was obtained from all study participants in accordance with the Declaration of Helsinki and national legal regulations. All LDS patients had a confirmed pathogenic variant in one of the 6 genes known to be responsible for the disease (TGBR1/2, SMAD2/3, or TGFB2/3). The diagnostic criteria for MFS patients were a confirmed pathogenic variant in FBN1 gene and a clinical diagnosis according to the revised Ghent nosology (10,11). 270 MFS and 55 LDS patients were screened for enrollment. Exclusion criteria were age under 18-year-old (pediatric patients were excluded to account for completely grown-up aortic morphology), insufficient imaging quality due
to motion artifacts and incomplete examinations (absence of a 3D volume setting of contrast-enhanced or unenhanced MRA) and a history of thoracic aortic surgical/endovascular treatment or aortic dissection at the time of enrollment without a previous CTA or MRA available. In addition, when the first CTA or MRA available was close to aortic surgical intervention or showed large aortic aneurysms, the patient was excluded as an expression of an advanced aortic disease, avoiding potential selection bias.

114 patients from the original dataset were enrolled, 95 MFS and 19 LDS. The aortic morphology was evaluated comparing aortic diameters, lengths, areas, tortuosity, anatomic variants, and arch type prevalence between the two groups. Additional measurements (length and diameters) ratios were considered. The thoracic aorta morphology was also analyzed comparing the two groups with a third cohort of 20 age and sex-matched controls with no history and no evidence of aortic disease. Clinical and epidemiological data were obtained from the outpatient Medical Reports for all the patients visited in the Marfan Centers and the comparative analysis between the two cohorts is summarized in Table 1.

IMAGING ANALYSIS

MRA imaging was performed with two 1.5-Tesla MR scanners (General Electric Medical System, Waukesha, Wis, and Philips Medical Systems, The Netherlands), while CTA imaging was conducted by a 16,128 and 192x2-channel scanners (Siemens Healthineers, Erlangen, Germany and Philips Medical Systems, The Netherlands). In our center we perform MRA as first choice to reduce the dose radiation burden in a relatively young population. CTA was used alternatively due to a higher system
availability. A complete detailed description concerning imaging techniques and protocols, aortic segmentation and measurements methodology is presented in the Supplementary Material, Supplementary Method section. MRA and CTA protocols always included a 3D angiographic arterial acquisition of the thoraco-abdominal aorta from the proximal supraortic vessels to the femoral bifurcation level. The thoraco-abdominal aorta was divided into several segments following widespread used clinical practice. Ascending aorta (AA) was measured at three levels: proximal AA, pulmonary bifurcation level and distal AA. The aortic diameter measurements were performed according to the most recent international guidelines (12,13) on at least two perpendicular planes using multiplanar reformatted reconstructions (MPR) with manual delineation and confirmed by the semiautomated Arterial Vessel Analysis software (Intelli Portal, Philips) that provides double oblique transverse-oriented images for every point of the selected aortic segment. The aortic root (AR) diameters were calculated measuring the three sinus-to-sinus distances (intercoronary, left coronary-non coronary, right coronary-non coronary) at the point of maximum expansion also to search for potential asymmetries. A per-segment analysis as well for total thoraco-abdominal aorta was performed for length, tortuosity index and areas calculations. All these measurements were applied using the Arterial Vessel Analysis software. The centerline approach was used for length and tortuosity measurements. The arch type was defined following the interventional classification proposed by Marrocco-Trischitta MM et al (14), based on the ratio between the distance of the IA ostium from the top of the aortic arch and the left common carotid artery caliber; a value <1 indicate a type I, >2 indicate the type III, type II arch correspond to a value between 1 and 2. The larger is the distance from the top of the arch, the highest is the degree of the aortic arch slope.
The elongated transverse aortic arch was identified following Kim et al definition (15). A retrospective review of all MRA and/or CTA examinations was independently conducted by two experienced readers (radiologists’ expert on cardiovascular imaging). The criteria used to choose on which imaging modality perform the measurements in patients when both CTA and MRA were available was the image quality. When this was equal we preferred the CT measures, because are easier to handle.

STATISTICAL ANALYSIS
All the analyses were conducted in SPSS version 23 [SPSS Inc., Chicago, IL, USA], Microsoft Windows version. Normality of data distribution was examined with the Kolmogorov-Smirnov test. Continuous variables are expressed as mean ± Standard Deviation or median with interquartile range as appropriate, anyway the second system has been used systematically due to several variables without a normal distribution for all groups. Categorical variables are expressed as a percentage. For the continuous variables, comparisons between two groups were made using t-tests while for three or more groups with ANOVA and Bonferroni test for multiple comparisons. The analysis of non-parametric variables used Mann Whitney test while for three or more groups Kruskall-Wallis test. For categorical variables we used the chi-square test. The most significant continuous variables were first tested for linearity of the association with pathologies using restricted cubic splines, ROC analysis have been constructed to identify the most appropriate cut-off value in order to discriminate between the two populations; p≤0.05 from 2-sided tests was considered statistically significant.
RESULTS

Ninety-five MFS and 19 LDS patients were included in the final analysis. The two cohorts were similar in age, sex and imaging modality used for the aorta examination. There were no statistically significant differences for all the comorbidities potentially affecting aortic morphology except a larger proportion of obesity among LDS (21% vs 4% \( p=0.02 \)) and a greater BSA in MFS (Median and interquartile range (IR) 1.9 m\(^2\), 1.75-2.09 m\(^2\) vs. 1.74, 1.68-1.84 m\(^2\); \( p=0.012 \)) as foreseen. MFS patients showed a higher prevalence of AA and AR dilation (82% vs 50%, \( p=0.005 \)), intended as Z-score\( \geq +2 \), Campens’s normograms (16). Conversely, among clinical and epidemiological features, LDS group differs significantly for its stronger familial history for aortic aneurysms (prevalence 66.7% vs 17%, \( p<0.001 \)) and the combined aortic pathology and sudden death events. All baseline features are summarized in Table 1.

COMPARATIVE ANALYSIS OF AORTIC DILATION

MFS group show diffusely larger aortic dimensions than LDS cohort, especially at the AR and suprarenal level, but also AA and isthmus, with significantly greater values of all the three sinus-to-sinus diameters (median and IR 40mm, 36-43.25 vs 36.5mm, 30.2-40.5mm for left-to-right coronary sinus diameter, \( p=0.005 \)) and both coronal and sagittal measures of suprarenal abdominal aorta (median and IR 19 mm, 14-20 mm vs 15.13-17.75 and 19.5 mm, 16-22 mm vs 17 mm, 14.25–19 mm respectively; \( p<0.05 \)), confirmed after adjusting the aortic diameters for BSA (median and IR non-coronary-to-right sinus diameter 21.06 mm/m\(^2\), 19.48-22.8 mm/m\(^2\) vs 18.52mm/m\(^2\), 16.4-22.77 mm/m\(^2\), \( p=0.041 \)). MFS patients also have greater iliac arteries dimensions and a higher
prevalence of iliac artery dilatation (18.1% vs 10.5%), especially left iliac artery (14.9% vs 5.3%), while interestingly LDS group tends to larger values in the distal arch and middle-to-distal descending thoracic aorta. The distribution of Z score values for AR and AA among the 3 cohorts are illustrated by frequency histograms (Figure 1). The absolute and BSA-indexed aortic diameters distribution and relative differences are also represented by box plots for AR, sino-tubular junction (STJ) and AA in the same cohorts (Figure 2). A clear distinction of MFS values from both LDS and controls is evident for AR diameters. LDS group shows larger overlapping of aortic dimensions with controls, with similar median values in AA. The comparison of the whole spectrum of absolute and BSA-indexed thoraco-abdominal aorta diameters is shown in Supplementary Table 1. Box-plots representations of aortic absolute diameters comparison of the whole thoraco-abdominal aorta among our cohorts are displayed by Supplementary Figure 1

MORPHOLOGIC PARAMETERS

MFS group has a significantly longer AR measured from the aortic annulus to the STJ (median and IR: 26mm, 23-29mm vs. 23 mm, 20-26mm; p=0.043). AR asymmetries are equally distributed in both syndromes, representing 25 - 30% of cases. LDS patients show longer length in several aortic segments, in particular show longer aortic arch and suprarenal aorta (median and IR: 37 mm, 30-46mm vs. 32 mm, 25-39mm; p=0.053 and 80 mm, IR 61-96mm vs. 69 mm, 56-80mm, p=0.038). Type 1 aortic arch is prevalent in MFS group (67.4% vs 47.4%) while LDS patients show a larger representation of type 2-3 aortic arch (52.6% vs 32.6%) and elongated aortic arch. Length measurements and the aortic arch morphologic patterns are summarized in Table 2. No significant
differences were noted in tortuosity index. The complete dataset concerning areas and tortuosity index are presented in Supplementary Table 2. Among the additional measurement ratios considered in the comparative analysis of aortic morphology, the AR-to-AA length/AR diameter ratio is significantly lower in MFS than LDS patients, while the AR/STJ and AR/AA diameter ratios are significantly higher in MFS population. These simple morphometric ratios could help to differentiate the two syndromes. The same analysis has been repeated between the two cohorts according to the presence/absence of AR and/or AA dilation. The significant differences of these measurement ratios between MFS and LDS population have been confirmed among the patients without associated aortic dilation (median and IR: AR-to-AA length/AR diameter 2.10, 1.95-2.27 vs. 2.26, 2.15-2.51, \( p = 0.027 \), AR/STJ diameter 1.25, 1.18-1.33 vs. 1.10, 1.06-1.15; \( p = 0.007 \) and AR/AA diameter, 1.22, 1.07-1.33 vs. 1.05, 0.95-1.11; \( p = 0.008 \) respectively). This result is of great relevance, reinforcing the idea of the discriminating role of these morphologic indexes especially at early aortic disease stages, suggesting their preemptive value considering the higher risk profile for aortic events in LDS. A further confirmation of the diagnostic value of these morphologic ratios comes from their interpolation curves, that identify cut-off values able to differentiate the two syndromes. Especially cut-off values have been identified for AR/STJ (≥1.19) and AR/AA diameter ratios (≥1.15) While specificity, positive predictive value and negative predictive value are respectively 63%, 91.3% and 35.3% and 58%, 90.4%, 35.5%.

The corresponding ROC curves illustrate a sensitivity to differentiate LDS from MFS patients of 76% (AUC: 0.69; 95% CI: 0.54-0.83) and 79% (AUC 0.724; 95% CI: 0.58-0.86) respectively (Figure 3). Moreover, the aortic isthmusdescending thoracic aorta
diameter ratio resulted to be greater in MFS than in LDS among patients with aortic dilation (median and IR 1.11-1.27 vs. 1.08, 1.03-1.09; p=0.015). The most relevant morphometric indexes are summarized in Table 3. Spline Interpolation and ROC curves of AR-to-AA length/AR diameter ratio are also shown in Supplementary Figure 2.

DISCUSSION

MFS and LDS are the most common and clinically relevant HTAD. Both syndromes derive from extracellular matrix components alterations and share a marked genetic heterogeneity and pleiotropism. More than 1800 mutations of FBN1 gene have been recognized in MFS (17,18), while LDS is characterized by mutation of several genes all coding for TGFβ signalling components (19,20). Cardiovascular manifestations and especially aortic complications account for the highest mortality and morbidity rates in both syndromes (21,22). Notably, LDS tends to manifest with greater severity, often leading to aortic dissection at an earlier age and at smaller aortic diameters, as evidenced by a lower median survival rate (22–24). Life expectancy has been progressively improved in MFS by early diagnosis and prophylactic surgical AR replacement based on aortic diameter measurements (25). Therefore, early recognition could have beneficial effects in terms of survival and disease management. Despite some distinctive and at times striking features, such as elongated arm span or arachnodactyly in MFS and the unique presence of hypertelorism, bifid uvula, or cleft palate in LDS, both syndromes exhibit considerable phenotypic overlap. This has been affirmed by the recent recognition of LDS as a distinct entity (19,26). Moreover, specific characteristics like widespread arterial aneurysms and peripheral vascular
tortuosity in LDS (27,28) or musculoskeletal characteristics in MFS often account for no more than 30-50% of subjects (29). The marked variability of disease phenotypic expression may also hamper their distinction from normal subjects, especially in the context of tall stature athletes.

MORPHOLOGIC INDEXES IN THE DIFFERENTIAL DIAGNOSIS

Our study confirms the preeminent dilation of the AR and AA in both syndromes with a significantly higher prevalence of aortic dilation in MFS. Additionally, the predominant arch morphologies in LDS were type 2-3, which are closer to the "gothic" arch geometry and have a higher risk of type B dissection (14,30-31). The elongated aortic arch is also more prevalent in LDS patients, and it is another feature potentially associated to a more severe aortic disease. These aspects correspond to the literature evidence of a more severe course of cardiovascular alterations in LDS (24,32). The per-segment analysis of aortic dimensions in LDS revealed a larger distribution of normal values. We observed a clear distinction between MFS patients and normal subjects, while LDS values may overlap with the normal pattern (Figure 1-2, Supplementary Table 1), revealing itself as a more insidious syndrome. Therefore aortic tortuosity or arch elongation observed in LDS despite normal diameters, as a comprehensive aortic phenotypic tool may represent a first red flag of disease suspicion respect to normal population, which in our control series lacks completely these morphologic features. The analysis of measurements ratios, especially at the level of AR and AA complex, was performed to highlight the morphologic differences evidenced between LDS and MFS. AR-to-AA length/AR diameter was significantly lower in MFS, while AR/STJ and AR/AA diameter are larger in Marfan patients. The corresponding ROC curves
illustrate the discrimination power of the cut-off values identified for these indexes with a sensitivity up to 80% for the AR/AA diameter ratio and AUC 0.724 with 95% CI 0.58-0.86 (Figure 3-4).

CLINICOPATHOLOGICAL IMPACT OF AORTIC PHENOTYPES

Crucially, our analysis revealed the exceptional discriminatory power of these ratios (Figure 4), especially in patients lacking aortic dilation at these levels. This emphasizes the presence of a distinct aortic phenotype before dilation occurs, signifying an early stage of aortic involvement in these diseases. Traditional clinical and imaging criteria often struggle to differentiate at this phase when genetic test results might not be readily available or conclusive. Early recognition of these syndromes could significantly enhance medical therapies, potentially maximizing their protective effect when initiated before advanced aortic disease sets in (33). These morphologic ratios are rapidly calculated using different imaging modalities and could be easily applied during the normal clinical practice both at tertiary or hub imaging centres and peripheral or secondary medical sites. Our analysis also shed light on the comprehensive morphology of the aorta and its primary segments, transcending mere aortic diameters. Particularly noteworthy is the proximal aorta complex; in MFS, it not only widens but also significantly elongates, assuming a distinctive "pear-shaped" configuration upon dilation (Figure 4). This unique morphotype, especially in the sinuses of Valsalva, could serve as a visual clue, raising strong suspicions of the underlying disease. Conversely, LDS lacks significant AR morphology alterations, maintaining normal anatomical relationships even when dilated. MFS cohort showed larger aortic diameters at several other segments, like the isthmus, suprarenal aorta and iliac arteries. The isthmus dilation
is typical when AA is already dilated and could represent another syndrome-specific phenotype. This morphotype could be a potential indicator of a more advanced disease status. Conversely, LDS patients displayed longer aortic segments, especially in the aortic arch and abdominal aorta, reflecting aortic tortuosity, a hallmark of LDS. The main imaging morphologic indexes and aortic phenotypes useful for LDS and MFS distinction are summarized in Table 3. These distinct aortic morphotypes, observed at various stages of hereditary thoracic aortic diseases, serve as practical tools for differentiation. They potentially reflect the diverse impact of pathogenetic mechanisms involving fibrillin 1 and TGF-beta on different aortic sections and their developmental processes, contributing to a deeper understanding of these intricate diseases (34).

In the realm of Thoracic Aortic Aneurysm and Dissection, where 37 genes are associated with genetic variants or mutations (35), many families with multiple affected members remain genetically elusive. For these patients, CTA and MRA aortic phenotyping could emerge as a valuable tool, guiding surveillance and treatment decisions amidst the complexity of genetic variability.

**STUDY LIMITATIONS**

The retrospective nature of the study has limited partly the number of patients analysed. Some advanced statistical analysis could not be conducted for the limited number of cohorts population. A possible selection bias may derive from the exclusion of many patients that came to our centres when already surgically treated and whose previous CTA or MRA were not available. These patients could represent a higher risk population with specific anatomic patterns. Morphologic differences may also reflect the diverse impact of some specific genotypes, but a genotype/phenotype correlation
analysis was beyond the aim of our study. Finally, the potential impact in prognosis of these anatomic differences is crucial but needs a focused long-term follow-up.

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syndrome: spectrum, prevalence, and cardiac MRI findings in a pediatric and young


Table 1: Clinical and demographic features of MFS and LDS cohorts.

<table>
<thead>
<tr>
<th></th>
<th>LDS (n = 19) †</th>
<th>MFS (n = 95) †</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at examination (years)</td>
<td>44 (32-52)</td>
<td>34 (25-46)</td>
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<tr>
<td>Weight (kg)</td>
<td>63 (60-78)</td>
<td>70 (60-78)</td>
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<tr>
<td>Height (m)</td>
<td>1.70 (1.63-1.76)</td>
<td>1.80 (1.73-1.90)</td>
<td>&lt;0.001&amp;</td>
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<tr>
<td>BSA (m²)</td>
<td>1.76 (1.68-1.85)</td>
<td>1.90 (1.74-2.07)</td>
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<tr>
<td>Gender (female)</td>
<td>14 (73.7%)</td>
<td>51 (53.7%)</td>
<td>0.100</td>
</tr>
<tr>
<td>Imaging modality (CTA)</td>
<td>13 (68.4%)</td>
<td>48 (50%)</td>
<td>0.150</td>
</tr>
<tr>
<td>Imaging modality (MR)</td>
<td>12 (63.2%)</td>
<td>68 (71.6%)</td>
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<td>Obesity/overweight</td>
<td>4 (21.1%)</td>
<td>4 (4.2%)</td>
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<tr>
<td>Smoking</td>
<td>0</td>
<td>8 (8.6%)</td>
<td>0.250</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (5.3%)</td>
<td>5 (5.4%)</td>
<td>0.730</td>
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<td>Diabetes</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
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<td>Hypercholesterolemia</td>
<td>2 (10.5%)</td>
<td>7 (7.5%)</td>
<td>0.470</td>
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<td>AoR</td>
<td>3 (18.8%)</td>
<td>32 (36%)</td>
<td>0.250</td>
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<td>Familial history of sudden death</td>
<td>7 (36.8%)</td>
<td>28 (29.8%)</td>
<td>0.540</td>
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<tr>
<td>Familial history of aortic aneurysm</td>
<td>12 (66.7%)</td>
<td>16 (17%)</td>
<td>&lt;0.001</td>
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<tr>
<td>Familial history of AD</td>
<td>6 (31.6%)</td>
<td>19 (20.2%)</td>
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<tr>
<td>Combined family history of Aortic disease/sudden death</td>
<td>15 (78.9%)</td>
<td>43 (45.7%)</td>
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</tr>
<tr>
<td>Aortic dilation prevalence ‡</td>
<td>10 (52.6%)</td>
<td>76 (80%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Aortic arch type 2-3</td>
<td>31 (32.6%)</td>
<td>10 (52.6%)</td>
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</tr>
</tbody>
</table>
† Values are expressed as median (IR) or number (%)
‡ AR and AA level
& statistical significant values are marked by bold numbers
AD, aortic dissection; AoR, aortic regurgitation; BSA, body surface area; CTA, Computed Tomography Angiography; IR, Interquartile range; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome; MR, Magnetic Resonance.
Table 2: Aortic segments lengths and main morphologic patterns in MFS and LDS patients.

<table>
<thead>
<tr>
<th>Aortic segments</th>
<th>Aortic Lengths (mm) †</th>
<th>Aortic indexed lengths (mm/m²) †</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LDS patients (n=19)</td>
<td>MFS patients (n=95)</td>
<td>LDS patients (n=19)</td>
</tr>
<tr>
<td>AR</td>
<td>25 (22-26)</td>
<td>26 (23-29)</td>
<td>0.047</td>
</tr>
<tr>
<td>AA</td>
<td>65 (56-79)</td>
<td>65 (56-73)</td>
<td>0.843</td>
</tr>
<tr>
<td>Aortic Arch</td>
<td>37 (30-46)</td>
<td>32 (25-39)</td>
<td>0.053</td>
</tr>
<tr>
<td>Aortic isthmus</td>
<td>28 (20-34)</td>
<td>31 (25-38)</td>
<td>0.063</td>
</tr>
<tr>
<td>DTA</td>
<td>142 (131-167)</td>
<td>153 (142-166)</td>
<td>0.110</td>
</tr>
<tr>
<td>Suprarenal Aorta</td>
<td>80 (61-96)</td>
<td>69 (56-80)</td>
<td>0.038</td>
</tr>
<tr>
<td>Infrarenal Aorta</td>
<td>91 (79-107)</td>
<td>98 (84-116)</td>
<td>0.143</td>
</tr>
<tr>
<td>Right iliac artery</td>
<td>67 (57-84)</td>
<td>63 (55-98)</td>
<td>0.361</td>
</tr>
<tr>
<td>Left iliac artery</td>
<td>66 (52-83)</td>
<td>62 (54-97)</td>
<td>0.884</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aortic arch morphology</th>
<th>LDS patients (n=19)</th>
<th>MFS patients (n=95)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic arch anomalies</td>
<td>0</td>
<td>2 (2.1%)</td>
<td>0.690</td>
</tr>
<tr>
<td>Arch Elongation</td>
<td>4 (21.1%)</td>
<td>10 (10.5%)</td>
<td>0.182</td>
</tr>
<tr>
<td>Type 2-3 Aortic Arch</td>
<td>10 (52.6%)</td>
<td>31 (32.6%)</td>
<td>0.097</td>
</tr>
</tbody>
</table>

† Values are expressed as median (IR) AR, aortic root; AA, Ascending aorta; DTA, Descending thoracic aorta; IR, Interquartile range; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome.
Table 3: Thoracic Aorta measurements ratios (all patients, dilated aorta, not dilated aorta)

<table>
<thead>
<tr>
<th></th>
<th>LDS patients ‡ (n=19)</th>
<th>MFS patients ‡ (n=95)</th>
<th>P</th>
<th>LDS patients ‡ (n=8)</th>
<th>MFS patients ‡ (n=75)</th>
<th>P</th>
<th>LDS patients ‡ (n=11)</th>
<th>MFS patients ‡ (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AR-AA length/AR diameter</td>
<td>2.21 (1.87-2.51)</td>
<td>1.96 (1.72-2.21)</td>
<td>0.002</td>
<td>1.86 (1.74-2.25)</td>
<td>1.94 (1.71-2.21)</td>
<td>0.799</td>
<td>2.3 (2.15-2.63)</td>
<td>2.12 (1.94-2.28)</td>
<td>0.043</td>
</tr>
<tr>
<td>AA length/AA diameter</td>
<td>2.20 (2.00-2.39)</td>
<td>2.18 (1.94-2.50)</td>
<td>0.997</td>
<td>2.16 (2.06-2.37)</td>
<td>2.16 (1.96-2.5)</td>
<td>0.918</td>
<td>2.20 (2.00-2.39)</td>
<td>2.10 (1.85-2.52)</td>
<td>0.918</td>
</tr>
<tr>
<td>AR diameter/STJ diameter</td>
<td>1.13 (1.07-1.13)</td>
<td>1.30 (1.20-1.42)</td>
<td>0.009</td>
<td>1.18 (1.07-1.40)</td>
<td>1.32 (1.20-1.45)</td>
<td>0.112</td>
<td>1.13 (1.06-1.37)</td>
<td>1.24 (1.18-1.34)</td>
<td>0.052</td>
</tr>
<tr>
<td>AR diameter/AA diameter</td>
<td>1.06 (1.025-1.31)</td>
<td>1.33 (1.20-1.43)</td>
<td>0.002</td>
<td>1.27 (1.03-1.44)</td>
<td>1.34 (1.21-1.46)</td>
<td>0.273</td>
<td>1.06 (1.00-1.18)</td>
<td>1.27 (1.07-1.33)</td>
<td>0.030</td>
</tr>
<tr>
<td>AA diameter/DTA diameter</td>
<td>1.52 (1.39-1.66)</td>
<td>1.47 (1.35-1.61)</td>
<td>0.152</td>
<td>1.63 (1.42-1.99)</td>
<td>1.50 (1.36-1.70)</td>
<td>0.130</td>
<td>1.50 (1.39-1.60)</td>
<td>1.27 (1.07-1.33)</td>
<td>0.011</td>
</tr>
<tr>
<td>Isthmus diameter/DTA diameter</td>
<td>1.11 (1.07-1.20)</td>
<td>1.16 (1.06-1.25)</td>
<td>0.344</td>
<td>1.08 (1.03-1.09)</td>
<td>1.21 (1.11-1.27)</td>
<td>0.015</td>
<td>1.13 (1.07-1.20)</td>
<td>1.10 (1.02-1.18)</td>
<td>0.090</td>
</tr>
</tbody>
</table>

† Dilated aorta refers to patients with AA and/or AR dilation. ‡ Values are expressed as median (IR); AR, aortic root; AA, Ascending Aorta; IR, Interquartile range; LDS, Loeys-Dietz syndrome; STJ, Sinotubular Junction; DTA, Descending thoracic aorta.
Figure 1. AR, AA Z-score frequency distribution in MFS, LDS and controls.

(A) A value $\geq +2$ indicates aortic dilation. Net distribution of MFS AR diameters to the right of +2 value indicates strong prevalence of dilated aorta. Controls show an opposite distribution. LDS values are equally distributed on both sides of the +2 value. (B) Same representation for AA diameters shows more similar values distribution between LDS and MFS. (C) AR Z-score values distribution represented by interpolation splines show a net separation between MFS and controls, LDS two-peak shape curve indicates a larger overlapping with normal subjects. AR, aortic root; AA, Ascending aorta; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome.

Figure 2. Proximal aortic segments dimensional profile in LDS, MFS and controls.

Absolute and size-indexed diameter box-plot representations for NC-to-RC (A and B), coronal STJ (C and D) and coronal AA (E and F). MFS AR diameters are distinct from the other groups; larger overlapping is evident between LDS and controls (A and B). Both syndromes show higher STJ diameters than controls, overlapping completely each other (C and D). LDS and MFS AA diameters are similar, but LDS more largely overlaps with controls showing almost the same median value (E and F). Lower and upper box borders represent 25th and 75th percentiles. The middle horizontal lines represents the median. The lower and upper whiskers represent minimum and maximum values of non-outliers. Extradots mark the outliers. AA, Ascending aorta; AR, Aortic root; cor, coronal; LDS, Loeys-Dietz Syndrome; MFS, Marfan Syndrome; NC, non-coronary sinus; R, right coronary sinus; STJ, sinotubular junction.
Figure 3. Performance of the main morphologic indexes for LDS and MFS differential diagnosis. Spline interpolation and corresponding ROC curves of AR/STJ diameters ratio (A and B) and AR/Prox AA diameters ratio (C and D) in LDS and MFS populations. Spline interpolation illustrates the discrimination effect of the cut-off value, while the ROC curves quantify their accuracy. AR, Aortic Root; AA, Ascending Aorta; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome.

Figure 4. CTI and MRI aortic morphology analysis provides aortic profiles and indexes as early tools to differentiate LDS and MFS patients., aortic diameter, length and tortuosity measurements are performed in selected cohorts of LDS, MFS and controls; the main derived diameter or diameter/length ratios for AR and AA in LDS and MFS patients are shown on representatives CT images on the left; the relative morphotypes, the derived indexes with cut-off values and the corresponding diagnostic accuracy are schematically represented on the top right; The main result and take-home messages are shown in the bottom right. AR, aortic root; AA, Ascending aorta; CTI, Computed Tomography imaging; D, Diameter; LDS, Loeys-Dietz Syndrome; L, length; MFS, Marfan Syndrome; MRI, Magnetic Resonance Imaging; STJ, sinotubular junction.

Supplementary Figure 1. Box plot representation of aortic absolute diameters distribution of the whole thoracoabdominal aorta (A-J) in LDS patients, MFS patients and controls. Aortic diameter differences between controls and MFS patients are greater than aortic diameter differences between controls and LDS patients. Lower and upper box borders represent 25th and 75th percentiles. The middle horizontal lines represent
the median. The lower and upper whiskers represent minimum and maximum values of non-outliers. Extradots mark the outliers. AR, aortic root; AA, Ascending aorta; Ao, Aortic; ch, chambers; cor, coronal; Diaph, Diaphragmatic L, Left coronary sinus; LD, Loeys-Dietz; MFS, Marfan syndrome; MT, Middle Thoracic; NC, non-coronary; Pulm Bif, Pulmonary bifurcation; R, right coronary sinus; sag, sagittal; SR, Suprarenal; STJ, sinotubular junction.

Supplementary Figure 2. Performance of AR-to-AA length/AR diameter ratio for LDS and MFS differentiation. Spline interpolation (A) and ROC curve (B) of AR-to-AA length/AR diameter ratio in LDS and MFS populations. The intersection of spline interpolation curve representing the two populations corresponds to the cut-off value; the respective curve position and trend illustrate its discriminating effect, while the ROC curve quantifies its accuracy. AR, Aortic Root; AA, Ascending Aorta; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome.
Aortic morphology MR/CT comparative analysis

Controls  LDS patients  MFS patients
A

B

C

D

**A**

LDS patients

MFS patients

Interpolation Curve

AR/STJ diameters ratio

<=1.18

1.19-1.29

1.30-1.42

>1.42

**B**

Value ≥ 1.19 for MFS identification

76% sensitivity

Sensitivity

1 - Specificity

AUC: 0.69 (0.54-0.83)

**C**

LDS patients

MFS patients

Interpolation Curve

AR/Prox AA diameters ratio

<=1.13

1.14-1.31

1.32-1.44

>1.44

**D**

Value ≥ 1.15 for MFS identification

80% sensitivity

Sensitivity

1 - Specificity

AUC: 0.72 (0.58-0.86)
A comparative retrospective CTI and MRI analysis of aortic morphology in three cohorts of LDS, MFS patients and controls

Patients diagnosed at advanced disease stage or with less than optimal image quality were excluded.

19 LDS patients, 20 controls, 95 MFS patients

- Ao diameters
- Diameters/length ratios
- Ao Lenghts and Tortuosity

This morphologic comparative study:

- Found some aortic profiles and indexes as easy tools to differentiate LDS and MFS patients at early disease stages, especially when genetic analysis is lacking
- Suggested further analysis and research to learn the different physiopathologic mechanisms and behavior of these two rare diseases