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Cardiovascular involvement and outcomes in Marfan syndrome: new observations on evolving aortic risk associations in a single-center cohort from Poland

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Key words: elective thoracic aortic surgery, *FBN1*, Marfan syndrome, thoracic aortic dissection, thoracic aortic events

Abstract

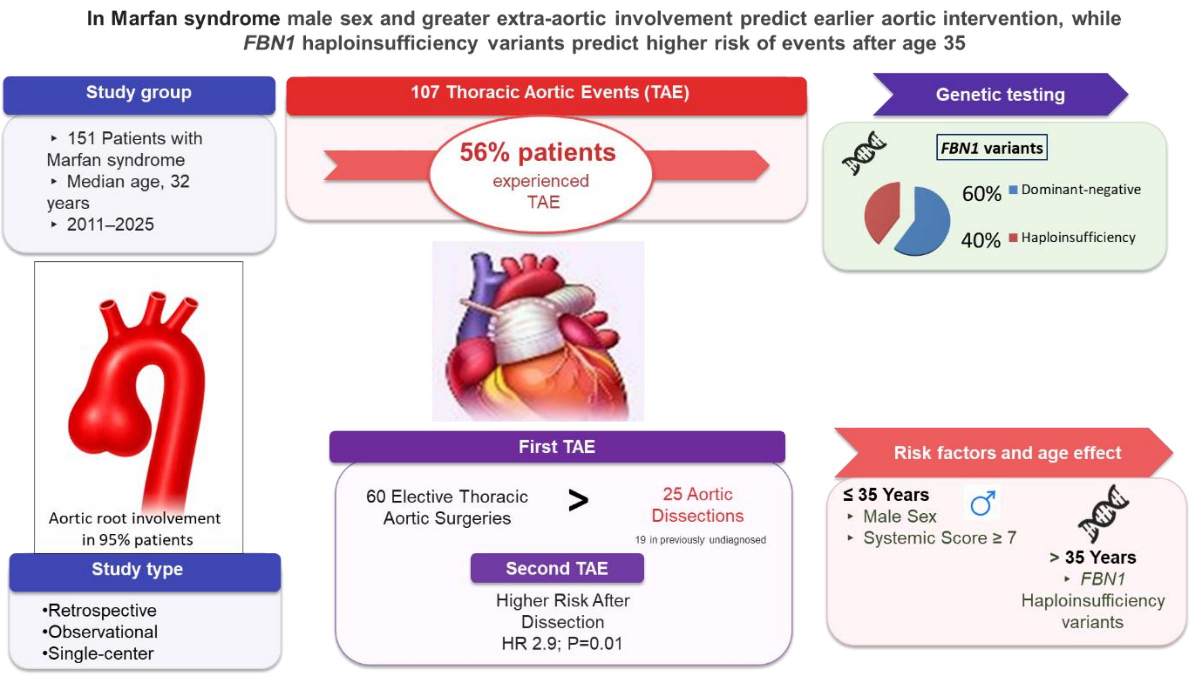
Introduction: Marfan syndrome (MFS) is a connective tissue disorder with aortic dilatation driving morbidity and mortality.

Objectives: To characterize cardiovascular profile, outcomes, and factors associated with the lifetime risk of thoracic aortic events (TAE) in a contemporary MFS cohort.

Patients and methods: We retrospectively analyzed data from MFS patients diagnosed based on revised Ghent criteria and followed for a median 6.8 (IQR 3–10) years at our tertiary center.

Results: The cohort comprised 151 patients (104 probands, median age 32 years, 58% female). Aortic root involvement was present in 95% patients, a positive family history in 69%, a systemic score of ≥7 points in 61%, and ectopia lentis in 36%. Among patients with identified *FBN1* variants, 60% carried dominant-negative and 40% haploinsufficiency variants, 27% variants were novel. Overall, 107 TAE occurred in 85 (56%) patients. The first TAE (median age 33 years) comprised 60 elective operations and 25 aortic dissections; 19 in previously undiagnosed individuals. TAE-free survival was shorter in men and in patients with high systemic score, mainly before age 35, whereas later haploinsufficiency variants were associated with TAE. A second TAE developed in 18 (21%) patients and was more frequent after dissection than elective surgery (HR 2.9, 95% CI 1.2–7.1, $P = 0.01$). Mitral valve surgery was performed in 13% of patients.

Conclusions: The majority of MFS patients experienced a TAE. The association of TAE risk with factors, such as male gender, extra-aortic features, and FBN1 variant type, varies with age group.



Introduction

Marfan syndrome (MFS) is the most common heritable thoracic aortic disease (HTAD)[1]. MFS affects approximately 1 in 5000–10 000 individuals in the general population and accounts for 6–9% of aortic dissection cases [1, 2]. It is caused by alterations in the *FBN1* gene, a large gene, located on the long arm of chromosome 15q21.1 and composed of 65 exons, which encodes fibrillin-1, a structural macromolecule (2871 amino acids) that polymerizes into extracellular matrix microfibrils[3]. It is expressed in the connective tissue of multiple organs, but is prominently found in the aortic wall, the ciliary zonules of the eye, and the perichondrium. This explains the pleiotropic nature of the MFS with predominant manifestations in the cardiovascular, ocular, and skeletal system. The diagnosis of MFS is currently made based on the 2010 revised Ghent criteria, which assigned key importance to aortic root dilatation and allowed for the diagnosis of MFS in combination with one of the following: ectopia lentis, a diagnostic systemic score (of at least 7 points) or a pathogenic *FBN1* variant [2]. A family history of MFS is considered an equivalent concomitant criterion.

To date, more than 3000 *FBN1* variants have been reported [4]. Some of them, resulting in single amino acid substitutions (missense variants) or insertion/deletion of single amino acids (in-frame indels), result in the production of an defective protein that interferes with the formation of normal microfibrils, exerting their dominant negative effect[3, 5]. Others, namely truncating (nonsense or frameshift) variants or large insertions/deletions encompassing multiple exons, result in the degradation of the defective protein, while its synthesis from the normal allele is insufficient and leads to its deficiency (haploinsufficiency)[6].

In the aortic wall, fibrillin-1 microfibrils form a connection between elastic lamellae and smooth muscle cells, which are subject to constant stretch and recoil and also participate in transforming growth factor β signaling. Defective or missing fibrillin-1 weakens the structural integrity of the aortic media and promotes progressive aortic root dilatation, which may ultimately lead to aneurysm formation and dissection. Thoracic aortic dissection (TAD) most often occurs in the ascending aorta (type A according to Stanford classification), but it can also occur in the descending aorta (type B), even if not significantly dilated[7]. TAD was the main cause of death in MFS before the era of cardiac surgery with the majority dying before the age of 45[8] . Nowadays, life expectancy is almost equal to the general population, but thoracic aortic events (TAE) still occur frequently, with a median age of approximately 40 years. Several risk factors for TAE have been identified, including male sex, larger aortic root diameter, faster aortic dilation rate, family history of dissection at a small aortic diameter, pregnancy, arterial hypertension, and type of *FBN1* variant (haploinsufficiency or cysteine-related) [9-12].

In this study, we aimed to evaluate the cardiovascular involvement in patients with MFS, and to evaluate risk factors for TAE over lifetime in the Polish population.

Patients and methods

Study cohort

The study cohort comprised adult patients with MFS under the care of the Unit for Screening Studies in Inherited Cardiovascular Diseases, National Institute of Cardiology, Warsaw, Poland, followed between 2011 and 2025 for a median 6.8 [IQR 3-10] years. The diagnosis of MFS was based on the revised Ghent criteria [2]. Cascade screening was offered to all patients' families. Demographic, genetic, phenotypic, and outcomes data were systematically recorded.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Bioethics Committee of the National Institute of Cardiology, Warsaw, Poland (Ref. No. 1880, 2061). All participants provided written informed consent.

Clinical assessment

In all patients, a three to four-generation pedigree was drawn and information on the family history of MFS, thoracic aortic involvement (dilation, aneurysms, dissections and surgeries) and other relevant diseases was obtained.

Cardiovascular involvement was assessed using transthoracic echocardiography and computed tomography angiography of the aorta. Aortic root diameter was normalized for age, sex and body size using an online calculator available at the Marfan Foundation website [13]. An aortic root Z-score of ≥ 2 was considered dilatation. Involvement of other systems was based on physical examination, medical history, imaging tests, and available medical records. To calculate the systemic score, we used an online calculator [14]. Left ventricular systolic dysfunction (LVSD) was defined as a left ventricular ejection fraction (LVEF) lower than 50%. Arterial hypertension was defined as repeated blood pressure measurements >140/90 mm Hg or current antihypertensive therapy.

We collected data on age at the diagnosis of MFS, thoracic aortic dilatation and the history of TAE, defined as TAD, elective thoracic aortic surgery (ETAS), or sudden death presumably due to acute aortic syndrome as judged by the investigators. We also recorded other major cardiovascular events, including other cardiac and vascular operations.

Patients' follow-up was continued until their last available clinical assessment before 31 July 2025. In several cases, follow-up data were obtained over the phone or from patients' relatives.

Genetic testing

Genetic testing in probands was performed using either next-generation whole-exome sequencing or different gene panels that included all the coding and splicing regions of the *FBN1* gene. Family cascade testing was performed via Sanger sequencing. Genetic testing at our center was offered to probands based on availability. Ten probands had previously been tested outside our center.

We analyzed variants found in the *FBN1*, as well as other genes associated with heritable aortopathy, located in coding or canonical splice regions with a population frequency of ≤0.001 in both gnomAD genomes and gnomAD exomes databases. Variant pathogenicity was assessed according to the American College of Medical Genetics and Genomics (ACMG) guidelines [15]. Pathogenic and likely pathogenic (P/LP) variants were considered causative. All causative variants were confirmed by Sanger sequencing in probands and followed in relatives.

Patients who met the clinical criteria for MFS (e.g., based on aortic root dilatation and systemic criteria) but did not carry a causal *FBN1* variant, and instead had a pathogenic variant in other HTAD-related genes, were diagnosed with other systemic forms of aortic aneurysm, primarily Loeys-Dietz syndrome (LDS), and were excluded from this study.

The identified *FBN1* variants were divided depending on the postulated mechanism of action into haploinsufficiency (HI) variants (frameshift, nonsense and splicing) and dominant negative (DN) variants (missense and small in-frame indels).

A variant was considered novel if it was absent from ClinVar, UMD, and LitVar2 databases.

Statistical analysis

All results for categorical variables were presented as counts and percentages. Due to the non-normal distribution of numerical variables (verified by the Shapiro-Wilk test), results were reported using the median and interquartile range (IQR). The chi-square independence or Fisher's exact test was used for comparison of binary variables. The differences between numerical variables were assessed by the non–parametric Mann–Whitney test.

Kaplan–Meier estimates were constructed for event-free survival calculated from birth to date of the first TAE, death or the end of follow-up, whichever came first. Therefore, among the potential risk factors we included variables that remain constant throughout life (sex, variant type) or usually do not change significantly in adulthood (systemic score, ectopia lentis). Differences for specific data subsets were compared by log-rank. Mutually exclusive outcomes (ETAS or TAD) related to specific features were determined with competing risk outcome analysis by the Fine and Gray method. Hazard ratios (HR) with 95% CI were calculated using the Cox regression model modified by Fine and Gray.

All hypotheses were two-tailed with 0.05 type I error. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Cary, NC, US).

Results

Study cohort characteristics

The study group consisted of 151 MFS patients. Baseline characteristics are shown in Table 1. The median age was 28 years at the diagnosis of MFS and 32 years at baseline evaluation in our center. The cohort comprised predominantly women (58%) and probands (69%). Arterial hypertension was present in 1/3 (34%) of all patients. Other classical risk factors included current smoking in 8 (5%) patients and hypercholesterolemia in 24 (16%) patients.

At baseline, all probands and 83% of relatives had thoracic aortic involvement. Extra-aortic features were common (Supplementary Table S1). The most prevalent manifestations were skeletal features, present in 84% of patients; among these, the most common were scoliosis and thoracolumbar kyphosis, observed in 67% of the cohort. Cutaneous features (striae), were present in 74% of patients, and ectopia lentis in 36%.

As shown in Table 1, of the 51 TAE prior to baseline evaluation, 22 (15% of the cohort) were TADs and 29 (19% of the cohort) were ETAS; three (2%) patients had both. Eight (5%) patients underwent another cardiac surgery. LVSD was observed in eight patients; it could be attributed to concomitant valvular heart disease in all cases.

5 (3%) patients had a bicuspid aortic valve, two (1%) had an atrial septal defect. In one patient described previously, concomitant fibromuscular dysplasia was found [16].

At the end of follow-up, the most commonly prescribed medications were beta-blockers, used in 142 patients (94%), followed by angiotensin receptor blockers in 83 (55%), angiotensin-converting enzyme inhibitors in 20 (13%), mineralocorticoid receptor antagonists in 22 (14%), diuretics in 30 (20%), calcium channel blockers in 24 (16%), other antihypertensive agents in 4 (3%), statins in 30 (20%), other lipid-lowering agents in 3 (2%), antiplatelet therapy in 17 (11%), vitamin K antagonists in 42 (28%), non-vitamin K antagonist oral anticoagulants in 6 (4%), and antidiabetic agents in 7 (5%).

Genetic results

In total, 68 of 104 probands were examined with next generation sequencing covering all *FBN1* exons (Figure 1). Sixty-two causative *FBN1* variants were identified in 62 (91%) probands, and subsequently in 39 (83%) relatives (see supplementary material Table S2). 17 (27%) of these variants were novel. In 6 (9%) of the tested probands, a causative variant was found neither in

FBN1 nor in other HTAD-related genes, and the MFS diagnosis was based solely on clinical criteria. Of note, one nonsense variant was found in two unrelated probands. In another proband, two different missense variants were identified (there were no relatives to test and we could not specify if they were in trans or cis position). All other variants were heterozygous.

The number of probands with different variant types is presented in Figure 1. Dominant negative variants were found in 36 (53%) of tested probands and their 24 relatives, whereas 26 (38%) probands and 15 relatives had haploinsufficiency variants.

In the tested probands, no P/LP variants in other HTAD-related genes were identified.

Diagnostic criteria

The hallmark of MFS is aortic root dilatation, was present in 95% of our patients (Figure 2). The second most common criterion was genetic burden, understood as positive family history for MFS and/or relevant *FBN1* variant. It was met in 82% of patients with aortic root dilatation and in all patients without it. Systemic score was diagnostic in 61% of patients and ectopia lentis was present in 36% of patients.

60% of patients met ≥3 diagnostic criteria, and 40% met 2 of them. Notably, genetic testing was necessary to diagnose MFS in only six cases. In one family, neither the proband nor two of his relatives had any significant systemic symptoms, and in three other probands, the systemic score was 5–6 points.

The diagnostic criteria met according to the revised Ghent nosology are presented in Supplementary Table S3, including the distribution of patients meeting two or more of the major diagnostic criteria needed for the MFS diagnosis.

Thoracic aortic events

Throughout the entire period from birth to the end of follow-up, 85 (56%) patients experienced at least one TAE (Figure 3). Overall, ETAS was more prevalent than TAD across all ages (Figure 3A). Event-free survival at 20, 40, and 60 years of age was 93%, 50%, and 20%, respectively. The cumulative incidences of ETAS at these ages were 7%, 37%, and 54%, respectively, whereas the cumulative incidences of TAD were 0%, 13%, and 27% (Supplementary Table S5). ETAS was the first TAE in 60 cases (71% of patients with TAE; 40% of the total cohort). The median aortic root diameter before ETAS was 51 mm [50–57]. In 25 patients (29% of patients with TAE; 17% of the total cohort), the first TAE was dissection (84% type A); among them, 19 (76% of those with TAD) had no MFS diagnosis at the time of TAD. The median aortic root diameter preceding type A TAD was 56 mm [47–60].

A second TAE occurred in 18 patients (21% of patients with TAE). The recurrence risk was higher after dissection than after ETAS (P = 0.01, Supplementary Figure S1). In patients after TAD, subsequent TAEs were elective surgeries, except for one patient who experienced a type B dissection 14 years after type A dissection. In contrast, in patients after ETAS, subsequent events were TAD, diagnosed in 8 cases (Figure 3B). These were primarily type B dissections with one case of type A dissection, which occurred 13 years after a Bentall procedure just above an aortic graft.

The analyses of survival curves revealed apparent differences in their relationships depending on the life stage, which prompted us to conduct additional analyses separately for the periods up to and above the age of 35.

TAE-free survival was significantly shorter in men (Figure 4). This difference was driven by the significantly higher rates of ETAS before the age of 35 (HR 2.5, 95% CI 1.3-4.6, P = 0.003). The incidence curves for aortic dissection were homogeneous.

TAE-free survival up to the age of 35 was the same regardless of the causative variant type (P = 0.99). After the age of 35, the risk of events was significantly higher in the HI group (HR 2.8, 95% CI 1.3-6.0, P = 0.005), primarily due to more frequent elective surgeries (Figure 5).

The risk of TAE was higher in patients with a systemic score of at least 7 points (Figure 5). In this group, the rate of ETAS was borderline higher before the age of 35 ($P = 0.053$) and significantly higher afterward (HR 5.5, 95% CI 2.1-14, $P < 0.001$), while the risk of dissection after the age of 35 was lower (HR 0.2, 95% CI 0.04-0.8, $P = 0.03$). In contrast, among patients aged ≥ 35 years, the risk of TAE was lower in patients with ectopia lentis than in those without it.

Other major cardiovascular events

By the end of the follow-up period, 20 (13%) patients underwent mitral valve surgery (with or without tricuspid annuloplasty), two of them due to infective endocarditis. Other major cardiovascular events included one surgical atrial septal defect closure in childhood, one myocardial infarction (fatal), ischemic strokes in 2 patients, elective interventions on abdominal aortic aneurysm in 3 patients (including a patient with chronically dissected aorta, and two other patients at the age of 60 and 75), carotid artery dissections in 2 patients (one pregnancy-related), venous thrombosis in 4 patients.

Two patients underwent cardioverter-defibrillator implantation due to severe LVSD persisting after mitral valve replacement.

During follow-up, 10 patients (7%) died at the median age of 48 [38-65] years: 2 of acute aortic dissection, 3 of complications after elective aortic surgery, 5 from other or unknown reasons.

Discussion

herein we summarize 15 years of experience of our tertiary center for MFS patients and their families. In this largest cohort from Poland to date, we identified 17 novel *FBN1* variants. We assessed the risk of TAE with the use of competing risk outcome analysis (ETAS vs. TAD) and with division into age ranges. This led to new observations that the relationship between the risk of TAE and established risk factors, such as male sex, *FBN1* variant type, and higher systemic score, may be age-dependent.

Following the first Polish report on the genetic characteristics of MFS patients by Wypasek et al.[17], only few works on various issues related to MFS in Poland were published[16, 18-20]. In this study, we report the cardiovascular phenotype, prevalence of extra-aortic features, risk factors and clinical outcomes in our MFS cohort. Our cohort was young, similarly to the large European study by Arnaud et al. (mean (SD) age: 34 (18) years vs 34 (13) years, respectively) [21]. As in studies from other European countries [9, 21, 22], we showed a phenotypic diversity, with aortic root dilatation present in 95% of patients, a positive family history of MFS in more than two thirds, systemic score ≥7 in nearly two thirds and ectopia lentis in more than one third of patients. The diagnosis in our cohort was confirmed in nearly two thirds of probands by genetic testing. For the vast majority of patients, a diagnosis of MFS could be established solely on clinical grounds and genetic testing was necessary for this purpose only in 4 probands with aortic dilation but no other clinical MFS criteria. Nevertheless, genetic testing remains essential to differentiate MFS from other HTAD, such as LDS, which can present with an overlapping phenotype [2, 7]. In a previously published paper [23], we presented 7 LDS patients who met the clinical criteria for MFS diagnosis, but were excluded from this study due to the detection of an LDS-related genetic variant and the absence of relevant *FBN1* variants. Another patient with aortic root dilatation and a systemic score of 9 points was also excluded after identifying a likely pathogenic *SKI* variant and diagnosing Shprintzen-Goldberg syndrome [24].

The UMD-*FBN1* mutation database provides a catalogue of P/LP *FBN1* variants [4]. Among 1,847 different *FBN1* variants listed there, the most common are missense variants (n=1015), followed by small deletions (n=268), nonsense variants (n=210), and splice-site variants (n=200)[4]. The distribution of variant types in our cohort was similar, with missense variants predominating. As highlighted by Xu et al., analysis of genomic variability may improve our understanding of phenotypic differences in MFS, although other factors, such as epigenetic modifications, modifier genes and chimerism, are also likely to contribute to the variability observed within and between families [25].

Our study confirms substantial aortic morbidity. TAE-free survival at the age of 60 years was only 20%, lower than 38% reported in the Danish nationwide cohort [26], which is probably due to the reference status of our center. In the Danish cohort, the median age at the first TAE, ETAS, and TAD was 37, 33, and 41 years, respectively [26]. In the Dutch CONCOR registry, Franken et al. reported a mean age of 39 years at ETAS and 48 years at TAD [22]. In our study, the first TAE, ETAS and TAD occurred earlier, at a median age of 33, 30 and 36 years, respectively.

In our cohort, in which the median age at diagnosis was 28 years, TAD was the presenting event in 13% of patients, whereas in the study by Robertson et al., with 283 MFS patients, this figure was lower, at 8%, probably due to the fact that the study population was younger (mean age 22 years) [27].

Survival analyses have shown that the risk of TAE varies across subgroups, similarly to other studies. A new finding is that the differences in the risk level are not constant throughout life but may change around the age of 35. Male patients had higher risk of aortic events (HR 1.8, 95% CI 1.2-2.7, p=0.008), and this difference was solely due to a higher risk of ETAS before the age of 35 (HR 2.5, 95% CI 1.3-4.6, p=0.003). Other studies have also demonstrated that men have prophylactic aortic surgery at a younger age than women [11, 21, 22, 26].

Prognostic information is also provided by the results of genetic testing. A recent meta-analysis, based on 11 studies which included 6000 adults, reported that *FBN1* HI variants (reduced fibrillin-1 content) confer an approximately 2.5-fold higher risk of adverse aortic outcomes compared with DN variants (abnormal fibrillin-1) [28]. In our study, the risk of TAE among HI vs DN variant carriers was not elevated before the age of 35, but significantly increased afterwards (HR 2.8, 95% CI 1.3-6.0, $p=0.005$) due to the higher incidence of ETAS. The rate of ETAS in patients with a systemic score of at least 7 points was higher throughout life (HR 2.4, 95% CI 1.4-4.2, $p<0.001$), while the risk of dissection in this group was lower after the age of 35 (HR 0.2, 95% CI 0.04-0.8, $p=0.03$), possibly because earlier ETAS in patients with more pronounced systemic features reduced their subsequent risk of dissection. In patients with ectopia lentis, a lower risk of TAE was observed only after the age of 35 and seemed to be driven mainly by a trend toward a lower incidence of aortic dissection. It should also be noted that the above-mentioned correlations with extra-aortic features may be secondary to the effects of the *FBN1* variant type, as in patients with HI variants, a systemic score of at least 7 points was more frequently observed, and ectopia lentis less frequently. This interpretation is consistent with previous reports showing that *FBN1* pathogenic variants linked with higher incidence of TAE, namely HI variants, are also associated with lower frequency of ectopia lentis but higher frequency of severe scoliosis [22].

These findings, suggesting that the influence of risk factors may change around the age of 35 years, are novel but, given the small sample size and low number of events, require confirmation in larger studies.

Long-term observations of the ageing MFS population, treated with ETAS have shown increasing numbers of type B TAD with time [29-31], underlining the need for systematic surveillance of the whole aorta [7]. In our study, 12 patients had type B dissections, 4 of them as the first TAE, and 8 after surgery on the ascending aorta. Recurrent TAE were more frequent after TAD than after ETAS, yet almost 80% of patients remained free of recurrence after their first TAE. In contrast to LDS [23, 27], multiple aortic events were relatively uncommon: only about 4% of patients experienced 3 TAE.

Of particular concern in this cohort was mitral valve prolapse, present in more than half of patients (56%), similarly to other studies (60-65%) [32]. 13% of the whole cohort required mitral valve surgery, which is substantially higher than in the study by Arnaud et. al. (6%)[21]. Congenital heart diseases were not common in our cohort and, unlike in some reports [19], we did not encounter co-occurrence with complex congenital anomalies.

Our study has several limitations. First, this is a single tertiary center, cohort study, and the referral bias is likely. Second, this is a retrospective study, with non-uniform follow-up policy prior to referral as majority (66%) of the patients had already been diagnosed with MFS before baseline visit in the Unit. Third, within-family clustering may have influenced genotype–phenotype and outcome associations. Also, we assessed adult population, and the more important correlations could be found while including children and adolescents. Furthermore, we did not assess the prognostic impact of factors that are highly variable over the lifespan, such as blood pressure control, medication or smoking, even if their prognostic relevance is well documented.

Although knowledge about MFS is increasing, still a significant proportion of Polish MFS patients experienced TAD before diagnosis. This problem could be alleviated by broader access to genetic testing and counselling, and by creating centers for rare diseases, including HTAD. Genetic testing, although not necessary in most cases to establish a diagnosis, can significantly facilitate it. It can also become an essential component of individualized approach in genotype-guided precision medicine in HTAD. The age-dependent associations observed in our cohort may contribute to more personalized risk stratification, tailoring surveillance and prophylactic interventions in patients with MFS.

Article information

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Table 1 Baseline characteristics of the Marfan syndrome cohort

Variable	Total cohort (n = 151)	Probands (n = 104)	Relatives (n = 47)	*P*value
Demographics and family history				
Age at Marfan syndrome diagnosis, years	28 [18–37]	27 [18–36]	31 [22–45]	0.02
Age at baseline evaluation, years	32 [21–41]	32 [21–39]	34 [24–46]	0.10
Male sex	63 (42%)	51 (49%)	12 (26%)	0.01
Family history of Marfan syndrome	104 (69%)	57 (55%)	47 (100%)	<0.001
Family history of thoracic aortic dissection	53 (35%)	28 (27%)	25 (53%)	0.003
Family history of sudden unexplained death	17 (11%)	9 (9%)	8 (17%)	0.22
Aortic involvement				
Prior thoracic aortic dissection	22 (15%)	19 (18%)	3 (6%)	0.10
Prior elective thoracic aortic surgery	29 (19%)	26 (25%)	3 (6%)	0.01
Aortic root, mm	43 [39–49]	45 [41–50]	40 [36–44]	<0.001
Aortic root Z-score	4.1 [2.3–5.8]	4.7 [3.1–7.1]	2.9 [2.1–4.6]	<0.001

Ascending aorta, mm	31 [28–34]	35 [30–41]	30 [26–34]	<0.001
Aortic valve replacement	29 (19%)	25 (24%)	4 (8%)	<0.001
Cardiac abnormalities				
Bicuspid aortic valve	5 (3%)	5 (5%)	0	0.33
Moderate or greater aortic regurgitation	9 (6%)	9 (9%)	0	0.06
Mitral valve replacement/repair	20 (13%)	18 (17%)	2 (4%)	0.06
Mitral valve prolapse	84 (56%)	62 (60%)	22 (47%)	0.20
Moderate or greater mitral regurgitation	24 (16%)	21 (20%)	3 (6%)	0.06
Left-ventricular end-diastolic dimension, mm	51 [47–55]	53 [48–56]	50 [47–54]	0.04
Left-ventricular ejection fraction, %	62 [57–66]	62 [57–65]	62 [58–66]	0.89
Left ventricular systolic dysfunction	8 (5%)	8 (8%)	0	0.06
Atrial fibrillation	15 (10%)	9 (9%)	6 (13%)	0.63
Risk factors and medication				
Arterial hypertension	51 (34%)	36 (35%)	15 (32%)	0.89
Obesity	11 (7%)	6 (6%)	5 (11%)	0.47
Diabetes	7 (5%)	4 (4%)	3 (6%)	0.79
Hypercholesterolemia	24 (16%)	15(15%)	8 (17%)	0.99
Beta-blocker use	135 (89%)	96 (92%)	39 (83%)	0.15

Angiotensin II receptor blocker use	78 (52%)	59 (57%)	19 (40%)	0.09
Values are given as counts (percentages) and medians [IQR]. The aortic root diameter refers to the diameter measured at baseline visit or before surgery in the case of patients operated prior to the visit. Aortic root Z-score for adults ≥2.0 indicates aortic root dilation and is a major Marfan syndrome diagnostic criterion				

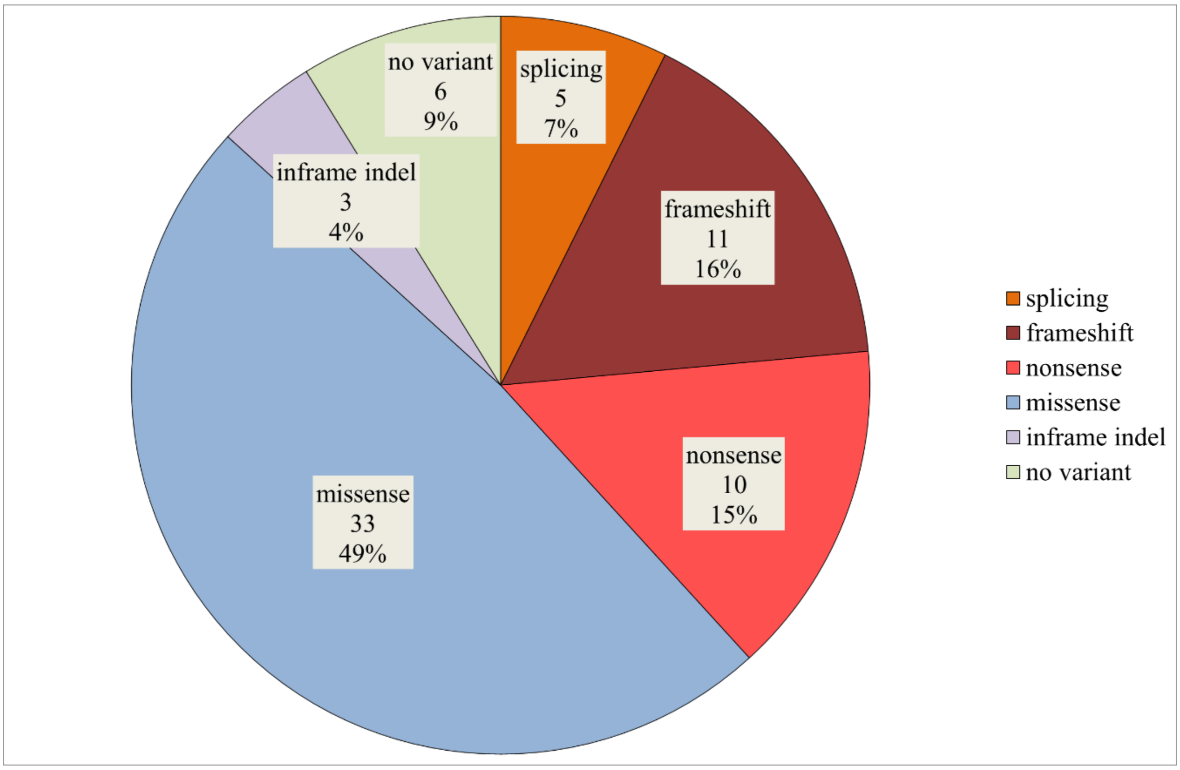

Figure 1 Distribution of *FBN1* variant types in the tested probands. *FBN1*, fibrillin-1 gene

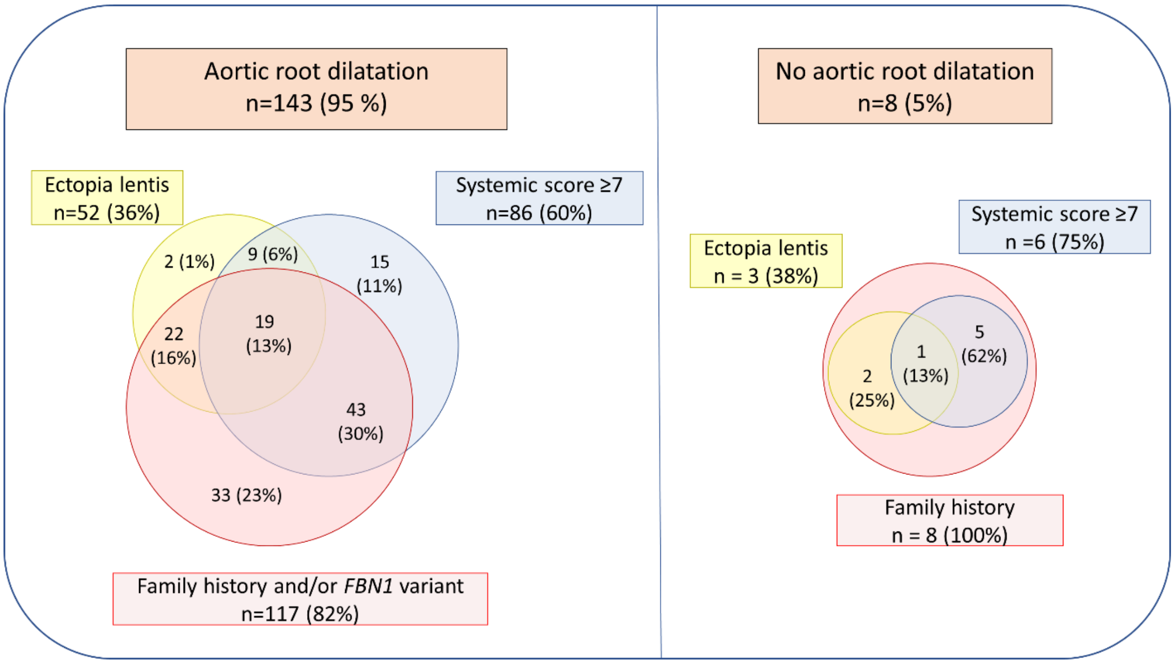

Figure 2 Distribution of diagnostic criteria for Marfan syndrome in the study cohort

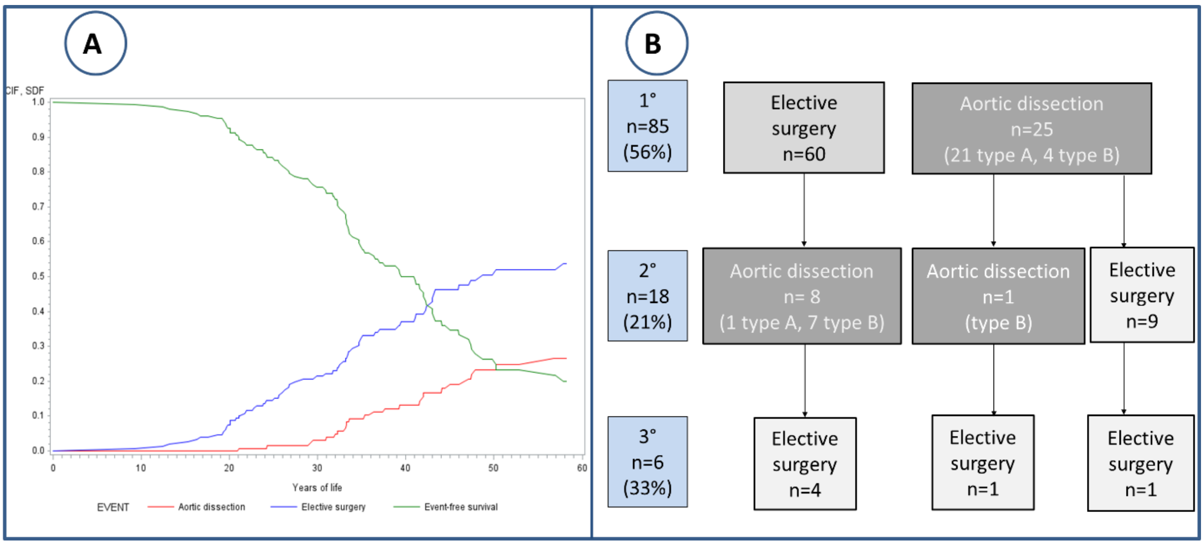

Figure 3 Thoracic aortic events in the study cohort; A – competing outcomes of first thoracic aortic events; B – the flowchart showing the number and type of first and subsequent thoracic aortic events

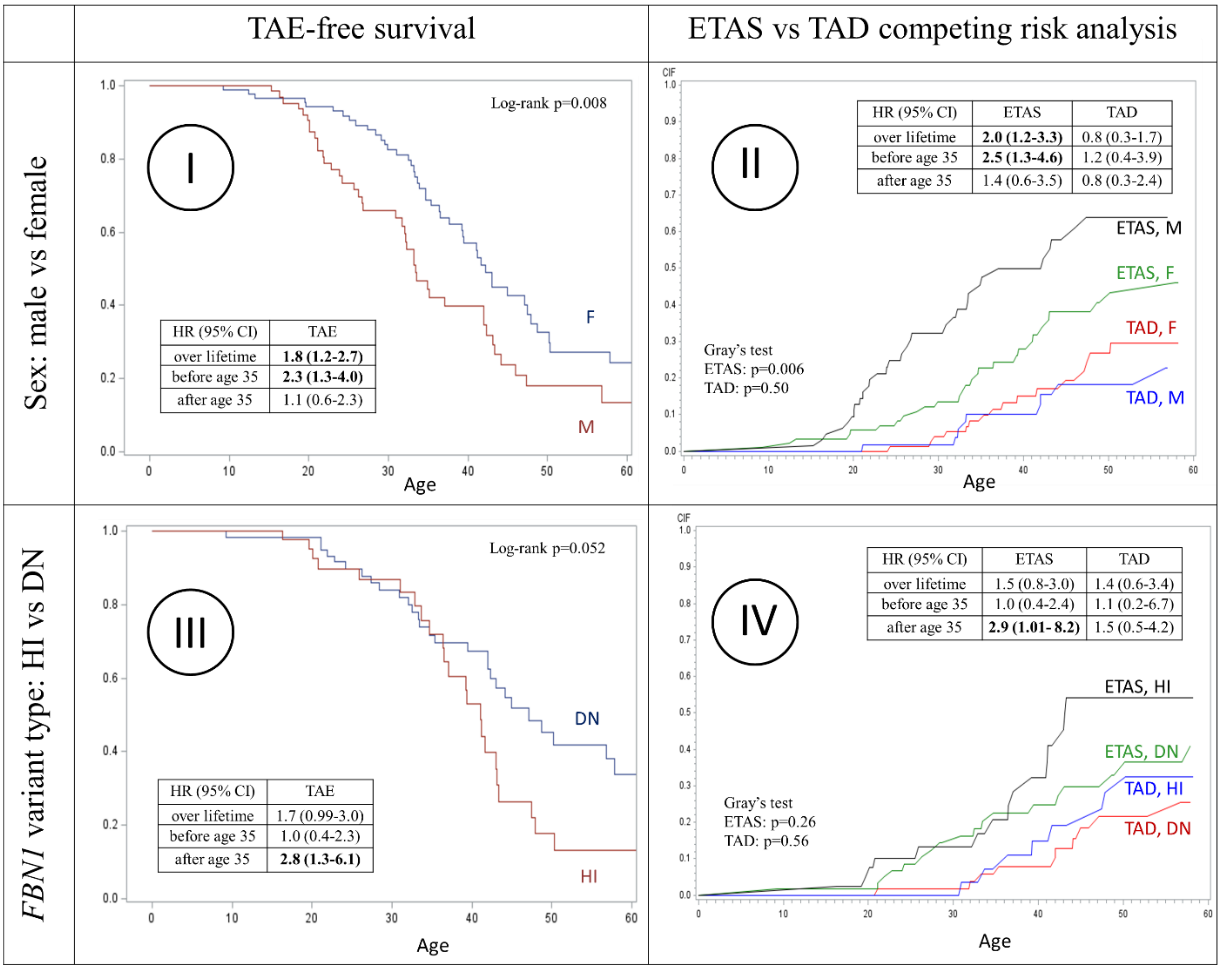

Figure 4 The risk of thoracic aortic events in the study cohort depending on sex and *FBN1* variant type. I. Survival without thoracic aortic event depending on sex. II. Competing risk analysis of elective thoracic aortic surgeries and thoracic aortic dissections depending on sex. III. Survival without thoracic aortic event depending on *FBN1* variant type. IV. Competing risk analysis of elective thoracic aortic surgeries and thoracic aortic dissections depending on *FBN1* variant type. Abbreviations: DN, dominant negative variant; ETAS, elective thoracic aortic surgery; *FBN1*, fibrillin-1 gene; HI, haploinsufficiency variant; TAD, thoracic aortic dissection

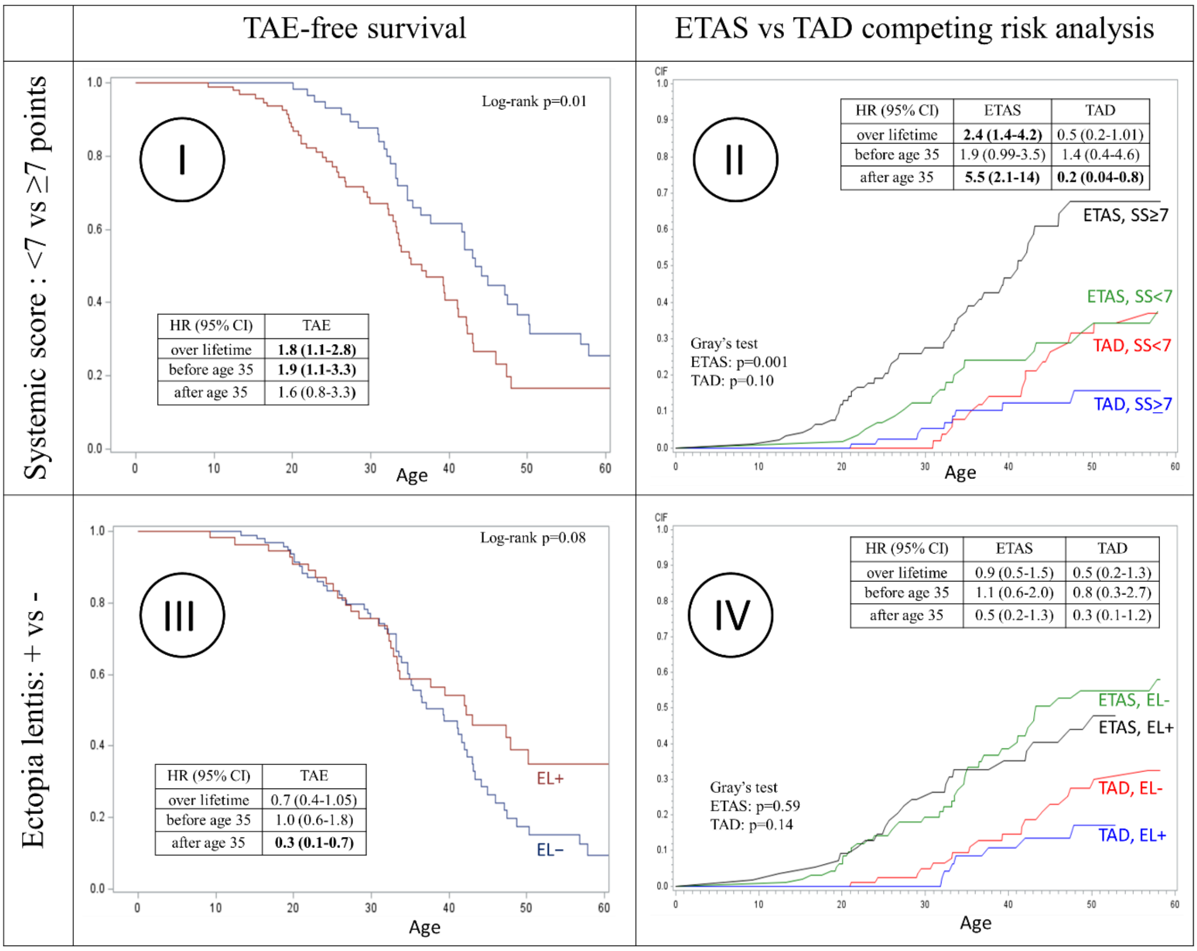

Figure 5 Association between the risk of thoracic aortic events and extra-aortic phenotypic features of Marfan syndrome. I. Survival without thoracic aortic event depending on the systemic score. II. Competing risk analysis of elective thoracic aortic surgeries and thoracic aortic dissections depending on the systemic score. III. Survival without thoracic aortic event depending on the presence of ectopia lentis. IVa/b. Competing risk analysis of elective thoracic aortic surgeries and thoracic aortic dissections depending on the presence of ectopia lentis. Abbreviations: EL, ectopia lentis; ETAS, elective thoracic aortic surgery; SS, systemic score; TAD, thoracic aortic dissection; TAE, thoracic aortic event.

Short title: New insights into evolving aortic risk associations in Marfan syndrome