The impact of sex and gender on aortic events in patients with Marfan syndrome

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ABSTRACT

Objectives:

Aim of this study was to explore sex and gender differences regarding aortic events in Marfan patients.

Methods:

We analysed all data from our connective tissue disorder database. Only patients with Marfan syndrome were included. For analysis, patients were divided by sex. Female patients were further divided into 2 subgroups; with vs without children. Aortic events were defined as Stanford type A or type B aortic dissection or any aortic intervention.

Results:

A population of 183 Marfan patients was analysed for the purpose of this study. One-hundred-four (57%) were male and 79 (43%) were female patients. Thirty-seven (47%) of the 79 female patients had at least one child. Male patients had a significantly higher probability of experiencing an aortic event (p=0.015) compared to female patients. However, there was no increased probability for recurrent events in male patients compared to female patients (p=0.063). Follow-up revealed no sex and gender differences in the occurrence of Stanford type A or B aortic dissection between male and female patients (p=0.324/p=0.534). While 11% of women with children suffered from peripartum aortic events, 24% experienced Stanford Type A aortic dissection unrelated to pregnancy.

Conclusions:

Male patients have a higher risk of aortic events than female patients. The majority of women were not aware of their Marfan syndrome diagnosis before conceiving. One out of ten women suffered from peripartum Stanford Type A or B aortic dissection. Twice as many female patients with children suffered from aortic dissection unrelated to childbirth. There were no sex and gender differences affecting mortality in Marfan patients.

Keywords: sex and gender, Marfan syndrome, aortic dissection, aortic aneurysm, childbirth

ABBREVIATIONS

AAD	Acute aortic dissection
MFS	Marfan syndrome
TAAD	Type A aortic dissection
TBAD	Type B aortic dissection
SD	standard deviation

INTRODUCTION

Marfan syndrome (MFS) is a connective tissue disorder inherited in an autosomal dominant fashion. Up to 25% of MFS patients have a de novo mutation. Prevalence is 1 in 5000 individuals, affecting both sexes equally [1]. The diagnosis of MFS is based on the revised Ghent nosology [2]. Patients with MFS show skeletal, ocular and cardiovascular manifestations. Up to 80% of patients with MFS have cardiovascular involvement, including aortic root disease, aortic dissection and mitral valve prolapse with or without mitral regurgitation. Aortic dissection is the main source of morbidity and mortality in patients with MFS.

Data regarding sex and gender-related differences in MFS patients is scarce. Most studies regarding pregnancy in MFS patients do not differentiate between female patients becoming pregnant while being aware of the disease and those who are not. It has been shown that female patients with MFS have an increased risk for aortic dissection during the last trimester of pregnancy and in the early postpartum period [3].

Therefore, we aimed at reporting on sex and gender differences in mortality and aortic events, defined as acute aortic dissection or any aortic intervention, in MFS patients.

METHODS

Ethics Statement

This study was approved by the cantonal ethics committee of the University of Bern (Approval-no: 2019-01534). Individual informed consent was obtained from the patients. In cases of minors, consent was obtained from the parent or the legal guardian.

Study population

We retrospectively analysed data from our database of patients with connective tissue disorders. This database comprises all patients with connective tissue disorders that were

seen in our tertiary-care referral center at least once between 1995 and end of 2020. All patients fulfilled Ghent criteria at the time of inclusion into the database.

Definition of aortic events

Aortic events were defined as Stanford type A (TAAD), type B (TBAD) aortic dissection or any aortic intervention. Aortic interventions include open or endovascular surgery involving all aortic segments. While the analysis of aortic events censors each patient after the 1st event, the recurrent events analysis allows to appreciate the differences in the number of interventions that each patient underwent. All aortic events during a patient's lifetime, from birth to either death or censoring, were considered.

Definition of peripartum period

According to established standards, the peripartum period was defined as pregnancy and three months postpartum [4].

Follow-up

Patients are referred to our tertiary care center because of clinically suspected MFS, an aortic event or a family history of MFS. Patients were actively follow-up in our MFS clinic at 3, 6 and 12 months after any aortic event (surgery or dissection) and then, depending on the findings, at least once a year. Patients without previous aortic events were followed on an annual basis with complete aortic imaging performed at least every 3 years. Patients were generally evaluated using echocardiography, CT-angiography or MR-imaging.

Surgical approach

Since 1995, we have gradually lowered our threshold for elective aortic root surgery in MFS patients from 55 mm to 50 mm or less. Currently the threshold is 45-50 mm in patients suitable for valve sparing aortic root replacement or those who have progressive aortic dilatation more than 3 mm per year.

Our operative technique has evolved since 1995 from the modified Bentall technique to the valve-sparing procedure, namely the David reimplantation technique. Prophylactic root replacement was offered to women wishing to conceive if aortic root size exceeds 40 mm. Operative strategy in patients with acute type A aortic dissection aimed at exclusion of any entry tear in the aortic root, ascending aorta or aortic arch. Recent years saw an increase in total arch replacements using the frozen-elephant-trunk procedure to facilitate subsequent treatment of the thoracoabdominal aorta.

Statistical analysis

Statistical analysis was performed using Stata version 17 (StataCorp, College Station, Tx). For analysis, patients were divided by sex. Female patients were further divided into those with children and those without. Two female patients underwent aortic surgery before pregnancy, and thus experienced their aortic event before childbirth. These patients were therefore included in the subgroup of female patients without children for descriptive as well as Kaplan-Meier analyses (see below). All other women who had children as well as aortic events experienced their aortic events after childbirth and are thus considered as having children at the time of the event in these analyses. Note that the Cox-regression model described below considers children as a time-varying exposure variable, i.e., women are considered as not having children before childbirth and as having children thereafter.

The distribution of continuous data was assessed by Shapiro-Wilk tests, quantile-quantile plots, and histograms. Data are presented as mean (standard deviation), median [quartiles] and number with percentage, according to the type and distribution of the data. Times from patients' birth to (A) first aortic events or (B) death were separately analysed by the Kaplan-Meier method followed by a log rank test to compare the event risk for males versus females, as well as between patients with and without children [5]. To address immortal time bias in comparing women with and without children, we used a Cox regression model with children as a time-dependent variable as detailed above. Hazard ratios and their 95% confidence intervals were estimated from the model, and the proportional hazards assumption was tested using

scaled Schoenfeld residuals. To address that several patients had more than one aortic event, recurrent aortic events were analysed by an Andersen-Gill model, with cluster-robust standard errors to account for multiple observations per patient and considering death as a competing risk for occurrence of aortic events. This model also considered children as time-dependent variable in the comparison of women with versus without children. Differences between the groups in continuous outcomes other than time-to-event data were assessed with unpaired Student' s t-test, Mann-Whitney U test or chi-squared tests, as appropriate. All p-values are two sided and p-values <0.05 were considered statistically significant, except for subgroup analyses of males versus females with children, males versus females without children, and females with children versus females without children, for which a Bonferroni-corrected significance threshold of 0.05/3 = 0.017 was used to denote statistical significance.

RESULTS

Among the 183 MFS patients, 104 (57%) were male and 79 (43%) were female patients. Thirty-seven (47%) of the 79 female patients had at least one child (*Figure 1*).

Seventy-two percent of all patients underwent genetic testing and 89% of these carried pathogenic FBN1 mutations.

Aortic events

Of the 104 male patients, 30 (29%, mean age at last follow-up 19.8 (SD:13.2) years, range 3.4 – 50.1 years) had no aortic events. Seventy-four (71%) male patients had at least one aortic event, including 19 TAAD and 17 TBAD (*Figure 1*). Male patients had 151 aortic events (median 1 [first and third quartile: 0,2], range 0 – 8) in total.

Thirteen (31%, mean age at last follow-up 15.2 (SD:18.3) years, range 1.0 – 71.5 years) of the 42 female patients without children had no aortic events. Twenty-nine (69%) female patients without children had at least one aortic event including four TAAD and four TBAD (*Figure 1*). Female patients without children had 42 aortic events (median 1 [0, 1], range 0 – 3) in total.

Among the 37 female patients with children, six (16%, mean age at last follow-up 42.7 (SD:10.6) years, range 30.2 – 59.5 years) had no aortic events. Thirty-one (84%) female patients with children had at least one aortic event, including twelve TAAD and ten TBAD (*Figure 1*). Female patients with children had 71 aortic events (median 1 [1, 3], range 0 – 7) in total.

During follow-up there is a significant difference in the occurrence of an initial aortic event between male and female patients (p=0.015), with a higher hazard rate of the occurrence of aortic events in male patients (HR 1.56, 95% CI 1.09 to 2.23, *Figure 2A*). However, there is no evidence for an increased probability for recurrent aortic events in male patients compared to female patients (SHR 1.33, 95%CI 0.98 to 1.79, p=0.063) (*Figure 3A*). In the subgroup analysis, there is a significant difference in the occurrence of an initial aortic event between male patients and female patients with children (HR 2.45, 95%CI 1.55 to 3.89, p<0.001), however there is no significantly increased probability for recurrent aortic events (SHR 1.49, 95%CI 1.04 to 2.15, p=0.032) (*Figure 2C and 3C*). There is no significant difference in the occurrence of an initial aortic event (HR 0.89, 95%CI 0.57 to 1.39, p=0.613) nor an increased probability for recurrent aortic events (SHR 1.13, 95%CI 0.77 to 1.66, p=0.542) in male patients compared to female patients without children (*Figure 2B and 3B*).

Moreover, female patients without children apparently have a higher probability of experiencing an aortic event during follow-up (HR 2.08, 95% CI 1.24 to 3.49, p=0.005) compared to female patients with children (*Figure 2D*). However, this difference vanishes after accounting for immortal time bias in the Cox regression model (HR 1.26, 95% CI 0.70 to 2.26, p=0.434). Likewise, there is no increased probability for recurrent aortic events in female patients without children compared to female patients with children (HR 1.32, 95% CI 0.83 to 2.13, p=0.240) (*Figure 3D*).

Stanford type A aortic dissection

Of the 74 male patients who had at least one aortic event, 19 had TAAD (mean age at time of TAAD 37.6 (SD:10.9) years, range 18.4 - 50.3 years). In 18 patients, TAAD occurred as first

aortic event. Only one was aware of his diagnosis prior to TAAD (Table 1). Of the 29 female patients without children who had at least one aortic event, four had TAAD (mean age at time of TAAD 36.5 (SD:21.6) years, range 15.3 – 64.5 years). In all four patients, TAAD occurred as first aortic event. Only one patient was aware of her MFS diagnosis prior to TAAD (Table 1). Among the 31 female patients with children, who had at least one aortic event, twelve had TAAD (mean age at time of TAAD 48.6 (SD:14.0) years, range 26.9 – 69.4 years). TAAD occurred as first aortic event in ten cases. Only three patients were aware of their diagnosis prior to TAAD (Table 1).

During long-term follow-up there is no statistically significant difference in the rate of TAAD between male and female patients (p=0.324), male and female patients without children (p=0.322), male and female patients with children (p=0.537) nor between female patients with children and those without (p=0.569). Male patients were significantly younger at the time of TAAD compared to female patients with children (p=0.020).

Stanford type B aortic dissection

Of the 74 male patients, who had at least one aortic event, 17 had TBAD (mean age at time of TBAD 39.0 (SD:10.0) years, range 24.2 – 57.4 years). TBAD as first aortic event occurred in only three patients. Two patients were aware of their diagnosis prior to TBAD (Table 1). Of the 29 female patients without children, who had at least one aortic event, four had TBAD (mean age at time of TBAD 42.7 (SD:10.2) years, range 34.4 – 56.1 years). TBAD as first aortic event occurred in two cases and only one was aware of her diagnosis prior to TBAD (Table 1).

Among the 31 female patients with children who had at least one aortic event, ten had TBAD (mean age at TBAD 48.4 (SD:12.3) years, range 23.8 – 62.5 years). TBAD as first aortic event occurred in three cases. Two patients were aware of their diagnosis prior to TBAD (Table 1).

During follow-up there was no statistically significant difference in the occurrence of TBAD between male and female patients (p=0.534), male and female patients without children (p=0.652), male and female patients with children (p=0.604) nor between female patients with

children and those without (p=0.989). Male patients were significantly younger at the time of TBAD compared to female patients with children (p=0.041).

Childbirth

Of the 79 female patients, 37 (47%) had at least one child (Figure 1). Mean maternal age at first childbirth was 25.8 (SD:3.5) years (range 19.8 – 34.8 years). Patients reported a total of 79 childbirth (range 0 – 4, three sets of twins). Miscarriages and abortions were excluded.

Prophylactic aortic surgery prior to conception

Prophylactic aortic surgery prior to conception was performed in two patients. In both patients, valve-sparing root replacement was performed. One female patient had one child, the other had three children. Follow-up after childbirth was uneventful in both patients.

Peripartum aortic events

Four (11%) of the 37 female patients with children experienced an aortic event during the peripartum period (Table 2). Three patients had TAAD during the third trimester prior to being diagnosed with MFS. One patient already diagnosed with MFS had uncomplicated TBAD in the postpartum period.

Confirmation of MFS diagnosis before aortic events and childbirth

Among 74 male patients with at least one aortic event, 55% (n=41) were aware of their MFS diagnosis before first aortic event (Table 1). Among 29 female patients without children with at least one aortic event, 79% (n=23) were aware of their MFS diagnosis before first aortic event (Table 1). Among 31 female patients with children with at least one aortic event, 55% (n=17) were aware of their diagnosis before the first aortic event (Table 1).

Among 37 female patients with children, only 22% (n=8) were aware of their MFS diagnosis before their first childbirth. Aortic dissections unrelated to pregnancy occurred in nine (24%) of the 37 female patients with children, five of whom were aware of their diagnosis prior to aortic

dissection. Mean time period between last childbirth and TAAD was 27.0 (SD:12.7) years. Mean time period between last childbirth and TBAD was 24.1 (SD:10.3) years (Figure 4).

Follow-up and Mortality

Mean follow-up from first contact until either death or censoring was 3.7 [0.5, 7.7] years for male patients and 4.9 [0.0, 11.5] years for female patients (p=0.662). The Clark index of all patients was 0.915.

Overall mortality did not significantly differ between male and female patients (HR 0.84, 95%CI 0.30 to 2.38, p=0.744), male and female patients without children (HR 0.76, 95%CI 0.18 to 3.13, p=0.703), male and female patients with children (HR 0.86, 95%CI 0.28 to 2.64, p=0.789) nor between female patients without children and female patients with children (HR1.55, 95%CI 0.36 to 6.63, p=0.549) (Figure 5). Thirty-day mortality was 5% (n=7). The majority of deaths (13 of 16, 81%) occurred in patients with a history of dissection. All causes of death are reported in supplemental table 1.

DISCUSSION

The impact of sex and gender on aortic events in patients with Marfan syndrome has only been reported in a limited number of clinical studies [6,7,8,9]. For decades, case series of peripartum acute aortic dissection or rupture have fostered the notion that women with MFS in general are at a higher risk for aortic events than men. It is only recently that data emerges contradicting this paradigm. Detaint et al. [7] recently reported a large series of MFS patients, where male patients less than 30 years of age were at higher risk for aortic dilatation and aortic events. Results from the Dutch Concor study [8] and from a nationwide Danish cohort [9] reported additional evidence for male sex and gender being a risk factor in patients with MFS. Recent data from a mouse model for MFS confirms these finding and provides mechanistic insights on a molecular level [10]. Further studies that investigated genotype/phenotype correlations

[11,12,13,14] showed that independently of the variants, male patients had more aortic events than female patients.

In our patient population there were no statistically significant differences in the rate of TAAD or TBAD between male and female patients, similar to the GenTAC registry report [15]. While our data on the rate of TAAD in MFS patients is in line with previous research that reported 16% to 28% of patients presenting with TAAD [16,17,18], we are able to provide more granular data regarding sex, gender and childbearing. In our patient population, 18% of male patients, 10% of female patients without children and 32% of female patients with children presented with TAAD. The rate of TBAD, 16% in men, 10% in female patients without children and 27% in female with children in this study is higher than previously reported [6,19]. Seventy-five percent of all aortic dissection (TAAD/TBAD) occurred as first aortic event in patients unaware of the MFS diagnosis at the time of their event. This is higher than previously reported in the Danish cohort [9].

There is little data regarding pregnancy in MFS patients. Only very few reports differentiate between female patients becoming pregnant while being aware of the disease and those who are not. The rate of women becoming pregnant not being aware of MFS diagnosis in this study (78%) is higher than in the GenTAC registry [4] where only 58% of female patients were not aware of their MFS diagnosis before pregnancy. The 2011 European Society of Cardiology (ESC) guidelines on management of cardiovascular disease during pregnancy recommend preventive aortic surgery in females with MFS contemplating pregnancy with an aortic root dilatation >45mm [20]. In the revision of 2018 [21], pregnancy is not recommended in female MFS patients with an aortic dilatation >45mm. According to the 2010 American Heart Association guidelines on thoracic aortic disease, preventive aortic surgery is recommended in females with MFS who are considering pregnancy with an aortic root dilatation >40mm [22]. In this study, only two patients underwent pre-conception aortic surgery. In both cases, a valve-sparing aortic root replacement using the reimplantation technique was performed. AAD in MFS patients most frequently occurs during the last trimester or early postpartum period, up until three months postpartum. However, female MFS patients have an increased risk of

dissection after delivery for at least 6 months to 1 year [23]. In the current patient population, 11% of female MFS patients had peripartum events. However, while pregnancy is regarded as an important risk factor for acute aortic dissection in women with MFS, in our patient population more than twice as many (24% vs. 11%) women with children suffered from acute aortic dissections unrelated to pregnancy. Mean time period between last childbirth was 27.0 (SD:12.7) years for TAAD and 24.1 (SD:10.3) years for TBAD. In the current study, there is no evidence for a difference in the number of events – neither primary nor recurrent aortic events – when appropriately modelling child as a time-varying variable.

In patients with a confirmed diagnosis of MFS, pregnancy and childbirth will most probably be uneventful given adequate surveillance is ensured and prophylactic measures according to current guidelines are performed. Nevertheless, women should be counselled that a small but significant risk for peripartum dissection remains. Especially peripartum TBAD is difficult to prevent as most patients dissect at diameters that are far from any threshold for intervention [18]. Factors influencing peripartum risk for aortic dissection have not been fully elucidated. Breastfeeding and its associated rise in oxytocin levels has been identified as a risk factor for aortic dissection in a mouse model for MFS [24] but robust data in humans is lacking.

This study covers a period of more than 25 years. Awareness for MFS and related disorders has significantly increased over time. Furthermore, growing experience with valve sparing root replacement has lowered the threshold for prophylactic aortic repair prior to conception. This has also certainly influenced the number of women now becoming pregnant despite the diagnosis of MFS. In counselling patients, the pregnancy-associated risk in women with MFS has to be balanced against the lifetime risk of aortic events in people with MFS in general. The current data shows that acute aortic dissection occurs more frequently unrelated to pregnancy and that the lifetime risk for aortic events in women with children is lower than in men. Identifying women in childbearing age at risk for acute aortic dissection remains the most important measure to lower mortality in this patient population.

CONCLUSION

In conclusion, our data suggest that male patients with MFS have a higher risk for aortic events than female patients. Furthermore, 78% of women were not aware of their MFS diagnosis before childbirth. One out of ten of these women suffered from peripartum acute aortic dissection. Twice as many female patients with children suffered from acute aortic dissection unrelated to childbirth. There was no evidence that sex and gender differences affect mortality in MFS patients.

LIMITATION

The current study carries all limitations associated with the retrospective and observational nature of this study, including the possibility of bias. In particular, confounding cannot be excluded. For example, female MFS patients with a strong phenotype or female MFS patients, who already had aortic events in younger age, may be more reluctant to have children. This is a clear confounder of our analysis.

We looked at a subset of patients who had been carefully chosen for the firm diagnosis of MFS. Although the study as a whole is underpowered to detect differences in survival, the fact that we were able to report a complete follow-up with a mean follow-up of more than a decade suggests that this analysis, despite its exploratory nature, provides important data to better counsel patients and help clinicians make an informed decision.

FUNDING STATEMENT

No founding was acquired.

CONFLICTS OF INTEREST STATEMENT

Conflicts of interest: none declared.

DATA AVAILABILITY STATEMENT

Raw data were generated at Inselspital, University of Bern. All relevant data are within the manuscript. Derived data supporting the findings of this study are available from the corresponding author on request.

AUTHOR CONTRIBUTION STATEMENT

Conceptualisation, M.N., P.P.H., B.L. and F.S.S.; methodology, M.N., P.P.H., B.L. and F.S.S.; validation, F.S.S.; formal analysis, M.N., M.Y., and P.S.; investigation, M.N., P.P.H., B.L., M.Y., and F.S.S.; resource, M.N. and F.S.S.; data curation, M.N. and M.M.; writing-original draft, M.N., P.P.H., P.S. and F.S.S.; preparation, M.N., P.P.H. and F.S.S.; writing–review and editing, M.N., P.P.H., B.L., S.J., M.M., P.S., M.M.L., M.Y. and F.S.S.; visualisation, M.N., P.P.H., B.L., S.J., M.M., P.S., M.M.L., M.Y. and F.S.S.; supervision, F.S.S..; project administration, F.S.S.. All authors have read and agreed to the published version of the manuscript.

FIGURE LEGENDS

Central Image

Central image summarizing the study population, study design and the important conclusions.

Figure 1

Flowchart depicting the entire study cohort. Patients are divided by sex and gender and whether female patients had children; see text for details. Aortic events are defined as Stanford type A or type B dissection or intervention on any aortic segment.

MFS: Marfan syndrome. TAAD: Stanford type A acute aortic dissection. TBAD: Stanford type B acute aortic dissection.

Figure 2

Kaplan-Meier plots for the time from birth to initial aortic events between males and females (panel A) and across subgroups (panels B-D). The hazard rate of aortic events defined as Stanford type A or B type dissection or intervention on any aortic segment, is higher in male compared to female patients (panel A). While there were no statistically significant differences between male and female patients without children (panel B), there hazard rate of events was lower in women with children compared to male patients (panel C) or female patients without children (panel D). Note that the finding in panel 2D vanishes after accounting for immortal time bias (see text for details).

Figure 3

Kaplan-Meier plots for recurrent aortic events. Aortic events are defined as Stanford type A or B type dissection or intervention on any aortic segment. While the analysis of aortic events in Fig. 2 censors each patient after the first event, the recurrent events analysis allows to appreciate the differences in the number of interventions that each patient underwent. There is no increased probability for recurrent aortic events nether between male and female patients

(panel A) nor in the subgroup analysis (male patients vs female patients without children (panel B) or male patients vs female patients with children (panel C) or female patients with children vs female patients without children (panel D)).

Figure 4

Timeline illustrating the temporal association of events in female patients with children that suffered from acute aortic dissection during follow-up.

AAD: acute aortic dissection. TAAD: Stanford type A acute aortic dissection. TBAD: Stanford type B acute aortic dissection.

Figure 5

Kaplan-Meier survival plots. All-cause mortality did not differ between male and female patients (panel A), male and female patients without children (panel B), male and female patients with children (panel C) nor between female patients with children and those without (panel D).

TABLES

Table 1: Confirmation of diagnosis prior to event

	Male patients (n=104)	Female patients without children (n=42)	Female patients with children (n=37)
Confirmation of MFS diagnosis before conceiving	n/a	n/a	22% (n=8)
Aortic events	71% (n=74)	69% (n=29)	84% (n=31)
Confirmation of MFS diagnosis before aortic event	55% (n=41)	79% (n=23)	55% (n=17)
TAAD	18% (n=19)	10% (n=4)	32% (n=12)
Confirmation of MFS diagnosis before TAAD	5% (n=1)	25% (n=1)	42% (n=5)
TBAD	16% (n=17)	10% (n=4)	27% (n=10)
Confirmation of MFS diagnosis before TBAD	65% (n=11)	75% (n=3)	70% (n=7)

Overview regarding confirmation of diagnosis and aortic events in male and female patients with or without children.

All MFS patients with aortic events divided by sex and gender and subgroups.

MFS: Marfan syndrome. TAAD: Stanford type A acute aortic dissection. TBAD: Stanford type B acute aortic dissection.:

Table 2: Peripartum events

Patient	Aortic event	1st aortic event	Age at childbirth / aortic event	Number of childbirth	Timepoint	Confirmation of MFS diagnosis before event	Outcome
1	TAAD	yes	34.2	1	3rd trimester	no	surgery + C-section
2	TBAD	yes	23.8	1	postpartum	yes	initially conservative, TAAAR 8 months postpartum
3	TAAD	yes	28.8	4	3rd trimester	no	surgery + C-section
4	TAAD	yes	26.9	1	3rd trimester	no	surgery + C-section

Overview of peripartum events in female patients with children. The peripartum period was defined as pregnancy and 3 months postpartum.

MFS: Marfan syndrome. TAAD: Stanford type A acute aortic dissection. TBAD: Stanford type B acute aortic dissection. TAAAR: thoracoabdominal aortic aneurysm repair

REFERENCES

1. Judge DP, Dietz HC. Marfan's syndrome. Lancet. 2005;366:1965-1976.
2. Loeys BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet. 2010;47:476-485.
3. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cífková R, De Bonis M, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy: The Task Force for the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(34):3165-3241.
4. Roman MJ, Pugh NL, Hendershot TP, Devereux RB, Dietz H, Holmes K, et al. Aortic Complications Associated With Pregnancy in Marfan Syndrom: The NHLBI National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC). J Am Heart Assoc. 2016;5:e004052.
5. Schober P, Vetter TR. Survival Analysis and Interpretation of Time-to-Event Data: The Tortoise and the Hare. Anesth Analg. 2018:127(3):792-798.
6. Roman MJ, Devereux RB, Preiss LR, Asch FM, Eagle KA, Holmes KW, et al. Associations of Age and Sex with Marfan Phenotype: the National Heart, Lung, and Blood Institute GenTAC (Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions) Registry. Circ Cardiovasc Genet. 2017;10(3):e001647.
7. Détaint D, Faivre L, Collod-Beroud G, Child AH, Loeys BL, Binquet C, et al. Cardiovascular manifestations in men and women carrying a FBN1 mutation. Eur Heart J. 2010;31(18):2223-2229.
8. Franken R, Groenink M, de Waard V, Feenstra HMA, Scholte AJ, van den Berg MP, et al. Genotype impacts survival in Marfan syndrome. Eur Heart J. 2016;37(43):3285-3290.
9. Groth KA, Stochholm K, Hove H, Kyhl K, Gregersen PA, Vejlstrup N, et al. Aortic events in a nationwide Marfan syndrome cohort. Clin Res Cardiol. 2017;106:105-112.

10. Anderson NK, Juzwiak EE, Dietz HC. A seX(XY) Article on Marfan Syndrom. J Am Heart Assoc. 2020;9(29):e018814.
11. Arnaud P, Milleron O, Hanna N, Ropers J, Ouail NO, Affoune A, et al. Clinical relevance of genotype-phenotype correlations beyond vascular events in a cohort study of 1500 Marfan syndrome patients with FBN1 pathogenic variants. Genet Med. 2021;23:1296-1304
12. Faivre L, Collod-Beroud G, Loeys BL, Child A, Binquet C, Gautier E, et al. Effect of Mutation Type and Location on Clinical Outcome in 1013 Proband with Marfan Syndrome or Related Phenotypes and FBN1 Mutations: An International Study. Am J Hum Genet. 2007;81:454-466.
13. Hernándiz A, Zúñiga A, Valera F, Domingo D, Ontoria-Oviedo I, Marí JF, et al. Genotype FBN1/phenotype relationsip in a cohort of patients with Marfan syndrome. Clin Genet. 2021;99:269-280.
14. Takeda N, Inuzuka R, Maemura S, Morita H, Nawata K, Fujita D, et al. Impact of Pathogenic FBN1 Variant Types on the Progression of Aortic Disease in Patients With Marfan Syndrome. Circ Genom Precis Med. 2018;11:e002058.
15. Holmes KW, Maslen CL, Kindem M, Kroner BL, Song HK, Ravekes W, et al. GenTAC registry report: Gender differences among individuals with genetically triggered thoracic aortic aneurysm and dissection. Am J Med Genet Part A 161A:779-786.
16. Cameron DE, Alejo DE, Patel ND, Nwakanma LU, Weiss ES, Vricella LA, et al. Aortic root remplacement in 372 Marfan patients; evolution of operative repair over 30 years. Ann Thorac Surg. 2009;87(5):1344-1349.
17. Girdauskas E, Kuntze T, Borger MA, Falk V, Mohr FW. Distal aortic reinterventions after root surgery in Marfan patients. Ann Thorac Surg. 2008;86(6):1815-1819.
18. Schoenhoff FS, Jungi S, Czerny M, Roost E, Reineke D, Matyas G, et al. Acute Aortic Dissection Determines the Fate of Initially Untreated Aortic Segments in Marfan Syndrome. Circulation. 2013;127(15):1569-1575.

19. den Hartog AW, Franken R, Zwinderman AH, Timmermans J, Scholte AJ, van den Berg MP, et al. The risk for type B aortic dissection in Marfan syndrome. J Am Coll Cardiol. 2015;65(3):246-254.
20. Regitz-Zagrosek V, Blomstrom-Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Disease during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2011;32(24):3147-3197.
21. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomström-Lundqvist C, Cifkova R, De Bonis M, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy: The Task Force for the Management of Cardiovascular Disease during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(34):3165-3241.
22. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/ SIR/STS/ SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Associa- tion Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation. 2010;121(13):e266–e369.
23. Meijboom LJ, Vos FE, Timmermans J, Boers GH, Zwinderman AH, Mulder BJM. Pregnancy and aortic root growth in the Marfan syndrome: a prospective study. Eur Heart J. 2005;26(9):914-920.
24. Habashi JP, MacFarlane EG, Bagirzadeh R, Bowen C, Huso N, Chen Y, et al. Oxytocin antagonism prevents pregnancy-associated aortic dissection in a mouse model of Marfan syndrome. Sci Transl Med. 2019:11(490):eaat4822.

Figure 1

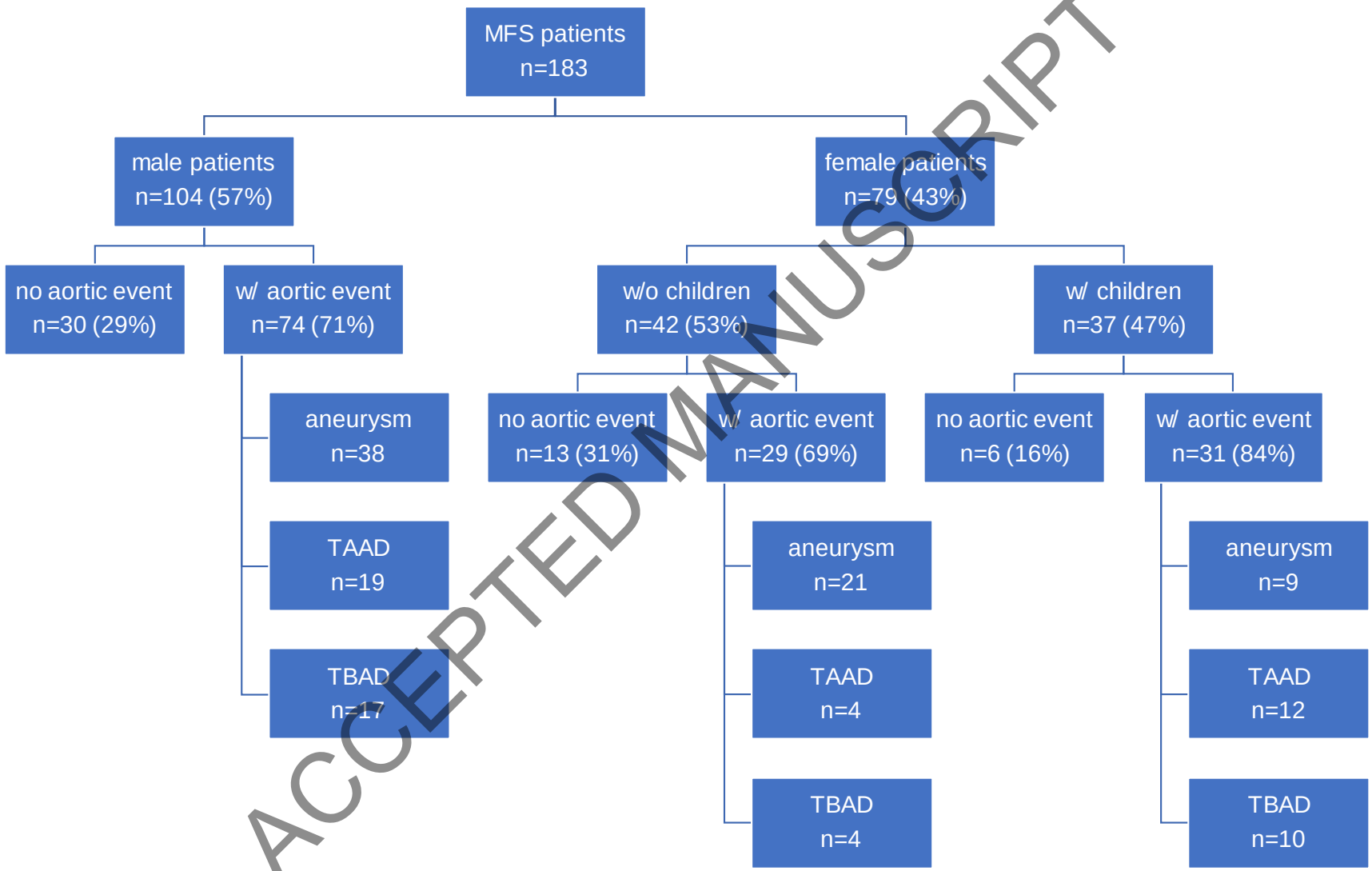
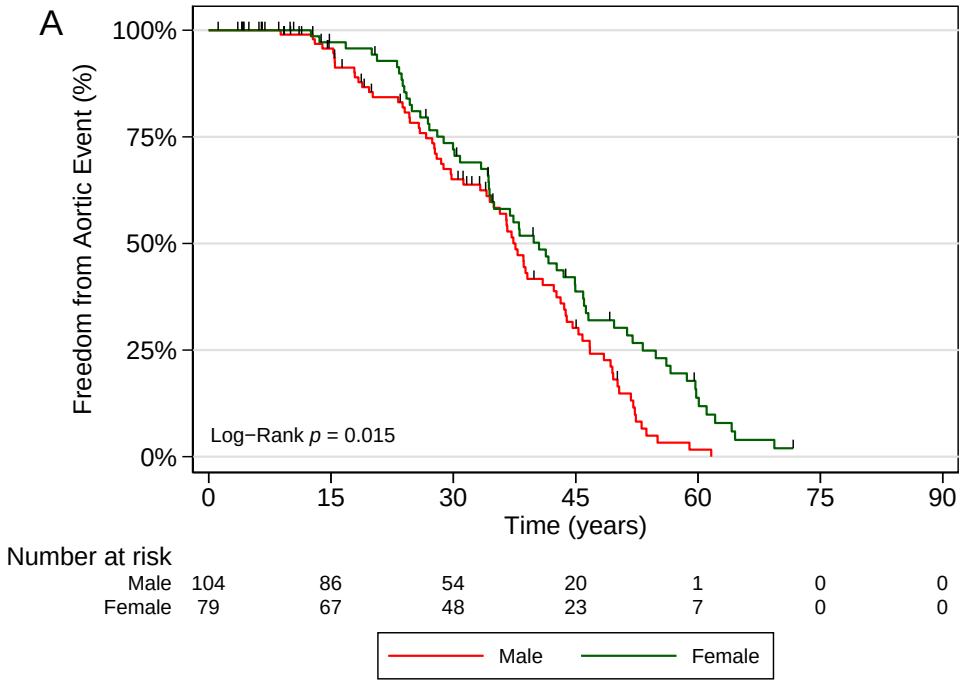
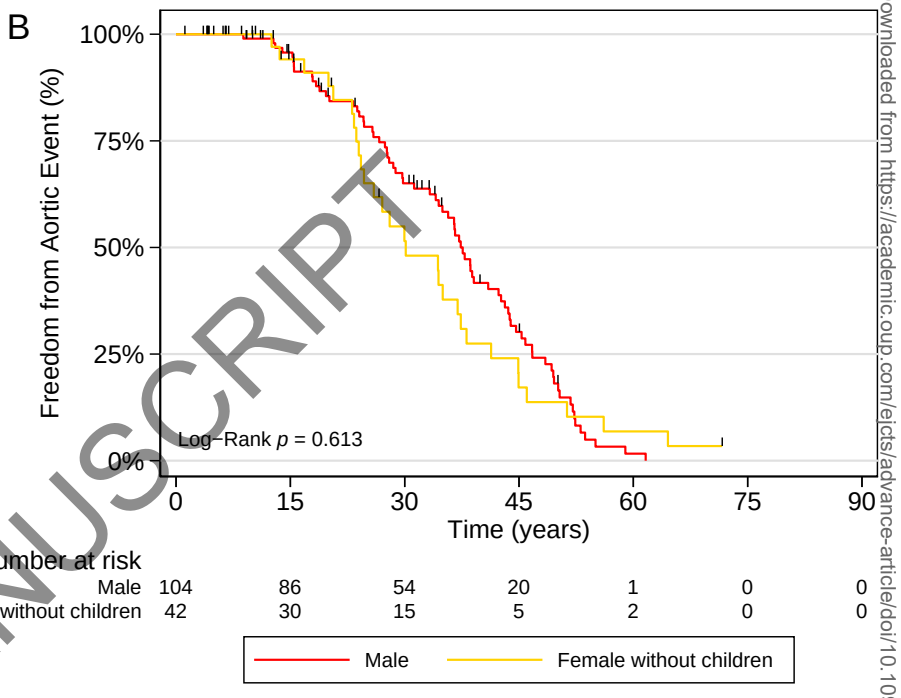
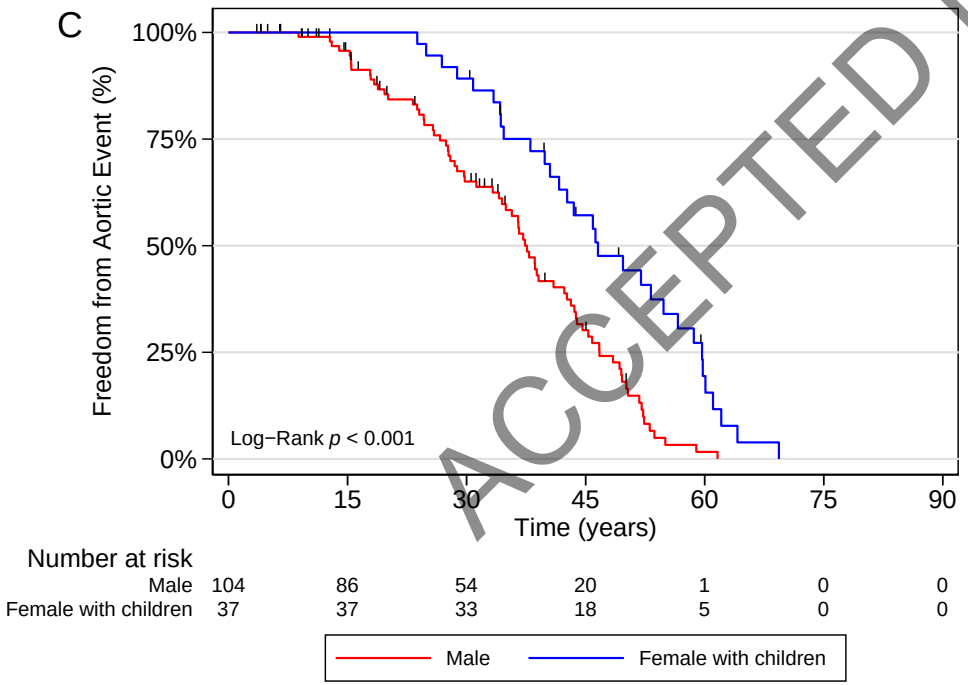
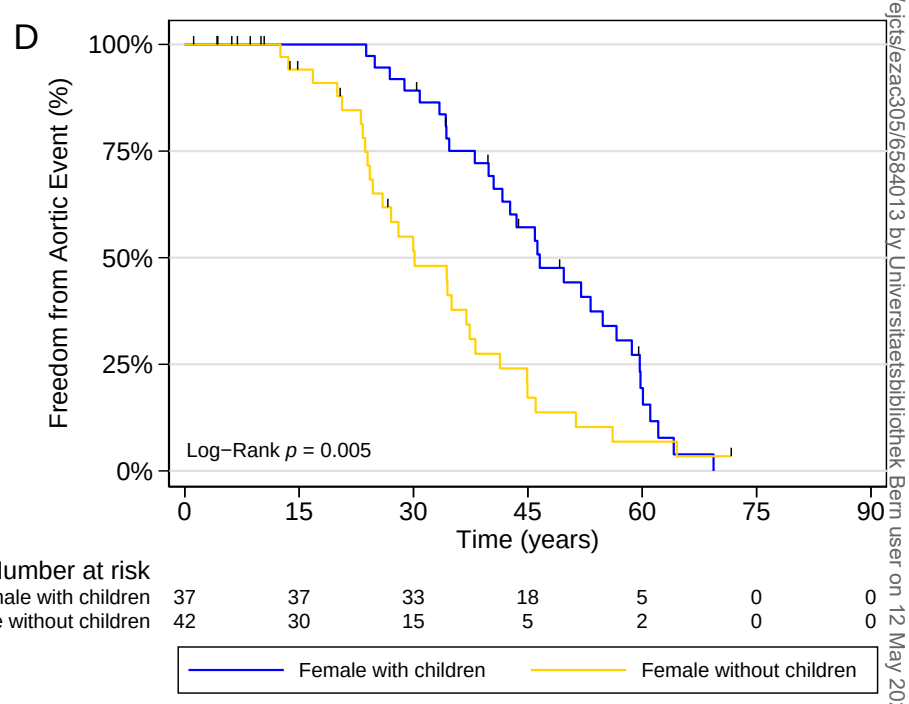


Figure 2









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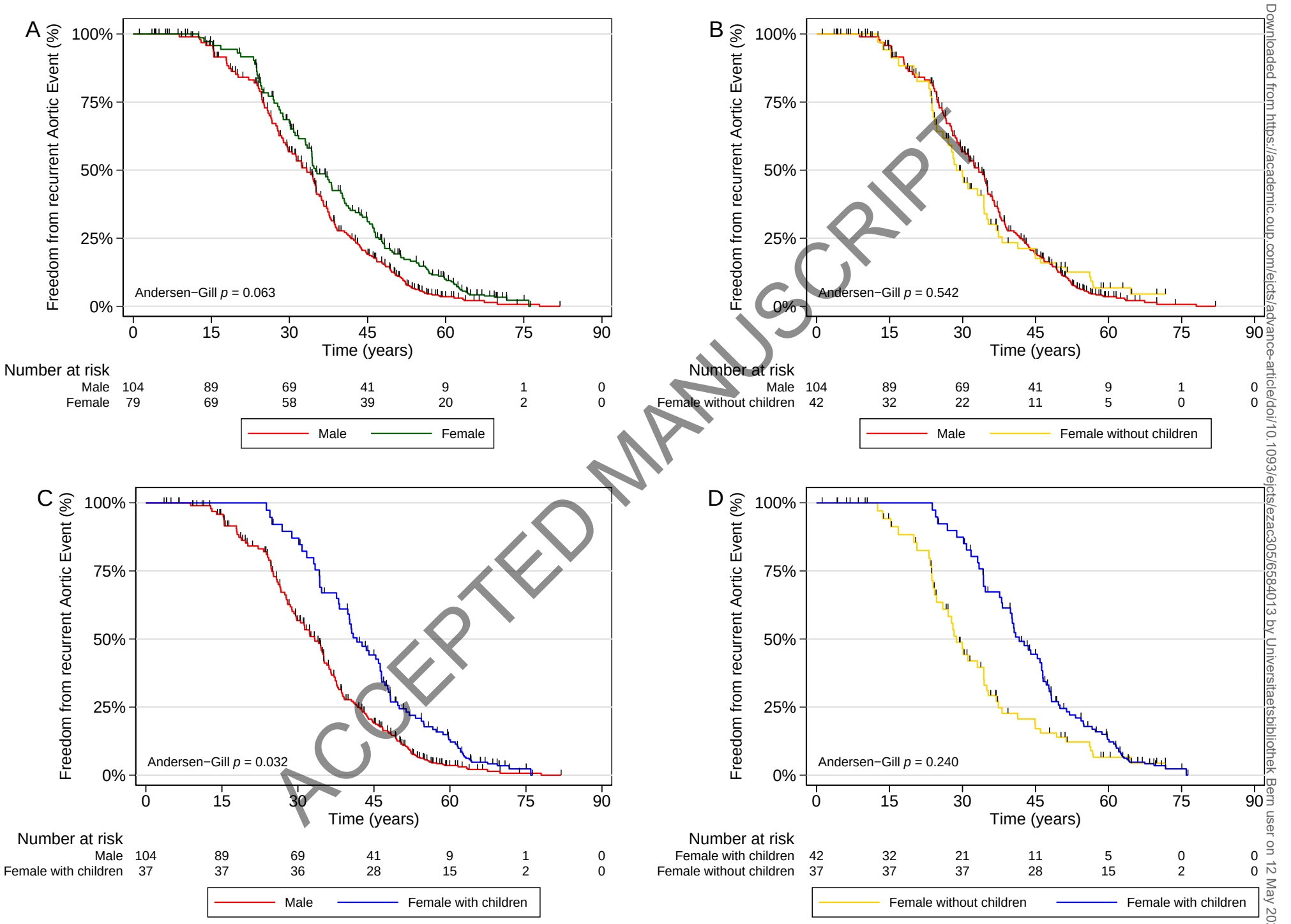

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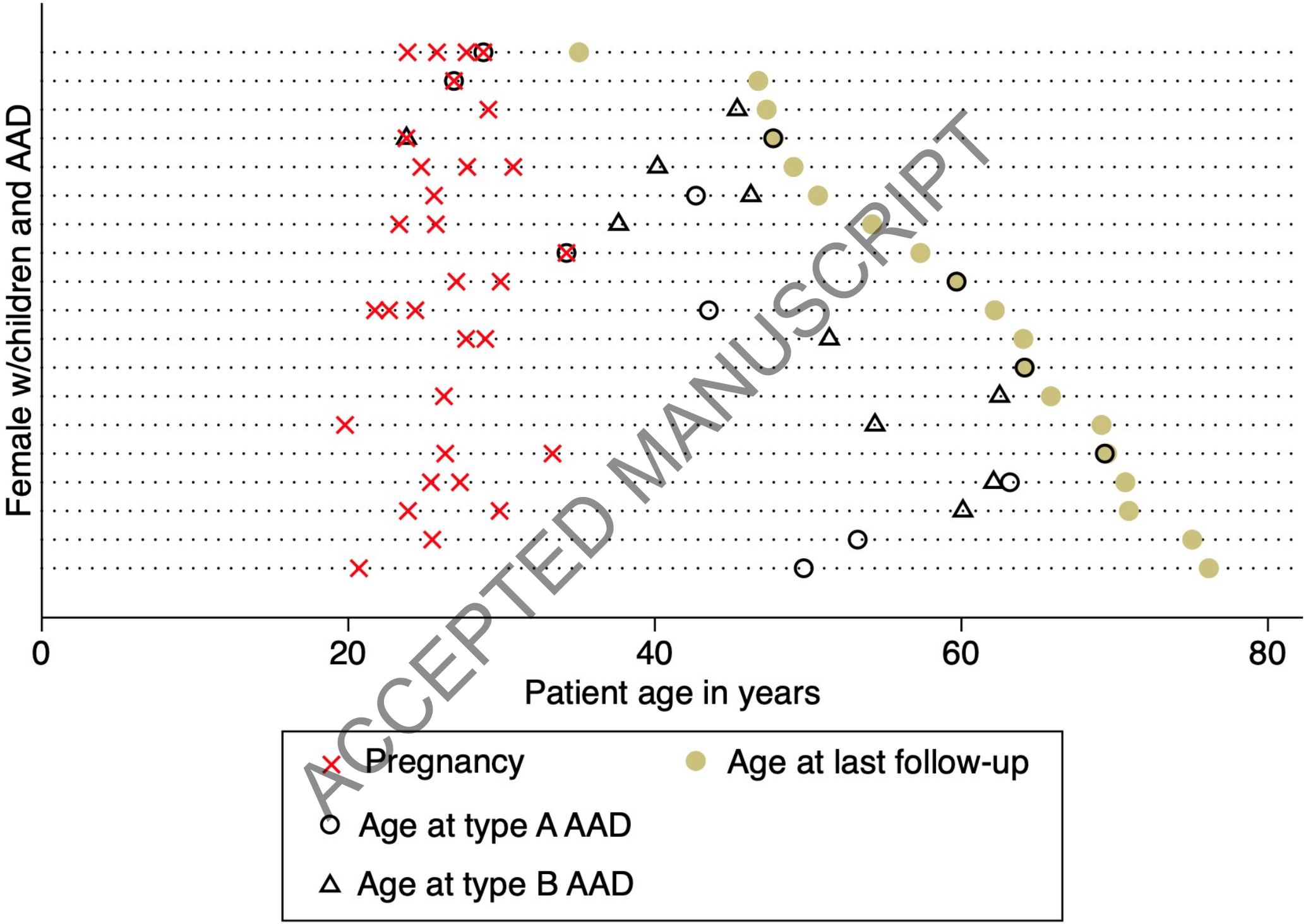

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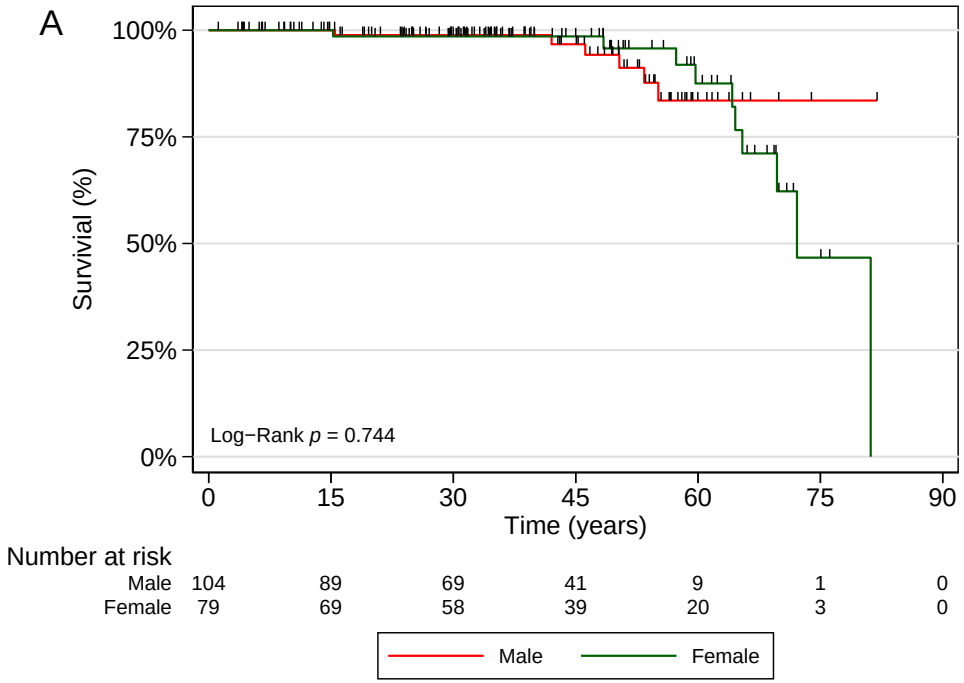

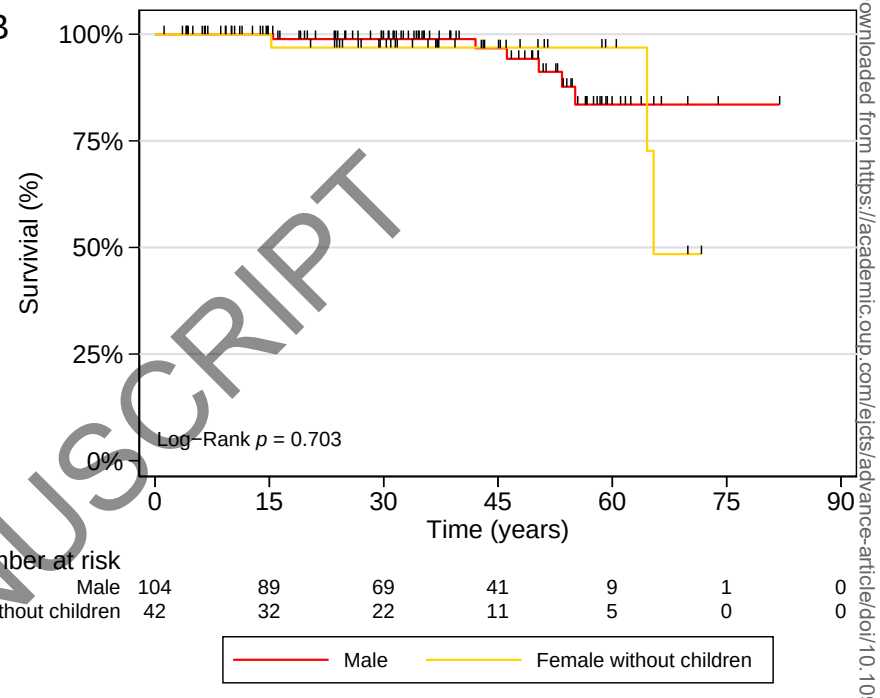

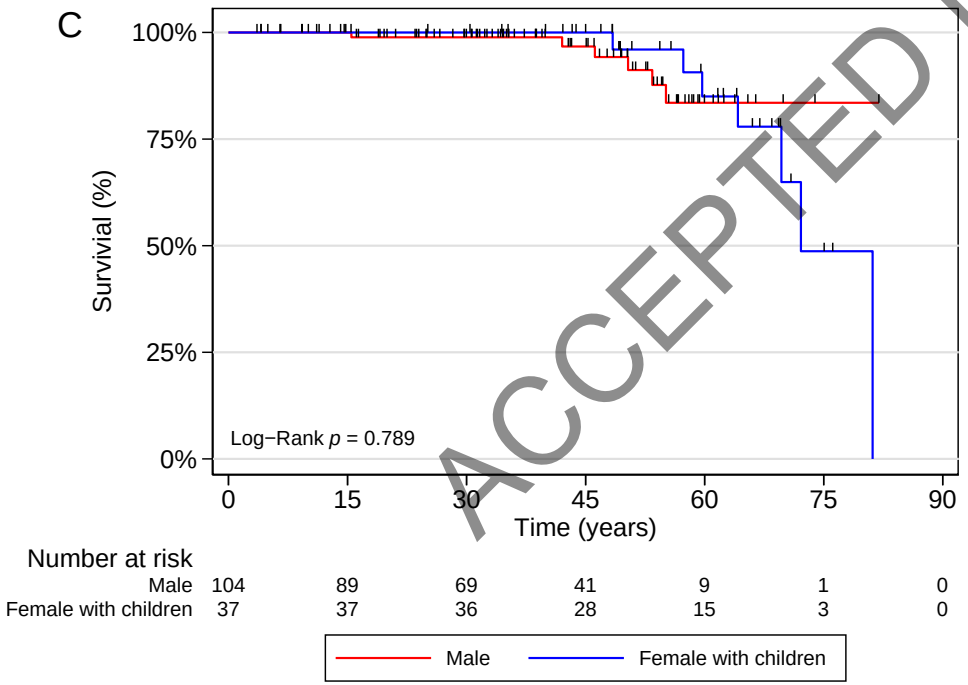

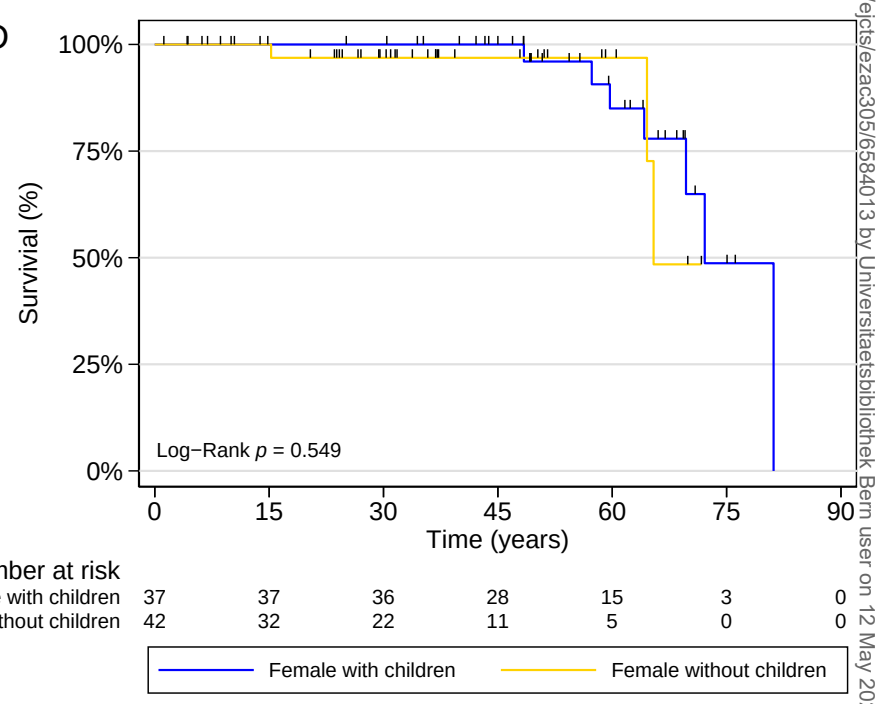

Central image

Key question

Are there sex and gender differences regarding aortic events in MFS patients?

Key finding(s)

No sex differences in occurrence of TAAD/TBAD. One out of ten women suffered from peripartum AAD.

Take-home message

Male patients have a higher risk of aortic events, but there are no sex differences affecting mortality.

The impact of sex and gender on aortic events in patients with Marfan syndrome

Population	Design	Results	Conclusions
183 MFS patients - 104 ♂ - 79 ♀	Observational retrospective single center study	71% of male patients had at least one aortic event, including 16 TAAD and 14 TBAD	Male patients have higher risk of aortic events No sex differences in occurrence of TAAD/TBAD No sex differences affecting mortality

Subgroup Analysis

Female patients	Results	Conclusions
79 female MFS patients - 42 w/o children - 37 w/ children (n=79)	69% of female patients w/o children and 84% of female patients w/ children had at least one aortic event.	One out of ten women suffered from peripartum TAAD/TBAD Twice as many female patients with children suffered from AAD unrelated to pregnancy