Aortic size predicts aortic dissection in Turner syndrome - A 25-year prospective cohort study

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ABSTRACT

Background: Women with Turner syndrome (TS) have an increased risk of aortic dissection. The current recommended cutoff to prevent aortic dissection in TS is an aortic size index (ASI) of $\geq 2.5$ cm/m$^2$. This study estimated which aortic size had the best predictive value for the risk of aortic dissection, and whether adjusting for body size improved risk prediction.

Methods: A prospective, observational study in Sweden, of women with TS, n = 400, all evaluated with echocardiography of the aorta and data on medical history for up to 25 years. Receiver operating characteristic (ROC) curves, sensitivity and specificity were calculated for the absolute ascending aortic diameter (AAD), ascending ASI and TS specific z-score.

Results: There were 12 patients (3%) with aortic dissection. ROC curves demonstrated that absolute AAD and TS specific z-score were superior to ascending ASI in predicting aortic dissection. The best cutoff for absolute AAD was 3.3 cm and 2.12 for the TS specific z-score, respectively, with a sensitivity of 92% for both. The ascending ASI cutoff of 2.5 cm/m$^2$ had a sensitivity of 17% only. Subgroup analyses in women with an aortic diameter $\geq 3.3$ cm could not demonstrate any association between karyotype, aortic coarctation, bicuspid aortic valve, BMI, antihypertensive medication, previous growth hormone therapy or ongoing estrogen replacement treatment and aortic dissection. All models failed to predict a dissection in a pregnant woman.

Conclusions: In Turner syndrome, absolute AAD and TS-specific z-score were more reliable predictors for aortic dissection than ASI. Care should be taken before and during pregnancy.

Keywords:
Risk factor
Prophylactic surgery
ROC curve
Aortic dissection
Echocardiography
Sensitivity

Abbreviations: AAD, Ascending aortic diameter; ASI, Aortic size index; BMI, Body mass index; ROC, Receiver operating characteristic; TS, Turner syndrome.

* All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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1. Introduction

Turner syndrome is a complex genetic disorder affecting 1/2500 live-born girls and is caused by a complete or partial absence of the X chromosome [1]. The same genotype generates highly variable phenotypes, but the classic Turner syndrome genotype (45,X) is usually associated with short stature, gonadal dysfunction, and congenital cardiovascular malformations, such as coarctation of the aorta and a bicuspid aortic valve. Women with Turner syndrome have an increased risk of aortic dissection which often results in sudden death at a young age [2,3]. It is therefore crucial to be able to predict which women might experience an aortic dissection.

Coarctation of the aorta, bicuspid aortic valve and hypertension are all risk factors for aortic dissection. These factors are currently used to predict the risk of aortic dissection in Turner syndrome, as well as an ascending aortic size index (ASI) which adjusts absolute ascending aortic measurements for body size [4,5].

An ascending ASI \( \geq 2.5 \text{ cm/m}^2 \) is considered to be associated with a high risk of aortic dissection in women with Turner syndrome >15 years of age. International guidelines recommend considering prophylactic elective surgery to replace the aorta when the ascending ASI is \( \geq 2.5 \text{ cm/m}^2 \) [4-6]. However, this threshold is based on weak evidence; no prospective longitudinal study of aortic dissection related to ascending ASI in Turner syndrome has been published, making it difficult to make a clear-cut distinction between those who will benefit from surgery and those who will not. On the one hand, patients with an ascending ASI of <2.5 cm/m\(^2\) sometimes experienced aortic dissection, and, on the other, prophylactic surgery of the ascending aorta has a mortality rate of 2.0–4.8%. Thus, the benefits of surgery must be weighed against the possible risks [7-11].

In this study, we address which aortic size has the best predictive value for the risk of aortic dissection, and whether adjusting for body size in these women with short stature improves the risk prediction. We use a large cohort of Swedish women with Turner syndrome followed for up to 25 years to answer these critical questions.

2. Material and methods

2.1. Study design and ethical considerations

This is a prospective, observational cohort study. From January 1995 to March 2021, resulting in a follow-up period of a maximum of 25 years, women with Turner syndrome were consecutively included in a special care schedule in order to follow them and study cardiovascular outcomes.

The number of patients with Turner syndrome in the area during the study period determined the study size. The study population was followed from the date of inclusion to the date of death or to the endpoint aortic dissection, or until March 2021, whichever came first. The National Cause of Death Register in Sweden was used to identify the cause of death in the patients with an unknown cause of death. The Swedish National Inpatient Register and the Swedish National Outpatient Register were used to identify the outcome (i.e. aortic dissection ICD 10 codes: I71.0, I71.1, I71.3, I71.5, and I71.8) in the patients who moved from the area during the study period and failed to attend follow-up visits. The study was approved by the Regional Ethical Review Board in Gothenburg and the Central Ethical Board in Stockholm and conducted in accordance with the Helsinki declaration [12]. All patients provided informed consent.

2.2. Participants

Patients with suspected or diagnosed Turner syndrome were recruited through an advertisement in the Turner patient magazine, by referral from hospitals or through transition from pediatric clinics in Sweden (10 million inhabitants) to the Turner Centers in Stockholm, Gothenburg, Malmö, and Linköping, Sweden. The inclusion criteria were phenotypic subjects with Turner syndrome, \( \geq 16 \) years of age, with partial or complete absence of an X chromosome in at least 5% of the leukocytes or buccal cells and at least one available echocardiographic report of the aorta. The exclusion criteria were death of unknown cause, aortic dissection Stanford type B, and prophylactic aortic surgery.

2.3. Examinations

The patients were monitored according to the current national and international guidelines for care and treatment of patients with Turner syndrome at the time of the study period [1,6,13,14]. All patients were examined every five years by an internal medicine specialist/endocrinologist and referred for echocardiography every 1–10 years depending on their risk profile. Coarctation of the aorta and bicuspid aortic valve, respectively, were mainly detected during childhood and in those cases known before transition to the adult clinic. If the diagnosis Turner syndrome was set after 16 years of age, and any aberrations were suspected at the first echocardiography, a magnetic resonance imaging (MRI) was performed for confirmation of the coarctation of the aorta and/or bicuspid aortic valve. Data on genotype and phenotype, including age, height, body weight, body mass index (BMI), blood pressure, smoking status, serum lipids, cause and date of death, all medication, previous growth hormone therapy, ongoing estrogen hormone replacement therapy, pregnancy and comorbidities, were collected, anonymized, and included in a study database.

2.4. Echocardiography and definitions

The patients underwent standard echocardiography performed by experienced investigators at the local hospital. The diameter of the proximal part of the ascending aorta obtained from a parasternal long-axis projection, was measured according to the inner edge to inner edge principle. Aortic dissection, both Stanford Type A (a dissection that involves any part of the aorta proximal to the origin of the left subclavian artery) and Type B (a dissection that arises distal to the left subclavian artery origin), that was recorded in the medical records or in the autopsy protocol were included in the database [15]. The ascending ASI was computed by dividing the diameter of the ascending aorta by the body surface area. Z-score was calculated in accordance with Quezada et al. [16].

Body surface area (BSA) was calculated with the Du Bois method [17]. Coarctation of the aorta was defined as a localized narrowing of the aortic lumen with a significant pressure gradient obtained with doppler ultrasound. The aortic valve (bicuspid or tricuspid) and coarctation of the aorta were classified by echocardiography or MRI in accordance with clinical practice.

2.5. Genotype

The genotype was defined by the karyotype based on conventional cytogenetic analysis of G-banded metaphases after 72–96 h of lymphocyte growth. Analyses were performed on \( \geq 25 \) metaphases with a chromosome quality of 400 bands. When Fluorescence In Situ Hybridization (FISH) of the buccal cells or the lymphocytes in blood was performed, \( \geq 100 \) cells were evaluated. Monosomy (45,X) was present if the analyses showed \( \geq 95\% \) loss of the second sex chromosome. The lower limit was defined in accordance with Homer et al. [18].

2.6. Statistical analysis

Continuous variables were described with means and standard deviations (SD) or medians and ranges, where applicable. For comparison between groups, Fisher’s Exact test was used for dichotomous variables and the Mann-Whitney U test for continuous variables. Odds ratios with 95% confidence intervals were calculated using logistic regression.
Receiver Operating Characteristic (ROC) curves were generated compared with a nonparametric method by DeLong et al. [19]. Area under the curve (AUC) was calculated, and a cutoff for each model was estimated by Youden’s J statistic.

All tests were two-tailed and \( p < 0.05 \) was considered significant. Aortic dissections that occurred during the 25-year study period were included in the analysis.

All analyses were performed using either SPSS version 24.0 for Windows (IBM, Armonk, NY, USA) or SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Study population

From January 1995 to March 2021, 404 patients met the inclusion criteria and consented to participate in the study. Four of these patients were excluded: one due to unknown cause of death, two due to prophylactic aortic surgery, and one due to aortic dissection, Stanford type B (Supplementary Fig. 1). A total of 400 patients were finally included in the study, which corresponds to approximately 67% of all known patients with Turner syndrome >16 years in Sweden. The average age at the time of inclusion was 27 years, ranging from 17 to 78 years. The mean follow-up time was 15 years (median 15, maximum 25 years). The average number of available echocardiography reports was 1.75 per individual, minimum 1, maximum 4.

3.2. Concomitant hormone therapy

The average dose of estrogen supplementation was 2 mg 17-beta-estradiol/day. Growth hormone treatment due to short stature had been given to 55% of the patients during childhood and adolescence (Table 1).

| Baseline characteristics in women with Turner syndrome with and without aortic dissection. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                 | All women with TS | Women with TS and aortic dissection | Women with TS and no aortic dissection | \( P \) value \(^\dagger\) |
| Age, years  \( n = 400 \) | 27.3 ± 11.4 | 32.8 ± 13.1 | 27.2 ± 11.4 | 0.041 |
| Height, cm  \( n = 388 \) | 154.1 ± 6.8 | 151.3 ± 6.9 | 154.2 ± 6.8 | 0.16 |
| Body weight, kg  \( n = 388 \) | 59.7 ± 12.2 | 67.1 ± 17.3 | 59.5 ± 12.0 | 0.095 |
| Body mass index, kg/m\(^2\)  \( n = 388 \) | 25.3 ± 6.0 | 29.4 ± 7.4 | 25.1 ± 5.9 | 0.013 |
| Body surface area, m\(^2\)  \( n = 388 \) | 1.54 ± 0.18 | 1.61 ± 0.19 | 1.54 ± 0.18 | 0.21 |
| Monosomy (45,X), n (%)  \( n = 388 \) | 234 (58.5) | 9 (75.0) | 225 (58.0) | 0.38 |
| Ascending aorta, cm  \( n = 388 \) | 2.7 ± 0.4 | 3.4 ± 0.5 | 2.7 ± 0.4 | 0.0007 |
| Aortic size index, cm/m\(^2\)  \( n = 388 \) | 1.9 ± 0.3 | 2.2 ± 0.3 | 1.9 ± 0.3 | 0.0003 |
| Bicuspid aortic valve, n (%)  \( n = 388 \) | 86 (21.9) | 5 (45.5) | 81 (21.3) | 0.14 |
| Coarctatio aortae, n (%)  \( n = 12 \) | 40 (10.1) | 2 (16.7) | 38 (9.9) | 0.69 |
| Systolic BP, mmHg  \( n = 388 \) | 122.8 ± 14.8 | 133.2 ± 18.9 | 122.5 ± 14.6 | 0.039 |
| Diastolic BP, mmHg  \( n = 388 \) | 76.8 ± 9.3 | 79.8 ± 9.6 | 76.8 ± 9.3 | 0.20 |
| GH therapy, n (%)  \( n = 388 \) | 220 (55.6) | 6 (50.0) | 214 (55.7) | 0.91 |
| Estrogen HRT, n (%)  \( n = 388 \) | 334 (85.4) | 8 (72.7) | 326 (85.8) | 0.41 |
| BP medication, n (%)  \( n = 388 \) | 63 (16.2) | 5 (41.7) | 58 (15.5) | 0.062 |
| Total cholesterol, mmol/L  \( n = 388 \) | 5.0 ± 2.6 | 5.2 ± 1.2 | 5.0 ± 2.6 | 0.27 |
| Smoker, n (%)  \( n = 388 \) | 17 (4.3) | 1 (8.3) | 16 (4.2) | 0.83 |
| Diabetes mellitus, n (%)  \( n = 388 \) | 16 (4.2) | 0 (0.0) | 16 (4.3) | 1.00 |

BP, Blood pressure; GH, growth hormone; HRT, hormone replacement therapy; TS, Turner syndrome.  
\(^\dagger\) \( P \) values are shown for comparisons between patients with Turner syndrome with and without aortic dissection using the Mann-Whitney U test/Fisher’s Exact test.

3.3. Aortic dissection versus no aortic dissection

The patients were divided into two groups: aortic dissection (\( n = 12 \)) or no aortic dissection (\( n = 388 \)). Patients with aortic dissection were older at inclusion, their systolic blood pressure was higher, and they had a wider absolute ascending aortic diameter and ascending ASI than the patients without aortic dissection. Height, body weight, and body surface area were similar in between the groups as were the proportions of coarctation of the aorta and treatment for hypertension (Table 1).

The following karyotypes were represented in the women with aortic dissection vs women without dissection: monosomy X (75% vs 58%), mosaic 45,X/46,XX (17% vs 14%), mosaicism with ‘Triple X’/polyplody (0% vs 2%), mixed gonadal dysgenesis/ Y material (0% vs 7%), deletions (0% vs 7%), ring X chromosome (8% vs 3%) and isochromosomes Xp; isodicentric Xp (0% vs 10%), other karyotypes (0% vs 3%). The aortic dissection was fatal in six of 12 (50%) patients. The mean aortic size was similar in the patients with aortic dissection who died and those with aortic dissection who survived. Eleven patients experienced dissection in the ascending aorta, and one patient from a dissection that involved the ascending and the proximal descending aorta. Their echocardiograms prior to dissection were performed at a mean of 2.6 years before the dissection (median 2.5 years, minimum same year, maximum eight years).

The mean age at aortic dissection was 40 years (standard deviation of ±15.5 years, median 37 years, min.-max. 25-71 years) (Table 2). There was no decreasing trend of aortic dissections, i.e., they were evenly distributed over the study period. The patient with the echocardiogram eight years prior to dissection had no other comorbidity, and she cancelled her planned five year follow up. She died of aortic dissection three years after the cancelled visit. The only woman who experienced an aortic dissection with an aortic diameter below 3 cm was pregnant, (Table 2).

3.4. Receiver operating characteristics curves and threshold levels

The ROC curves compare the true positive rate (sensitivity) in function of the false positive rate (1- the specificity) for the ascending ASI, the absolute ascending aortic diameter and the Turner syndrome specific z-score in predicting aortic dissection. The area under the curve was 0.81 (95% CI 0.68;0.94) for the ascending ASI, 0.87 (95% CI 0.76;0.99) for the absolute ascending aortic diameter and 0.86 (95% CI 0.74;0.99) for Turner syndrome specific z-score (Fig. 1). Comparison between the models showed that there was a significant difference; the AUC of both absolute ascending aortic diameter and Turner syndrome
specific z-score were superior to ascending ASI (Wald test, \( p = 0.01 \) for absolute ascending diameter vs \( p = 0.01 \) for Turner specific z-score).

There was no significant difference between the absolute ascending diameter model and the Turner syndrome specific z-score model. The best cutoff for predicting aortic dissection was calculated for each model; 3.3 cm for the absolute ascending aortic diameter, 2.06 cm/m\(^2\) for ascending ASI and 2.12 for Turner syndrome specific z-score of the ascending aorta (Table 3).

Fig. 2 presents the relationship between aortic size and age at the latest echocardiogram prior to dissection for each model in women with Turner syndrome.

Table 2

<table>
<thead>
<tr>
<th>Timing of last echo prior to dissection (years)</th>
<th>Ascending aorta (cm)</th>
<th>ASI (cm/m(^2))</th>
<th>Comorbidities and karyotype</th>
<th>Age at dissection (years)</th>
<th>Dissection year</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3.5</td>
<td>2.19</td>
<td>Hypertension, 45,X/46,XX</td>
<td>25</td>
<td>1999</td>
</tr>
<tr>
<td>1</td>
<td>4.0</td>
<td>2.19</td>
<td>BAV, CoA, hypertension, 45,X</td>
<td>37</td>
<td>2002</td>
</tr>
<tr>
<td>&lt;1</td>
<td>3.3</td>
<td>2.13</td>
<td>BAV, 45,X</td>
<td>30</td>
<td>2005</td>
</tr>
<tr>
<td>4</td>
<td>3.9</td>
<td>2.41</td>
<td>45,X/46,XX,r(X)</td>
<td>28</td>
<td>2006</td>
</tr>
<tr>
<td>8</td>
<td>3.4</td>
<td>2.50</td>
<td>45,X</td>
<td>71</td>
<td>2008</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>1.45</td>
<td>Pregnancy, 45,X/46,XX</td>
<td>28</td>
<td>2009</td>
</tr>
<tr>
<td>&lt;1</td>
<td>3.3</td>
<td>2.39</td>
<td>45,X</td>
<td>57</td>
<td>2011</td>
</tr>
<tr>
<td>&lt;1</td>
<td>3.3</td>
<td>2.14</td>
<td>BAV, CoA, hypertension, 45,X</td>
<td>63</td>
<td>2012</td>
</tr>
<tr>
<td>&lt;1</td>
<td>4.3</td>
<td>2.20</td>
<td>BAV, hypertension, 45,X</td>
<td>38</td>
<td>2013</td>
</tr>
<tr>
<td>6</td>
<td>3.7</td>
<td>2.06</td>
<td>Hypertension, 45,X</td>
<td>42</td>
<td>2018</td>
</tr>
<tr>
<td>2</td>
<td>3.8</td>
<td>2.53</td>
<td>BAV, 45,X</td>
<td>37</td>
<td>2019</td>
</tr>
<tr>
<td>3</td>
<td>3.5</td>
<td>2.06</td>
<td>45,X</td>
<td>25</td>
<td>2019</td>
</tr>
</tbody>
</table>

BAV, bicuspid aortic valve; CoA, coarctation of the aorta.

Table 3

<table>
<thead>
<tr>
<th>Model</th>
<th>Cutoff</th>
<th>Sensitivity, (%)</th>
<th>Specificity, (%)</th>
<th>LHR+</th>
<th>LHR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascending aortic size index (cm/m(^2))</td>
<td>2.50(^a)</td>
<td>17</td>
<td>95</td>
<td>3.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Ascending aortic size index (cm/m(^2))</td>
<td>2.06(^b)</td>
<td>92</td>
<td>77</td>
<td>4.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Absolute ascending aortic diameter (cm)</td>
<td>3.30(^b)</td>
<td>92</td>
<td>86</td>
<td>6.7</td>
<td>0.1</td>
</tr>
<tr>
<td>Turner-specific z-score</td>
<td>2.12(^b)</td>
<td>92</td>
<td>85</td>
<td>6.3</td>
<td>0.1</td>
</tr>
</tbody>
</table>

LHR+, positive likelihood ratio; LHR-, negative likelihood ratio.

\(^a\) The recommended cutoff according to international guidelines [4–6].

\(^b\) The best cutoff for predicting aortic dissection in each model.
Fig. 2. The relationship between absolute ascending aortic diameter, ascending aortic size index, Turner syndrome specific z-score, and age in women with Turner syndrome with or without aortic dissection. The aortic measurements are from the latest echocardiography reports prior to dissection. The different cutoffs for each model are marked in the figures. The woman with aortic dissection who had the lowest values in the figures was pregnant. (A) Age and absolute ascending aortic diameter. Dotted line at the best absolute aorta diameter cutoff, 3.3 cm. (B) Age and ascending ASI. Dotted line at the ascending ASI value of $2.5 \text{ cm/m}^2$, which is the current recommended cutoff for considering prophylactic surgery in patients with Turner syndrome according to international guidelines [4–6]. Dashed line at the best ascending ASI cutoff, 2.06 \text{ cm/m}^2. (C) Age and Turner syndrome specific z-score. Dotted line at the best z-score cutoff, 2.12.
Turner syndrome with or without aortic dissection. The ascending ASI model shows both the best cutoff of ascending ASI (2.06 cm/m²) and the recommended ascending ASI cutoff (2.5 cm/m²).

3.5. Comparison of cutoffs: Ascending ASI versus absolute ascending aortic diameter and z-score

Using an ascending ASI of 2.5 cm/m² as the cut-off value predicted two out of 12 patients with dissection (17% sensitivity) but missed ten (83%). By using the calculated ascending ASI cutoff of 2.06 cm/m² instead of the recommended cutoff, the sensitivity improved to the same level as the absolute ascending aortic diameter cutoff value of 3.3 cm and the z-score cut off value of 2.12 (92%). Both the absolute ascending aortic diameter and the z-score predicted all patients with aortic dissections, except for one pregnant patient who had an absolute ascending aortic diameter of 2.5 cm, ascending ASI of 1.45 and a z-score of −0.29. The specificity, the positive likelihood ratio, and the negative likelihood ratio were almost equal between absolute ascending aortic diameter and z-score of the ascending aorta. The specificity was 77% for the ascending ASI cutoff of 2.06 vs 86% and 85% for the absolute ascending aortic diameter cutoff of 3.3 cm and z-score cutoff of 2.12, respectively (Table 3).

3.6. Risk factors for aortic dissection in Turner syndrome

Systolic blood pressure > 120 mmHg (OR 1.05, 95% CI 1.01–1.09), antihypertensive medication (OR 3.9, 95% CI 1.20–12.72), and absolute ascending aortic diameter ≥ 3.3 cm (OR 69.32, 95% CI 8.77–547.99) were associated with an increased risk of aortic dissection. Neither coarctation of the aorta, bicuspid aortic valve, nor monosomy (45,X) or BMI were associated with an increased risk of aortic dissection. Aortic growth could not be analyzed because most of the women with aortic dissection only had one echocardiography performed prior to dissection.

A subgroup analysis of all women with Turner syndrome and an aortic diameter ≥ 3.3 cm (n = 64) irrespective of aortic dissection was performed. This showed that an aortic diameter ≥ 3.3 cm was the only factor that distinguished those who experienced an aortic dissection (n = 11) from those who did not (n = 53) irrespective of other risk factors (coarctation of the aorta, bicuspid aortic valve, antihypertensive medication, systolic blood pressure, BMI, previous growth hormone therapy, estrogen treatment and monosomy).

4. Discussion

This study, based on a national cohort of 400 women with Turner syndrome followed for up to 25 years, was designed to collect data for calculation of a cutoff value for the aortic size to predict aortic dissection which occurred in 12 patients (3%). The aim was also to compare the absolute ascending aortic diameter with an ascending ASI of 2.5 cm/m², which is the current recommended cutoff value for considering prophylactic surgery to prevent aortic dissection in women with Turner syndrome, according to international guidelines [4–6]. The results presented in this study show that the strategies currently used to predict the risk of an aortic dissection are insufficient.

4.1. ROC curves to predict aortic dissection

In the present study, the ROC curves demonstrated that the absolute ascending aortic diameter and z-score were superior to ascending ASI in predicting aortic dissection in Turner syndrome. Adjusting for body size did not improve the predictions, which is consistent with results for abdominal aortic aneurysm in the general population [20].

4.2. Comparison of cutoffs: Ascending ASI versus absolute ascending aortic diameter and z-score

The most important task in predicting aortic dissection in these models is to set the cutoff. A test with 100% sensitivity and specificity rarely exists, as an increase in sensitivity will decrease the specificity. When a test is used to identify a serious but treatable disease, high sensitivity is considered the most important feature [21]. The recommended ascending ASI cutoff of 2.5 cm/m² was not superior to chance, as it only predicted two out of 12 dissection patients (sensitivity 17%). The cutoffs, 3.3 cm for absolute ascending aortic diameter, 2.06 for ascending ASI and 2.12 for z-score, predicted all the aortic dissections, except for in one pregnant woman (sensitivity 92%). However, the specificity for ascending ASI cutoff 2.06 cm/m² was lower (77%) compared to the absolute ascending aortic diameter cutoff 3.3 cm and z-score cutoff 2.12 (85% vs 86%). The pregnant woman who was missed had an aortic diameter of 2.5 cm, an ascending ASI of 1.45 cm/m² and z-score of −0.29, but neither coarctation of the aorta, bicuspid aortic valve nor hypertension. This underscores the risk of aortic dissections in pregnant women with Turner syndrome, even with smaller aortic measures [22,23]. In Marfan syndrome and Loeys-Dietz syndrome (both genetic connective tissue disorders involving a high risk of aortic dissection) the cutoff for considering aortic surgery to prevent aortic dissection is an absolute ascending aortic diameter of 5 cm [24]. In the general population, this cutoff is 5.5 cm [25]. The cutoff estimated in this study for patients with Turner syndrome of 3.3 cm is considerably lower, probably due to short stature.

Due to the low prevalence of aortic dissection, positive and negative likelihood ratios were calculated instead of positive and negative predictive values, as the likelihood ratios are independent of the disease prevalence. The positive likelihood ratios, LHR+ (probability of positive test in those with disease/probability of positive test in those without disease) were similar at an absolute ascending aortic diameter cutoff of 3.3 cm, and a z-score cutoff of 2.12 (6.71, 95% CI 4.96–9.08, vs. 6.32, 95% CI 4.70–8.50) and showed a moderate increase in the likelihood of aortic dissection when the test was positive. However, the negative likelihood ratio, LHR- (probability of negative test in those with disease/probability of negative test in those without disease) in these models was 0.1 (95% CI 0.01–0.64), which implies that a negative test result is ten times more likely to be truly negative than falsely negative. The corresponding negative likelihood ratio of 0.87 (95% CI 0.68–1.13), at an ascending ASI cutoff of 2.5 cm/m² reduces the likelihood to only 1.15 times, which means that if the test is negative this cutoff can hardly distinguish the individuals with dissection from those without.

4.3. Risk factors

The results of the present study demonstrate that an absolute ascending aortic diameter of 3.3 cm and a z-score of 2.12 are more reliable cutoff levels in predicting aortic dissection in Turner syndrome than the current recommended ascending ASI cutoff of 2.5 cm/m². The ASI model and the z-score model are both adjusted for body size, but the ASI model is not based on a Turner syndrome-based reference population as the z-score model is [16]. This may explain why the z-score model is superior to the ASI model. However, with these thresholds, (absolute ascending aortic diameter of 3.3 cm or a z-score of 2.12) unnecessary prophylactic surgery will be performed on patients who might never have experienced aortic dissection (false positives). Elective surgery of the ascending aorta has a reported mortality of 2.0–4.8%; thus, the advantages of surgery must be weighed against the possible risks and the decision of surgery should be made by a multidisciplinary team [7–9,26]. Hypothetically, there would have been 1–3 unnecessary deaths due to prophylactic surgery with the absolute ascending aortic diameter cutoff of 3.3 cm or the z-score cutoff of 2.12 in this study. On the other hand, these cutoffs might have saved nine of the ten patients from aortic dissection that the ASI > 2.5 cm/m² cutoff failed to identify.
The present strategy for determining who should be recommended prophylactic surgery is insufficient, and more studies are needed before considering a change to the current guidelines.

Since this study spans several decades, the guidelines have been updated and changed during the follow-up time. This means that some patients have not been followed according to the current cardiovascular guidelines and have therefore not had an echocardiography at the time intervals that are currently recommended [4]. Unfortunately, in most cases with aortic dissection, only one echocardiography report prior to dissection was available so aortic growth rate was not possible to estimate.

Bicuspid aortic valve, coarctation of the aorta, and monosomy are considered as risk factors in previous studies, but that could not be confirmed in this study [6,10]. This could be due to the relatively small sample size of patients with aortic dissection. The prevalence of bicuspid aortic valve in women with aortic dissection varies greatly in different studies; Carlson et al. reported 27% (14/51) in a review of aortic dissections in women with Turner syndrome, but later the same author reported a prevalence of (90%) in a study of 20 cases with aortic dissection [10,11]. In the present study, the prevalence of bicuspid aortic valve in the patients with aortic dissection was similar as in a recently published study by Yetman et al., who also reported 12 patients with type A dissections, of whom six had bicuspid aortic valve (50%) [27]. Different study designs and selection bias are likely the reason for the varying results.

Secular trends based on more knowledge and data on Turner syndrome worldwide have been adopted in the guideline revisions during the last 20 years [1,6,14]. For example, blood pressure has been treated more aggressively with an even lower treatment goal than for women in the general population because of the high risk for aortic dissection in women with Turner syndrome. Unfortunately, no decreasing trend in aortic dissection has been seen in the present study. These results stress the importance of further research of preferably pooled data in order to create a risk score of multiple factors to determine who will benefit from prophylactic surgery weighed by the risk for unnecessary operation. Furthermore, Turner syndrome should be suspected when an aortic dissection is detected in a young woman, especially if she has features such as short stature, hypertension, or congenital cardiovascular disease.

4.4. Strengths and limitations

This is the first prospective cohort study of aortic dissection related to ascending ASI, Turner syndrome specific z-score of the ascending aorta and absolute ascending aortic diameter in Turner syndrome, respectively. It is a national multicenter study with a large cohort of women from the age of 16, and a long, standardized follow-up time. Some measurements in this study were several years old, and it cannot be excluded that progressive aortic enlargement occurred after their most recent echocardiogram. However, this is the same limitation as in the previously published literature [10,28]. The echocardiography measurements of aortic dimensions were not performed by a core lab. We can only speculate if centralizing the measurements could have affected the results. Most likely, the results have not been biased in any direction (over- or underestimation), using measurements from a nationwide multicenter study performed over a 25-year period. However, the results might have been more precise if the measurements had been repeated in a core lab. No girls below age 16 were included in the cohort, so no conclusions can be drawn on the risk of aortic dissection in children with Turner syndrome based on aortic size. It is difficult to assess the additional risk increase that other comorbidities (coarctation of the aorta, bicuspid aortic valve, hypertension or karyotype, etc.) might contribute to due to the small sample size of the outcome and the rare nature of the aortic dissection disease. To address this limitation, a larger international multicenter study would be needed to achieve statistical power to investigate the risk factors and to establish a risk score for aortic dissection in Turner syndrome.

5. Conclusion

Adjusting the aortic measurement for body size in an echocardiogram did not improve the predictions of aortic dissection in women with Turner syndrome in the present study. The absolute ascending aortic diameter of 3.3 cm and Turner syndrome specific z-score of 2.12 were more reliable cutoffs than the current ascending ASI cutoff (≥ 2.5 cm/ m²). The results contribute important information in the effort to predict a potentially fatal aortic dissection in patients with Turner syndrome. Larger pooled cohorts should focus on developing a risk assessment score to aid decision-making in the timing of prophylactic aorta surgery in women with Turner syndrome. Special care is needed before and during pregnancy in women with Turner syndrome.

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Disclosures

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