Cardiac abnormalities in girls with Turner syndrome: ECG abnormalities, myocardial strain imaging, and karyotype–phenotype associations

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Abstract
Turner syndrome (TS) is a chromosomal condition which is associated with an increased prevalence of cardiac morbidity and mortality. In this cross-sectional study, Minnesota-based electrocardiographic (ECG) abnormalities, aortic dimensions, routine- and myocardial strain echocardiographic parameters, and karyotype-cardiac phenotype associations were assessed in girls with TS. In total, 101 girls with TS (0–18 years) were included. The prevalence of major ECG abnormalities was 2% (T-wave abnormalities) and 39% had minor ECG abnormalities. Dilatation of the ascending aorta (z-score > 2) was present in 16%, but the prevalence was much lower when using TS-specific z-scores. No left ventricular hypertrophy was detected and the age-matched global longitudinal strain was reduced in only 6% of the patients. Cardiac abnormalities seemed more common in patients with a non-mosaic 45,X karyotype compared with other karyotypes, although no statistically significant association was found. Lowering the frequency of echocardiography and ECG screening might be considered in girls with TS without cardiovascular malformations and/or risk factors for aortic dissection. Nevertheless, a large prospective study is needed to confirm our results. The appropriate z-score for the assessment of aortic dilatation remains an important knowledge gap. The karyotype was not significantly associated with the presence of cardiac abnormalities, therefore cardiac screening should not depend on karyotype alone.

KEYWORDS
cardiovascular abnormalities, electrocardiogram, global longitudinal strain, karyotype, turner syndrome

1 | INTRODUCTION

Turner syndrome (TS) is a chromosomal condition that affects females who have one intact X-chromosome and complete or partial absence of the second sex chromosome (Gravholt et al., 1998). Short stature and premature ovarian failure are the cardinal features of TS, with a variety of associated problems including cardiac involvement (Gravholt et al., 1998). The latter can be divided into congenital malformations, such as a bicuspid aortic valve (BAV), aortic coarctation (COA), and partial anomalous pulmonary venous return (PAPVR), and acquired problems such as ascending aortic dilatation and aortic dissection (Bondy, 2008a, 2008b; Gravholt et al., 2006; Mortensen, 2006; Mortensen, 2006).
Hypertension is another common comorbidity in patients with TS, which could lead to left ventricular hypertrophy, and eventually left ventricular dysfunction (Mortensen, Gravholt, et al., 2012; Sozen et al., 2009; Tancredi et al., 2011). However, little is known on the prevalence of these abnormalities in girls with TS.

Besides cardiovascular malformations, electrocardiogram (ECG) abnormalities, mainly QTc prolongation, have been reported (Atici et al., 2018; Bondy, Ceniceros, et al., 2006; Bondy, Van, et al., 2006; Dalla Pozza et al., 2006; Dalla Pozza et al., 2009; Sozen et al., 2008; Trolle et al., 2013). We recently found no increased prevalence of QTc prolongation using Hodges formula in a large cohort of girls (n = 101) and women (n = 251) with TS, as was confirmed by Harrahil et al. in 112 women with TS (Harrahil et al., 2020; Noordman et al., 2020). ECG is mostly performed at every clinical visit of patients with TS. Reports on ECG abnormalities other than QTc prolongation are limited (Bondy, Ceniceros, et al., 2006; Bondy, Van, et al., 2006), and the clinical consequences of ECG abnormalities remain unclear.

Routine echocardiography enables the assessment of cardiac malformations, dimensions, and function in patients with TS. For children, it is common to calculate z-scores of left ventricular- and aortic dimensions taking the body surface area (BSA) into account (Silberbach et al., 2018). Z-scores of aortic dimensions can be calculated using different methods, but no uniform method has been established. Myocardial strain analysis, mainly global longitudinal strain (GLS), can be used to detect subtle changes in left ventricular systolic function, that are not detectable with the left ventricular ejection fraction (EF) (Lang et al., 2015; Tops et al., 2017). However, this sensitive technique has only been investigated in very small cohorts of patients with TS, with contradicting results (AbdelMassih et al., 2018; Oberhoffer et al., 2020; Oz et al., 2014).

Previous studies have explored the relationship between karyotype and phenotype, including cardiovascular malformations, and have reported different results (Cameron-Pimblett et al., 2017; El-Mansoury et al., 2007; Gotzsche et al., 1994; Noordman et al., 2018; Noordman et al., 2019; Prandstraller et al., 2009). Most studies have suggested that the prevalence of cardiovascular malformations is higher in patients with a monosomy 45,X karyotype, compared with other karyotypes. However, associations between karyotype and specific cardiac function tests such as ECG or GLS, have hardly been described (Bondy, Ceniceros, et al., 2006).

We aim to assess the prevalence of specific cardiac abnormalities in childhood, including ECG abnormalities, aortic dimensions, routine- and myocardial strain parameters, and to look for karyotype - cardiac phenotype associations in a large cohort of girls with TS.

2 | METHODS

2.1 | Patients

Girls with TS, aged 0–18 years, visiting the TS outpatient clinic from April 2010 to June 2017 at the department of pediatrics, Amalia Children’s Hospital, Radboudumc, Nijmegen were eligible for this retrospective study. Diagnosis of TS was based on clinical features and cytogenetic analysis. Patients were excluded if the cardiac follow-up was performed outside our institution, if the quality of the echocardiography was insufficient to perform strain analysis, if cytogenetic analysis showed <5% cells with karyotype 45,X or if the patient had other genetic abnormalities that could lead to cardiac problems. This study was approved by the local ethics committee (CMO Arnhem-Nijmegen). The current study population is partially overlapping with the study population of two previous publications (Noordman et al., 2018; Noordman et al., 2020).

Karyotypes were classified and divided into seven subgroups: monosomy 45,X, mosaicism 45,X/46,XX, isochromosome (e.g., 45,X/46,i(Xq) or 46,XX,i(Xq)). deletion (e.g., (45,X)/46,XX,del(Xp) or (45,X)/46,XX,del(Xq)), polyploidy (e.g., 45,X/47,XXX), ring X (e.g., 45,X/46,X,r(X)), and Y-material (e.g., 45,X/46,XY). The karyotype was examined in lymphocytes (30 cells) and/or buccal cells (100 cells). If available, the karyotype of the buccal cells was used for classification (Freiks et al., 2013). Patients with a monosomy 45,X karyotype were compared with patients with other karyotypes. To describe characteristics of the population, data on age, height, and weight were collected. For the assessment of cardiac abnormalities, the most recent ECG and echocardiogram at the time of inclusion were studied. Definition of COA was based on history of surgical or catheter intervention. Presence of hypertension was defined as the need for anti-hypertensive treatment, and associations between hypertension and other cardiac abnormalities were investigated.

2.2 | Electrocardiography

Resting 12-lead ECGs were scored for type of heart rhythm, heart rate, PR, QRS and QT intervals, QRS axis and morphology of the P wave, QRS complex, and ST segment. The QT interval was measured manually and the corrected QT interval (QTc) was calculated using Hodges’ formula (Gravholt et al., 2017). Abnormal ECG findings were coded according to the Minnesota Code (Prinas, & R.S.; Zhang, Z-M., 2009). The ECG abnormalities in this study were classified into “major” and “minor” ECG abnormalities as binary, not mutually exclusive, variables and are shown in Appendix 1a and 1b (Healy & Lloyd-Jones, 2016). ECG intervals were adjusted for age at time of the ECG, according to Sharieff et al. (Sharieff & Rao, 2006). A prolonged QRS interval was defined as >100 ms and a prolonged QTc interval as >450 ms (Davignon et al., 1980; Rautaharju et al., 2009; Surawicz et al., 2009). The heart rate of girls with TS was compared with the heart rate of healthy girls from the same age groups, derived from the literature (Rijnbeek et al., 2001).

2.3 | Echocardiography

2.3.1 | Aortic dilatation

Assessment of cardiac morphology and cardiac function was carried out using a routine echocardiography scanner (GE, Vingmed
Ultrasound, Horten, Norway) with a 3.0 and a 5.0 MHz transducer. The aortic root was measured at three levels (aortic annulus in systole, sinus of Valsalva, and ascending aorta both in diastole) and z-scores were calculated according to the method of Gautier et al. (providing normative data of 353 healthy children) (Gautier et al., 2010). Second, specific z-scores for patients with TS were calculated according to Quezada et al., providing standard values for the aortic size of healthy girls and women with TS (Quezada et al., 2015). Dilatation for all measurement levels was defined as a z-score > 2. Additionally, the aortic size index (ASI; ascending aortic diameter/BSA; cm/m²) was calculated for girls ≥15 years (Silberbach et al., 2018). Associations between aortic dilatation (according to Gautier et al.) and other cardiac abnormalities were investigated.

2.3.2 | Routine- and myocardial strain parameters

Z-scores of left ventricular dimensions were based on normal values of M-mode measurements of a healthy population as given by Kampmann et al., using an online z-score calculator (Dyar, 2020; Kampmann et al., 2000). The left ventricular systolic function was indicated using fractional shortening (FS) and ejection fraction (EF). LV mass (LVM) was calculated using the formula first described by Devereux et al. (Devereux et al., 1986), and LV mass for height z-scores were calculated according to Foster et al. (Foster et al., 2008).

Global longitudinal strain (GLS) of the left ventricle was assessed offline using 2D speckle-tracking echocardiography as described earlier by our group (Mavinkurve-Groothuis et al., 2009). Analysis was performed using echocardiographic quantification software (EchoPAC version 113; GE Medical Systems, Horten, Norway). Strain results were compared with age- and vendor-specific normative values (Klitsie et al., 2013; Levy et al., 2016), and compared with results reported in other TS populations (AbdelMassih et al., 2018; Oberhoffer et al., 2020).

2.4 | Statistical analysis

Statistical analysis was carried out using SPSS 25 (SPSS inc, Chicago, IL). Baseline characteristics were expressed as frequency and percentage for categorical variables and as mean or median for continuous variables. Associations between cardiac abnormalities, ECG abnormalities, and karyotype were analyzed with an independent t-test, or a Mann–Whitney U test for non-normally distributed variables. In addition, odds ratios (ORs) and 95% confidence intervals (95%CI) were calculated. A one sample t-test was used to compare the heart rate and strain parameters of the study cohort with values of a reference population derived from the literature (Klitsie et al., 2013; Rijnbeek et al., 2001). Analyses were performed if a subgroup consisted of at least three cases. A p-value <.05 and OR with a 95%CI excluding 1 were set as statistically significant or relevant, respectively.

3 | RESULTS

3.1 | Baseline characteristics

Data from 139 patients with a confirmed diagnosis of TS were available for this study. A total of 38 patients were excluded from this study, of whom 23 patients without an available echocardiogram in our study center, 13 patients whose quality of the echocardiogram was not sufficient for offline strain analysis, one patient with < 5% 45,X cells in buccal cell analysis, and one patient with another genetic abnormality that could lead to cardiac problems. After exclusion, the final study cohort consisted of 101 girls with TS. Data of patient characteristics, karyotype, and cardiac malformations are shown in Table 1. Age, height, weight, karyotype, and prevalence of cardiac malformations of the excluded patients were not significantly different from those of our study cohort (data not shown). Eleven girls had a history of cardiac surgery, including repair of aortic valve (n = 2) and aortic coarctation (n = 8). One girl had surgery for both indications, including repair of ascending aortic aneurysm. None of the girls with PAPVR (n = 2) underwent surgery. Hypertension was present in seven girls (7% of the population).

The most common karyotype was monosomy 45,X (31%). Buccal cell analysis was available in 86% of the patients with a 45,X monosomy in lymphocytes. In five of these girls (16%), buccal cell analysis showed a second cell line with a mean percentage of 26 (5–70)% 46,XX cells. These patients were eventually classified as mosaicism 45,X/46,XX.

3.2 | Electrocardiography

ECG intervals and abnormalities according to the Minnesota criteria in girls with TS are described in Table 2. The heart rate of girls with TS was higher compared with the heart rate of healthy age-matched girls, derived from the literature (data not shown). None of the patients had (a history of) severe arrhythmia or QTc prolongation. Only two girls (aged 8 and 15 years) had major ECG abnormalities (isolated T-wave abnormalities). No patients with a short PR interval met the criteria of Wolf-Parkinson White syndrome. Girls with hypertension did not have an increased prevalence of ECG abnormalities (OR 95%CI: 1.5 [0.3–7.6]). Details about the QTc interval and associated factors can be found in our previous study (Noordman et al., 2020).

3.3 | Echocardiography

3.3.1 | Aortic dilatation

The aortic root dimensions of girls with TS and z-scores using different methods are shown in Table 3. Eight patients (9%, aged 3–18 years) had a z-score > 3 of the ascending aorta according to Gautier et al., while no patients had a current z-score > 3 according to...
Quezada et al. All girls with a z-score > 3 according to Gautier et al. had at least one cardiac abnormality. The mean ASI in girls ≥15 years was 1.5 cm/m²; only one girl had an ASI >2 cm/m² (2.1 cm/m²), which corresponded with a z-score of 3.2 according to Gautier et al. Ascending aortic dilatation was associated with the presence of a BAV (OR 95%CI: 12.4 [3.5–43.1]), COA (OR 95%CI: 5.4 [1.3–23.2]), and a history of cardiac surgery (OR 95%CI: 6.0 [1.5–23.3]). Ascending aortic z-scores were not significantly higher in girls with hypertension (0.9 vs. 0.7; p = .683) and presence of aortic dilatation was not associated with age (p = .616), even when girls with cardiac malformations or a history of cardiac surgery were excluded from the analyses.

Routine- and myocardial strain parameters
Table 3 shows the routine- and myocardial strain parameters. None of the patients had a FS <28% or an EF <55%. The mean GLS in girls with TS was −21.3 ± 3.0% and did not significantly differ from the values of age-matched healthy children derived from the literature (Klitsie et al., 2013). According to those values, 6% of the girls had an abnormally low GLS for their age, without association with cardiac malformations or heart rate. Presence of hypertension was not associated with the LVM z-score (−1.2 vs. −1.4; p = .662) or GLS (−19.8 vs. −21.5%; p = .145).

| TABLE 1 | Description of patient characteristics, karyotype, and cardiac malformations in girls with Turner syndrome undergoing detailed cardiac evaluation |
|----------|---------------------------------------------------------------------------------------------------------------|
|          | N = 101                                                                                                       |
| Age in years | Median (min-max) 11 (0–18)                                                                                     |
| Height SDS | Median (min-max) −2.0 (−3.3–0.7)                                                                               |
| Weight for height SDS | Median (min-max) 1.0 (−1.6–3.7)                                                                               |
| Karyotype | n (%)                                                                                                          |
| Monosomy 45,X | 31 (31%)                                                        |
| Mosaicism 45,X/46,XX | 26 (26%)                                                        |
| Isochromosome | 19 (19%)                                                        |
| Deletion | 9 (9%)                                                            |
| Polyploidy | 7 (7%)                                                            |
| Ring X | 5 (5%)                                                            |
| Y-material | 4 (4%)                                                            |
| Cardiac malformations | n (%)                                                                                       |
| BAV | 22 (22%)                                                         |
| (History of) COA | 9 (9%)                                                            |
| Aortic stenosis | 5 (5%)                                                            |
| Aortic regurgitation | 7 (7%)                                                            |
| PAPVR | 2 (2%)                                                            |
| Persistent left vena cava superior | 1 (1%)                                                      |
| Patent ductus arteriosus | 1 (1%)                                                            |
| Previous cardiac surgery | 11 (11%)                                                        |
| Previous aortic dissection | 0 (0%)                                                            |

| TABLE 2 | ECG abnormalities and intervals in 94 girls with Turner syndrome |
|----------|---------------------------------------------------------------|
| Intervals | Mean | SD |
| Heart rate, beats/minute | 94 | 18 |
| PR, ms | 127 | 21 |
| QRS, ms | 82 | 8 |
| QT, ms | 333 | 30 |
| QTc, ms (Hodges) | 392 | 18 |

| Major ECG abnormalities (Minnesota Code) | N | % |
|----------------------------------------|---|---|
| T wave Items | | |
| T amplitude negative or biphasic with negative phase >1.0 mm, but not as deep as 5.0 mm in aVF (5.2) | 2 | 2.1 |
| Other | | |
| QTc prolongation (>450 ms, Hodges) | 0 | 0 |
| Any other | 0 | 0 |
| Total number of ECGs with at least one major ECG abnormality | 2 | 2.1 |

| Minor ECG abnormalities (Minnesota Code) | N | % |
|----------------------------------------|---|---|
| QRS axis deviation | | |
| Right-axis deviation (2.2) | 5 | 5.3 |
| High Amplitude R waves | | |
| R amplitude in V5 or V6 plus S amplitude in V1 > 35.0 mm (3.3) | 3 | 3.2 |
| T wave Items | | |
| T amplitude zero with less than 1.0 mm negative phase (5.3) | 1 | 1.1 |
| AV conduction defect | | |
| Long PR interval (6.3) | 2 | 2.1 |
| Short PR interval (6.5) | 4 | 4.3 |
| Ventricular conduction defect | | |
| Incomplete right bundle branch block (7.3) | 22 | 23.4 |
| Arrhythmias | | |
| Ventricular premature beats (8.1.2) | 1 | 1.1 |
| Regular supraventricular rhythm (8.4.1) | 4 | 4.3 |
| Sinus tachycardia (8.7) | 1 | 1.1 |
| Sinus bradycardia (8.8) | 2 | 2.1 |
| Any other | 0 | 0 |
| Total number of ECGs with at least one minor ECG abnormality | 37 | 39.4 |

Note: Abnormal ECG findings were coded according to the Minnesota Code (Prineas, 2009). The ECG abnormalities were corrected for age according to Sharieff et al. (Sharieff & Rao, 2006). The ECG abnormalities were not mutually exclusive; patients may have had more than one abnormality. Abbreviation: ms, millisecond.
No statistically significant association was found between karyotype (non-mosaic 45,X vs. other) and any of the cardiac abnormalities (Table 4), although the prevalence of cardiac malformations in patients with a non-mosaic 45,X karyotype seemed higher compared with the other karyotypes. A more detailed subgroup analysis could not be executed due to small numbers in each subgroup.

### 4.1 | Electrocardiography

The value of a routine ECG in patients with TS is under debate. The clinical TS guideline advises to perform at least one ECG at diagnosis.
and in clinical practice it is often performed during every cardiac evaluation. The evidence for (recurrent) ECG examination is weak, and reports on ECG abnormalities (other than QTc prolongation) in patients with TS are rare (Gravholt et al., 2017). To our best knowledge, two studies of Bondy et al. are the only studies that have investigated ECG abnormalities in 78 girls and 100 women with TS (Bondy, Ceniceros, et al., 2006; Bondy, Van, et al., 2006). In general, we found similar ECG abnormalities to Bondy et al., although in a lower prevalence. Most importantly, we showed a low prevalence of major ECG abnormalities according to the Minnesota Criteria in the current study. This is not surprising since major ECG abnormalities in general, for example signs of myocardial infarction or T-wave abnormalities, are less common in children compared with adults. Although ECG data of healthy children are scarce and definition of an abnormal ECG differs, the prevalence of ECG abnormalities in our study is similar to two earlier, large studies (Chandra et al., 2014; Marek et al., 2011). These studies included healthy (non-athlete) subjects aged 14–35 years and found an abnormal ECG in 2.5%–49%.

Clinical relevance of the ECG findings may be as follows: First, presence of right axis deviation (RAD) may indicate the presence of a PAPVR (van den Hoven et al., 2017). In the current study, we found a relatively high prevalence of RAD compared with the general population (reported prevalence 0.13%–0.8% in children and young adults) (Chandra et al., 2014; Marek et al., 2011). Two out of the five patients with RAD had a PAPVR, but this association could not be analyzed due to the small amount of numbers. The low prevalence of PAPVR in our study might be explained by the use of echocardiography solely without cardiac magnetic resonance imaging (CMR) (Obara-Moszynska et al., 2018). The undetected PAPVR are probably hemodynamic unimportant and did not lead to right atrial or right ventricular dilatation. Second, QTc prolongation in the general population is known to be associated with arrhythmias or even sudden cardiac death (Yap & Camm, 2003). However, there is no evidence for a higher mortality rate in patients with TS due to QTc prolongation, and we found no patients with QTc prolongation using Hodges’ formula in a previous study (Noordman et al., 2020; Silberbach et al., 2018). Third, an excessive sympathetic drive has been described in patients with TS (Silberbach et al., 2018; Sozen et al., 2008). This might be confirmed by the increased heart rate and the relatively high prevalence of a short PR interval found in our cohort. The PR interval in children varies with heartrate and is therefore usually shorter in children with a higher heartrate (e.g. young children) (Rijnbeek et al., 2001; Sharieff & Rao, 2006). The clinical consequences of a short PR interval in girls with TS are unclear; none of the patients met the criteria of Wolff-Parkinson-White syndrome.

Regarding minor ECG abnormalities, an incomplete right bundle branch block (IRBBB) was the most common abnormality (23%) in our population, a higher prevalence than in the normal pediatric population (3%) (Meziab et al., 2018). However, an IRBBB is considered as a benign conduction disturbance of unknown etiology that usually disappears in adulthood. We support the general opinion that this specific finding does not have clinical implications, also for girls with TS.

4.2 | Echocardiography

4.2.1 | Aortic dilatation

The prevalence of ascending aortic dilatation (z-score > 2) in girls with TS is known to be significantly increased, and the results in this study using z-scores according to Gautier et al. match those in the literature (Kim et al., 2011). With the use of the advised TS-specific z-score, prevalence of aortic dilatation was relatively low (Gravholt et al., 2017; Quezada et al., 2015; Silberbach et al., 2018), although the differences in methods of measuring the aortic root should be taken into account.
A disadvantage of both of these z-scores is that they are based on BSA, which could lead to over- or underestimation of aortic dilatation in patients with a relatively high or low weight for their height (Braley et al., 2017). Correcting the aortic diameter using height instead of BSA could partly solve this problem (Duijnhouwer et al., 2019). Recently, a new screening tool was reported, but only for relatively tall patients with connective tissue disease (e.g. Marfan) (Wozniak-Mielczarek et al., 2020). A tool for patients with TS and short stature has not yet been reported. The authors believe that seeking international agreements which z-score should be used in TS and building a TS-specific curve of progression of aortic dilatation with time is mandatory. In other words, more research is needed in larger TS populations, as well as prospective studies of the same patients from childhood into adulthood, in order to be able to follow the patients with abnormal ascending aortic z-scores.

### 4.2.2 Routine- and myocardial strain parameters

The LVM z-score in this study was relatively low, and not in line with previous studies reporting on normal left ventricular parameters or even left ventricular hypertrophy in girls and women with TS (AbdelMassih et al., 2018; Mortensen, Gravholt, et al., 2012; Oberhoffer et al., 2020; Sozen et al., 2009). This might be partly due to the differences in methods used to calculate the LVM (e.g., LVM/BSA, LV mass-for-height, LVM index). Although this cannot completely explain why our results contradicted those in the literature, it is clear that no signs of left ventricular hypertrophy in our pediatric patients with TS were found.

Abnormal (decreased) GLS is regarded as a sensitive marker for discrete abnormalities of left ventricular systolic function, even before decreased FS or EF is detected (Tops et al., 2017). Studies reporting on strain parameters in patients with TS showed contradictory results. Oberhoffer et al. reported comparable mean strain values in 38 young adults with TS (Oberhoffer et al., 2020), whereas Abdelmassih showed lower mean GLS values (−13.2 ± 1.1%) in 36 girls with TS compared with controls (−18.3 ± 2.4%) (AbdelMassih et al., 2018). In our large cohort, the mean GLS in girls with TS was comparable with the normal values in healthy children reported in the meta-analysis of Levy et al. (Levy et al., 2016), even as the mean GLS of healthy children from matched age groups derived from the literature (Klitsie et al., 2013). However, we found that 6% had an abnormal low GLS for their age, which was not associated with cardiac malformations or heart rate (Klitsie et al., 2013). Whether the abnormal GLS in these girls is a marker for (discrete) myocardial damage or increased afterload, remains to be assessed in a prospective longitudinal study.

### 4.2.3 Risk factors for acquired heart disease

The risk factors for aortic dilatation in girls with TS found in this study partially correspond to the risk factors described in girls and women with TS (Cleemann et al., 2010; Duijnhouwer et al., 2019). We found that BAV and COA were associated with ascending aortic dilatation. Hypertension is another important risk factor known to be associated with aortic dilatation, although this association was not found in our cohort (Elsheikh et al., 2001). This might be due to our definition of hypertension, resulting in lower prevalence of hypertension in this cohort (7%) compared with the literature (25%–40%) (Los et al., 2016).

In general, hypertension and other cardiac malformations such as COA or aortic valve stenosis could lead to left ventricular hypertrophy and eventually to left ventricular dysfunction (Drazner et al., 2004; Rinnstrom et al., 2016). We could not find any of these associations in our cohort. It is possible that left ventricular hypertrophy and subsequently ventricular dysfunction will develop later in life and are not yet present in our young population. Another possible explanation could be that early correction of cardiac abnormalities, e.g., COA or aortic stenosis, prevented the development of left ventricular hypertrophy and/or dysfunction.

### 4.3 Karyotype-phenotype associations

Cardiac abnormalities are often found in patients with monosomy 45,X, but are also present in patients with other karyotypes (Cameron-Pimblett et al., 2017; El-Mansoury et al., 2007; Mazzanti & Cacciari, 1998; Noordman et al., 2018; Noordman et al., 2019; Prandstraller et al., 2009). In our cohort, patients with a non-mosaic 45,X karyotype seemed to have a higher prevalence of cardiac malformations, for example BAV or COA, and ECG abnormalities compared with other patients. However, no statistical significance was measured, possibly due to insufficient power in this study to demonstrate an effect. Another explanation might be the relatively lower prevalence of monosomy 45,X in our cohort (31%). This is partly due to our search for undetected cell lines in buccal smears of 45,X monosomy patients, which revealed a mosaic pattern in five girls. In addition, all girls with short stature are being screened for TS in the Netherlands, which might lead to a more frequent diagnosis of (low grade) mosaicism. These factors may explain the differences between our study and others.

### 4.4 Limitations

Our study is a retrospective study which comes with its limitations. We analyzed ECGs and echocardiograms performed during routine clinical care, yet only in a large cohort of girls and not in a mixed population as often reported in other studies. The small numbers in some subgroups might have hampered the finding of significant associations. No data on healthy controls were available and differences in height between patients with TS and healthy subjects make it difficult to compare these two groups. To reduce this bias, we decided to use different z-scores.

### 5 Conclusion and recommendations

This study investigated cardiac abnormalities in a large cohort of girls with TS, including ECG abnormalities, aortic dimensions, myocardial...
strain analysis, and karyotype – cardiac phenotype associations. We found a low prevalence of major ECG abnormalities, no QTc prolongation, and no severe arrhythmias. Although the prevalence of minor ECG abnormalities was high (39%), these were mainly nonspecific and of no clinical relevance. In contrast to other studies, no evidence for left ventricular hypertrophy was found. Mean GLS was comparable with age-matched controls derived from literature while an abnormal low GLS was rare. Although the prevalence of most cardiac abnormalities was higher in patients with a non-mosaic 45,X karyotype compared with other karyotypes, no statistically significant association could be detected.

Our results suggest that cardiac screening of patients with TS should not depend on the karyotype alone. Furthermore, lowering the frequency of cardiac echocardiography and ECG screening might be considered in girls with TS without cardiovascular malformations and/or risk factors for aortic dissection. Nevertheless, a large prospective study, for example using a registry database, is needed to confirm these statements. Last, the appropriate z-score to be used for the assessment of aortic dilatation remains an important knowledge gap.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTION
Design of the study: Iris D. Noordman, Zina Fejzic, Anthonie L. Duijnhouwer, Marlies Kempers, Janielle A.E.M. van der Velden, Livia Kapusta. Methodology: Iris D. Noordman, Zina Fejzic, Melanie Bos, Anthonie L. Duijnhouwer, Gert Weijers, Marlies Kempers, Remy Merkx, Janielle A.E.M. van der Velden, Livia Kapusta. Formal analysis and investigation: Iris D. Noordman, Zina Fejzic, Melanie Bos, Anthonie L. Duijnhouwer, Gert Weijers, Marlies Kempers, Remy Merkx, Janielle A.E.M. van der Velden, Livia Kapusta. Writing – original draft preparation: Iris D. Noordman, Melanie Bos, Anthonie L. Duijnhouwer, Janielle A.E.M. van der Velden, Livia Kapusta. Writing – review and editing: Iris D. Noordman, Zina Fejzic, Melanie Bos, Anthonie L. Duijnhouwer, Gert Weijers, Marlies Kempers, Remy Merkx, Janielle A.E.M. van der Velden, Livia Kapusta. Supervision – Anthonie L. Duijnhouwer, Zina Fejzic, Janielle A.E.M. van der Velden, Livia Kapusta.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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