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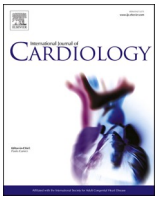

Cardiac manifestations in children with osteogenesis imperfecta: A single-center observational study☆

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ABSTRACT

Background: Osteogenesis imperfecta (OI) is a rare hereditary connective tissue disorder characterized by defective type I collagen synthesis. In the cardiovascular system, type I collagen provides tensile strength and structural integrity to the myocardium, cardiac valves, chordae tendineae and great vessels. OI may therefore predispose affected individuals to various cardiovascular diseases. Limited existing literature suggests an increased risk of developing heart failure and valvular diseases in adults with OI, but data on cardiac involvement in pediatric OI remains limited.

Objectives: This study aimed to investigate the prevalence and characteristics of structural and functional cardiac abnormalities in children with OI.

Methods: In 78 children (aged 1–18 years) with OI, pediatric cardiologists performed standardized ECG and echocardiographic evaluations. *Z*-scores were calculated using pediatric reference values and compared between OI subtypes.

Results: None of our patients had clinically significant arrhythmias or required cardiovascular medication. Congenital heart defects were identified in 13 % of patients, most commonly ASD and PDA. Mild aortic or mitral valve regurgitation were observed in 7.3 % and 8.7 % of patients and aortic root dilation in 8.7 %, predominantly in moderate to severe OI. Aortic root and annulus diameters correlated with disease severity. Left ventricular systolic function and diastolic function were normal in all patients.

Conclusions: Clinically relevant cardiovascular disease is rare in children with OI, but mitral and aortic valve regurgitations and aortic root dilation are more prevalent in severe phenotypes. Echocardiographic screening should be considered before transition to adult care in patients with moderate to severe OI.

1. Introduction

Osteogenesis imperfecta (OI) is a rare hereditary connective tissue disorder with an estimated incidence of 1 in 10,000 to 20,000 live births. It is characterized by increased bone fragility, recurrent fractures, and skeletal deformities.

The primary molecular defect in the majority of OI cases involves mutations in the *COL1A1* and *COL1A2*, which encode the α1 and α2 chains of type I collagen, respectively [1]. In the last decade however, mutations in a wide range of genes, encoding proteins that are involved in the synthesis of type I collagen, its processing, secretion and post-translational modification have been identified. These mutations lead to quantitative or qualitative abnormalities in type I collagen, impairing its function in bone matrix formation. Since type I collagen is a major component of the matrices of other connective tissues, OI is commonly accompanied by non-skeletal manifestations, including joint laxity, blue sclerae, dentinogenesis imperfecta, and hearing impairment [2].

Type I collagen is a vital component of the heart valves, ventricular septum, aortic wall, chordae tendineae, and the annulus fibrosus that anchors the mitral and tricuspid valves [3,4]. Within the myocardium, collagen fibers provide tensile strength and support the structural integrity of the myocyte network [5]. The disruption of collagen synthesis in OI may therefore predispose these patients to cardiovascular complications, similar to other connective tissue disorders like Marfan

☆ 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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and Ehlers-Danlos syndrome.

The literature suggests an increased prevalence of valvular heart defects and heart failure in adults with OI [6,7], but the literature on cardiac involvement in children with OI remains scarce. Some small studies have indicated a higher prevalence of congenital heart defects and early cardiac dysfunction in this population compared to healthy peers [8–11]. However, the sample sizes in these studies are usually small due to the rarity of OI, and the documented prevalence is inconsistent across studies. To provide optimal and comprehensive care for patients with OI, it is important to understand the true prevalence of structural and functional cardiac defects in this condition, so that clinicians can determine appropriate protocols and timing for cardiac screening and monitoring.

This study aimed to investigate the presence of cardiovascular abnormalities by electrocardiography and echocardiography in a large cohort of children with OI.

2. Methods

2.1. Study design

This retrospective, single-center study was designed to investigate the prevalence of cardiac malformations and dysfunction in pediatric patients with OI treated at our specialized center for rare skeletal diseases. Cardiac examinations, including electrocardiography and echocardiography, were performed by specialized pediatric cardiologists.

2.2. Inclusion and exclusion criteria

Children younger than 18 years with a clinically or genetically (classified as “pathogenic” or “likely pathogenic” according to the ACMG criteria) confirmed diagnosis of OI were included in the study. Patients older than 18 years, those with additional skeletal dysplasias, or those with poor echocardiographic image quality that prevented accurate evaluation were excluded from the study.

2.3. Data collection

Demographic patient data, including age, weight, height, body surface area (BSA), genotype, medication, and family history of cardiac disease, were collected from outpatient clinic records. Patients were categorized into mild (type I), moderate (type IV) or severe (type III) OI based on the *Sillence* classification system, which includes localization and number of fractures, severity of bone deformities and mobility. Patients were also asked about symptoms such as palpitations, dizziness, syncope, dyspnea, reduced exercise capacity, and chest pain. For patients too young to reliably report their own symptoms, parental reports were used to identify any potentially cardiac-related signs and symptoms.

2.3.1. Electrocardiography (ECG)

Standard 12-lead electrocardiograms (ECGs) were recorded using the Cardiovit MS-2015 (*Schiller AG, Switzerland*). These included extremity leads, based on the Einthoven and Goldberger configurations, as well as precordial leads following the Wilson method. Resting heart rates, rhythm, PR intervals, QRS duration, QRS axis, and QT intervals were examined and interpreted by experienced cardiologists.

2.3.2. Echocardiography

Echocardiographic evaluations were conducted following a standardized protocol adherent to the recommendations of the *American Society of Echocardiography* [12]. The examinations were performed by pediatric cardiologists, using the GE Vivid E9 ultrasound system (*GE Healthcare, Chicago, IL, USA*) equipped with an M5Sc probe. Whenever possible, the examinations were performed in the left lateral decubitus position, or in the supine position if required, after a 20-min rest period. However, in patients with severe OI-related scoliosis and immobility, optimal positioning of the patient was not possible. Each patient’s data were analyzed twice by the same examiner. The mean values from these evaluations were then compared with the mean values obtained by a second examiner to ensure inter-observer reliability.

Cardiac structural abnormalities were identified using 2D echocardiography. Left ventricular end-diastolic diameter (LVEDd) and end-systolic diameter (LVEDs) were measured from the parasternal long-axis view. Cardiac function was evaluated through M-mode echocardiography to measure the fractional shortening (FS). The left ventricular ejection fraction (LVEF) was assessed using the biplane Simpson method. For patients where the biplane EF assessment was not feasible due to limited image quality, LVEF was estimated based on FS measurements from the long-axis view. Color Doppler was utilized to evaluate blood flow dynamics and pressure gradients within the heart and adjacent vessels. It enabled the detection of shunts and valvular stenosis and insufficiency. Tissue Doppler Imaging (TDI) was used to measure myocardial velocities and assess diastolic function. The E/A ratio, calculated from the early diastolic (*E*-wave) and late diastolic (A-wave) velocities over the mitral valve in the apical four-chamber view, provided insights into diastolic filling. Additionally, the E/E’ index, derived from the ratio of peak *E*-wave velocity to myocardial tissue velocity (E’) near the mitral annulus (measured at septal and lateral walls), was used to further evaluate left ventricular diastolic function.

2.4. Statistics

For statistical analysis, *Z*-scores were calculated based on pediatric reference values to standardize the values of ECG and echocardiography in relation to body surface area (BSA) or age. For the calculation of the BSA the following formula by Haycock et al. (1978) was used: $\text{BSA}\ (m^2) = \text{Weight(kg)}^{0.5378} \times \text{Height(cm)}^{0.3964} \times 0.024265$ [13].

The specific references that we used are indicated in the results section. *Z*-scores above +2 or below −2 were defined as pathologic [14]. Additionally, the Z-scores of the patients were compared across different severity grades of OI using one-way ANOVA. Unpaired *t*-test was used for group comparison. Spearman correlation coefficient was calculated to test for a correlation between aortic *Z*-scores and patient age. A *p*-value of <0.05 was considered statistically significant. For data analysis and graphical representation, GraphPad Prism (Version 10.4.1) was used.

2.4.1. Ethics

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki and was formally approved by the institutional ethics committee, with assigned reference number 20–1115.

3. Results

3.1. Study population

Between November 2016 and December 2018, 78 children between age 1 and 18 years were included in our study. The majority of patients (80.8 %) had moderate (type IV) to severe (type III) OI. Due to patient compliance and technical limitations, not all parameters could be measured in every patient. ECG examination was feasible in 76 patients; echocardiographic evaluation was possible in 69 patients. A detailed overview of the patient population and characteristics is presented in

Table 1
Patient characteristics and family history.

Parameter	Value
Total number of patients, n (%)	78 (100.0)
Age, mean ± SD (years)	8.96 ± 4.60
Male, n (%)	38 (49.0)
BSA, mean ± SD (m^2)	0.86 ± 0.39
Genetic results	
COL1A1/ COL1A2, n (%)	53 (68.0)
Other OI-related gene, n (%)	11 (14.1)
BMP1, n	4
LEPRE1, n	1
SERPINF1, n	2
IFITM5, n	2
CRTAP, n	1
PLOD2, n	1
Patients without genetic testing[a], n (%)	14 (18.0)
Clinical phenotype	
Mild (type I), n (%)	15 (19.2)
Moderate (type IV), n (%)	30 (38.5)
Severe (type III), n (%)	33 (42.3)
Family history of cardiovascular diseases, n (%)	6 (7.7)
Congenital cardiac malformations, n	3
Sudden cardiac arrest, n	1
Coronary artery disease and chronic heart failure, n	2
Patients requiring cardiovascular medication, n	0

Data are presented as numbers and percentages or mean ± standard deviation.
[a] In patients without genetic results testing was not done.

Table 2
ECG values of all patients.

Parameter	Value
Cardiovascular symptoms[a]	
Palpitations, n (%)	0 (0.0)
Dizziness, n (%)	0 (0.0)
Syncope, n (%)	0 (0.0)
Chest pain, n (%)	0 (0.0)
ECG[b]	
Heart rate z-score, mean ± SD	+0.50 ± 1.28
PR interval z-score, mean ± SD	−0.68 ± 1.32
QRS complex z-score, mean ± SD	−1.43 ± 1.11
QTc interval z-score, mean ± SD	+0.05 ± 1.34
Normal axis, n (%)	20 (26.0)
Vertical axis, n (%)	37 (49.0)
Left axis deviation, n (%)	14 (18.0)
Right axis deviation, n (%)	5 (7.0)
Incomplete right bundle branch block, n (%)	6 (7.9)
Other ECG abnormalities, n	2
Flattened T waves, n	1
LV hypertrophy, n	1

[a] Symptoms could not be assessed reliably in 15 patients under 5 years of age.
[b] ECG was feasible only in 76 patients.

Table 1. No patient reported symptoms suggestive of cardiovascular disease (CVD). Dyspnea is a common symptom in patients with severe OI due to thoracic deformities and was not interpreted as a cardiac symptom if it was not accompanied by other typical symptoms, such as new-onset exercise intolerance, dizziness, or palpitations. Furthermore, no patient required medications for CVD.

3.2. ECG and echocardiography

The electrocardiographic assessments revealed no clinically relevant pathological findings in our patients. *Z*-scores for the interpretation of ECG data were calculated based on age-matched data of the normal population [15]. ECG findings of all patients are summarized in Fig. 1 and Table 2. Ten participants had heart rates exceeding the physiological range, yet no cardiac arrhythmias were detected. Additionally, eight individuals presented with shortened PR intervals, though without evidence of atrioventricular conduction disturbances. Importantly, the QRS intervals and QTc durations remained within the physiological range for all patients, and no bundle branch blocks or repolarization abnormalities were observed.

Congenital heart defects were identified in 9 out of 69 patients (13 %), including persistent foramen ovale (PFO), persistent ductus arteriosus (PDA), atrial septal defects (ASD) (detailed in Table 3). One patient with an ASD type II underwent interventional closure during follow-up. Additionally, two patients had dysplastic aortic valves. Mild aortic and mitral regurgitation were the most frequent findings and occurred in 7.3 % and 8.7 % of all patients, respectively, but only in patients with moderate to severe OI. Two of the patients with mitral regurgitation also had aortic regurgitation. Most structural heart defects were observed in patients with 'classical forms' of OI, i.e. in patients with collagen (*COL1A1/COL1A2*) variants (Table 3).

The *Z*-scores for the aortic valve annulus and aortic root were calculated using BSA-matched reference values [16]. In most patients, the diameters of the aortic valve annulus and aortic root were within the physiological range (Table 4, Fig. 2). However, dimensions of the aortic annulus and root increased with severity of OI. Children with OI type III had larger diameters of the aortic root compared to patients with the milder form, OI type IV, and especially compared to patients with type I (mean *Z*-score of aortic root: in OI type III: +1.10 (± 1.66 SD) vs. -0.22 ± 0.97 in OI type I, $p = 0.03$, mean *Z*-scores of aortic annulus: in OI type III: +0.94 ± 1.27 vs. +0.50 ± 0.75 in OI type I, $p = 0.33$, Fig. 2).

We wanted to assess whether the enlargement of the aortic root and annulus develops with progressive ageing of the patients. However,

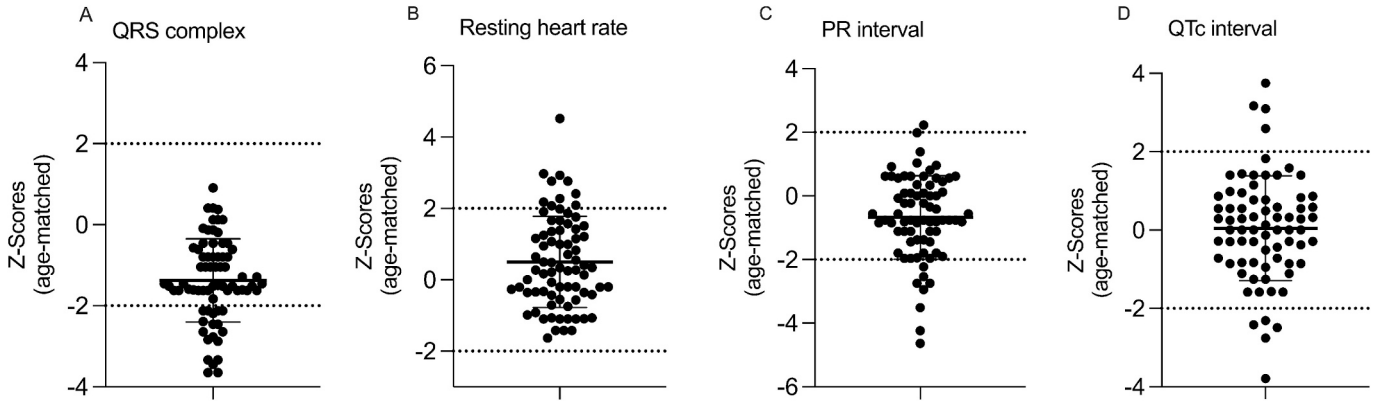

Fig. 1. ECG data. ECG parameters are presented as age-matched Z-scores. Each point represents an individual patient. The dotted lines indicate the physiological reference range (−2 to +2). Error bars denote the mean ± standard deviation.

Table 3
Overview of structural heart defects.

Parameter	Value
Number of patients with structural heart defects, n (%)	23 (33.3)
PFO, n (%)	3 (4.4)
ASD type II, n (%)	2 (2.9)
VSD, n (%)	1 (1.5)
Aortic regurgitation, n (%)	5 (7.3)
Dysplastic aortic valve, n (%)	2 (2.9)
Aortic root ectasia, n (%)	6 (8.7)
Prolapse of mitral valve, n (%)	1 (1.5)
Mitral regurgitation (mild), n (%)	6 (8.7)
Persistent left superior vena cava, n (%)	1 (1.5)
Hypertrophy of LVOT, n (%)	1 (1.5)
Hypertrophy of left ventricle, n (%)	2 (2.9)

Echocardiographic examination was successfully done in 69 out of 78 patients. Some patients had more than one structural heart defect. 10 patients (of 56 where echocardiography was feasible) with structural defects had a variant in *COL1A1/COL1A2*. 3 patients (of 5 where echocardiography was feasible) had a non-collagen mutation (PFO and aortic regurgitation in two patients with a *LEPRE1* variant, dysplastic aortic valve in one patient with a *CRTAP* variant). In 10 patients with structural heart defects, there was no genetic testing available. Abbreviations: PFO: Patent foramen ovale; ASD: Atrial septal defect; VSD: Ventricular septal defect; LVOT: Left ventricular outflow tract. Data are presented as numbers and percentages.

Table 4
Echocardiographic measurements of children with OI. Data are presented as mean ± standard deviation.

Parameter	Value
LVEDd, mean ± SD (mm)	35.37 ± 5.85
LVEDd Z-scores[a], mean ± SD	+0.06 ± 1.07
OI type I	+0.33 ± 0.66
OI type III	+0.04 ± 1.15
OI type IV	−0.05 ± 1.20
LVEDs, mean ± SD (mm)	+22.31 ± 4.89
LVEDs Z-scores[a], mean ± SD	−0.06 ± 1.33
OI type I, mean ± SD	+0.24 ± 0.74
OI type III, mean ± SD	−0.24 ± 1.68
OI type IV, mean ± SD	−0.06 ± 1.26
Left ventricular ejection fraction, mean ± SD (%)	+65.29 ± 6.84
Left ventricular ejection fraction Z-score, mean ± SD	−0.54 ± 1.27
OI type I, mean ± SD	−0.74 ± 1.25
OI type III, mean ± SD	−0.51 ± 1.31
OI type IV, mean ± SD	−0.44 ± 1.30
E velocity, mean ± SD (cm/s)	+99.71 ± 14.56
E velocity Z-score[b], mean ± SD	−0.31 ± 0.94
A velocity, mean ± SD (cm/s)	+59.12 ± 10.18
A velocity Z-score[b], mean ± SD	+0.80 ± 1.02
E/A ratio, mean ± SD	+1.74 ± 0.36
E/A ratio Z-score[b], mean ± SD	−0.35 ± 0.78
E/e' ratio, mean ± SD	+6.82 ± 1.29
E/e' ratio Z-score[b], mean ± SD	−0.45 ± 0.89
AV annulus diameter Z-score[a], mean ± SD	+0.87 ± 1.13
OI type I, mean ± SD	+0.50 ± 0.75
OI type III, mean ± SD	+0.94 ± 1.27
OI type IV, mean ± SD	+0.99 ± 0.27
Aortic root diameter Z-score[a], mean ± SD	+0.56 ± 1.42
OI type I, mean ± SD	−0.22 ± 0.97
OI type III, mean ± SD	+1.10 ± 1.66
OI type IV, mean ± SD	+0.44 ± 1.17
AV peak velocity, mean ± SD (m/s)	+1.20 ± 0.19
PV peak velocity, mean ± SD (m/s)	+0.99 ± 0.17
Tricuspid valve pressure gradient, mean ± SD (mmHg)[c]	+21.21 ± 4.96

Abbreviations: AV: Aortic valve; PV: Pulmonary valve. E velocity: Early diastolic mitral inflow velocity; A velocity: Late diastolic mitral inflow velocity.

[a] BSA matched *Z*-score.

[b] age-matched Z-score.

[c] In 31 patients no tricuspid insufficiency was detected and therefore pressure gradient was not measurable for these patients.

there was no significant correlation between age and the *Z*-scores of the aortic root ($r = 0.264$, $p = 0.07$) or the aortic annulus ($r = 0.161$, $p = 0.28$).

LVEDd and LVEDs *Z*-scores were calculated with BSA-matched reference values [17]. Mean Z-scores were higher in patients with mild OI compared to those with moderate or severe OI, but overall remained within the physiological range in all patients (mean *Z*-score of LVEDd in OI type I: +0.33 (± 0.66 SD) vs. in OI type III: +0.04 (± 1.15 SD) vs. in OI type IV: −0.05 (± 1.20 SD), $p = 0.57$. Mean *Z*-score of LVEDs in OI type I: +0.24 (± 0.74 SD) vs. - 0.24 (± 1.68 SD) in OI type III vs. -0.06 (± 1.26 SD) in OI type IV, $p = 0.63$ (Fig. 3 **and** Table 4).

One patient with a severe OI type III and a LVEDd Z-score > + 2 had a *LEPRE1* variant and another patient with a type IV OI had a variant in *COL1A1*. One patient with a LVEDs Z-score of +2.2 had a *COL1A1* mutation.

LVEF and FS Z-scores were calculated based on age-matched references (18) and were in the physiological range for most patients (Fig. 3). Three patients with OI type I, one patient with type IV and five patients with the most severe form, OI type III, had reduced LVEF values below −2 SDs compared to age-matched references (Fig. 3). Six of these patients with reduced LVEF carried a collagen mutation, and in three patients, no genetic result was available.

The E/A and E/E' ratio *Z*-scores were calculated based on age-specific references (19, 20) and within the normal range in all patients, suggesting preserved left ventricular diastolic function (Fig. 3).

4. Discussion

In this study, we investigated cardiac manifestations in a relatively large cohort of 78 children between age one and 18 years with OI. Interestingly, we did not observe an increased prevalence of clinically significant cardiac malformations or dysfunction in this population. However, patients with severe OI exhibited larger aortic root dimensions compared to healthy individuals and those with mild OI. Our results can help establish guidelines for recommended screening for cardiovascular diseases in children with OI.

Recent Danish cohort studies have shown a significantly higher rate of heart failure diagnosis in patients with OI [6]. This data is supported by animal models of OI demonstrating structural and functional defects in cardiovascular tissue [21], and small clinical studies in children and adults reporting structural abnormalities such as ventricular dilation, thickening of ventricular walls, reduced function, and valvular defects [8–10].

Despite these findings, our study population suggests the overall burden of CVDs is low in children with OI. We investigated 1) symptoms of CVD, 2) the need for cardiovascular medications or interventions, 3) arrhythmias on ECG, 4) congenital heart defects, 5) other potentially acquired structural abnormalities, and 6) reduced diastolic or systolic function. However, we found no increased prevalence in any of these aspects, even in this heterogeneous group of very young to almost adult patients.

None of our patients had clinical symptoms or required cardiac medication. However, it needs to be considered that children with severe OI are generally limited in their physical activity and thorax deformities could potentially confound the assessment of dyspnea arising from underlying cardiac dysfunction.

Previous studies suggested that collagen forms an isolation shell surrounding cardiac conduction cells together with elastin, and therefore might be important for the proper conduction of electrical impulses within the heart [22]. One population-based study suggested an increased prevalence of atrial arrhythmias in adults with OI [6]. However, in our study, no significant arrhythmias or conduction abnormalities were detected on standard 12-lead ECGs, and none of the patients reported symptoms of palpitations, syncope, or pre-syncope. Right or

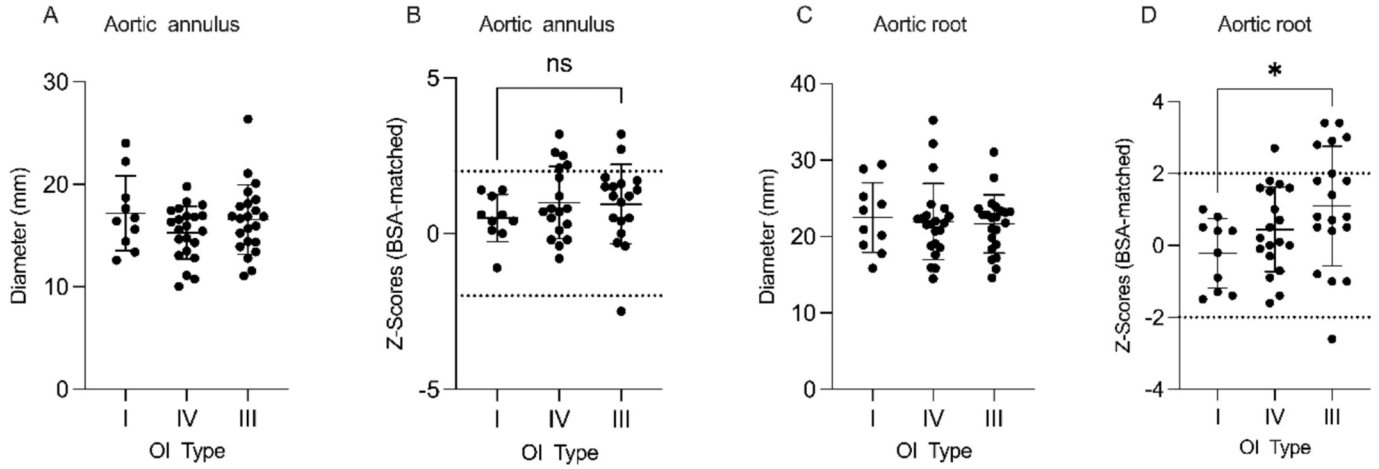

Fig. 2. Diameters of aortic annulus and aortic root. Data are presented as absolute values or age-matched Z-scores. Each point represents an individual patient. The dotted lines indicate the physiological reference range (−2 to +2). Error bars denote the mean ± standard deviation. *ns*: p = 0.33 in panel **B**; * $p = 0.030$ in panel **D**.

left axis deviation was detected in 25 % of patients, which may be explained by severe thoracic deformities affecting the positioning of the heart within the thoracic cavity. Our findings suggest that, although clinically significant arrhythmias may still develop later in life, there is no increased risk of such arrhythmias in children with OI.

Congenital heart defects (CHD) were observed in 13 % of our study population. One patient required interventional closure of an ASD. However, this is a procedure which is also performed regularly in children without OI, since atrial and ventricular septal defects are among the most common congenital heart defects in the general population [23,24]. Although our study cohort was too small to draw definitive conclusions regarding the overall prevalence of CHD in OI, our findings suggest a potentially increased prevalence compared to the general German population, where CHD occurs in approximately 1 % of live births [24]. However, no large case-control studies with OI patients are available to directly compare our findings. A recent systematic review reported a CHD prevalence of 5.7 % among 492 OI patients across six studies, with atrial septal defects (ASD) and patent ductus arteriosus (PDA) being the most frequently observed anomalies [7]. Our observed prevalence of 13 % might overestimate the true prevalence of CHD in OI patients. Nevertheless, a slightly increased risk of congenital cardiac malformations in OI cannot be excluded.

The most frequently observed valvular abnormalities in our study were structural and non-symptomatic functional defects of the aortic and mitral valves. Approximately 9 % of the children in our cohort with moderate to severe OI had aortic root ectasia, 7 % had aortic regurgitation, and 9 % had mitral regurgitation. The left-sided heart valves must withstand significant mechanical stresses and therefore contain abundant, stable collagen type I. Moreover, collagen type I is the predominant protein component of the aortic adventitia, providing structural integrity [25]. Patients with severe OI in our population had markedly larger aortic root diameters than those with mild OI, suggesting a correlation between the degree of aortic enlargement and OI severity. Clinically insignificant aortic regurgitation has been described in small cohorts of adult [26,27] and pediatric [9,10,28] OI patients. It remains unclear whether these findings may progress to clinically significant forms over time [7]. In our population, the occurrence of aortic root and annulus enlargement was not age-dependent, but studies have shown that mice with a deletion in the *COL1A1* gene develop age-dependent aortic dissection and rupture, potentially due to a higher requirement for collagen content in the aortas of older animals [25]. Furthermore, a few case reports have described aortic dissections and aneurysms in adults with OI [29].

Chronic mitral and aortic valve regurgitation may result in progressive LV volume overload, ultimately leading to LV dilation and impaired systolic function. The children in our study cohort did not exhibit LV enlargement, including those with severe forms of OI. Furthermore, our patients demonstrated no systolic dysfunction, neither in echocardiographic assessment of ejection fraction and myocardial contraction, nor clinically. The existing literature also currently lacks clear evidence of early cardiac dysfunction in children with OI [9]. Only one small study of 8 pediatric OI patients observed a reduction in diastolic function [8]. However, some previous studies have reported LV dilation in adult OI patients [27,30] and an increased prevalence of heart failure [6,27,30] and diastolic dysfunction [26,27]. Children with severe OI should receive regular cardiac ultrasounds due to their risk of aortic and mitral valve regurgitation with the potential to progress to LV failure in early adulthood.

A limitation of this study is the absence of a standardized control group, requiring the use of various reference sources, which may introduce inaccuracies due to differences in population characteristics and measurement techniques. Given the cross-sectional study design, no longitudinal data were available to assess the progression of cardiac abnormalities over time. Thoracic deformities also posed challenges in obtaining standardized echocardiographic measurements in some patients. In patients with pronounced scoliosis, body height may have been underestimated. This could have led to an overestimation of *Z*-scores for echocardiographic parameters that are indexed to body size. Further research needs to elucidate if specific mutations or causative genes have an influence on the development of cardiovascular involvement in OI. Despite these limitations, this study provides valuable insights due to its relatively large and heterogeneous pediatric OI cohort, a rare disease with limited available data.

In conclusion, contrary to previous concerns, this study found no increased prevalence of clinically significant cardiovascular disease in children with OI. However, there appears to be an elevated frequency of aortic root dilation and aortic and mitral valve regurgitation, particularly in patients with severe forms of OI. Clinicians should be therefore vigilant for the possibility of valvular disease when encountering OI patients presenting with cardiac symptoms and should promptly initiate further diagnostic evaluation. At least one echocardiographic screening for aortic dilation and valve regurgitations should be considered before transition to adult care in patients with OI.

Clinical trial registration

Not applicable.

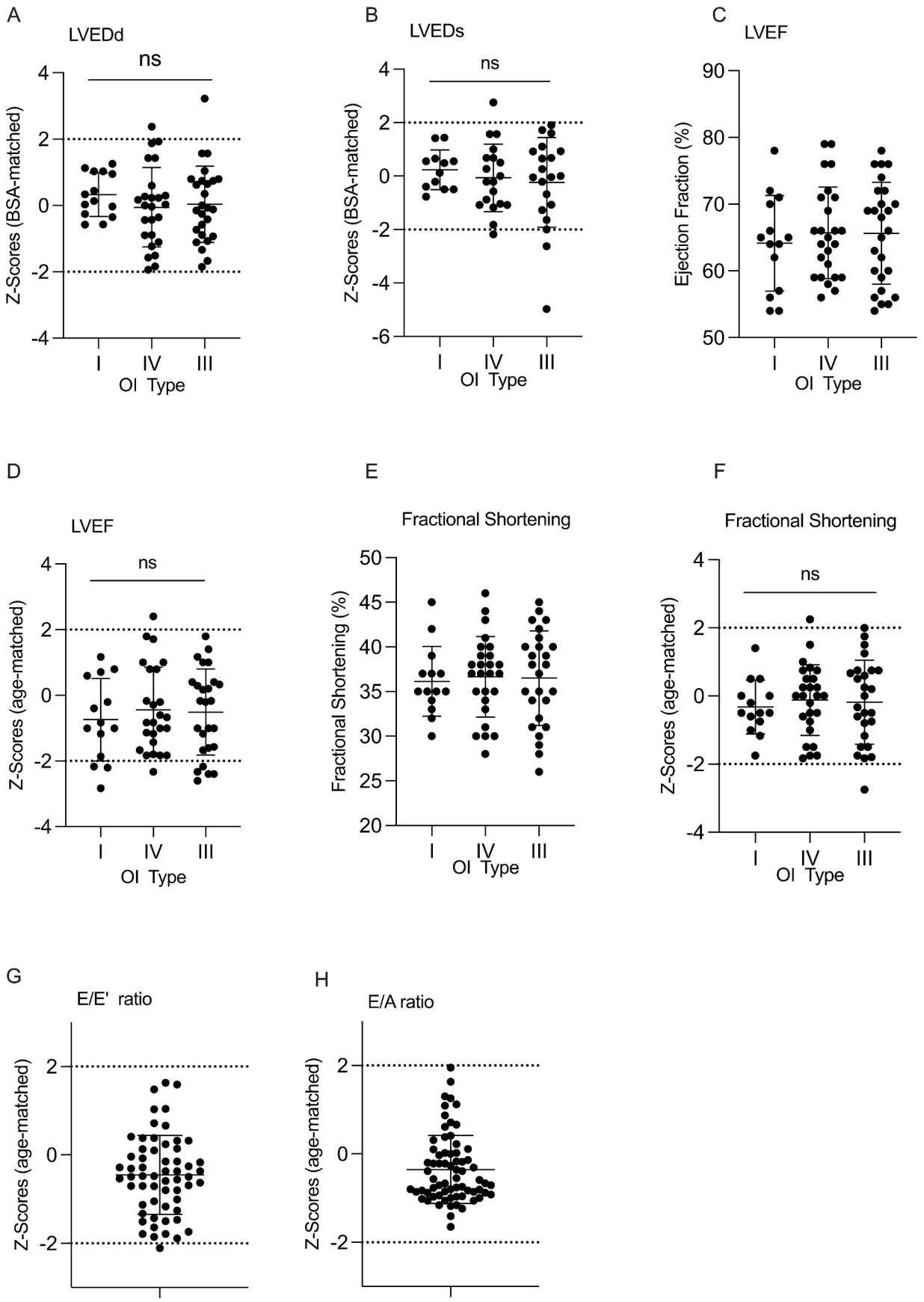

Fig. 3. Left ventricular morphology and function Parameters are presented as age- or body surface area (BSA)-matched Z-scores. Each point represents an individual patient. The dotted lines indicate the physiological reference range (−2 to +2). Error bars denote the mean ± standard deviation. *ns*: p = 0.57 (panel A), p = 0.63 (panel B), $p = 0.84$ (panel F).

CRediT authorship contribution statement

Stefanie Stasek: Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Julia Kronenberger:** Writing – review & editing, Formal analysis, Conceptualization. **Ingo Germund-Maiwald:** Writing – review & editing, Formal analysis, Data curation, Conceptualization. **Shino Junghänel-Welzing:** Writing – review & editing, Conceptualization. **Susanna Reincke:** Writing – review & editing. **Oliver Semler:** Writing – review & editing, Supervision, Resources, Project administration, Conceptualization. **Heike Hoyer-Kuhn:** Writing – review & editing, Supervision, Resources, Methodology, Conceptualization. **Mirko Rehberg:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Patient consent statement

Written informed consent was obtained from all patients' parents or legal guardians prior to participation in the study.

Ethics approval statement

The study was approved by the local ethics committee (approval number: 20–1115) and conducted in compliance with Good Clinical Practice (GCP) and Good Scientific Practice (GSP) guidelines.

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Declaration of competing interest

The authors declare no conflicts of interest.

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Data availability

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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