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Comparison of the 1-year survival rate in infants with congenital heart disease diagnosed by prenatal and postnatal ultrasound

A retrospective study

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Abstract

The impact of prenatal diagnosis on the survival outcome of infants with congenital heart disease (CHD) is still unclear. This study aimed to compare the 1-year survival rate between the prenatally and postnatally diagnosed infants with CHDs.

A single-center population-based retrospective cohort study was performed on data from all infants diagnosed with CHD born between January 1998 and December 2017. Among infants with isolated CHDs, the 1-year Kaplan–Meier survival probabilities for prenatal and postnatal diagnosis were estimated. Cox proportional hazard ratios were adjusted for critical CHD (CCHD) status and gestational age.

A total of 424 (40 prenatally and 384 postnatally) diagnosed infants with CHDs were analyzed. Compared with non-CCHDs, infants with CCHDs were more likely to be prenatally diagnosed (55.0% vs 18.0%; $P < .001$). Among the 312 infants with isolated CHDs, the 1-year survival rate for the prenatally diagnosed was significantly lower than postnatally diagnosed (77.1% vs 96.1%; $P < .001$). For isolated CCHDs, the 1-year survival rate for the prenatally diagnosed was significantly lower than postnatally diagnosed (73.4% vs 90.0%; $P < .001$). The 1-year survival rate was increased with the increase of age at diagnosis. Among infants with isolated CHDs and CCHDs, the adjusted hazard ratios for 1-year mortality rates for the prenatally versus postnatally diagnosed were 2.554 (95% confidence interval [CI], 1.790, 3.654; $P < .001$) and 2.538 (95% CI: 1.796, 3.699; $P < .001$), respectively.

Prenatal diagnosis is associated with lower 1-year survival rate for infants with isolated CCHDs. This could probably due to variation in the disease severity among the CCHD subtypes.

Abbreviations: AS = aortic stenosis, ASD = atrial septal defect, CCHD = critical congenital heart disease, CGH = comparative genomic hybridization, CHD = congenital heart disease, CoA = coarctation of the aorta, DORV = double outlet right ventricle, EA = Ebstein anomaly, FISH = fluorescence in situ hybridization, HLHS = hypoplastic left heart syndrome, IAA = interrupted aortic arch, MLPA = multiplex ligation-dependent probe amplification, MSAFP = maternal serum alpha-fetoprotein, NTD = closed neural tube defect, PA = pulmonary atresia, PDA = patent ductus arteriosus, PS = pulmonary artery stenosis, PTA = persistent truncus arteriosus, SV = single ventricle, TA = tricuspid atresia, TAPVR = total anomalous pulmonary venous return, TGA = transposition of the great arteries, TNGS = targeted next generation sequencing, TOF = tetralogy of Fallot, TOP = termination of pregnancy, VSD = ventricular septal defect.

Keywords: 1-year survival rate, critical congenital heart disease, fetal echocardiography, non-critical congenital heart disease, postnatal diagnosis, prenatal diagnosis

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1. Introduction

The use of ultrasound in the diagnosis of congenital heart disease (CHD) has been increasing in recent years. At birth, the incidence of cardiovascular anomalies is 6.5 times higher than that of chromosomal anomalies.[1] Detail fetal echocardiography is essential as many of the congenital heart malformations have been easily missed during routine obstetric ultrasound examination. Ultrasound screening is generally performed at 18 to 22 weeks gestation. However, at present, more and more centers perform early pregnancy scan (11–14 weeks) along with chromosomal abnormality screening. Some fetal structural abnormalities are able to be detected and confirmed at this stage.[2] Prenatal echocardiography examination has been able to detect CHDs in some low risk pregnancies.[3]

Prenatal diagnosis allows more time for parents to weigh the pros and cons between continuing pregnancy and early termination of pregnancy (TOP).[4] It also helps to improve survival outcome of fetal CHDs, as it allows proper treatment on time. For those who opted to continue their pregnancies, continuous observation of the disease progress and monitoring can be done.

Previously, there had been cases of children with undiagnosed CHDs but were later diagnosed at autopsy.[5] Studies have shown that for severe CHDs requiring intervention, prenatal diagnosis may have benefits in postnatal surgery. Besides, it can reduce adverse events in the perioperative period.[6–10] Research findings have prompted researchers to conclude that prenatal diagnosis can improve long-term neurological outcome.[7,8]

However, the impact of prenatal diagnosis on the survival outcome of infants with CHDs is still unclear. For example, conclusions from previous studies on whether prenatal diagnosis can reduce the preoperative and postoperative mortality in patients with hypoplastic left heart syndrome (HLHS)[8,11,12] and transposition of the great arteries (TGA)[9,11] are contradictory. There is no definitive evidence on the relationship between the 2, partly because it is difficult to collect sufficient samples for a particular disease. In addition, scholarly studies on survival outcome after the perioperative period are relatively scarce.

In this study, we compared the survival rate of the prenatally and postnatally diagnosed infants with CHDs. We hypothesized that there would be a significant difference in the survival rate between the prenatally and postnatally diagnosed infants with CHDs. In addition, factors associated with the different outcomes following prenatal and postnatal diagnosis were explored.

2. Materials and methods

2.1. Ethical approval

This retrospective study was approved by the Ethics Committee of Shandong Weihai Municipal Hospital and the requirement for informed consent was waived.

2.2. Study design and setting

This was a single-center population-based retrospective cohort study.

2.3. Study subjects

Data from infants with CHD born between January 1998 and December 2017 in Shandong Weihai Municipal Hospital were collected and identified via chart review. Information gathered included type of CHD, gestational age at birth, family living standard, birth weight, maternal age, and 1-year survival after birth.

Inclusion criteria: all infants born between January 1998 and December 2017, prenatally or postnatally diagnosed with CHD.

Exclusion criteria: CHD with other associated major anomalies or chromosomal syndromes, prenatally diagnosed CHDs which were aborted.

According to the time of initial ultrasound screening, the infants were divided into prenatally and postnatally diagnosed group. Those of the prenatally diagnosed were further divided into 2 groups: early trimester group, in which the diagnosis of CHD was made in the first trimester (11^{+0} week–13^{+6} week); mid-trimester group, in which the diagnosis of CHD was made in the second trimester (14^{+0} week–28^{+0} week). Second trimester screening at 18^{+0} to 22^{+0} weeks of gestation was recommended as the standard of care for all pregnancies to determine the approximate gestational age, confirm fetal viability, identify multiples, detect closed neural tube defect (NTD)s which were not usually detected by maternal serum alpha-fetoprotein (MSAFP) screening, or screen for other congenital anomalies. In most areas, it was considered as the optimal time frame for prenatal ultrasound scanning. Those beyond 22 weeks of gestation were considered late pregnancy. The flow diagram for patient enrollment was shown in Fig. 1.

2.4. Equipment and operators

All examinations were performed by experienced obstetrician sonologists. More complex cases were diagnosed by an expert consultation. Voluson-730 (GE Healthcare, Zipf, Austria) and Voluson-E8 (GE Healthcare, Zipf, Austria) color Doppler ultrasound diagnostic apparatus with probe frequency of 3 to 5 MHz were used as diagnostic apparatus.

2.5. Types of congenital heart disease

In this study, critical congenital heart disease (CCHD)s were defined as 12 defects that are likely to require intervention within the first year of life. These included 7 critical lesions typically present with hypoxemia: HLHS, tetralogy of Fallot (TOF), TGA, pulmonary atresia (PA), tricuspid atresia (TA), persistent truncus arteriosus (PTA) and total anomalous pulmonary venous return (TAPVR) and 5 lesions that sometimes produce hypoxemia but less consistently: coarctation of the aorta (CoA), double outlet right ventricle (DORV), Ebstein anomaly (EA), interrupted aortic arch (IAA), and single ventricle (SV).[13]

Non CCHDs were defined as defects that do not require intervention or oxygen monitoring after birth. Types of defect collected in this study included aortic stenosis (AS), atrial septal defect (ASD), patent ductus arteriosus (PDA), pulmonary artery stenosis (PS), and ventricular septal defect (VSD).

2.6. Potential associated covariates

Potential covariates for the association between timing of diagnosis (prenatal vs postnatal) and 1-year mortality rate included CHD status (critical vs noncritical), gestational age at birth ($\leq$36 weeks vs >36 weeks), standard of living (<20% of population living in poverty vs $\geq$20%), birth weight (<2500 g vs $\geq$2500 g), and maternal age.

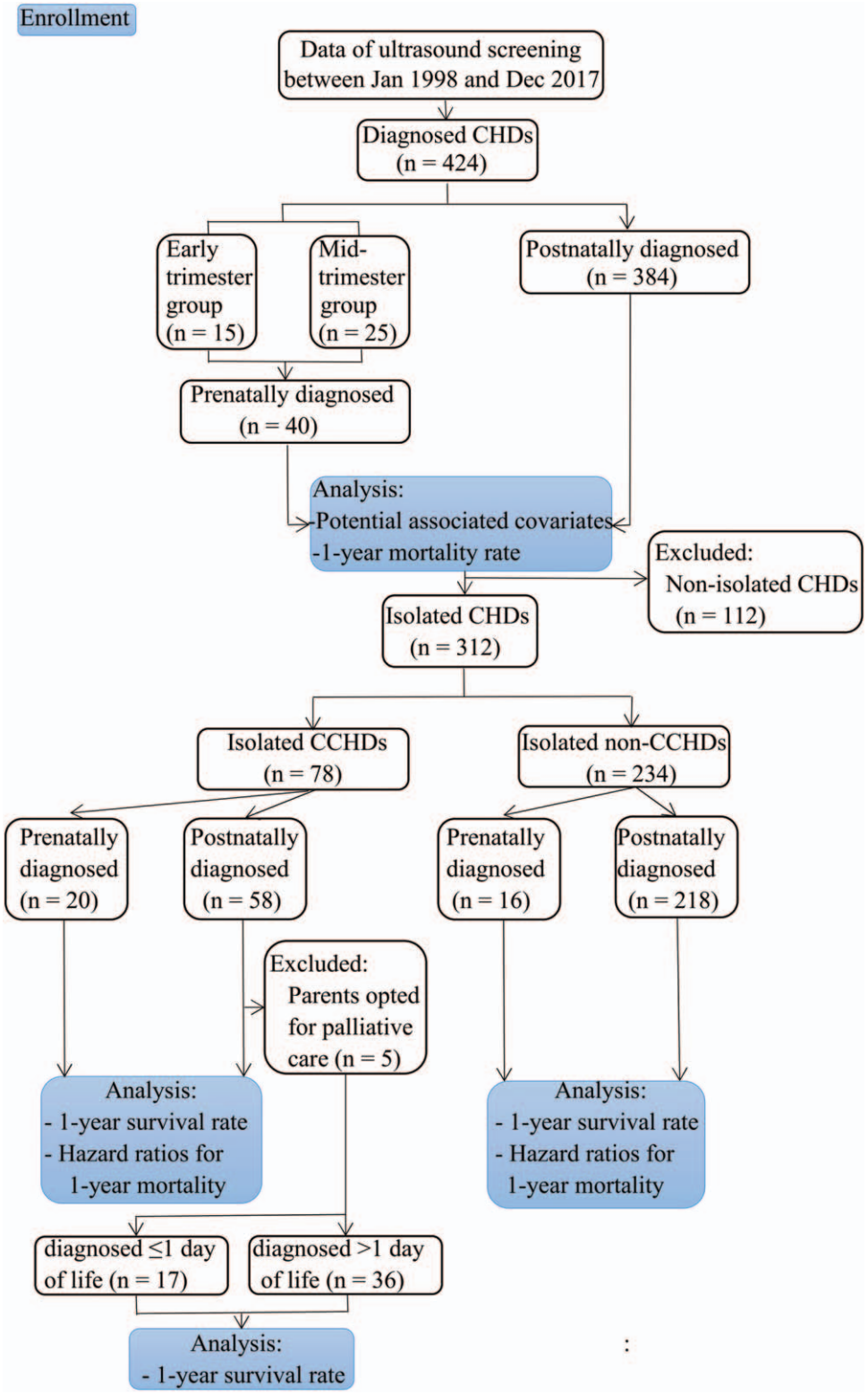

Figure 1. Flow diagram for patient enrollment. Note: CCHD = critical congenital heart disease; CHD = congenital heart disease.

2.7. Genetic examination

Prenatally diagnosed infants with CHDs underwent genetic screening and prenatal karyotype examination. Fetal cytology and molecular genetic analysis were determined with chorionic villus sampling or amniocentesis. Postnatally diagnosed infants with CHDs completed genetic screening postpartum. Comparative genomic hybridization (CGH) chip was used for karyotype analysis. Fetuses with suspected DiGeorge syndrome were detected with fluorescence in situ hybridization (FISH) or multiplex ligation-dependent probe amplification (MLPA) tech-

niques. Targeted next generation sequencing (TNGS) was performed in selected patients with a family history of CHD and all the above test results were negative.

2.8. Statistical analysis

Data analysis was performed with SPSS 16.0 software (SPSS Inc., Chicago, IL). Chi-square tests were performed to compare the baseline characteristics of the associated covariates between the prenatally and postnatally diagnosed cohorts. Survival probabilities were estimated using Kaplan–Meier methods, and log-rank test was used to determine significance ($P < .05$). Infants with isolated CHDs were included in the Kaplan–Meier survival curves or proportional hazards analyses. The potential covariates were also analyzed using univariate logistic regression modeling, with death at 1 year as the outcome. Covariates that were significantly different between prenatal and postnatal cohorts and were also significantly associated with 1-year mortality rate ($P < .05$) were identified as potential confounders and included in the Cox proportional hazards models to obtain adjusted hazard ratios for mortality. The multivariate analysis model was completed with corrected values of gestational age. Finally, a separate Kaplan–Meier curve was constructed to compare and analyze the 1-year survival rate based on the timing/age of diagnosis for the isolated CCHDs: prenatal diagnosis versus early postnatal diagnosis (≤1 day of age) versus late postnatal diagnosis (>1 day of age).

2.9. Outcome measures

The primary outcome measure was the difference of the 1-year survival rate between the prenatally and postnatally diagnosed infants with CHDs.

The secondary outcome measure was the factors associated with the different outcomes following prenatal and postnatal diagnosis.

3. Results

3.1. Comparison of baseline characteristics

A total of 424 cases with CHDs were included, of which 40 (9.4%) were prenatally diagnosed. Among the prenatally diagnosed cases, 15 (37.5%) were diagnosed in the early trimester. Significant differences were seen with respect to the proportion of infants with CCHDs and gestational age between the prenatally and postnatally diagnosed CHDs ($P < .001$). There were no significant differences with respect to family living standard, low birth weight, or maternal age. All covariates were significantly associated with 1-year mortality rate by logistic regression. In all selected cases with CHDs, those diagnosed prenatally had a significantly greater unadjusted 1-year mortality rate compared with those diagnosed postnatally (35.0% vs 9.1%, respectively; $P < .001$) (Table 1). Types of heart defects among CCHDs and non-CCHDs were summarized in Tables 2 and 3, respectively.

Table 1

Baseline characteristics for prenatally and postnatally diagnosed infants with CHDs.

	Prenatally diagnosed					
Variable	Early trimester (n = 15)	Mid-trimester (n = 25)	*P* value (early trimester vs mid- trimester)	Total (n = 40)	Postnatally diagnosed (n = 384)	*P* value (prenatally vs postnatally diagnosed)
CCHD	10 (66.7)	12 (48.0)	<.001*	22 (55.0)	69 (18.0)	<.001*
Associated defects						
Isolated CHD	6 (40.0)	14 (56.0)	<.001*	20 (50.0)	292 (76.0)	<.001*
Multiple CHD	3 (20.0)	3 (12.0)	.002*	6 (15.0)	34 (8.9)	.002*
Chromosomal abnormality	5 (33.4)	5 (20.0)	<.001*	10 (25.0)	42 (11.0)	<.001*
Trisomy 21	2 (13.3)	1 (4.0)		3 (7.5)	16 (4.2)	
Trisomy 18	1 (6.7)	1 (4.0)		2 (5.0)	9 (2.3)	
Trisomy 13	1 (6.7)	0 (0.0)		1 (2.5)	3 (0.8)	
Turner syndrome	1 (6.7)	1 (4.0)		2 (5.0)	6 (1.6)	
22q11.2 deletion syndrome	0 (0.0)	1 (4.0)		1 (2.5)	2 (0.5)	
Others	0 (0.0)	1 (4.0)		1 (2.5)	6 (1.6)	
Gestational age, wks						
≤36	4 (26.7)	6 (24.0)		10 (25.0)	100 (26.0)	
37–38	6 (40.0)	8 (32.0)	<.001*	14 (35.0)	92 (24.0)	<.001*
39–40	5 (33.3)	8 (32.0)		13 (32.5)	127 (33.1)	
>40	0 (0.0)	3 (12.0)		3 (7.5)	65 (16.9)	
Family living standard (poverty level)						
0.0–4.9%	5 (33.3)	8 (32.0)	.68	13 (32.5)	131 (34.1)	.66
5.0–9.9%	4 (26.7)	7 (28.0)		11 (27.5)	108 (28.1)	
10.0–19.9%	4 (26.7)	6 (24.0)		10 (25.0)	96 (25.0)	
≥20%	2 (13.3)	4 (16.0)		6 (15.0)	49 (12.8)	
Low birth weight (<2500 g)	4 (26.7)	7 (28.0)	.26	11 (27.5)	92 (24.0)	.23
Maternal age (years old)						
<20	2 (13.3)	2 (8.0)		4 (10.0)	32 (8.3)	
20–24	2 (13.3)	5 (20.0)	.18	7 (17.5)	69 (18.0)	.15
25–29	3 (20.0)	5 (20.0)		8 (20.0)	91 (23.7)	
≥30	8 (53.4)	13 (52.0)		21 (52.5)	192 (50.0)	
1-year mortality	7 (46.7)	7 (28.0)	<.001*	14 (35.0)	35 (9.1)	<.001*

Data were presented as number of patients with percentage (%), n = total number of patients. CCHD = critical congenital heart disease; CHD = congenital heart disease.
* *P* indicated statistically significant.

Table 2

Types of heart defects among CCHDs.

Cardiac abnormality	Prenatally diagnosed			Postnatally diagnosed (n = 69)
	Early trimester (n = 10)	Mid-trimester (n = 12)	Total (n = 22)	
HLHS	2 (20.0)	1 (8.3)	3 (13.6)	8 (11.6)
TOF	1 (10.0)	1 (8.3)	2 (9.1)	12 (17.4)
TGA	1 (10.0)	1 (8.3)	2 (9.1)	10 (14.5)
PA	1 (10.0)	1 (8.3)	2 (9.1)	3 (4.4)
TA	1 (10.0)	1 (8.3)	2 (9.1)	4 (5.8)
PTA	1 (10.0)	1 (8.3)	2 (9.1)	4 (5.8)
TAPVR	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)
CoA	1 (10.0)	1 (8.3)	2 (9.1)	7 (10.1)
DORV	1 (10.0)	2 (16.7)	3 (13.6)	5 (7.2)
EA	1 (10.0)	1 (8.3)	2 (9.1)	5 (7.2)
IAA	0 (0.0)	1 (8.3)	1 (4.5)	4 (5.8)
SV	0 (0.0)	1 (8.3)	1 (4.5)	5 (7.2)

Data were presented as number of patients with percentage (%), n = total number of patients. CCHD = critical congenital heart disease; CoA = coarctation of the aorta; DORV = double outlet right ventricle; EA = Ebstein anomaly; HLHS = hypoplastic left heart syndrome; IAA = interrupted aortic arch; PA = pulmonary atresia; PTA = persistent truncus arteriosus; SV = single ventricle; TA = tricuspid atresia; TAPVR = total anomalous pulmonary venous return; TGA = transposition of the great arteries; TOF = tetralogy of Fallot.

Table 3

Types of heart defects among non-CCHDs.

Cardiac abnormality	Prenatally diagnosed (n = 18)	Postnatally diagnosed (n = 315)
AS	2 (11.1)	81 (25.7)
ASD	1 (5.6)	74 (23.5)
PDA	0 (0.0)	39 (12.4)
PS	8 (44.4)	86 (27.3)
VSD	7 (38.9)	35 (11.1)

Data were presented as number of patients with percentage (%), n = total number of patients. AS = aortic stenosis; ASD = atrial septal defect; CCHD = critical congenital heart disease; PDA = patent ductus arteriosus; PS = pulmonary artery stenosis; VSD = ventricular septal defect.

3.2. Comparison of 1-year survival rate

3.2.1. Isolated CHDs. Isolated CHDs accounted for 312 cases from 1998 to 2017. Kaplan–Meier survival curves showed significantly lower 1-year survival rate for the prenatally diagnosed versus postnatally diagnosed CHDs (77.1% vs 96.1%, respectively; $P < .001$) (Fig. 2).

3.2.2. Isolated non-CCHDs. No difference in 1-year survival rate was seen among isolated non-CCHDs for the prenatally versus postnatally diagnosed infants (93.3% vs 96.4%, respectively; $P = .7$) (Fig. 3).

3.2.3. Isolated CCHDs. Among isolated CCHDs, the prenatally diagnosed infants had significantly lower 1-year survival rate compared with those postnatally diagnosed (73.4% vs 90.0%, respectively, $P < .001$) (Fig. 4).

3.2.4. Analysis by age at diagnosis. The Kaplan–Meier survival curve for the CCHD cohort showed an increase in the 1-year survival rate with the increase of age at diagnosis. On further analysis of the postnatally diagnosed infants, the 1-year survival rate was 96.0% for those diagnosed >1 day of life and 85.2% for those diagnosed ≤1 day of life ($P < .001$) (Fig. 5).

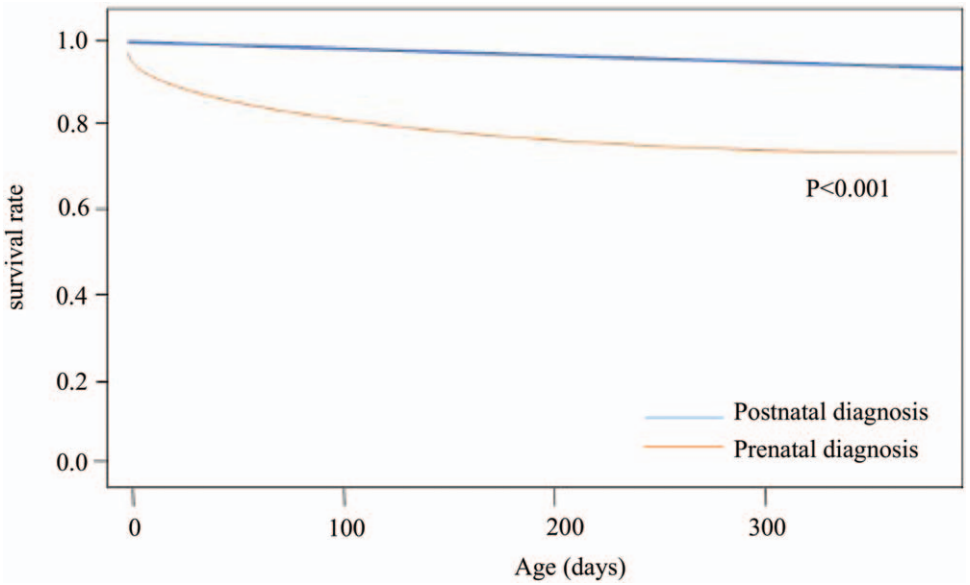

Figure 2. One-year survival rate for infants with isolated CHDs by prenatal and postnatal diagnosis. CHD = congenital heart disease.

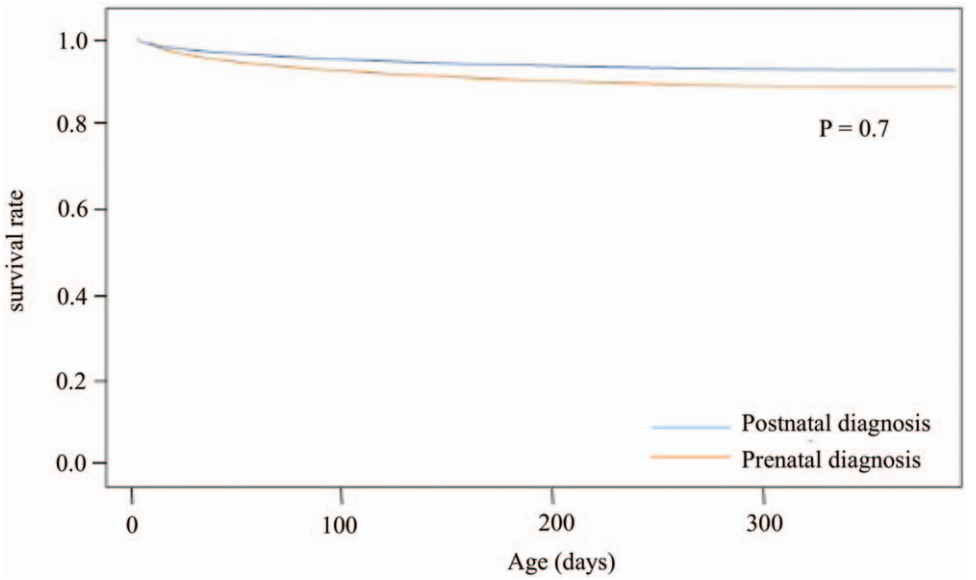

Figure 3. One-year survival rate for infants with isolated non-CCHDs by prenatal and postnatal diagnosis. CCHD = critical congenital heart disease.

3.3. Proportional hazard ratios for 1-year mortality rate

Through adjusted values, more convinced conclusions could be drawn. When examining the 1-year mortality rate using proportional hazards regression modeling among isolated CHDs, the prenatally diagnosed infants had a hazard of mortality 2.554 times greater than those postnatally diagnosed (95% CI: 1.790, 3.654; $P < .001$), adjusted for gestational age. When the analysis was limited to the CCHD cohort, the adjusted hazard ratio for prenatally versus postnatally diagnosed infants was 2.538 (95% CI: 1.796, 3.699; $P < .001$). Among non-CCHDs, the adjusted hazard ratio for prenatally versus postnatally diagnosed infants was 1.003 (95% CI: 0.135, 7.370; $P = .12$) (Table 4).

4. Discussion

Congenital heart defects are the most common type of birth defects and have been reported to occur in 4 to 8 of every 1000 live births,[14–16] accounting for 30% to 50% of birth defects-induced infant mortality.[17,18] Previous studies showed that prenatal detection of CHD may improve pregnancy outcome of fetuses with specific types of cardiac lesions.[19] In this study, 424 (0.8%) infants were identified as CHDs between 1998 and 2017. Overall, 40 (9.4%) infants were diagnosed prenatally, with increased rate from 6.8% (16% for CCHDs and 3.6% for non-CCHDs) in 1998 to 2007 to 11.9% (32% for CCHDs and 6.5% for non-CCHDs) in 2008 to 2017. The prenatal detection rates

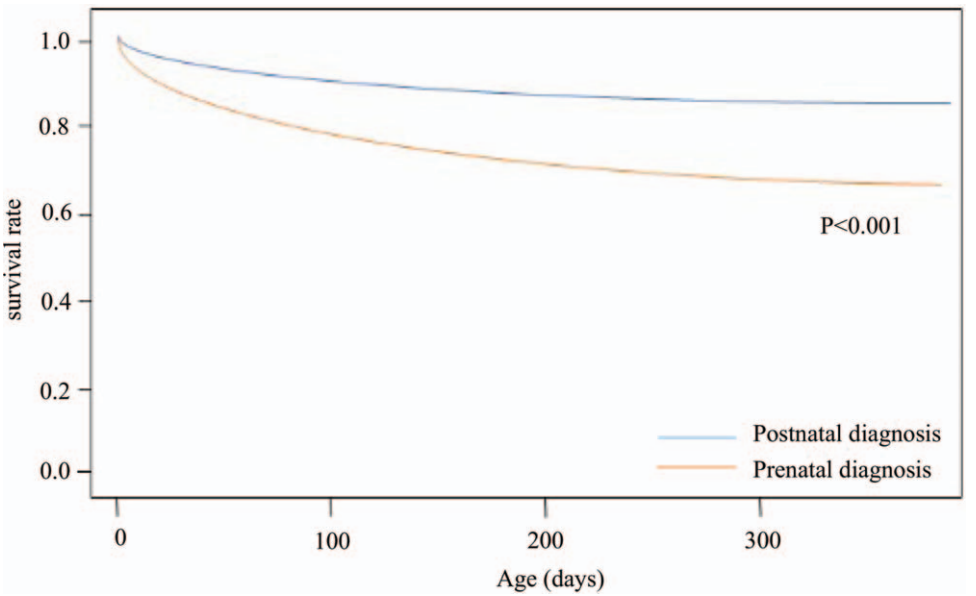

Figure 4. One-year survival rate for infants with isolated CCHDs by prenatal and postnatal diagnosis. CCHD = critical congenital heart disease.

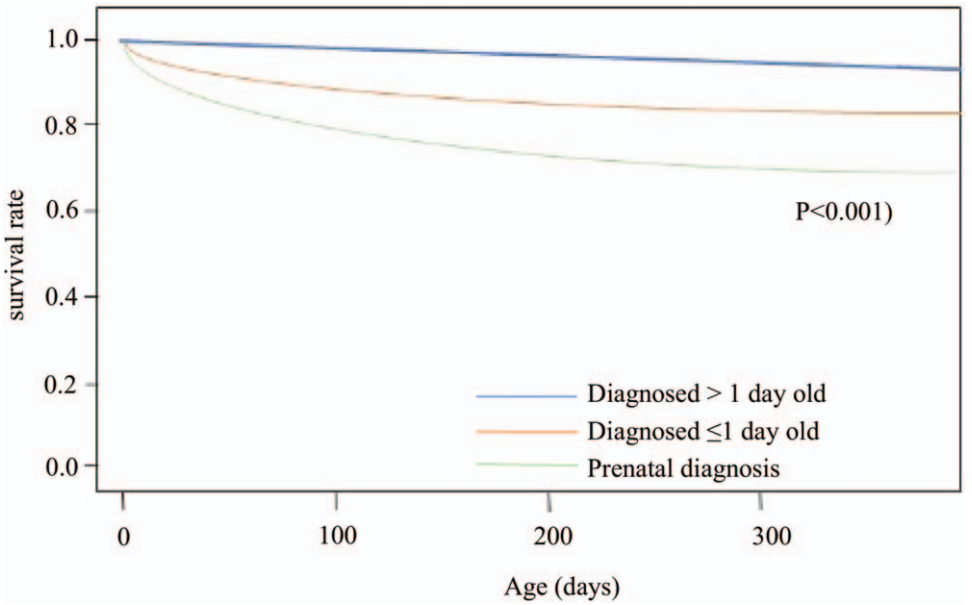

Figure 5. One-year survival rate for infants with isolated CCHDs by age at diagnosis. CCHD = critical congenital heart disease.

for CCHDs were illustrated in Table 2, with the highest detection for HLHS and DORV (13.6%) and lowest detection for TAPVR (0.0%). The reason for low prenatal detection rate for CHD was possibly due to most parents opted for TOP by induction of labor following a prenatal diagnosis of cardiac malformation and few patients chose to continue their pregnancy. The prenatally diagnosed cases of non-CCHDs were mainly detected in the mid trimester. There were more postnatally diagnosed cases, mainly due to missed diagnosis and unclear diagnosis caused by various prenatal reasons, and most of these were non-CCHDs.

Prenatal detection rates may vary by the patient's geographic region and defect type. Previous studies showed that there may be significant variation across the country by region or state.[20] Some of the variation can be attributed to the examiner experience, maternal obesity, transducer frequency, abdominal scars, gestational age, amniotic fluid volume, and fetal position.[21,22] Defects associated with an abnormal 4 chamber view were found to be more likely to have prenatal identification than those require outflow tract views.[20,23] Adding ventricular outflow tract view to assessment of the standard 4-chamber view in prenatal screening could improve detection of CHD,[24] while addition of 3-vessel or 3-vessel with trachea views to the standard 4-chamber and outflow tract views have been shown to improve detection such as CoA.[25,26]

Table 4

Stratified Cox proportional hazard ratios for 1-year mortality for prenatally and postnatally diagnosed infants with CHDs.

Variable	Hazard ratio	95% CI	*P* value
Prenatal versus postnatal			
All isolated CHDs	2.554	1.790, 3.654	<.001*
Isolated non-CCHDs	1.003	0.135, 7.370	.12
Isolated CCHDs	2.538	1.796, 3.699	<.001*

All hazard ratios adjusted for gestational age. CCHD = critical congenital heart disease; CHD = congenital heart disease.
* *P* indicated statistically significant.

In this population-based study, we found significantly lower 1-year survival rate among infants with prenatally diagnosed isolated CHDs compared with those postnatally diagnosed. Despite Tworetzky et al[12] and Franklin et al[19] reporting a survival benefit among the prenatally diagnosed HLHS and CoA, respectively, several other studies have failed to demonstrate such benefit. A retrospective study[27] of HLHS patients presented from 1999 to 2010 found no survival-to-discharge advantage among the prenatally diagnosed, a finding which has been similarly demonstrated in other single-center studies with regard to HLHS and TGA,[8,10,11,28] as well as PA with intact ventricular septum.[29] A previous study showed that prenatal diagnosis of complex CHD may lead to improved preoperative morbidity, particularly in patients with ductal-dependent cardiac anomalies, however, no survival benefits were noted.[30] A recent systematic review suggested that prenatal diagnosis of CCHDs may improve overall newborn survival.[31] However, Słodki et al[32] found that prenatal identification of fetuses at increased risk of developing CoA may reduce mortality and improve outcome only in neonates with severe CoA, which symptoms appeared within the first 7 days after birth. Study by Alabdulgader[33] revealed no statistically significant difference in survival outcome between prenatal and postnatal diagnosis of HLHS.

In our cohort studies, infants with CHDs in the prenatal diagnosis group had higher ratio of CCHDs, which may contribute to the worse outcome of the 1-year survival rate. Similar studies have also attributed the worse outcome of prenatal diagnosis with CHDs due to severity of the disease.[34] A recent comprehensive study conducted in Czech Republic found that prenatal ultrasound screening diagnosed more CCHD cases and was associated with overall high mortality rate.[35] It has been reported that it was easier to determine CCHDs during prenatal period. This might be partly due to higher possibility of detecting significant anatomical or structural abnormalities in the

routine obstetric ultrasound examination.[36–38] A study in metropolitan Atlanta found that among the infants whose congenital cardiac defect was diagnosed prenatally, 30.9% died before 5 years of age, and almost 10% were stillborn, reflecting the severity of the conditions.[39] A study by McCandless et al[40] found that neonates with prenatally diagnosed coarctation had smaller left heart structures than those diagnosed after first week of age, were more likely to require extensive arch reconstruction under cardiopulmonary bypass, and had longer hospital stays.

The definition of CCHD in this study was different from the so-called "complex" or "severe CHD" in other studies. We excluded isolated non-CCHDs which are prone to be found during obstetric examination such as visceral heterotaxy, and included some abnormalities which can only be detected by visual inspection of the heart flow tract and where technical feasibility is not always satisfactory. Although the classification method of cardiac malformations was different, we also found that CCHDs were much easier to be diagnosed prenatally, and the 1-year mortality rate among the prenatally diagnosed infants was higher. This finding is consistent with the study by Gedikbaşi et al[41] in Turkey which concluded that serious deformities resulted in worser outcome. Gedikbaşi et al[41] conducted a study on the survival rate of 155 infants with prenatally diagnosed CHD. Classification of CHD was performed according to the Allan–Huggon grading system, and it was found that the survival rates for low, moderate, and high risk CHDs were 89.2%, 66.7%, and 13.5%, respectively.

Chung et al[42] conducted a study on infants with CHD admitted to NICU with "complex" heart disease, including all cases of atresia and SVs; "significant" heart disease, including TGA and TOF; and "simple" heart disease, which referred to cases not requiring intervention. Among the CHD infants who were admitted in 2004 to 2006, the 1-year survival rates for "complex," "significant," and "simple" CHD were 73.0%, 94.0%, and 100%, respectively. In this study, as the classification of cardiac malformations into CCHDs and non-CCHDs is relatively broad, we further divided the age at diagnosis into 3 categories. This classification can be used as a rough correlation with severity of CHDs. CHDs which were diagnosed prenatally were defined as "severe"; CHDs which were diagnosed within 24 hours after birth were defined as "moderate," while CHDs which were diagnosed after 1 day of birth were defined as "mild." In order to minimize bias, parents who opted for palliative care among infants with postnatally diagnosed CCHDs were excluded from analysis. The Kaplan–Meier survival curve showed an increase in the 1-year survival rate with the increase of age at diagnosis. Based on our clinical observation, in CCHDs, the more severe the disease, the earlier the symptoms would appear, and the easier for it to be diagnosed in the early stage. One day of age was chosen as the cut-off point in this study, as in clinical practice, for those with poor postnatal scores, the obstetricians will require to perform a bedside echocardiography on the same day, while those with a good postnatal score will undergo echocardiography the next day, or even after discharge. One day of age cut-off for timing of diagnosis was also found to be most closely reflects the timing of potential diagnoses for CCHDs in a proposed pulse oximetry screening algorithm.[43] Diagnostic timing is important; the goal is to improve survival for current cases experiencing delay in diagnosis.

Since 1992, first trimester prenatal screening has developed progressively. In China, early pregnancy screening is only carried out in a few centers.[44] Currently, ultrasound screening for fetal anomalies are typically conducted in regional tertiary obstetric centers and secondary obstetric hospitals, and are performed by physicians experienced in obstetric ultrasonography rather than sonographers.[45]

Prenatal diagnosis of CCHD depends upon recognition of structural heart defects by ultrasound or fetal echocardiography. However, some CCHDs are more amenable to visualization through these methods than others,[14] which may contribute to the variation in the prenatal detection rates.[45–49] For instance, HLHS has been shown to be detected prenatally quite frequently, with estimates ranging from 53% to 88%,[47–49] while TAPVR is much less likely to be detected prenatally. CoA is infrequently diagnosed before birth, with studies estimating that only 11% to 37% of cases have a prenatal diagnosis,[47–49] while DORV seems to be diagnosed prenatally more frequently. When the discrepancy of 4-chamber size is not obvious, cardiac abnormalities such as CoA may be missed diagnosis.[50] Infant/fetal characteristics associated with increased prenatal diagnosis included the presence of other birth defects or chromosomal syndromes, as well as increasing complexity of CCHD. Maternal factors associated with increased rates of prenatal detection are multiple gestations, increased maternal age, maternal diabetes, and family history of CCHD, while non-Hispanic White maternal race/ethnicity and increased prepregnancy body mass index have been associated with decreased rates of prenatal diagnosis.[47,51]

Previous studies showed that the sensitivity of echo-views increased with the advance of gestational age.[50] It was suggested that although certain types of fetal CHD can be detected after 13 weeks of pregnancy, early fetal echocardiography should be followed by echocardiography at second and third trimesters.[52–54] Some views may be inadequate for assessment of normality or abnormality during the early scan. This is perhaps due to both the distance of the fetus from the maternal abdominal wall and the small size of heart structures.[55] Nonetheless, the feasibility and utility of early fetal echocardiography have been shown in previous studies. Axt-Fliedner et al[56] found that a left heart obstruction diagnosed in the first trimester can progress to left heart hypoplasia in early second trimester. Gholkar et al[2] reported a confirmed diagnosis case of HLHS in a first trimester aneuploidy screening at 13 weeks. This highlights the significance of early fetal echocardiography. The findings could help in early decision making, safe termination if opted for, and minimizing emotional trauma. Previous study showed that early prenatal diagnosis could help to detect a HLHS case in low risk pregnancy.[3] There is also strong evidence in the literature supporting the view that fetal echocardiography performed in high-risk pregnancies for congenital heart defects by expert operators is reliable for diagnosing most major structural heart defects in the first and early second trimesters of pregnancy, thus allowing optimization of management to parents through early counseling or TOP.[3]

At our center, prenatal genetic examination was performed for cases of high-risk factors such as advanced maternal age (≥35), high risk for Down syndrome, and nuchal translucency thickening. Prior to 2012, the fees for collecting fetal DNA from venous blood of the pregnant women were relatively high, which were about 3000 yuan, and the technology was not mature, thus the main method of screening was through amniotic fluid testing. Some pregnant women were concerned about the invasive procedure and did not undergo the amniocentesis test. In this study, 32 cases (80.00%) in the prenatal diagnosis group and

177 cases (46.09%) in the postnatal diagnosis group underwent genetic examination. The prenatal diagnosis group has a higher proportion of genetic testing. This was probably due to the parents were quite concerned about the possibility of developmental defects in other organ systems as well, which abnormality might be found during the fetal period, and thus the acceptance for undergoing the genetic test was better. In the postnatal diagnosis group, the pregnant women generally did not undergo amniocentesis or other DNA tests, as the fetal heart was thought to be "normal" before birth. After birth, as the organ development of the newborn could be assessed by other means, thus not all of them carried out the genetic tests. Since this study mainly focused on the effect of severity of fetal heart malformation on prognosis, the influence of chromosomal factors would be explored in subsequent studies.

Although our study does not show that prenatal diagnosis is associated with a 1-year survival benefit, however, it has been well described to be associated with improvements in preoperative condition, reductions in morbidity such as hypoxemia, the need for invasive respiratory support, and metabolic acidosis to some extent.[57–59] Early screening allows better advice for parental counseling and delivery planning.[41,60,61] Several population-based studies from countries around the world have focused on the relation of prenatal diagnosis with 1-year survival rate. It was found that the increase in prenatal diagnosis resulted in a corresponding increase in 1-year survival rate. This indicates that prenatal fetal echocardiography contributes to the overall increase of survival rate.[62,63] However, the difference is that, these conclusions were based on comparison over different study periods, and not the same as our study, which compared the impact of prenatal and postnatal diagnosis on survival rate over a specific period of time. A recent study by Wright et al[64] on infants (aged <1 year) who underwent surgery for CHDs from 2006 to 2011 at a single institution found that infants diagnosed prenatally had significantly higher 1-year mortality rate, as well as significantly longer intensive care unit and hospital stays compared with those diagnosed postnatally, and prenatal diagnosis likely captures patients with more severe phenotypes.

A major strength of this study is its well-classified system. We sorted the information collected, and forward to the pediatric cardiologist to analyze, to ensure the accuracy of the study.[65] This system allowed our study to limit analysis to isolated CHDs, and minimized the possibilities that the findings are due to poorer outcomes associated with chromosomal abnormalities and extracardiac defects. The data were obtained from a single center rather than hospital discharge coding data, and the diagnoses were directly reviewed.

However, our study is not without limitations. After adjustment, we still obtain the conclusion that prenatal diagnosis significantly increased the risk of mortality of CCHDs. To explain this condition, we cannot draw conclusions based solely on the CCHD ratio. One possible reason is that there is a difference in the disease severity among the CCHD subtypes. Lowenthal et al[66] in a recent study on prenatal diagnosis of HLHS found that the 2-year survival rate of patients with varying degrees of atrial septal restrictions were significantly lower than those without. The data we collected for the present study does not include detailed information on the severity of individual illness, and also lack of information on clinical visits, surgical intervention and surgical mortality. Therefore, we cannot incorporate these factors into our study. Worse cardiac or extracardiac diseases not taken into account in the modeling, and differences in the management strategy that negatively affect the survival of the prenatally diagnosed fetuses could also be the possible factors. Further studies with a larger sample size are needed to confirm the evidence generated in this study. Comparison of survival rate between the early and mid trimester diagnosed infants may also be evaluated with larger samples.

Although there was no specific information on surgical treatment and its related outcome, we managed to provide the parents of the prenatally diagnosed CHDs a direction to decide the appropriate type of treatment. There was a series of studies focused on factors that influence the parents' choice of treatment.[67–70] Development of modern surgical techniques has led to a reduction in the importance of conservative treatment recommended by physicians.[71] Prenatal diagnosis may allow parents more time to decide and consider conservative management over surgical intervention.[72] However, our findings did not suggest that the difference in survival rate between the prenatally and postnatally diagnosed groups was mainly due to more parents with a prenatal diagnosis of CHD opted for conservative treatment, and it persisted for even >1 month after birth. In addition, another factor that affected the parents' choice of conservative treatment upon prenatal diagnosis was when the child was found to be associated with chromosomal abnormalities. However, the present study did not conduct an in-depth analysis on this. Although it was not possible for the present study to make an analysis on the impact of prenatal diagnosis on TOP, other researchers did find that there was a stable relationship between the two. In a previous study, parents of CHDs diagnosed before 22 weeks of gestation were found to be more likely to opt for TOP.[73] Subsequent studies may focus to explore other factors associated with prenatally diagnosed CHDs that may affect the infant survival rate, such as time and mode of delivery.[74–77] Trento et al[78] and other scholars found that prenatal diagnosis of CHD increased the likelihood for planned delivery. In the Landis study,[59] the same conclusion was reached, and the correlation between prenatal diagnosis of CHD and induction of labor was also discussed. However, none of these studies have found any significant implications on short-term mortality. Perhaps these points could help us examine and analyze some of the factors in a larger size sample.

5. Conclusion

Fetal echocardiography remains an effective prenatal screening method for CHD. However, detection of some severe CHDs in the early stage of pregnancy resulted in a decrease in 1-year survival rate among the prenatally diagnosed infants compared with those postnatally diagnosed. Therefore, subsequent studies on the impact of prenatal echocardiography on survival rate should be performed on a larger population with serious structural defects, and focus to explore the significant factors affecting incidence and mortality, and clarify how prenatal diagnosis affects these factors.

Author contributions

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