

## Research Article

# Diagnosis of Neonatal Congenital Heart Disease: A Combination of Heart Murmur, SpO<sub>2</sub> Abnormality, Tachypnea, and Extracardiac Malformations

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Congenital heart disease (CHD) is one of the commonest congenital malformations that are mostly asymptomatic at birth, which challenges the diagnosis of neonatal CHD. An early accurate prenatal diagnosis will give parents a choice, as well as the opportunity to plan the delivery and improve the postnatal outcome. The purpose of the study is to evaluate the value of heart murmurs, SpO<sub>2</sub> abnormalities, tachypnea, and extracardiac malformations in screening neonatal CHD. All 4500 newborns in the obstetrics department of our hospital from January 2019 to January 2020 are selected as study subjects. Newborns were grouped according with the presence of heart murmurs, tachypnea, transdermal SpO<sub>2</sub> < 95%, and extracardiac malformations alone or in combination (≥3). Patients with murmur, tachypnea, and abnormal SpO<sub>2</sub> were assigned into group A, those with murmur, tachypnea, and extracardiac malformations into group B, those with murmurs, SpO<sub>2</sub>, and extracardiac malformations into group C, those with SpO<sub>2</sub>, tachypnea, and extracardiac malformations into group D, and those with all four into group E. The color echocardiography identified 65 children with CHD (1.4%) among the included 4,500 newborns. When murmur, tachypnea, abnormal SpO<sub>2</sub>, and extracardiac malformation were independently used to diagnose CHD, the sensitivity ranged from 30.68% to 51.26%, with specificity ranging from 47.36% to 82.65% and Youden's index (YI) ranging from 0.13 to 0.36. When murmur, tachypnea, abnormal SpO<sub>2</sub>, extracardiac malformation were together used to diagnose CHD, 91.23% sensitivity, 95.26 specificity, and 0.91 YI were observed. In conclusion, a combination of four indicators, murmur, tachypnea, abnormal SpO<sub>2</sub>, and extracardiac malformation yielded good performance in diagnosing neonatal CHD.

## 1. Backgrounds

Congenital heart disease (CHD) is a congenital malformation caused by the abnormal development of the heart and large blood vessels during the fetal period, which seriously endangers the lives and quality of life of children [1]. In China, the total prevalence of CHD at birth increases continuously over the past 40 years. Significant differences in sex, geographical regions, ethnicity, income levels, and monitoring models were witnessed [2, 3]. Despite advances in prenatal and newborn screening, it may present undiagnosed to the emergency department. CHD has variable signs and symptoms or is often nonspecific, which makes recognition and treatment challeng-

ing [4]. The concept of CHD is extensive, and some children with mild CHD do not need intervention and can heal naturally, but some severe children do not receive timely intervention and can be life threatening within a few days after birth [5]. So far, the great progress in the field of the diagnosis and treatment of CHD has been achieved. Noninvasive imaging diagnostic techniques, including echocardiography, magnetic resonance imaging and multislice spiral CT, has been developed, leading to more and more accurate diagnosis of CHD in the neonatal period [6]. Children with CHD, especially severe CHD, should be cured as soon as possible to restore their normal hemodynamics and provide the most basic guarantee for the development of important organs in children.

### 1.1. Theoretical Basis for Early Radical Cure

**1.1.1. Benefit to the Lungs.** The growth of the lungs in the first year after birth includes the development of new alveoli and pulmonary blood vessels, which reduces the pressure and flow of the pulmonary circulation to normal, so that the pulmonary vascular system will recover in the first year after birth. It can transform and develop normally.

**1.1.2. Benefit to the Brain.** The most serious sequela of children with critically ill CHD are hypoxic-ischemic brain damage and structural defects [7]. Studies have confirmed that children with bruising heart disease have up to 30% of the risk of brain hypoplasia during the fetal period [8]. The newborn's brain weighs about 350 grams, which is about a quarter of that of an adult. The human brain grows rapidly in the first year after birth. Therefore, the early cure of cardiovascular disease and the restoration of normal hemodynamic perfusion can contribute to the development and growth of the brain.

**1.1.3. Provide Protection: Reduce the Risk of Death.** The risk of the first-stage surgery in the neonatal period is significantly less than the risk of not being able to perform the first-stage surgery in the later period. The risk of the initial palliative surgery plus the second-stage radical surgery is much higher.

**1.1.4. Benefit to the Family.** Children with CHD are a huge family pressure. Parents always live in a place of great fear. Early radical treatment can enable parents to treat their children and live normally.

**1.1.5. Good for Society.** Early surgery can improve the quality of life of children, and the resources and costs required for staged surgery will greatly increase. Research data at home and abroad shows that for some complicated CHD, as well as early cases of severe cyanosis and cardiac insufficiency, if the diagnosis can be obtained in the neonatal period, it can provide more adequate opportunities and conditions for early intervention and give the necessary drug intervention and interventional therapy, or early surgical correction can significantly improve the prognosis of children and avoid death.

Recently, CHD screening has received an increasing attention. Some researchers focus on identification of molecular biomarkers for heart diseases [9, 10]. CHD presents distinct symptoms owing to conditions of different types of heart defects, including rapid heartbeat, shortness of breath, excessive sweating, fatigue, poor feeding, chest pain, blue tinge to the skin (cyanosis), and clubbed fingernails [11]. CHD develops shortly after birth and the symptoms do not develop until early childhood or teenage years. However, some complications may develop during adulthood such as the infections of the respiratory tract and lungs, heart infection, endocarditis, pulmonary hypertension, high blood pressure, and the heart failing to pump enough blood finally leading to a heart failure [12]. Therefore, early diagnosis of CHD and effective intervention can effectively increase the survival rate of births, improve the physical fitness of the

people, and reduce the burden on families and society. Herein, we explore the values of heart murmurs, SpO<sub>2</sub> abnormalities, tachypnea, and extracardiac malformations in the screening of neonatal CHD, in order to find a reliable and easy-to-promote screening method for neonatal CHD.

## 2. Materials and Methods

**2.1. Study Subjects.** All 4,500 newborns born in the Obstetrics Department of our hospital from January 2019 to January 2020 are initially enrolled into this retrospective study. Among these newborns, the male to female ratio is about 1.07:1, for 2326 and 2174 cases, respectively. The preterm to term newborn ratio is about 1.94:1, for 2970 and 1530 cases, respectively. The average gestational age at birth was  $39.21 \pm 1.23$  weeks, and the average birth weight was  $3236 \pm 324$  g. Newborns meeting the following inclusion criteria were included as eligible subjects: born in the Obstetrics Department of our hospital, regardless of gender; no death before discharge; birth weight of more than 1000 g or the gestational age of more than 28 weeks; the age ranging from 0.5 to 12 months; and an informed consent obtained from the guardian. Newborns were excluded from the study if they had been diagnosed with CHD before birth, their guardians were unwilling for newborn receiving the color Doppler echocardiography, and they were required for oxygen treatment. The study was approved by the Ethics Committee of our hospital.

**2.2. Subject Grouping.** Newborns with heart murmurs, tachypnea, transdermal SpO<sub>2</sub> < 95%, or differences between upper and lower extremities > 3% were classified as positive screening cases. Positive screening cases were arranged into the following groups: murmur group, tachypnea group, abnormal SpO<sub>2</sub> group, and extracardiac malformation group. Additionally, mixed groups where newborns with 3 or 4 positive indicators were set as follows: murmur, tachypnea, and abnormal SpO<sub>2</sub> are in group A; murmur, tachypnea, and extracardiac malformations are in group B; murmurs, abnormal SpO<sub>2</sub>, extracardiac malformations are in group C; SpO<sub>2</sub>, tachypnea, and extracardiac malformations are in group D; all four items are in group E.

**2.3. Echocardiography Examinations.** Cardiac sonographers performed echocardiography examinations to confirm the diagnosis of CHD among these 4,500 newborns. Newborns was lying from a supine to lateral position and their long axis of the left ventricle, apical four chamber, short axis of great artery, and suprasternal fossa were screened by echocardiography (iE33, Philips Healthcare, Hamburg, Germany).

**2.4. Examinations of Heart Murmur, Tachypnea, Abnormal SpO<sub>2</sub>, and Extracardiac Malformations.** All 4,500 newborns were screened by trained and qualified pediatricians and child health doctor to evaluate the presence of heart murmur, tachypnea, abnormal SpO<sub>2</sub>, and extracardiac malformations. The child health doctor was responsible for transcutaneous oxygen saturation measurement, and the pediatrician was responsible for cardiac auscultation to ensure that the results of transcutaneous oxygen saturation measurement

are accurate. Newborns with grade II at cardiac auscultation was considered positive for heart murmur [13]. Respiratory status was also assessed at cardiac auscultation and newborns with breathing frequency > 60 times/min, deep breathing, and irregular rhythm were considered positive for tachypnea [14]. Measurement of transcutaneous SpO<sub>2</sub> was performed on the transcutaneous oxygen saturation tester (RAD-5, Masimo Corp., Irvine, CA, USA). During the test, the child should be in a quiet state and the value of transcutaneous oxygen saturation should be stable for more than 3 s before recording the value to ensure the accuracy of the data. A right hand or any foot less than 95% was considered as positive for abnormal SpO<sub>2</sub> [15]. Each newborn will undergo color echocardiography within 3–7 days after birth to screen for extracardiac malformations [16]. Extracardiac malformations included central nervous system malformation, urinary system malformation, digestive system malformation, maxillofacial abnormality, visceral inversion, fetal edema, limb abnormality, respiratory system malformation, and abdominal wall abnormality. The color echocardiographic results will be the gold standard for CHD diagnosis, except for mild valve regurgitation.

**2.5. Statistical Analysis.** All data were processed by the SPSS 23.0 software. The counting data were described by ratio or percentage and analyzed by the chi-square test. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the diagnostic value. A level of  $P < 0.05$  was considered statistically significant.

### 3. Results

**3.1. CHD Detection Was Associated with Newborns' Month Old.** Among 4,500 newborns, 517 newborns were positive for heart murmur, tachypnea, abnormal SpO<sub>2</sub>, and/or extracardiac malformations. The positive rate was 11.5%. Among 517 newborns, there were 275 female newborns and 242 male newborns. Female newborns (275/2,174) showed a higher positive rate than male newborns (242/2,326). The difference was statistically significant ( $\chi^2 = 5.176$ ,  $P = 0.018$ ). Preterm newborns (398/2,970) showed a higher positive rate than term newborns (119/1,530). The difference was statistically significant ( $\chi^2 = 25.349$ ,  $P < 0.001$ ). These 517 newborns were screened by color echocardiography, and 65 newborns were identified with CHD (Table 1), mainly including 18 cases with ventricular septal defects, 12 cases with atrial septal defects, 8 cases with patent ductus arteriosus, and 8 cases with pulmonary valve stenosis. The incidence rate of CHD was 1.4%. Next, age-stratified analysis was performed to evaluate the association between detection rates of CHD and newborns' month old. As shown in Table 2, the incidence of CHD was correlated with newborns' month old ( $\chi^2 = 4.982$ ,  $P = 0.023$ ). Among 65 cases of CHD, there were 55 preterm newborns and 10 term newborns.

**3.2. Diagnostic Performance of Heart Murmur, Tachypnea, Abnormal SpO<sub>2</sub>, or Extracardiac Malformations for CHD.** Heart murmur, tachypnea, abnormal SpO<sub>2</sub>, or extracardiac malformations were separately used to diagnose CHD. As

TABLE 1: Types of 65 cases of CHD.

Type	Number (%)
Ventricular septal defect	18 (27.7%)
Atrial septal defect (diameter > 5 mm)	12 (18.5%)
Patent ductus arteriosus	8 (12.3%)
Pulmonary valve stenosis	8 (12.3%)
Atrioventricular septal defect	4 (6.2%)
Tricuspid atresia with ventricular septal defect	4 (6.2%)
Right ventricular double outlet	2 (3.1%)
Aortic stenosis	2 (3.1%)
Coarctation of the aorta	2 (3.1%)
Complete ectopic pulmonary venous drainage	3 (4.6%)
Mitral valve atresia	1 (1.5%)

TABLE 2: The month old of included newborns and positive rates for heart murmur, tachypnea, abnormal SpO<sub>2</sub>, and/or extracardiac malformations.

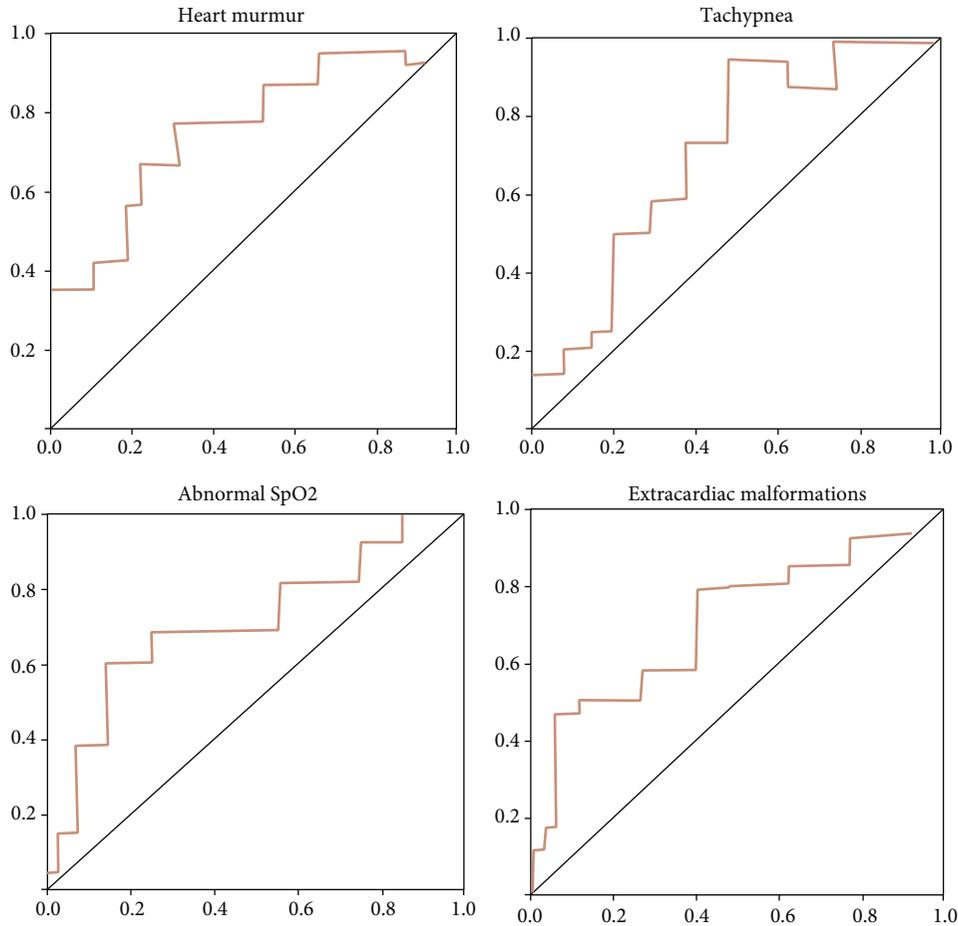
Age (month)	Total number	Positive number	Detection rate (%)
0–3	1980	42	2.1
4–6	1640	17	1.0
7–12	880	6	0.7
Total	4500	65	1.4

shown in Table 3, the sensitivity ranged from 30.68% to 51.26% and the specificity ranged from 47.36% to 82.65% and Youden's index ranged from 0.13 to 0.36. The AUC when heart murmur, tachypnea, abnormal SpO<sub>2</sub>, or extracardiac malformations were separately used to diagnose CHD ranged from 0.315 to 0.684, and the average AUC was 0.492 (Figure 1).

**3.3. Diagnostic Performance of Heart Murmur, Tachypnea, Abnormal SpO<sub>2</sub>, and Extracardiac Malformations in Combination for CHD.** Newborns positive for heart murmur, tachypnea, and abnormal SpO<sub>2</sub> are classified into group A. Newborns positive for murmur, tachypnea, and extracardiac malformations are classified into group B. Newborns positive for murmurs, abnormal SpO<sub>2</sub>, and extracardiac malformations are classified into group C. Newborns positive for SpO<sub>2</sub>, tachypnea, and extracardiac malformations are classified into group D. Newborns positive for four indicators are classified into group E. Heart murmur, tachypnea, abnormal SpO<sub>2</sub>, and extracardiac malformations in combination were used to diagnose CHD. As shown in Table 4 and Figure 2, the AUC (95% CI) of group A was 0.685 (0.514–0.759), with the sensitivity of 55.6% and the specificity of 89.65%; the AUC (95% CI) of group B was 0.714 (0.621–0.802), with the sensitivity of 81.6% and the specificity of 91.23%; the AUC (95% CI) of group C was 0.701 (0.638–0.798), with the sensitivity of 78.69% and the specificity of 89.65%; the AUC (95% CI) of group D was 0.723 (0.6435–0.814), with

TABLE 3: Diagnostic performance of heart murmur, tachypnea, abnormal SpO<sub>2</sub>, or extracardiac malformations alone for CHD.

Index	Murmur group	Tachypnea group	Abnormal SpO <sub>2</sub> group	Extracardiac malformation group
Sensitivity (%)	40.32	31.25	51.26	30.68
Specificity (%)	47.36	78.98	82.65	54.23
Youden's index	0.21	0.15	0.36	0.13

FIGURE 1: The AUC when heart murmur, tachypnea, abnormal SpO<sub>2</sub>, or extracardiac malformations were separately used to diagnose CHD.TABLE 4: Diagnostic performance of heart murmur, tachypnea, abnormal SpO<sub>2</sub>, and extracardiac malformations in combination for CHD.

Index	A group	B group	C group	D group	E group
Sensitivity (%)	71.6	55.6	62.39	68.65	91.23
Specificity (%)	89.65	91.23	89.65	94.68	95.26
Youden's index	0.57	0.71	0.75	0.65	0.91

the sensitivity of 68.65% and the specificity of 94.68%; the AUC (95% CI) of group E was 0.912 (0.841–0.987), with the sensitivity of 91.23% and the specificity of 95.26%. These results indicated that heart murmur, tachypnea, abnormal SpO<sub>2</sub>, and extracardiac malformations in combination yield a best diagnostic performance for CHD.

**3.4. Follow-Up Data.** Due to the particularity of childhood diseases in growth and development, some cases with mild CHD can heal naturally during the growth and development process. Follow-up was performed on 65 confirmed cases of cardiac color Doppler ultrasound after 3 months (Table 5). Among them, there were 18 patients with ventricular septal defect in the neonatal period. A total of 4 cases were perimembranous ventricular septal defects with a defect diameter < 5 mm, and they self-healed after 3 months, with a self-healing rate of 22.2%; of the 12 cases of atrial septal defect, 3 cases of atrial septal defect did not detect the shunt bundle again, indicating that septal defect healed spontaneously, with a self-healing rate of 25.0%; 8 patients with patent ductus arteriosus were detected, of which 3 were self-healing with a cure rate of 37.5%, and the self-healing rate of other types of patients was 22.2%.

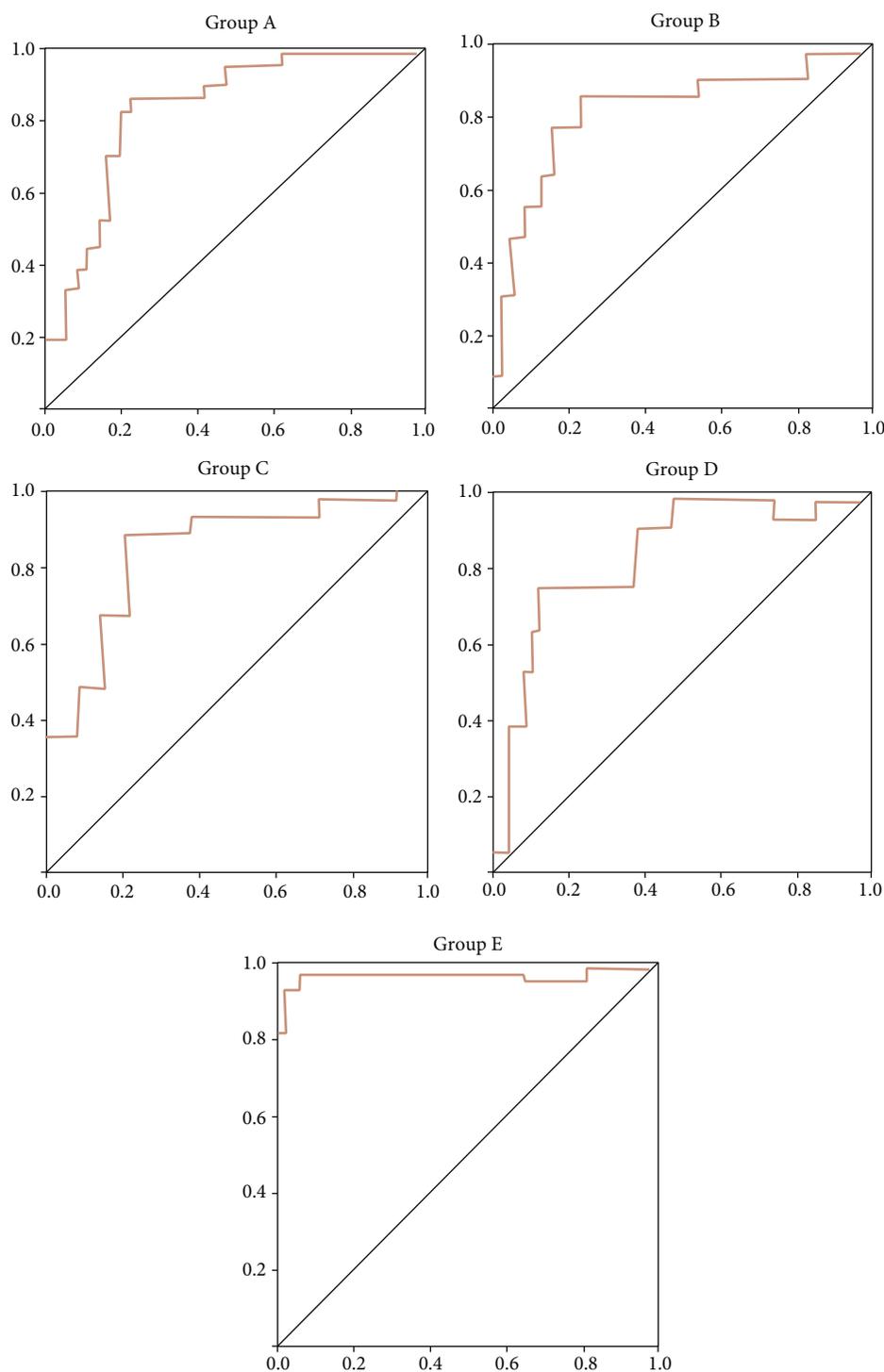


FIGURE 2: The AUC when heart murmur, tachypnea, abnormal SpO<sub>2</sub>, and extracardiac malformations were used in combination to diagnose CHD. Newborns positive for heart murmur, tachypnea, and abnormal SpO<sub>2</sub> are classified into group A. Newborns positive for murmur, tachypnea, and extracardiac malformations are classified into group B. Newborns positive for murmurs, abnormal SpO<sub>2</sub>, and extracardiac malformations are classified into group C. Newborns positive for SpO<sub>2</sub>, tachypnea, and extracardiac malformations are classified into group D. Newborns positive for four indicators are classified into group E.

#### 4. Discussion

CHD is a cardiovascular malformation caused by the abnormal development of the heart and blood vessels in the fetus. It is the most common heart disease in children. Foreign liter-

ature reports that the incidence of CHD is 9/1,000, most of which are mild or moderate CHD, do not require treatment, or only need post infant treatment [17]; among them, about 1/4 of children have CHD and need to be treated in infants. During the period, surgery or catheter intervention is

TABLE 5: Follow-up data after 3 months.

CHD classification	Neonatal period	After 3 months	Self-healing rate
Ventricular septal defect	18	14	22.2%
Atrial septal defect	12	9	25.0%
Patent ductus arteriosus	8	5	37.5%
Others	27	21	22.2%

required as soon as possible, most of which need to be treated in the neonatal period [1]. The incidence of congenital heart disease among newborns in my country in recent years is 7‰–8‰, and about 140,000 new children are newly diagnosed each year, accounting for the first birth defect in recent years. Among them, 60% die within one year of age and only 20% are actually treated. CHD is one of the important causes of neonatal death. Therefore, early screening of neonatal CCHD and early intervention and treatment can significantly reduce the occurrence of serious adverse consequences.

According to past experience, the diagnosis of critically ill congenital heart disease is mainly completed by prenatal ultrasound diagnosis and postnatal newborn physical examination, which makes up to 30% of infants not diagnosed with critically ill congenital heart disease before discharge from the hospital [18]. When these children return to the hospital with serious consequences of heart failure and shock, severe brain damage may occur during the period and some children may become disabled. At present, more and more institutions use transcutaneous oxygen saturation meters to screen for congenital heart disease. The United States will directly advocate that newborns receive pulse oximeters for early screening for CCHD, which will provide mature, noninvasive, and painless pulses. The oximeter screening is included in the routine monitoring of newborns to increase the detection rate of CCHD [19]. Murmur is an important sign of CHD and the main reason for CHD visits. Gum is more common in newborns, but it is mainly caused by accelerated blood flow and patent ductus arteriosus. Tachypnea in newborns can be manifested as rapid breathing rate, rhythm, strength, depth, and imbalance between inhalation and exhalation. SpO<sub>2</sub> is an important indicator of oxygen metabolism in the body. Normal neonates SpO<sub>2</sub> < 95% or difference between upper and lower limbs > 3% indicates hypoxia or abnormal blood shunting in the body, and cardiovascular disease should be watched out for. If the SpO<sub>2</sub> drop alone is more obvious, you should be wary of it being more critical CHD [20].

The test results showed that 4,500 newborns were screened by color echocardiography to identify 65 children with CHD and the preliminary statistics of the incidence of CHD were 1.4%. When murmur, tachypnea, abnormal SpO<sub>2</sub>, and extracardiac malformation were independently used to diagnose CHD, the sensitivity ranged from 30.68% to 51.26%, with specificity ranging from 47.36% to 82.65% and Youden's index (YI) ranging from 0.13 to 0.36. Com-

pared with the individual screening index, the related evaluation of the mixed group is relatively ideal, with a sensitivity of 89.36 and a specificity of 90.36%. When murmur, tachypnea, abnormal SpO<sub>2</sub>, extracardiac malformation were together used to diagnose CHD, 91.23% sensitivity, 95.26 specificity, and 0.91 YI were observed, suggesting that the use of the four mixed indicators for screening has better curative effects and is worthy of clinical promotion.

Due to the particularity of childhood diseases in growth and development, some mild congenital heart diseases can heal naturally during the growth and development process. Follow-up on confirmed cases of cardiac color Doppler ultrasound after 3 months was done. Among them, there were 18 patients with ventricular septal defect in the neonatal period and 4 patients healed themselves after 3 months, with a self-healing rate of 22.2%; of the 18 patients with atrial septal defect, 3 cases of atrial septal defect did not detect the shunt again, indicating that atrial septal defect healed spontaneously, with a self-healing rate of 25.0%; 8 patients with patent ductus arteriosus were detected, of which 3 were self-healing with a cure rate of 37.5% and the self-healing rate of other types of patients was 22.2%.

The above data show that the combined screening of 4 indicators including murmur, SpO<sub>2</sub> abnormality, tachypnea, and extracardiac malformations has better results and is worthy of clinical promotion.

## Data Availability

The data used to support the findings of this study are included within the article.

## Conflicts of Interest

All authors declare that they have no conflict of interest.

## Authors' Contributions

Kai Chen and Jiao Wang contributed equally to this work.

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