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Screening Tools for Diagnosis of Congenital Heart Diseases in New born Infants

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ABSTRACT
Congenital heart disease (CHD) is a common heart disease, which can be caused by the abnormal development of the heart and blood vessels during embryonic development, or the failure of related channels to close after birth, and it ranks first among all birth defects. There are many types of CHD. Early detection of CHD improves patient outcomes in relation to both morbidity and mortality. screening tests for CHD identification include prenatal ultrasonography and postnatal clinical examination of neonates. screening tool are Pulse oximetry, heart auscultation and echocardiography. Pulse oximetry is a promising alternative newborn screening strategy but further evaluation is needed to obtain more precise estimates of test performance and to inform optimal timing, diagnostic and management strategies.
This review article aims to assess the value of clinical evaluation, Oxygen saturation & blood pressure of four limbs and Echocardiography in early detection of congenital heart diseases.

Keywords: Oxygen, screening, CHD, review

INTRODUCTION

Congenital heart disease (CHD) is a common heart disease, which can be caused by the abnormal development of the heart and blood vessels during embryonic development, or the failure of related channels to close after birth, and it ranks first among all birth defects.(1) There are many types of CHD, the most common being ventricular septal defect, atrial septal defect, patent ductus arteriosus, pulmonary artery stenosis, coarctation of the aorta, tetralogy of Fallot, and complete transposition of the great arteries.The prevalence of congenital heart defects (CHDs) is around 7-9 per1000 live births(2).
The majority ofpatients with CHD fail to be diagnosed atthe early stages after birth (3, 4)usually asymptomatic at birth and some of them were recognized in 25% of living infants after discharge(5).This preventsinfants from receiving effective surgicalrepair or palliation in a timely fashion(6).Early detection of CHD improves patient outcomes in relation to both morbidity and mortality. Key screening tests for CHD identification include prenatal ultrasonography and postnatal clinical examination of neonates(5).
Pulse oximetry has been recommended as a reliable screening tool of CHD for newborns in a number of developed countries(7, 8) and can improve detection of CHDs to around 75–90%(9).Currently, measuring the difference in blood oxygen saturation (SpO2) in zones of blood supply above and below the open arterial duct has been proposed forearly diagnosis of asymptomatic CHD(10).
In addition, heart auscultation and echocardiography still play an important role indiagnosing CHD(11, 12).ECHO has become thegold standard for diagnosis of CHD in pediatric patientwith cardiac murmurs and its use has expanded with advances in technology(13).

Congenital heart disease

Congenital heart disease (CHD) is the most common birth defect, affecting nearly 1% of all live births. CHD encompasses a wide spectrum of defects from simple malformations with a favourable prognosis to more complex and severe lesions that require multiple catheter-based or surgical interventions with uncertain long-term outcomes. Although CHD remains a leading cause of morbidity and mortality in childhood, the population of adults with CHD is dramatically expanding. Now, more than 90% of children with CHD survive into adulthood due to significant advances in disease recognition and improved medical and surgical management across the lifespan (14).

Therefore, understanding the genomic architecture of CHD is increasingly clinically important. While there have been significant advances in the elucidation of the genetic etiologies for other forms of inherited cardiac disease such as cardiomyopathy and arrhythmias, it has only been with the increased understanding of the molecular pathways regulating cardiovascular development over the past couple of decades that the genetic basis of CHD has become more defined[15]. However, the detailed genetic architecture of CHD and how disruption of these underlying regulatory mechanisms result in the spectrum of CHD phenotypes is actively being investigated[16].

While numerous genes have been discovered to be implicated in the pathogenesis of syndromic CHD, the identification of the genetic contributors of non-syndromic CHD is more challenging due to genetic heterogeneity, incomplete segregation and potentially oligogenic or polygenic origins. The initial discoveries of disease-causing genes were primarily restricted to milder forms of CHD in non-syndromic and syndromic cases by using linkage analysis to study large families with autosomal dominant disease or by targeted sequencing of candidate genes in affected populations. Remarkable advances in genetic sequencing technologies, such as massively parallel or next-generation sequencing (NGS) have enabled the discovery of rare variants in new candidate genes that are likely contributing to non-syndromic CHD [17].

Although in vivo and in vitro genetic models have allowed for assessment of the potential functional deficits of specific variants on gene function, these sequencing studies still have practical challenges in establishing pathogenicity of identified variants. Recent advances in powerful new technologies known as single-cell RNA sequencing (scRNA-seq) have facilitated the discovery of the role of individual cells during cardiac development and pathogenic mechanisms by which small subset of cells affected by genetic mutations lead to cardiac malformations [18].

- **Epidemiology**

The birth prevalence of heart defects has increased dramatically over the past few decades, as it is now 9 for every 1000 live births, whereas previous reports indicated that there was only 1 for every 1000 births in 1930. Because the yearly number of births across the globe is approximately 150 million births, this equates to 1.35 million live births each year that are affected by CHD. In light of this, it is the duty of the health system to work toward minimizing the incidence of heart defects. This emergence in birth prevalence might not actually represent a true upsurge; rather, it might be the result of advances in diagnostic and screening technology[19].

Additionally, advancements in the field of surgery have contributed significantly to the dramatic rise in the patient survival rate and life expectancy. Due to the variety of approaches taken by epidemiologists, it is challenging to access and evaluate data on birth prevalence by region. In developing nations in particular, there may be a substantial sampling bias due to regional variations in healthcare availability and quality.Although CHD is on the rise across all age groups, from children to adults, more adults are affected by the disease because a more severe form of CHD is more common in adults. A new phenomenon, adult congenital heart disease, has emerged as a direct result of the improved care given to CHD patients from birth [20].

- **Etiology**

Both environmental and genetic factors play a role in the development of congenital heart disease.Common environmental influences include maternal health conditions such as diabetes, rubella, and systemic lupus erythematosus, as well as the use of certain teratogenic medications like lithium, isotretinoin, and antiseizure drugs. Maternal age is a known risk factor for genetic conditions like Down syndrome, which can include heart defects. However, it is still unclear if maternal age alone increases the risk of congenital heart disease. Paternal age might also be a contributing factor[21].

Certain chromosomal anomalies, such as trisomy 21 (Down syndrome), trisomy 18, trisomy 13, and monosomy X (Turner syndrome), are closely linked to congenital heart disease, though they only account for about 5 to 6% of all cases[22].

Many other cases involve subchromosomal deletions (microdeletions), duplications, or single-gene mutations. These genetic alterations often result in syndromes that impact multiple organs, including the heart. Examples include DiGeorge syndrome, which is linked to a microdeletion on chromosome 22q11.2, and Williams syndrome, associated with a microdeletion on chromosome 7p11.23. Mutations in specific genes like fibrillin-1 (Marfan syndrome), TBX5 (Holt-Oram syndrome), and PTPN11 (Noonan syndrome) are also known to cause congenital heart defects, either as part of a syndrome or as isolated (non-syndromic) defects. In about 72% of congenital heart disease cases, no genetic cause can be identified[16].

- **Pathophysiology of congenital heart anomalies**

Congenital heart defects (CHD) identified at birth are categorized into three levels of severity: mild, moderate, and severe. Severe CHD encompasses conditions such as large ventricular septal defect (VSD), large patent ductus arteriosus (PDA), critical aortic stenosis (AS), critical pulmonary stenosis (PS), critical coarctation of the aorta, and atrioventricular septal defect (AVSD). These defects typically require immediate medical

intervention. On the other hand, moderate CHD, including conditions such as mild to moderate aortic or pulmonary stenosis, non-critical coarctation of the aorta, and large atrial septal defect (ASD), generally requires less intensive treatment. Mild CHD, exemplified by small ASD, PS, PDA, or mild AS, often resolves spontaneously and is usually asymptomatic[23].

Congenital heart disease (CHD) can be classified into non-cyanotic and cyanotic forms, with the cyanotic type also known as critical congenital heart disease (CCHD). CCHD can be further divided into three categories: obstructive lesions of the right heart, obstructive lesions of the left heart, and lesions involving the mixing of blood **(Table 1)**[24, 25].

Table 1: Classification of congenital heart diseases [26]

Classification	Examples
Acyanotic	
Left to right shunt	Ventricular septal defect Atrial septal defect Patent ductus arteriosus Atrioventricular septal defect
Obstructive	Pulmonic stenosis Aortic stenosis Aortic coarctation Hypoplastic left heart syndrome
Cyanotic	
	Tetralogy of Fallot Transposition of the great arteries Tricuspid atresia Pulmonary atresia Persistent truncus arteriosus Total anomalous pulmonary venous return

- **Clinical presentation**

Neonates with CHD might present with symptoms like feeding difficulties, rapid breathing, cyanosis, cardiovascular collapse, or congestive heart failure, often in combination. While some infants may have isolated heart defects, many exhibits multiple abnormalities [27].Many patients with congenital heart defects (CHD) experience severe complications such as hypoxia, cardiac dysfunction, and pneumonia, often due to delays in diagnosis and management. Early detection and intervention, ideally before symptoms arise, can significantly improve outcomes and potentially save infants with critical and severe CHD by preventing the progression of their condition [28]

- **Diagnosis**

For a newborn suspected of having critical CHD, the initial evaluation includes[29]:

1) A detailed physical examination.
2) Measurement of blood pressures in all four limbs.
3) Assessment of preductal and post-ductal oxygen saturations, a hyperoxia test.
4) Chest x-ray**.**
5) Echocardiography is usually sufficient for diagnosis, but in some situations, cardiac MRI or CT angiography can offer more detailed anatomical information.

Three levels of prevention and treatment exist for congenital heart disease (CHD): preventing the fundamental cause, diagnosing and intervening during pregnancy, and treating the condition after delivery**[30]**.Currently, screening for critical congenital heart disease (CCHD) in newborns is a standard practice, though this was not always the case. In 2011, CCHD screening was incorporated into the U.S. Recommended Uniform Screening Panel (RUSP), and within the following four years, nearly all states adopted this recommendation[31].

- **Screening**

Congenital heart disease in neonates can sometimes present with subtle or no symptoms. If critical congenital heart disease is not detected early, especially in the 10 to 15%dia of neonates who need immediate surgical or medical treatment, it can result in neonatal mortality or serious health issues. Therefore, universal screening for critical congenital heart disease using pulse oximetry is advised for all newborns before they are discharged from the hospital[32].

This screening should be conducted when infants are at least 24 hours old and is considered positive if any of the following criteria are met[32]:

1) Any oxygen saturation reading is below 90%.

2) Oxygen saturation in both the right hand and foot is below 95% in three separate measurements taken one hour apart.
3) There is more than a 3% absolute difference between the oxygen saturation in the right hand (preductal) and the foot (post-ductal) in three separate, paired measurements taken one hour apart.
4) Neonates who have a positive result from the screening should receive a thorough evaluation to identify congenital heart disease or other causes of low oxygen levels, such as respiratory issues, central nervous system problems, or sepsis. This evaluation typically involves a chest X-ray, ECG, echocardiography, and sometimes blood tests. Pulse oximetry screening has a sensitivity of just over 75%, with left heart obstructive lesions (like coarctation of the aorta) being the most frequently missed congenital heart defects.

- **Prenatal screening**

In the prenatal period, ultrasound exams and nuchal translucency (NT) measurements are valuable for screening congenital heart disease (CHD). NT is an ultrasound test conducted in the first trimester, between 18 and 20 weeks of gestation, to assess the amount of fluid behind the fetus's neck. Elevated fluid levels detected by this test can indicate an increased risk of chromosomal, genetic, or fetal abnormalities[33].

The early fetal anomaly scan (EFAS) is a detailed ultrasound examination designed to detect structural abnormalities in the fetus, typically performed between 18 and 21 weeks of gestation. However, there is ongoing discussion about the most appropriate timing and the accuracy of NT measurements and EFAS screening in relation to gestational age. When the NT and EFAS screenings were conducted at 12 and 18 weeks, they identified 11% and 15% of CHD cases, respectively, without a statistically significant difference in detection rates between these two time points. A first-trimester anomaly scan can identify 55.80% of cardiac anomalies in low-risk populations and 67.74% in high-risk populations[34].

Routine fetal echocardiograms are conducted during the prenatal period to screen for heart disease,these echocardiograms can be performed using either a transabdominal or endovaginal approach. According to data from tertiary neonatal centres, prenatal echocardiography can detect 85–95% of major congenital heart diseases (CHDs)[35].

The success of prenatal detection of CCHD depends on several factors, including the quality of available technology, the skill level of the sonographer (since detecting CCHD requires more specialized experience than standard prenatal scans), and the accessibility of screening services, which can be affected by location and costs. Prenatal diagnosis and newborn screening are essential for early detection of CCHD, with prenatal diagnosis offering the advantage of allowing for more careful planning and coordination with families and care providers [36].

Clinical examinations in the early days of life have a sensitivity of less than 50% for detecting critical congenital heart disease (CCHD), likely due to a "diagnostic gap" that arises from the delayed transition from fetal to neonatal circulation. To address this gap, pulse oximetry screening has been suggested as a complementary method[37]. However, it is important to note that this screening does not replace the need for a thorough clinical examination. Even the slightest cyanosis, often paired with tachypnea, the primary symptomcan be identified by observant parents and should be carefully evaluated[38]

- **Cardiac auscultation**

While ultrasound remains the primary method for diagnosing congenital heart disease (CHD), auscultation of heart sounds is also a valuable tool for diagnosis and screening. Stethoscope-based auscultation is non-invasive and doesn't require costly equipment, making it especially beneficial in regions with limited medical resources and economic challenges[39]. However, auscultation depends heavily on the cardiologist's subjective experience, leading to significant variability in diagnoses among different practitioners. As a result, developing computer-assisted auscultation algorithms and systems is essential for more accurate CHD detection. Such technology not only enhances screening and diagnosis but also serves as a valuable tool for retrospective analysis and clinical education[39].

The heart and lungs should be assessed when the infant is calm and quiet, the clinician listens for the loudest heart sounds to check for dextrocardia, a normal heart rate ranges from 100 to 160 beats per minute, and the rhythm should be steady, although slight irregularities due to early contractions are possible. A murmur detected in the first 24 hours is often due to a patent ductus arteriosus, which typically resolves within three days, as confirmed by daily heart exams.Femoral pulses are compared with brachial pulse. A weak or delayed femoral pulse may signal aortic coarctation or another blockage in the left ventricular outflow tract. Central cyanosis may indicate congenital heart disease, lung problems, or sepsis[40].

To evaluate the respiratory system, the clinician should count the infant's breaths for a full minute, as newborns often have irregular breathing patterns; the normal rate is 40 to 60 breaths per minute. The chest should be inspected for symmetry, and lung sounds should be equal on both sides. Signs of respiratory distress include grunting, flaring nostrils, and chest retractions [41].

- **Murmurs**

Left-to-right shunts and obstructive lesions often produce systolic murmurs. The intensity of these murmurs and any associated thrills is usually greatest near their source, which helps in diagnosing the condition. An increased flow through the pulmonary or aortic valves creates a midsystolic crescendo-decrescendo (ejection systolic) murmur. Conversely, regurgitant flow through an atrioventricular valve or through a ventricular septal defect leads to a holosystolic (pansystolic) murmur that tends to mask the first heart sound (S1) as its intensity rises [(42)].
A patent ductus arteriosus usually produces a continuous murmur that persists throughout both systole and diastole because blood flows through the ductus during both phases. This murmur has a two-toned quality, being louder during systole due to higher pressure and quieter during diastole. Other physical examination findings might include symptoms of circulatory shock, poor blood flow, and abnormal heart sounds. These can manifest as a single or widely split-second heart sound (S2), a systolic click, a gallop rhythm, or an irregular heart rate that may be too slow or too fast [(43)].

- **Pulse oximetry**

Pulse oximetry screening is a cost-effective and non-invasive method for detecting CHD. It is capable of identifying 50–70% of CHDs that were previously undiagnosed [(31)].

- **Principles of operation and limitations**

The Beer–Lambert–Bouguer law explains how light is diminished as it passes through materials, Oxygenated blood primarily absorbs red light at a wavelength of 660 nm, while deoxygenated blood absorbs light in the infrared range at 940 nm[(44)]. To calculate oxygen saturation, calibration algorithms analyse signals from both non-pulsatile sources (such as venous and capillary blood, bone, and skin) and pulsatile arterial blood flow at the specified red and infrared wavelengths. A microprocessor filters out the constant signal from non-pulsatile tissues, leaving only the pulsatile arterial signal, which is then shown as a plethysmography waveform on the pulse oximeter display[(45)].
To use pulse oximetry safely, it's important to understand its limitations. Several factors can introduce errors, especially in neonates, leading to inaccurate readings. These factors include movement artifacts, poor blood flow or cold skin at the measurement site, irregular heart rhythms, ambient light, phototherapy or electromagnetic interference, skin pigmentation, jaundice, incorrect probe placement (penumbra effect), venous pulsations, intravenous dyes, and the presence of abnormal hemoglobin molecules[(46)].
Pulse oximetry is widely used in various aspects of newborn care, from resuscitating newborns in the delivery room to routine monitoring in the operating room. A study explored the normal oxygen saturation ranges in full-term newborns during their first days of life. A study assessed normal oximetry readings at sea level, from the time of admission to the newborn nursery until discharge. Variables such as the newborn's sex, gestational age, birth weight, mode of delivery, Apgar scores, pre- or postductal measurement site, and the infant's status during measurement (sleeping, quiet, or crying) were also considered. Measurements were taken at admission, 24 hours of life, and at discharge. The average oxygen saturation was 97.2% ± 1.6%. The study found a slight increase in oxygen saturation over time for both the right hand (preductal) and right foot (postductal), with postnatal age and the infant's activity being the only variables showing a statistically significant rise[(47)].
With an average pulse oximetry reading of 97.2% in newborns during their first few days, pulse oximetry is a valuable tool for identifying subtle signs of low oxygen levels, especially in newborns with certain congenital heart defects (CHD). These defects, including transposition of the great arteries, truncus arteriosus communis, hypoplastic left heart syndrome, total anomalous pulmonary venous connection, tricuspid atresia, tetralogy of Fallot, and pulmonary atresia, often cause reduced oxygen levels soon after birth. If these conditions are not detected early, they can lead to serious health issues or even death[(48)].
The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) identified these seven CHDs as critical targets for pulse oximetry screening in newborns, based on expert advice.By 2011, SACHDNC, along with the American Academy of Pediatrics, the American College of Cardiology Foundation, and the American Heart Association, formed a group to develop guidelines for using pulse oximetry to screen newborns for CHD;afteranalysing data from large studies in Sweden and the UK, the group created a screening protocol that involves measuring oxygen saturation in the right hand (preductal) and one foot (postductal). According to the SACHDNC guidelines, a newborn would fail the screening if, at 24 hours or later[(49)]:

1) The oxygen saturation is less than 90% in either the right hand or foot.
2) The oxygen saturation is less than 95% in both the right hand and foot on three separate checks taken one hour apart.
3) There is a consistent difference of more than 3% between the oxygen saturation readings of the right hand and foot on three separate checks taken one hour apart.

If an infant has an oxygen saturation of 95% or higher in either the right hand or foot, with a difference of 3% or less between the preductal (right hand) and postductal (foot) readings, the screening is considered negative, and

no further evaluation is required. Many states that have implemented pulse oximetry screening have adopted this protocol or a modified version of it[50].

Not all congenital heart defects (CHDs) present with hypoxemia, yet early detection is crucial to prevent severe complications and end-organ damage. Among CHDs, left-sided obstructive lesions are particularly prevalent. Emerging diagnostic technologies, such as the peripheral perfusion index (PPI), hold promise for improving early detection. PPI, available in some advanced pulse oximeters, quantifies the ratio of pulsatile to nonpulsatile components in the pulse oximetry signal. This measurement helps evaluate changes in arterial perfusion at the site of measurement, potentially identifying lesions that might not be detected through standard oxygen saturation screening alone[51].

Pulse oximetry can identify hypoxemic, non-cardiac conditions, facilitating earlier detection and treatment in asymptomatic newborns. However, acyanotic congenital heart diseases (CHDs), such as tetralogy of Fallot (TOF), ventricular septal defect (VSD), and coarctation of the aorta (CoA), may not be detected by pulse oximetry screening[52]. Oxygen saturation levels can fluctuate considerably during the first 24 hours of life, which can lead to false-positive results[53]

It is essential to determine the optimal timing for conducting screenings, particularly for infants discharged from the hospital before 24 hours of age. Healthcare providers measure oxygen saturation at two sites: the right hand for pre-ductal saturation and the right foot for post-ductal saturation. Assessing post-ductal saturation is important for detecting right-to-left shunting of poorly oxygenated blood through the ductus arteriosus (DA), which may indicate potential structural defects. Although specific guidelines may differ between facilities and policies, a saturation level below 95% is considered abnormal and necessitates an echocardiogram for further evaluation. Early diagnosis of congenital heart disease (CHD) through pulse oximetry screening enhances quality-adjusted life years for infants, reduces illness-related years lost, minimizes unnecessary healthcare visits, shortens hospital stays, and lowers mortality risk by preventing the extension of hypoxic conditions[54]

Critical Congenital Heart Disease (CCHD) in newborns often presents with symptoms such as shock, cyanosis, or respiratory distress, which can be easily confused with other neonatal conditions. Missing an early diagnosis can lead to severe outcomes, including sudden cardiovascular collapse and even death. Pulse oximetry screening is an effective tool for differentiating between newborns with CCHD and those with other potentially life-threatening hypoxemic conditions. When echocardiography is not feasible, it is crucial to initiate treatment with continuous prostaglandin E1 (PGE1) infusion in any newborn who shows signs of deterioration within the first few days of life**(Figure 1-Figure 2)**[55].

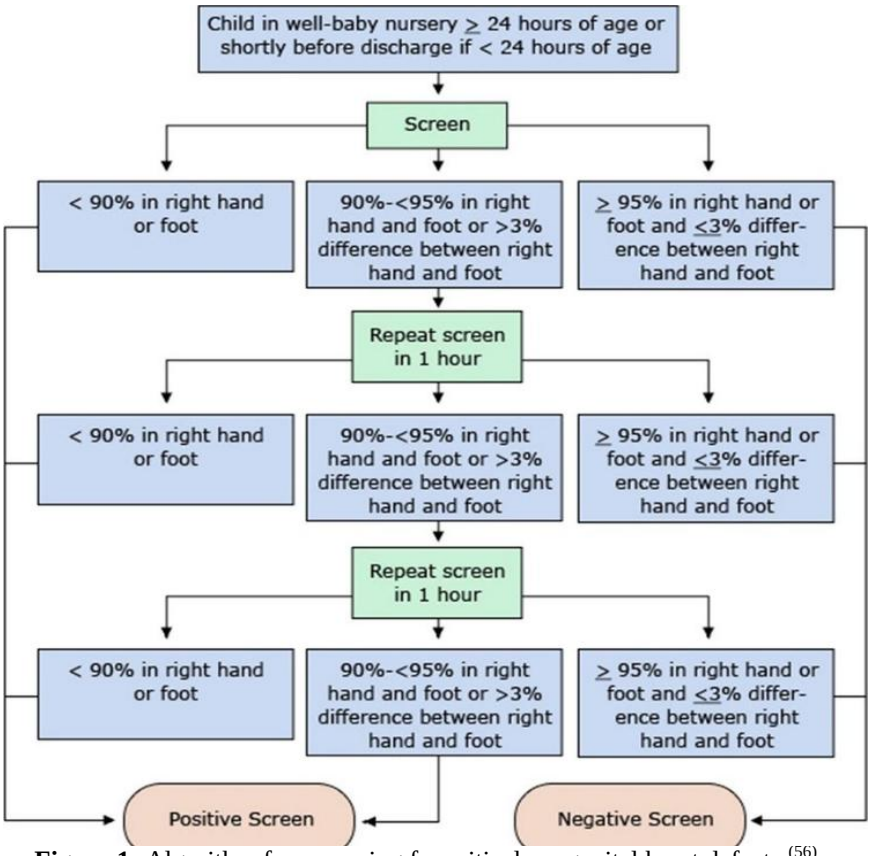

Figure 1: Algorithm for screening for critical congenital heart defects [56]

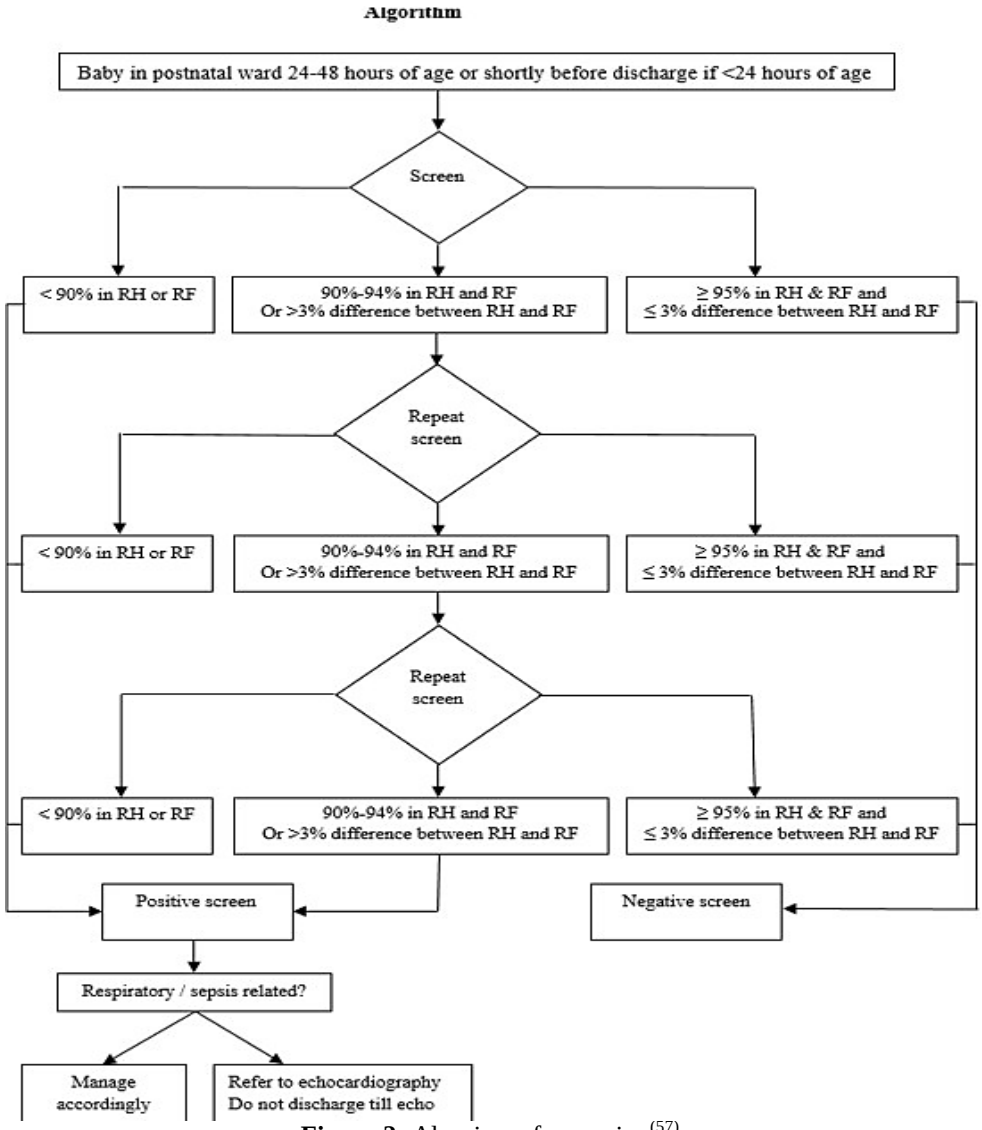

Figure 2: Algorism of screening[57]

- **Echocardiography**

Echocardiography, particularly when conducted by pediatric cardiologists, is widely utilized for diagnosing congenital heart disease (CHD) and can be more effective in detecting critical congenital heart disease (CCHD) in newborns with greater sensitivity compared to other screening methods [58]. The sensitivity of prenatal echocardiography for detecting CHD is 60.3% in the first trimester, 60.9% in the second trimester, and 77.4% in the third trimester. For CHD diagnosis, prenatal echocardiograms have a sensitivity of 45.4% in low-risk pregnancies and 85.1% in high-risk pregnancies [59]. Echocardiography, with the use of Doppler and color Doppler, has emerged as the primary diagnostic tool for CHD and reduces the need for invasive procedures such as cardiac catheterization [29].

Echocardiography is a crucial tool in diagnosing congenital heart disease (CHD) due to its widespread availability, portability, safety, and user-friendliness. It enables detailed anatomical assessment, hemodynamic evaluation, and outcome measurement. The echocardiographic techniques encompass 2-dimensional (2D) imaging, color flow Doppler (CFD), Doppler-tissue imaging (DTI), pulse wave Doppler (PWD), agitated saline studies, ultrasound-enhancing agents, stress echocardiography, and transesophageal echocardiography (TEE). Over the past decade, advancements in digital signal processing have introduced harmonic imaging, 4-dimensional (4D) imaging, and speckle tracking echocardiography, enhancing the diagnostic capabilities of this modality[60].

- **2D and Doppler echocardiography**

When assessing a patient with adult congenital heart disease (ACHD), 2D echocardiography (2DE) is often the most cost-effective and easily accessible test. It effectively identifies congenital anomalies and associated complications while minimizing the patient's exposure to radiation[60].

- **Contrast echocardiography**

Advancements in contrast echocardiography have resulted in the creation of contrast agents featuring a heavier gas molecule at their core. This innovation has significantly enhanced the stability of these agents within the bloodstream, improving the quality of imaging and diagnostic accuracy[61].

- **Stress echocardiography**

Stress echocardiography is primarily used to assess ischemia. The common stress protocols include exercise-induced stress using a treadmill or bicycle, pharmacological stress with agents like dobutamine, and symptom-limited tests such as the Master two-step test[62].

- **4D echocardiography**

Echocardiography has seen significant advancements over the past few decades, evolving from M-mode imaging to 2D imaging and Doppler echocardiography, and further expanding into 3D and 4D echocardiography (4DE)[60].

- **Treatment**

Treatment for heart failure involves several approaches, including[63]:

1) Medical stabilization: This may involve using diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, digoxin, spironolactone, salt restriction, and, in some cases, supplemental oxygen or prostaglandin E1.
2) Surgical or transcatheter interventions: These are needed to address the underlying issue and usually follow the stabilization of acute symptoms or cyanosis. However, certain conditions like ventricular septal defects that may close over time or mild valve dysfunction might not require immediate surgical intervention.

Transcatheter procedures include[64]

1) Balloon atrial septostomy: Used to palliate severely cyanotic neonates with transposition of the great arteries.
2) Balloon dilation: Performed for severe aortic or pulmonic valve stenosis.
3) Transcatheter closure: For cardiac shunts, such as atrial septal defects or patent ductus arteriosus.
4) Transcatheter placement: Insertion of a pulmonary valve.
5) Balloon dilation: With or without stenting of vascular stenoses, commonly used for pulmonary artery stenosis.

Treatment often includes using a diuretic, such as furosemide, administered at 0.5 to 1 mg/kg IV or 1 to 3 mg/kg orally every 8 to 24 hours, with dosage adjustments as needed. An ACE inhibitor like captopril, given at 0.1 to 0.3 mg/kg orally three times daily, is also commonly used. Potassium-sparing diuretics like spironolactone (1 mg/kg orally once or twice daily, with potential increases up to 2 mg/kg per dose) may be beneficial, especially if high doses of furosemide are needed. For children with chronic congestive heart failure, beta-blockers such as carvedilol or metoprolol are frequently added. Newer heart failure medications used in adults, including sacubitril/valsartan and sodium-glucose cotransporter-2 (SGLT-2) inhibitors, may also be helpful, but data on their effectiveness in pediatric patients are limited[65].

Digoxin is less commonly used now, but it may still be beneficial for children with heart failure, particularly those with large left-to-right shunts or certain postoperative conditions related to congenital heart disease. Dosage varies by age (refer to the Oral Digoxin Dosage in Children table). Notably, digoxin has been shown to reduce mortality in single-ventricle patients after the Norwood procedure and before the second-stage surgery[66]However, the use of digoxin as a first-line treatment for neonatal supraventricular tachycardia has decreased, as it is associated with higher mortality compared to propranolol[67]

Comparison between different diagnostic tools

- **Auscultation and echocardiography**

Auscultation of the heart is one of the most important tools of physical examination in neonates, which is very helpful in the diagnosis or rejection of congenital heart diseases (CHDs). A previous study was conducted within the period of 18 months on neonates hospitalized in neonatal unit whose heart murmur, diagnosed through examination, and echocardiography was conducted to investigate the existence of CHD. A total of 14.5% of the hospitalized neonates suffered from innocent murmur, and the rest with heart murmur had abnormal echocardiography and suffered from CHD (85.5%). Heart murmur in neonates could be a symptom of CHD, and timely echocardiography is very important in diagnosing the type of disease[68].

Only 25% of patients had innocent heart murmur; most were secondary to pulmonary artery branch stenosis or tricuspid regurgitation (TR). The most common murmur diagnosis in the neonatal intensive care unit was VSD in contrast with Geggel report in a similar study. In older children and infants, clinical cardiovascular examination is a very accurate and sensitive method of screening for the underlying heart disease, and

echocardiogram is less likely to reveal clinically unsuspected heart disease. This condition did not hold true in neonates with heart murmur, in whom echocardiography is important whenever CHD is suspected[69].
It was showed that in a neonatal tertiary care center, the sensitivity of clinical examination alone in detection of pathological murmurs by a neonatologist and cardiologist was only 78 and 83%, respectively, whereas both groups' accuracy (neonatologists and cardiologists' groups) in detection of innocent murmurs was unsatisfactory. This supports the fact that echocardiography has drastically improved the accuracy of neonate's diagnosis of CHD, and it is a good tool in neonates with heart murmur evaluation[70].
Previous studies have assessed the diagnostic accuracy of pediatricians' clinical auscultation skills to assess murmurs in children and cardiac simulators. It was concluded that general pediatricians were good at diagnosing innocent murmurs, whereas a study concluded that pediatric cardiologists have excellent diagnostic accuracy. However, previous study showed that pediatric residents had only 33% diagnostic accuracy. It was showed that the sensitivity of the senior house officer's examination to assess the clinical significance of the neonatal murmur was 71% and the specificity was 91%; the positive predictive value was 71% and the negative predictive value was 91%. Echocardiogram is still needed to reach the accurate diagnosis of CHD in neonates even if a pediatric cardiologist is consulted[71].
Heart murmur is one of the clinical symptoms that imply CHD in neonates. Therefore, it is important to pay special attention to heart sound auscultation in neonates, although innocent and pathologic murmur could not be distinguished from each other only through auscultation. Since 85.5% of the hospitalized neonates suffered from pathologic murmur, conducting timely echocardiography by experienced pediatric cardiologist is necessary for the diagnosis of this type of heart defect and deciding about the type of treatment to be considered[68].

- **POX and auscultation**

Pulse oximetry (POX) is easy to operate and requires only 2 to 3 minutes to analyze the results. Besides, POX as an adjunct to current routine practice is likely to be a cost-effective strategy in the light of currently accepted thresholds. It is highly specific in detecting CCHD with moderate sensitivity, and had been widely employed [72].As a large maternal and child healthcare facility, the studied hospital delivers more than 20,000 babies annually. Providing quick, convenient, and accurate screening tools for CHD detection among newborns are crucial for the local community in the absence of echocardiologist. Since 2018, this health center implemented a new strategy of combined auscultation and POX in CHD screening among newborns. When suspected CHD babies are identified by POX or auscultation, an echocardiography was requested for confirmation[73].
The most intriguing finding in this clinical evaluation was that there was no overlap of CHD spectrums between POX detection and auscultation detection. In contrast to common CHDs detected by auscultation, POX-detected CHDs were rare and critical, including COA, CTA, PAPVC, TAPVC, TGA, and TOF, which were consistent with the primary and second target lesions presenting at least mild hypoxemia during the neonatal period [46].Cardiac auscultation detected the majority of CHD (95.6%) cases while POX only screened (4.4%) cases. Interestingly, no CHD case was detected by both auscultation examination and POX screening. Auscultation detected most of the common types of CHD, but POX excelled in identifying rare and critical cases. addition of pulse oximetry to routine cardiac auscultation could be used as an accurate and feasible screening for early screening of CHD in newborns in large-scale clinical practice.Moreover, in one of two previous studies with a large population of 167,190 asymptomatic newborn infants, most POX-recognizable CHD cases were only detected via auscultation [74].
It was manifested the complementary aspects of POX and auscultation in early screening of CHD among newborns, shedding light on the effectiveness of combined use of both methods in comprehensive neonatal screening, especially regions lacking echocardiologists. when auscultation and POX combined in CHD screening, it can generate quick and accurate outcomes in an economic way, which can benefit facilities in low-income area and hospitals short of ward resource[73].

- **Pulse oximetry and screening echocardiography**

The rationale for considering pulse oximetry as a screening test for congenital heart defects lies in the observation that infants with life-threatening defects are not detected by clinical screening and that many of these defects are associated with cyanosis but not an audible murmur. Hence pulse oximetry which estimates arterial oxygen saturation by measuring the absorption of light in human tissue beds may preferentially detect infants whose cyanosis escapes clinical detection. Normal values for pulse oximetry are generally assumed to be the same as those for arterial oxygen saturation in the newborn. These values may be influenced by altitude but in general, levels below 95% are considered to be abnormal[44].
Pulse oximetry shows promise as a newborn screening test. It is a relatively cheap technology, is portable and appears to be well validated in newborn infants. The screen-positive rate does not appear to result in a huge increase in infants being referred for echocardiograms and the positive predictive value of a low oxygen saturation seems high in all three studies. However, existing experience is based on too small a sample to define the detection rate overall and for specific defects, and infants with COA and TAPVC have been missed.

Interestingly, an unintended benefit of this screening test is the detection of infants who are ill for non-cardiac reasons and who may also benefit from earlier recognition of their illness. However, this also has implications for the diagnostic assessment protocols as a negative echocardiogram may not necessarily be reassuring. It has been suggested that larger studies are required[75].Echocardiography is used postnatally in high-risk infants for the diagnosis or exclusion of congenital heart defects and for assessment of cardiovascular function. There is only limited experience in the literature of its use in low-risk populations as a screening test[76].
Mothers were randomised before delivery to screening echocardiogram or routine clinical screening examination. Screening was performed at 48 hours by a trained ultra-sonographer in the maternity hospital. This included infants with VSDs, PDA, PS and ASDs. No increase in the detection of life-threatening congenital heart defects was demonstrated. Pulse oximetry detects the presence of cyanosis, which may not always be apparent on clinical inspection[77].

In conclusion

- Early detection through newborn screening potentially can improve the outcome of congenital heart defects.
- Pulse oximetry is a promising alternative newborn screening strategy, but further evaluation is needed to obtain more precise estimates of test performance and to inform optimal timing, diagnostic and management strategies.
- Improving antenatal detection of congenital heart defects increases the cost per timely postnatal diagnosis afforded by any newborn screening strategy but does not alter the relative effects of the strategies.
- Timely management of screen-positive infants is essential if outcomes are to improve.
- The following areas are suggested for further study:
  - Refining the detection rate and other aspects of pulse oximetry.
  - More direct evaluation of antenatal screening strategies.
  - Investigating the psychosocial effects of newborn screening for congenital heart defects.

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