

## Early Pulse Oximetry Screening for Congenital Heart Disease in Asymptomatic Newborn Infants

### Abstract

**Background:** Critical congenital heart disease (CCHD) is an important cause of newborn death. Early diagnosis is very important for the outcome, but screening methods miss 50% of the affected neonates who can be detected by pulse oximetry. **Patients and Methods:** This study was carried out on all the neonates within the first 12 hours after delivery at Benha University Hospital (from July 2021 to December 2021). In asymptomatic infants, if the oxygen saturation was below 90%, echocardiography was performed. If the value was 90–94%, a second measurement was performed after 1 hour and repeated for the third time. If the measurement was below 95%, the newborn was evaluated and echocardiography was performed. **Results:** This study included 460 neonates, 26 were symptomatic, 11 had congenital heart disease (CHD) identified prenatally and 423 were asymptomatic. The asymptomatic neonates had hypoplastic heart disease, transposition of great arteries and tricuspid atresia (3 patients for each disease), pulmonary atresia, double outlet right ventricle (DORV) (2 patients for each disease), Fallot's tetralogy, common Av canal, and mild pulmonary hypertension (1 patient for each disease). Pulse oximetry (POX) plus cardiac auscultation showed sensitivity 87.5%, specificity 99.5%, positive predictive value 87.5%, negative predictive value 99.5% and diagnostic accuracy 99.1%. The area under the ROC curve (AUC) result was 0.84 and the P-value was 0.001. **Conclusion:** From our results, it will be concluded that using oximetry plus physical examination will help in the detection of a more significant number of neonates with CHD.

**Keywords:** congenital heart disease, pulse oximeter, Screening asymptomatic neonate.

### Introduction

Prenatal congenital heart diseases (CHDs) affect between 5 and 15 of every 1,000 live births (1). These cardiac diseases account for 40% of deaths in the first year of life due to congenital heart defects (2), as late postnatal diagnosis results in a worse prognosis, increased hospital admissions, increased costs during childhood (3), and prolonged hospital stays. Because signs and symptoms suggestive of CCHD do not always manifest themselves in the first days of life, physical examination does not always identify newborns with CCHD (4). Clinical examination is the first line of defense against heart disease, even more so in the presence of a murmur. However, the prevalence of murmurs in neonates varies between 0.6 and 77.4 percent during the first week of life, and the majority of heart murmurs are caused by postnatal circulatory changes. Additionally, their detection is contingent upon postnatal age, the examiner's experience, and the study population (5). Following the publication of several studies on test accuracy, numerous countries adopted pulse oximetry screening as a routine screening method (6). Apart from its accuracy, studies have shown that pulse oximetry is both acceptable to parents and clinical staff, as well as cost-effective (7). Preventing cardiovascular collapse in neonates with critical congenital heart diseases (CCHDs) is critical for optimizing outcomes following surgical or catheter intervention (8). Thus, the American Academy of Pediatrics, the American Heart Association, and clinical studies advocated for the routine use of pulse oximetry in asymptomatic neonates in conjunction with clinical examination (5). Pulse oximetry screening of neonates is being considered for national implementation in the United Kingdom with the goal of detecting affected neonates early, particularly those with duct-dependent pulmonary or systemic blood flow (9). Pulse oximetry screening is non-invasive, safe, and simple to perform. It has been shown to improve the detection of critical congenital heart disease in newborns. However, the test has not yet been implemented as a routine screening procedure in Egypt. The current screening procedure highlights critical details and recommendations (10). Pulse oximetry can determine the saturation of oxygen in the blood by shining light at specific wavelengths through tissue (most commonly in the fingernail bed). Oxygenated and deoxygenated hemoglobin absorbs light at distinct wavelengths (660 and 940 nm, respectively), and the light absorbed is processed by an algorithm to display a saturation value in the pulse oximeter. According to some studies, a 7 percent difference in saturation between the (preductal) right upper extremity and the (post ductal) lower extremity in the first six hours of life or saturation of 92 percent is considered abnormal (5). Pulse oximetry is not a policy for newborn screening in Egypt, despite the fact that detecting CHDs in the neonate is critical for the survival of affected newborns. The purpose of this study was to evaluate pulse oximetry as a method for screening full-term neonates for critical congenital heart diseases (CCHDs).

## **Patients and Methods:**

This study was unicenter prospective observational screening study and it was carried out on all neonates within the first 12 hours after delivery who were born over a period of six months (from July 2021 to December 2021) at the post-natal ward of Benha University Hospitals. It included 460 neonates, 26 were symptomatic neonates who were transported to the NICU after birth. There were 11 cases of CHD identified prenatally. Asymptomatic newborns were 423. They were screened by the pulse oximeter. The study was under the following inclusion and exclusion criteria, **Inclusion criteria:** Infants who were born at Benha University Hospital (from July 2021 to December 2021), irrespective of the mode of delivery. Newborn infants who were asymptomatic at the time of pulse oximetry screening. Newborn infants more than 34 weeks gestation. **Exclusion criteria:** Premature infants equal to or below 34 weeks of gestation. Newborns who required NICU admission. Newborns with any disease other than CHD. **Methods:** All the neonates in this study were subjected to: Full **history** taking stressing on: maternal history and family history as congenital heart diseases run in families e.g. hypertension, alcoholics, anemia, epilepsy, diabetes mellites, rubella and teratogenic drugs. **Clinical examination** stressing on: **General examination** (color, activity and temperature of the newborns). **Heart examination** was the initial method for diagnosis, especially in the presence of heart rate not within the normal range, irregular heartbeats or abnormal sounds such as certain murmurs or clicks. **Chest examination:** The respiratory rate was counted. The air entry was auscultated bilaterally. All areas were auscultated sequentially and compared with the corresponding areas of the opposite side. If any abnormal sounds were heard in the lungs; the lungs were evaluated. **Abdomen:** Examination of the liver as an important organ that becomes swollen when the balance of the body's water is abnormal. Examination for ascites. **Extremities:** neonate arms and legs were felt to check the pulse. Absent or strong pulses meant heart disease. The nail beds were examined as they show important information about the heart. **Pulse oximeter measurements** were performed by a nurse at the postnatal ward, on the right hand and either the left or right foot of the neonate when the infant is calm. As soon as the pulse oximeter measurement showed a good pulse wave, the maximum heart rate was noted. The measurement didn't exceed 2 minutes. The oxygen saturation cut-off value was 95%. If oxygen saturation was below 95%, the pediatrics resident performed clinical examination of the infant. If the infant had oxygen saturation below 90% or any signs of a CHD, echocardiography was performed and the patient was referred to the department of pediatric cardiology. In the case of an asymptomatic infant with values (90–94%), a second measurement was performed after 1 hour and was repeated for the third time. If the measurement was below 95%, the newborn was evaluated and echocardiography was performed. Neonates with CHD diagnosed prenatally had pulse oximeter measurement prior to the postnatal echocardiography, usually between 1 and 3 hours.

## **Ethical Consideration:**

Ethical permission for the study was obtained from the parents who were fully informed about all the study procedures and their consent was obtained prior to the children's enrollment in the study. This study was approved by the ethical committee of the faculty of medicine, Benha University.

## **Statistical analysis:**

The data were recorded on an "Investigation report form". These data were tabulated, coded then analyzed using the computer program SPSS (Statistical package for social science) version 26 to obtain descriptive statistics which were calculated for the data in the form of; Mean  $\pm$  Standard deviation ( $\pm$ SD), number and percent. In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests: Student's *t*-test to compare between the means of two groups of numerical (parametric) data or the chi-square test ( $X^2$ -value) for inter-group comparison of categorical data. The sensitivity and specificity were calculated, ROC curve analysis was performed to determine the diagnostic power of the test. *P* values  $<0.05$  were considered statistically significant.

**Results:**

Unicenter prospective observational screening study was conducted at Benha University Hospital from July 1, 2021, to December 31, 2021. All consecutive asymptomatic newborn infants were included (newborn more than 34 weeks gestational age, asymptomatic at the time of screening), but newborn infants with prenatally diagnosed CHD, newborns symptomatic after birth and those below or equal 34 weeks were excluded.

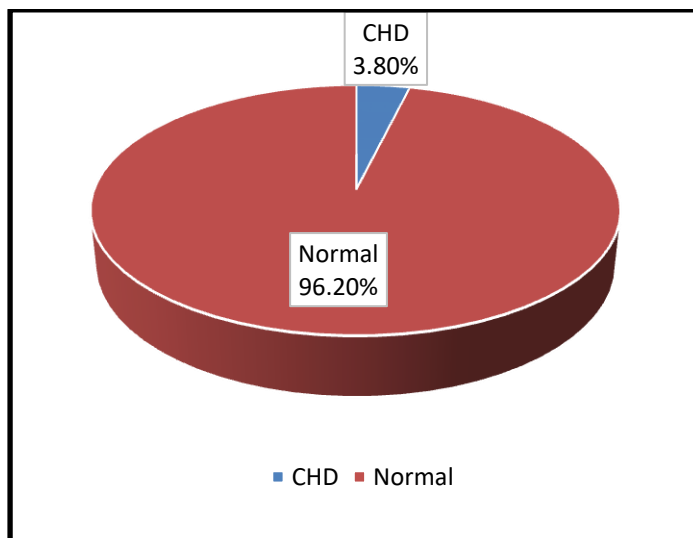
**Table (1):** Characteristics of the study group

|                                    |          |                |
|------------------------------------|----------|----------------|
| Maternal age/years (mean $\pm$ SD) |          | 28.1 $\pm$ 5.2 |
| Sex<br>No. (%)                     | Female   | 214 (50.6%)    |
|                                    | Male     | 209 (49.4%)    |
| Gravida<br>No. (%)                 | $\leq$ 3 | 320 (75.6%)    |
|                                    | > 3      | 103 (24.4%)    |
| Para<br>No. (%)                    | $\leq$ 3 | 360 (85.1%)    |
|                                    | > 3      | 63 (14.9%)     |
| Mode of delivery<br>No. (%)        | C/S      | 322 (76.1%)    |
|                                    | NVD      | 101 (23.9%)    |
| Gestational age/Weeks              |          | 38.1 $\pm$ 1.5 |
| Weight /K. G                       |          | 3.3 $\pm$ 0.3  |

Table 1 summarizes the characteristics of the study group which show the following: mean maternal age 28.1 $\pm$ 5.2 years, 51.1% females, 48.9% males, gravida (No. & %)  $\leq$  3 were 320 (75.6%), and > 3 were 103 (24.4%), para (No. & %)  $\leq$  3 were 360 (85.1%) and > 3 were 63 (14.9%), Mode of delivery (No. & %) C/S 322 (76.1%) and NVD 101 (23.9%), mean gestational age/weeks 38.1 $\pm$ 1.5 and weight /Kg 3.3 $\pm$ 0.3.

**Table (2):** CHD patients among the study group

|        | No. | Percent |
|--------|-----|---------|
| CHD    | 16  | 3.8     |
| Normal | 407 | 96.2    |

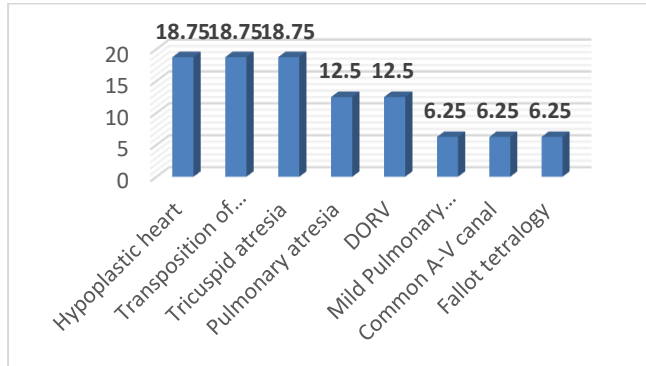


**Fig 1** Pie chart showing CHD patients among the studied sample

**Table (3):** frequency distribution of CHD's among the study group

|                                 | No. | Percent |
|---------------------------------|-----|---------|
| Hypoplastic heart               | 3   | 18.75   |
| Transposition of great arteries | 3   | 18.75   |
| Tricuspid atresia               | 3   | 18.75   |
| Pulmonary atresia               | 2   | 12.5    |
| DORV                            | 2   | 12.5    |
| Mild Pulmonary hypertension     | 1   | 6.25    |
| Common A-V canal                | 1   | 6.25    |
| Fallot tetralogy                | 1   | 6.25    |
| Total                           | 16  | 100.0   |

This table demonstrates that hypoplastic heart disease, transposition of great arteries, and tricuspid atresia were present in 3 patients for each disease, pulmonary atresia, DORV were found in 2 patients for each disease and that Fallot tetralogy, common a- v canal, and mild pulmonary hypertension were detected in 1 patient for each disease.

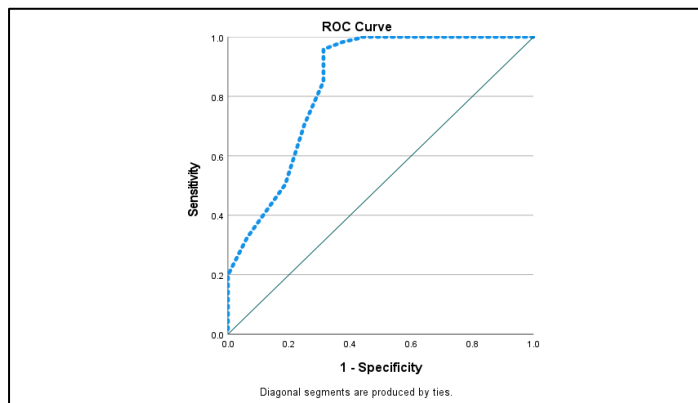


**Fig 2** Distribution of CHD among the study group

**Table (4):** Diagnostic Accuracy of POX plus cardiac auscultation for detection of CHD's

|                           |      |
|---------------------------|------|
| Number of patients        | 423  |
| True positives            | 14   |
| False negatives           | 2    |
| True negatives            | 405  |
| False positives           | 2    |
| Sensitivity (%)           | 87.5 |
| Specificity (%)           | 99.5 |
| Positive predictive value | 87.5 |
| Negative predictive value | 99.5 |
| Diagnostic accuracy       | 99.1 |

ROC curve for evaluation of POX



Area Under the Curve

| Area | P-value | Asymptomatic 95% Confidence Interval |             |
|------|---------|--------------------------------------|-------------|
|      |         | Lower Bound                          | Upper Bound |
| 0.84 | 0.001   | 0.71                                 | 0.97        |

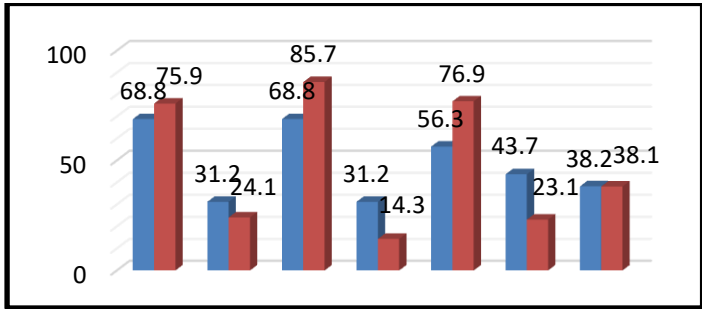
The area under the ROC curve (AUC) results were considered

- Excellent for AUC values between 0.9-1,
- Good for AUC values between 0.8-0.9,
- Fair for AUC values between 0.7-0.8,
- Poor for AUC values between 0.6-0.7
- Failed for AUC values between 0.5-0.6

**Table (5):** Study groups regarding pregnancy data

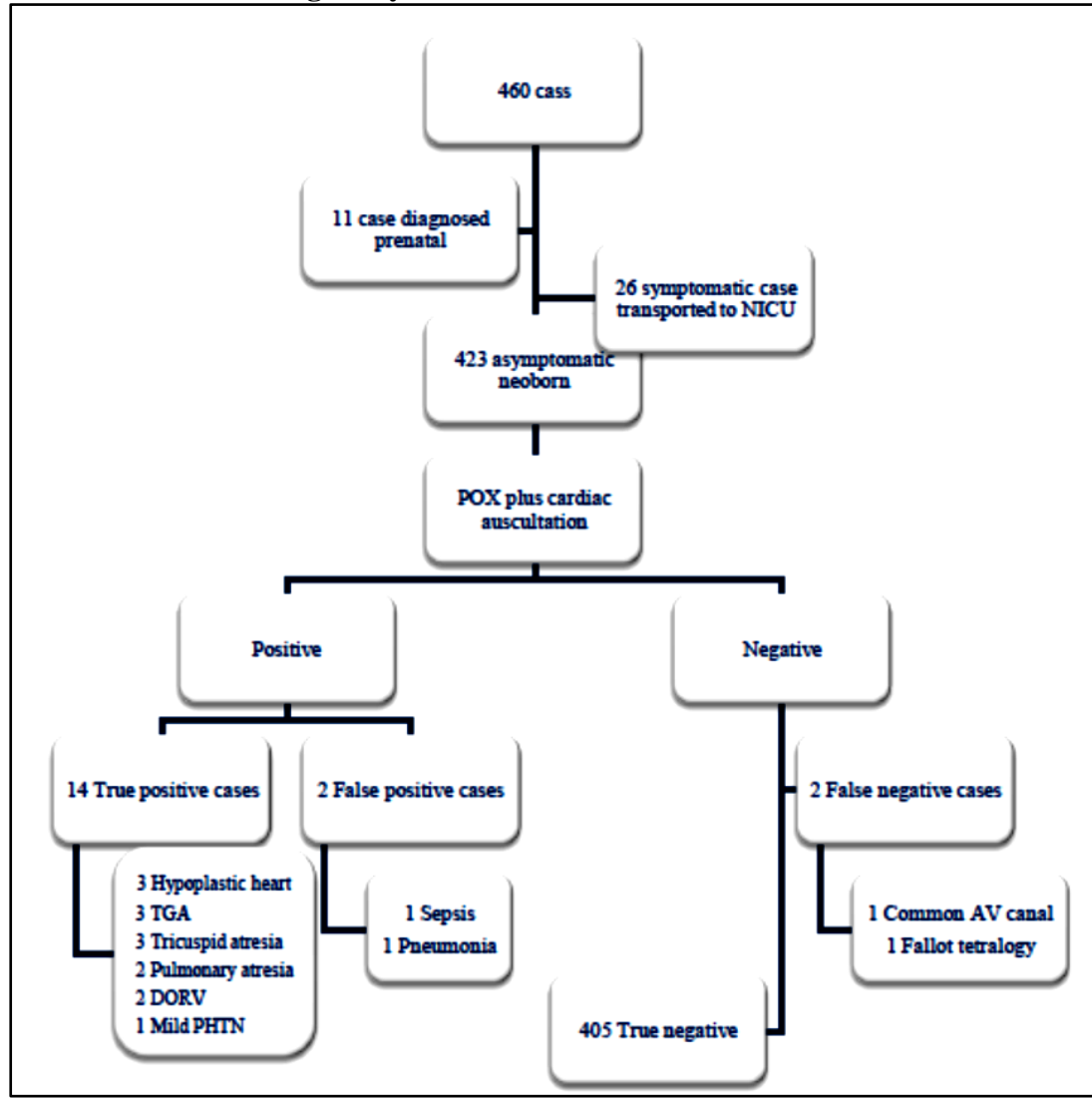
| Pregnancy data              |     | CHD<br>(n=16) | Normal<br>(n=407) | Test of sig. | p-value |
|-----------------------------|-----|---------------|-------------------|--------------|---------|
| Gravida<br>No. (%)          | ≤ 3 | 11 (68.8%)    | 309 (75.9%)       | 0.4          | 0.5     |
|                             | > 3 | 5 (31.2%)     | 98 (24.1%)        |              |         |
| Para<br>No. (%)             | ≤ 3 | 11 (68.8%)    | 349 (85.7%)       | 3.5          | 0.06    |
|                             | > 3 | 5 (31.2%)     | 58 (14.3%)        |              |         |
| Mode of delivery<br>No. (%) | C/S | 9 (56.3%)     | 313 (76.9%)       | 3.6          | 0.06    |
|                             | NVD | 7 (43.7%)     | 94 (23.1%)        |              |         |
| Gestational age/Weeks       |     | 38.2±1.4      | 38.1±1.5          | 0.1          | 0.7     |

This table shows that there was no significant differences between the study groups regarding the gestational age.



**Fig.3.**Bar chart showing Study groups regarding data of pregnancy

**Profile of the screening study**





#### **4. DISCUSSION**

Critical congenital heart diseases (CCHDs) are defined as congenital heart diseases (CHDs) that require early detection and cardiac catheterization or surgical intervention within the first twenty-eight days of life in order to maintain life. Major congenital heart diseases are defined as CHDs that require early detection, cardiac catheterization, or surgical intervention within the first year of life in order to maintain survival (11). It can result in deterioration and death if detection and treatment are delayed (12).

Cardiovascular diseases are significant causes of morbidity and mortality in neonates. Early detection has become a critical goal in the context of a screening strategy involving oximetry, an aspect of importance given that in addition to cardiac sequelae, late detection is associated with cognitive neurological sequelae, economic burden and social consequences. The medical literature recommends screening for CHDs classified as "life-threatening diseases" due to the risk of collapse and sequelae in neonates' development. Among the CCHDs that can be detected using a pulse oximeter are interrupted aortic arch, dextro-transposition of the great arteries, coarctation of the aorta, hypoplastic left heart, Ebstein's anomaly syndrome, pulmonary atresia, truncus arteriosus, tricuspid atresia, single ventricle, tetralogy of Fallot, and total anomalous pulmonary venous return (1).

Through the definition of key operative characteristics, this review aims to validate the importance of pulse oximetry as a screening method for CHDs. The data in our study suggest that clinical examinations performed in isolation do not provide adequate sensitivity for the detection of CCHDs in neonates, a finding that has been observed in the majority of studies. However, the clinical examination's specificity was high, which was consistent with clinical expectations. According to data, when the clinical examination is supplemented with oximetry, the sensitivity of the screening is significantly increased. The described likelihood values tend to favor the adjunctive use of oximetry (1).

This study included 460 neonates; 26 were identified as symptomatic neonates who were transported to the NICU following birth; 11 cases of congenital heart disease were identified prenatally, and 423 were asymptomatic during the first 12 hours after birth.

Of the 423 neonates in the study group, 50.6 percent were females, while 49.4 percent were males. Male neonates had CHD at a rate of 56.3 percent, while female neonates had a rate of 43.7 percent. Male predominance was similar to previous Swedish, Californian, and French studies that observed male predominance for the majority of cyanotic CHDs (13).

Similar to our results, a Portuguese study reported a 1.12:1 male-to-female ratio of CHD among live-born neonates but did not report the sex ratio for unaffected neonates (14). Similarly, another study covering 664,218 live births reported a predominance of males with transposition of the great arteries (male to female ratio: 2.11:1), hypoplastic left heart syndrome (male to female ratio: 2.25:1), and double outlet right ventricle (male to female ratio: 2.68:1), in comparison to more females than males with tetralogy of Fallot (15). In an Australian study that included only live births, similar findings were reported regarding tetralogy of Fallot and transposition of the great arteries, both of which showed male predominance (16). In contrast to our study, the study (17) found no difference in rates of neonatal gender.

Concerning the maternal age, we found no significant difference between the study groups, similar to a Swedish study that discovered no association between maternal age and CHDs after parity adjustment (16).

Despite the fact that an increased risk of Fallot tetralogy with increasing maternal age could not be confirmed in subsequent studies, such as the one conducted in Hawaii or the one conducted using data from the Metropolitan Atlanta Congenital Defects Program, our study against the (18) study found that for every year increase in maternal age, the risk of mortality increased by 1%.

Regarding birth weight and gestational age, no significant differences between the study groups was observed, similar to a previous research indicating that the majority of children with isolated CHD were born at average birth weight and full-term (18).

Our study discovered no significant difference in the parity of the mothers in the study group. In comparison, the study (19) discovered a 6% increase in the risk of coronary heart disease per live birth. However, there was no evidence that verified the association between parous versus nulliparous women and the risk of CHDs.

Folic acid is a critical vitamin, and a link between folic acid and birth defects has been extensively studied. It has been established that a deficiency would result in severe congenital malformations, most notably congenital heart defects and neural tube defects. Additionally, mothers who had more fetuses had shorter inter-pregnancy intervals, which have been shown to increase the risk of co-morbidity (19).

In our study, which was conducted in Benha University Hospitals, eight infants with CCHD and eight infants with serious CHD were identified from the asymptomatic neonates, whereas another 26 were identified as symptomatic neonates who were transported to the NICU following birth. Eleven cases of CHD were identified prenatally. There were 16 cases of congenital heart disease (CHD) among 423 consecutive asymptomatic newborns,

and the overall prevalence of major CHD was 3.8% (16 out of 423). The prevalence was higher when compared to (20) study, which reported a prevalence of major CHD of 2.23 percent, which was lower than our study's due to fewer cases diagnosed by prenatal 4D in our study due to lack of awareness of the importance of antenatal medical care.

Our study showed sensitivity of 87 percent which was lower than that of (20) study (92%) because we used POX plus cardiac auscultation, and was lower than in (1) study where sensitivity was 92% when echocardiograms were used as a reference pattern. The National Institute for Health Research (NIHR) reported a sensitivity value of 63.16 percent which is lower than our result because it was limited to pox. The (2) study discovered a moderate degree of sensitivity (76.3 percent). The (21) study reported a sensitivity of 64.5 percent, as it was a POX-specific sensitivity. In our study, specificity (99.5 percent) was higher than those of (1) (98 percent) and (20) (98.9) percent, but lower than those of (2) (99.9 percent) and (21) (99.7 percent).

The positive predictive value in our study was 87 percent, which was higher than that of a previous study's value of 66.7 percent (21). The negative predictive value in our study (99.5 percent) was less than those in the study (20) (100 percent) and study (21) (99.6 percent).

The diagnostic accuracy in our study was 99.1%, which was higher than the 98.9% reported in (20) and the 95% reported in (2) studies.

When physical examination and oximetry were combined, the receptor operational characteristics (ROC) area under the curve (AUC) value was 0.84, which was lower than the 0.95 (95 percent confidence interval, 0.93-0.97) value in (1) study.

One of our concerns with our study is that some infants with CHDs may have been overlooked during follow-up. Clinical follow-up was performed at 6 weeks of age, in conjunction with parental feedback regarding cardiac symptoms or any other clinical symptom of CHDs.

To determine the likelihood of missing major CHD, through follow-up and feedback from parents of infants screened negative by POX plus cardiac auscultation screening, we called the parents and discovered two serious defects (0.4 percent), indicating that only a few cases of major CHD were missed in our study, compared to 0.1 percent in the study (20). All newborn infants who developed symptoms or were in critical condition were admitted to our NICU. We validated the high sensitivity and specificity of POX plus cardiac auscultation in screening for major CHD in our study.

This screening method was 87.5 percent sensitive for CHD. Additionally, our study's false-positive ratio (FPR) was significantly lower at 0.47 percent, compared to 1.1 percent in the (20) study and 0.8 percent in the (22) study. The overall FPR in our study was 0.47 percent CHD, which was reasonable given the screening's high sensitivity. It was lower than that of the (23) study, with a false-positive rate of (0.8%) and 0.14 percent in the (2) study. Therefore, it would be preferable to screen within the first 12 hours of life and follow up after six weeks. However, 26 symptomatic newborns were transported to the NICU without being screened at birth hospitals in our cohort.

With significant evidence from previous studies, CCHD screening is now being implemented globally (24). The debate over whether to implement a low-cost, quick and painless screening for CCHD with the potential to save lives is over (3). There does not appear to be a need to confirm the benefits of pulse oximetry screening for CCHD. However, POX testing alone may result in a missed diagnosis of those with CHD who do not have right-to-left shunt defects and may result in the progression of some common but serious lesions, such as large septal defects, heart failure, or Eisenmenger syndrome (20).

It is worth noting that the majority of previous studies were conducted in developed countries, with an emphasis on POX. There appeared to be a greater emphasis on clinical assessment, such as cardiac auscultation. We demonstrated in our study that POX in conjunction with physical assessment can be successfully implemented in a typical hospital setting with few barriers, and that using POX in conjunction with physical assessment results in a high detection rate of major CHD and CCHD. Thus, we propose that POX combined with cardiac examination be used to screen for all major CHDs, including CCHD and serious defects (20).

While the benefits of CHD screening are widely recognized, obstacles to screening implementation abound (25). The first point of contention is the false-positive screening results. That study, in particular, examines the burden of false positives and the demand for paediatric echocardiography services. The researchers demonstrated in a meta-analysis that the FPR of POX screening for CCHD was significantly lower when performed after 24 hours of birth than when performed before 24 hours (26). This information must be emphasized when determining the optimal time to conduct CHD screening; we must balance the risk of false positives against the likelihood of diagnosis at the time of screening.

The second issue is the lack of resources; pediatricians outnumber births, with the average facility delivering five to ten infants per day. The availability of pediatricians and screening time, as well as whether screening would increase pediatricians' workload, are critical considerations. Our findings demonstrated that all facilities were capable

of successfully implementing major CHD screening. The time spent on screening did not result in a significant increase in the time doctors worked. Screening and diagnostic echocardiography rates reflect this.

Thirdly, economic data from US studies indicate that the cost of screening an infant range between \$5.10 and \$14.20 (20). Echocardiography is available in several hospitals throughout Egypt for a fee of 25 Egyptian pounds. As a result, screening and diagnostic echocardiography costs are lower than in developed countries, making them affordable for patients without health insurance.

The fourth issue is how to address the urgent need for cardiologic evaluation following a positive screening test result. Pediatric cardiology and cardiac surgery advancements have enabled the diagnosis and treatment of the majority of cases of CCHD. Major pediatric cardiac centers have established policies that prioritize surgical treatment of neonatal CCHD.

Our FPRs were reduced for a variety of reasons. To begin, our study began in 2021, after we gained experience and training in quality control for our screening protocol through a previous study. Second, all pediatricians who participated in the study were trained to perform auscultation. Clearly, in the current study, it was easier to monitor the quality of auscultation performance.

### **5. Limitations**

The present study shows some limitations e.g. the number of neonates who were born in our hospital wasn't high, we were limited to neonates born in this hospital, poor compliance of the parents on follow up or in telephone review, the hospital need more facilities, follow up should be on a long-duration such as one year and lack of prenatal diagnosis because of low compliance of people in follow up during pregnancy.

### **6. Conclusions**

From this study, it is concluded that the use of pulse oximetry added to the conventional physical examination will help in the detection of a more significant number of neonates with CCHDs, without a significant increase in the number of false-positive results, a finding that reduces the morbidity and mortality associated with hospital discharge of neonates without a timely diagnosis.

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