REGULAR ARTICLE

Pulse oximetry could significantly enhance the early detection of critical congenital heart disease in neonatal intensive care units

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ABSTRACT

Aim: Limited data have been available regarding critical congenital heart disease (CHD) screening in neonatal intensive care unit (NICUs). This study evaluated the feasibility of screening for CHD by adding pulse oximetry (POX) to clinical evaluation in a NICU in Shanghai, China.

Methods: We screened 4128 eligible consecutive NICU admissions using POX plus clinical evaluation. Infants with positive screening results were then evaluated with echocardiography. Those with negative screening results were put under observation, and they also underwent echocardiography if their oxygen saturation fell below 95% on room air during hospitalisation.

Results: This enhanced procedure detected 19 critical CHD cases, and seven of these diagnoses would have been delayed if POX had not been incorporated into the screening strategy. This means that the addition of POX increased the detection rate of critical CHD from 63.2 to 100%. The false-positive rate of critical CHD screening using POX plus clinical evaluation was higher in NICU patients with high morbidity rates.

Conclusion: When pulse oximetry screening was added to clinical evaluation, it increased the number of critical CHD cases that were detected in our NICU. This method could provide a useful screening protocol for critical CHD cases.

INTRODUCTION

Critical congenital heart disease (CHD) is generally defined as a congenital heart defect that leads to death or requires surgery or catheter intervention within 28 days of life (1). Early detection can improve the outcome of newborn infants, especially in the case of critical duct-dependent lesions in which closure of the ductus arteriosus can result in acute cardiovascular collapse, acidosis and death (2). Pulse oximetry (POX) is useful in the detection of critical CHD before hospital discharge and has been successful in decreasing missed cases to 4% (3,4). In the United States, some states have established legislation to make POX screening of CHD mandatory before newborn infants are discharged from hospital. In most of the previous studies, the screening that was performed was similar to that performed in the normal newborn nursery on the infants with a gestational age of 35 weeks and above. However, limited data are available regarding critical CHD screening in neonatal intensive care unit (NICUs).

Approximately 10–12% of newborns are admitted to a NICU. Many NICUs monitor oxygen saturation (SpO$_2$) for all admissions (5). But POX has seldom been used in NICUs for critical CHD screening, and there has been a lack of a strategy for physicians to detect critical CHD. Lyengar et al. reported 250 patients admitted to a NICU at Northwestern University, USA, who received critical CHD screening using POX, but did not report any positive results (6). In the United States, many state authorities recommend universal screening and do not differentiate between infants cared for in NICUs and those admitted to nurseries for newborn infants (7). Patients that fall into the following categories may be missed if their physical signs are absent or overlooked by clinicians: (i) infants with critical CHD who do not undergo a foetal or postnatal echocardiogram in the NICU (ii) and/or those infants who undergo

Key notes
- Limited data are available regarding critical congenital heart disease (CHD) screening in neonatal intensive care unit (NICUs).
- Our study of more 4000 patients showed that adding pulse oximetry increased the detection rate of critical CHD from 63.2 to 100% in the NICU.
- It supports the feasibility of using POX plus clinical evaluation as a screening protocol for critical CHD in this paediatric setting.

Abbreviations

CHD, Congenital heart disease; NICU, Neonatal intensive care unit; POX, Pulse oximetry; SpO$_2$, Blood oxygen saturation.

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echocardiography to evaluate patent ductus arteriosus but fail to receive a complete evaluation of the heart for structural malformations (iii) and/or those whose SpO_2 is only low in a limb, where a pulse oximeter probe is not applied during the entire hospital stay (8).

In the current study, we conducted a single-centre study to evaluate the feasibility of screening for critical CHD using POX plus clinical evaluation in the NICU, with a view to providing evidence for critical CHD screening in the NICU.

METHODS

Study populations

The current study focused on 4185 newborn infants who were consecutively admitted to the NICU at the Children's Hospital of Fudan University, Shanghai, China, from October 1, 2012 to September 30, 2014. The NICU, which is the largest one in East China, receives patients from the city of Shanghai and the surrounding areas who are critical, were born in an unstable condition or have complex diseases. We excluded 57 newborn infants because they were prenatally diagnosed with CHD and had received a postnatal echocardiogram prior to screening. This meant that 4128 babies were eligible for screening, including 56.2% preterm infants with a gestational age of <35 weeks. All the babies were aged more than two hours because they were transferred to our NICU from other hospitals. As shown in Table 1, there were 113 babies with an extremely low birthweight and 662 with a very low birthweight and 58.6% of them were male. The screening was completed within the first day of admission.

The current study was approved by the Ethics Committee of the Children's Hospital of Fudan University. All parents were informed of the study details, and verbal informed consent was obtained from the parents.

Screening and data collection

The screening was performed when the babies were admitted to the NICU (Fig. 1). The clinical evaluations were performed by trained physicians, based on five well defined components, which were a family history of CHD, central cyanosis, heart murmur, particular facial features and extracardiac malformations. Any newborn infant with one of these abnormal findings was considered to have screened positive.

Pulse oximetry testing was performed by the trained nurses, where the Radical-5v (Masimo Corporation, Irvine, CA, USA) was used with a LNOP YI multisite reusable sensor (Masimo Corporation), based on the measurement criteria proposed by the United States Secretary of Health and Human Services (9). The functional saturations were measured in the right hand and either foot in a nonspecified order and the sensor secured around the palm of the baby's hand and sole of the foot with a disposable wrap. The POX testing was repeated four hours later if the first SpO_2 measurement was between 90 and 95%. The screening was considered positive if: (i) an SpO_2 of <95% was obtained on both the right hand and either foot during two measurements separated by four hours, (ii) the difference between the two extremities was >3% for two measurements separated by four hours or (iii) any measurement of SpO_2 was <90%.

Echocardiography was undertaken within 48 hours for all babies who were classified as test positive. For those who were screened negative, but their SpO_2 was less than 95% at a later stage during their hospitalisation, bedside echocardiography was undertaken before discharge. All the detected cases of CHD were registered.

Definition of critical CHD

We defined critical CHD as the following seven conditions recommended by the Secretary's Advisory Committee on Heritable Disorders in Newborn and Children (9): hypoplastic left heart syndrome, pulmonary atresia, tetralogy of Fallot, transposition of great vessels, truncus arteriosus, tricuspid atresia and total anomalous pulmonary venous return. Those significant defects that sometimes,

Table 1 Characteristics of newborns

|	Total	GA ≤35 weeks	GA >35 weeks
Screening cases (%)	4128	2319 (56.2)	1809 (43.8)
Male sex (%)	2418 (58.6)	1338 (32.4)	1080 (26.2)
Gestational age (weeks)	34.7 ± 3.9	31.9 ± 2.5	38.4 ± 1.8
Age at screening (hours)	25 (2–506)	24 (2–278)	27 (2–506)
Birthweight (g)	2366.6 ± 861.6	1781.4 ± 515.1	3116.7 ± 593.4
BW ≤ 1000 g (%)	113 (2.7)		
1000 < BW ≤ 1500 g (%)	662 (16.1)		
BW > 1500 g (%)	3353 (81.2)		
Test-positive cases (%)	2866 (69.4)	1670 (40.5)	1196 (29.0)
Pulse oximetry alone (%)	2308 (55.9)	1390 (33.7)	918 (22.2)
Clinical evaluation alone (%)	963 (23.3)	486 (11.8)	477 (11.6)
Pulse oximetry or clinical evaluation (%)	2485 (60.2)	1461 (35.4)	1024 (24.8)
Echocardiography test (%)	3092 (74.9)	1891 (45.8)	1201 (29.1)
Oxygen therapy (%)	2402 (58.2)	1430 (34.6)	972 (23.6)
NICU stay (days)	13.7 ± 17.7	25.4 ± 21.8	6.3 ± 8.2
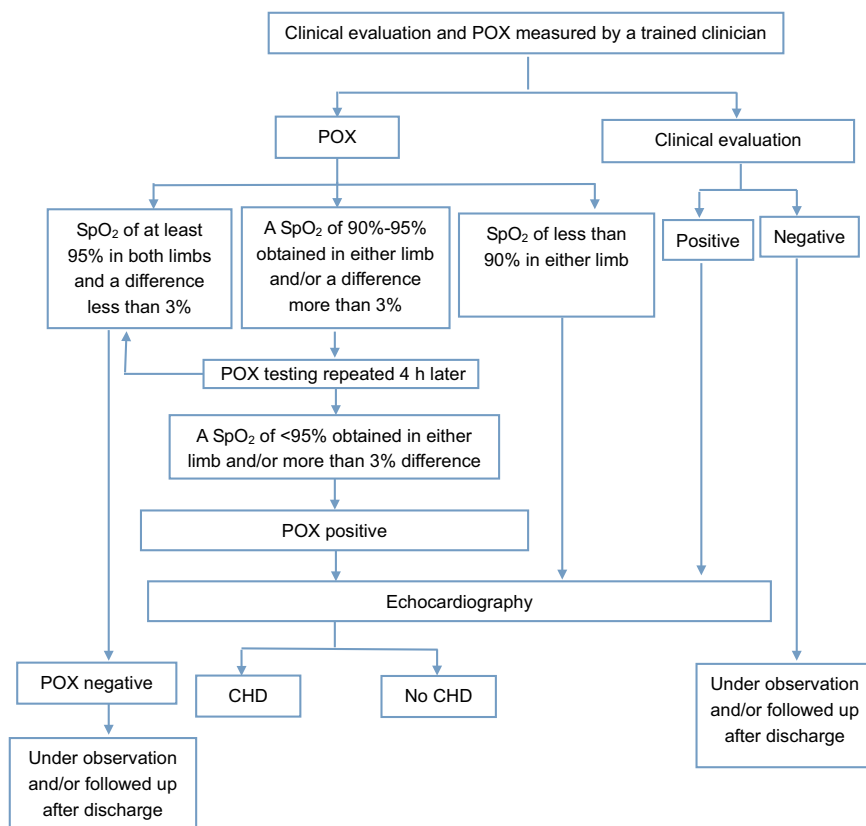
Figure 1 Critical CHD screening diagram in NICU.

but less consistently, cause hypoxaemia were also defined as critical CHD, for example, coarctation of the aorta, pulmonary stenosis, double outlet right ventricle, single ventricle, interrupted aortic arch and Ebstein anomaly, which needed surgery within 28 days of birth (10).

Statistical analysis

The number of critical CHD cases in the NICU and the distribution of critical CHD in different gestational ages was calculated in terms of sensitivity, specificity, positive and negative predictive value, negative and positive likelihood ratio and the 95% confidence interval (95% CI) of screening critical CHD by just POX, by just clinical evaluation and by POX plus clinical evaluation, respectively. The t test was used for the comparison between continuous variables and the chi-square test for nonparametric statistics.

RESULTS

Critical CHD detection

A total of 4128 newborn infants consecutively admitted to NICU without the prenatal diagnosis of CHD underwent the unit screening protocol. Of those, 69.4% of the infants screened positive, while 30.6% screened negative. A total of 19 critical CHD cases were detected (Fig. 2, Table 2). For those whose gestational age was less than 35 weeks, CHD was detected in the form of pulmonary stenosis, tetralogy of Fallot, single ventricle, transposition of great vessels, double

outlet right ventricle, total anomalous pulmonary venous return, tricuspid atresia and Ebstein in addition to the most common forms of CHD, such as patent ductus arteriosus, atrial septal defect, ventricular septal defect. If POX had not been incorporated into the screening strategy, there would have been seven delayed diagnoses of critical CHD, including two tetralogy of Fallot, one single ventricle, two transposition of great vessels, one tricuspid atresia and one pulmonary atresia. Patent ductus arteriosus was observed in 1115 preterm infants (48.1%): 38 of these underwent surgical ligation and 156 received prostaglandin inhibitors to achieve closure. However, of the 1809 infants that had a gestational age of more than 35 weeks, 670 (37.0%) had patent ductus arteriosus, with only two receiving surgical ligation and another two being treated with prostaglandin inhibitors. Persistent pulmonary hypertension was observed in 1233 infants, including 1044 who also had other forms of CHD. Incorporating POX into the screening strategy prevented six persistent pulmonary hypertension cases from being delayed.

The accuracy of different screening indicators for critical CHD

As shown in Table 3, just using POX as a screening method detected 16 of the 19 (84.2%) cases of critical CHD and just using clinical evaluation as a screening method detected 12 of the 19 (63.2%) cases of critical CHD. But when POX and clinical evaluation were both used, this detected all 19
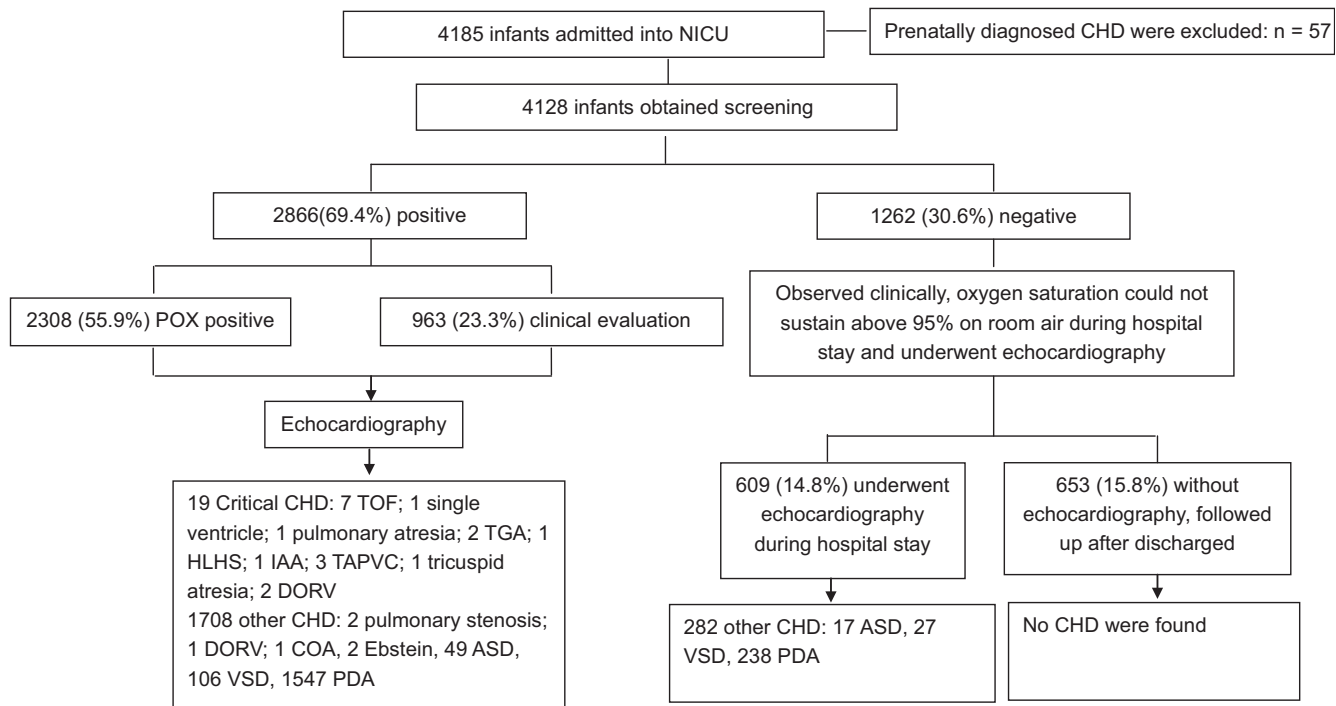
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┌─────────────────────────────────────────┐        ┌──────────────────────────────────────────┐
│      4185 infants admitted into NICU     │────────│ Prenatally diagnosed CHD were excluded: n = 57 │
└─────────────────────────────────────────┘        └──────────────────────────────────────────┘
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│        4128 infants obtained screening   │
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| 2866(69.4%) positive | | 1262 (30.6%) negative |

| 2308 (55.9%) POX positive | 963 (23.3%) clinical evaluation |

Observed clinically, oxygen saturation could not sustain above 95% on room air during hospital stay and underwent echocardiography

Echocardiography

19 Critical CHD: 7 TOF; 1 single ventricle; 1 pulmonary atresia; 2 TGA; 1 HLHS; 1 IAA; 3 TAPVC; 1 tricuspid atresia; 2 DORV
1708 other CHD: 2 pulmonary stenosis; 1 DORV; 1 COA, 2 Ebstein, 49 ASD, 106 VSD, 1547 PDA

609 (14.8%) underwent echocardiography during hospital stay

653 (15.8%) without echocardiography, followed up after discharged

282 other CHD: 17 ASD, 27 VSD, 238 PDA

No CHD were found

Figure 2 Profile of the study.

Table 2 Spectrum of CHD diagnosed by echocardiography

Predominant defect	Number	Gestational age ≤35 weeks	Gestational age >35 weeks	Description
Critical CHD				
TOF	7	3	4	Five of them were premature infants (two of them with SGA and one of them with malformation); the other two were omphalocele
Single ventricle	1	1	0	Premature infant (one of the twins)
Pulmonary atresia	1	0	1	Term baby with malformation
TGA	2	1	1	One was SGA, another one was premature infant with hypoglycaemia
HLHS	1	0	1	Term infant with asphyxia
IAA	1	0	1	Premature infant (infant of diabetic mother, IDM)
TAPVC	3	1	2	Term infant with aspiration pneumonia; the other two were premature infants with NRDS and hypoglycaemia
Tricuspid atresia	1	1	0	Combined with right ventricular dysplasia, premature infant
Other CHD				
Pulmonary stenosis	2	1	1	
DORV	3	1	2	2 cases underwent surgery during neonatal period, defined as CCHD. Both of them were SGA with transient tachypnea of newborn
COA	1	0	1	
Ebstein	2	1	1	
ASD	66	36	30	Combined with PDA or PPHN
VSD	133	71	62	Combined with PDA or PPHN
PDA	1785	1115	670	40 cases underwent surgery, 38 cases whose GA ≤35 weeks; 158 cases were treated by medication; 365 cases closed naturally; and the remaining 1222 cases were followed up after discharge
Total	2009	1232	777	

(100%) cases of critical CHD. Using just POX as a screening indicator showed that three critical CHD cases were missed, and just using clinical evaluation indicated that seven critical CHD cases were missed. But when POX was combined with clinical evaluation, no critical CHD cases were missed.

Table 3 Accuracy of screening method for Critical CHD in NICU

	POX	Clinical evaluation	POX + clinical evaluation
True positives	16	12	19
False negatives	3	7	0
False positives	2292	951	2466
True negatives	1817	3158	1643
False-positive rate (%)	55.8	23.1	60.0
Sensitivity (%)	84.2 (62.43, 94.48)	63.2 (41.04, 80.85)	100 (83.18, 100)
Specificity (%)	44.22 (42.71, 45.74)	76.86 (75.54, 78.12)	39.99 (38.50, 41.49)
Positive predictive value (%)	0.69 (0.43, 1.12)	1.25 (0.71, 2.17)	0.77 (0.49, 1.19)
Negative predictive value (%)	99.84 (99.52, 99.94)	99.78 (99.54, 99.89)	100 (99.77, 100)
Diagnostic accuracy (%)	44.44 (42.89, 45.92)	76.79 (75.48, 78.06)	40.26 (38.78, 41.77)
Positive likelihood ratio	1.51 (1.47–1.55)	2.73 (2.48–3.01)	1.666 (1.665–1.668)
Negative likelihood ratio	0.36 (0.19–0. 69)	0.48 (0.36–0.63)	0.00

Data: number or percentage (95% CI).

Table 4 False-positive rate of screening methods for detecting Critical CHD between different gestational ages in NICU

	POX		Clinical evaluation		POX + clinical evaluation	
	≤35 weeks	>35 weeks	≤35 weeks	>35 weeks	≤35 weeks	>35 weeks
True positives	6	10	3	9	7	12
False negatives	1	2	4	3	0	0
False positives	1384	908	483	468	1454	1012
True negatives	928	889	1829	1329	858	785
False-positive rate (%)	59.9	50.5	20.9	26.0	62.9	56.3
Sensitivity (%)	85.7	83.3	42.9	75.0	100	100
	(48.7, 97.4)	(55.2, 95.3)	(15.8, 75.0)	(46.8, 91.1)	(64.6, 100)	(75.8, 100)
Specificity (%)	40.1	49.5	79.1	74.0	37.1	43.7
	(38.2, 42.2)	(47.2, 51.8)	(77.4, 80.7)	(71.9, 75.9)	(35.2, 39.1)	(41.4, 46.0)

Data: number or percentage (95% CI).

DISCUSSION

Before we carried out this study, there was no agreement about whether critical CHD should be screened in our NICU and no clear strategy for such screening. Many clinicians working in level three neonatal units, where high-risk babies are cared for, are now facing the question of whether critical CHD screening using POX should be instituted in NICUs as well. This study will help individual NICUs to make decisions about, and institute policies about, carrying out critical CHD screening in their NICU. Kemper et al. (7) suggested detecting critical CHD by POX in stable late preterm infants and term infants in well infant and intermediate care nurseries. But there was no evidence-based protocol for POX screening infants in the NICU. The importance of screening critical CHD in the NICU had been recognised, and neonatologists have voiced concern that only screening babies in well infant and intermediate care nurseries would miss detecting critical CHD babies in the NICU. One study reported that approximately 10–15% of American babies who were treated in the NICU each year who underwent multiple physical examinations and were continuously monitored for their SpO_2 (10). But there has been limited literature on the use of POX to screen

critical CHD in the NICU. The results of our current study showed that the POX screening protocol, as employed in our previous national study (11), could also be applied in the NICU.

In our hospital, we adopted the third option recommended by Suresh (8), which was to screen all infants admitted to the NICU. The advantage of this approach was that it could detect critical CHD in preterm babies aged less than 35 weeks. As preterm infants face an equal or higher risk of having CHD than term infants, it is wise to screen them as well. As recommended by Suresh, screening all infants would allow the NICU to operate in an unambiguous manner, as it would be easier to implement a reliable system of screening if it was applied to all NICU infants instead of just a subset of NICU infants. A clear unified screening protocol can also help NICU staff to develop good screening compliance.

As no effective screening strategy for critical CHD was available for the NICU, we designed a screening protocol based on our own resources. The clear indicators and timings of screening can facilitate clinicians to make decisions in the NICU and routine screening can avoid a delayed diagnosis of critical CHD. In our current study,

19 critical CHD cases were detected in a timely manner after admission and therefore treated promptly. If we hadn't undergone simultaneous preductal and postductal SpO_2 monitoring to screen critical CHD, we would have missed one case of transposition of the great vessels and six persistent pulmonary hypertension cases, resulting in delayed treatment. If there had been no screening strategy that included POX, these critical CHD could still have been detected, but it would have taken a certain amount of time to reach a clear diagnosis. If the detection of duct-dependent lesions had been delayed, this could have led to serious consequence. And if clinical evaluation had not been included in the strategy, the detection of two tetralogy of Fallot and one double outlet right ventricle would have been delayed.

One significant difference between neonates not admitted to a NICU and our neonates was the high rate of false-positive screening results in the NICU population. Meta-analyses of large population-based studies of newborn pulse oximetry screening conducted after the first 24 hours after delivery among asymptomatic newborn infants demonstrated a low false-positive rate of 0.035–0.05% (12). In our current study, the false-positive rate was high because it was conducted in a NICU and, for example, the population included sepsis, pneumonia and more premature babies. Actually, if there had been no screening, at least half of the admissions to our NICU would have had an echocardiogram for medical indications. In this study, we carried out 640 additional confirmatory echocardiography to ensure positive screening results. However, all the CHD cases were found in a timely manner, including patent ductus arteriosus, which was a particular issue for preterm babies. In China, one echocardiography costs 200 Chinese Yuan, which is equivalent to approximately 30 U.S. dollars, which is not expensive. This means that the results were of greater significance in terms of saving those neonatal cases of critical CHD. Other costs were not precisely defined, but it seemed that no additional burden was imposed on the clinicians because they had no trouble accepting POX monitoring in the NICU, as every infant underwent continuous POX monitoring in the NICU until discharge. Actually, only 22 infants were measured for POX again four hours after the first measurement in our study. The clinicians were well trained, and the simple test took little time, with no additional human resources and equipment costs incurred.

It is difficult to determine the optimal timings for screening critical CHD in the NICU. Because infants admitted to the NICU usually suffer from acute cardiorespiratory disease, they tend to be put on oxygen therapy. Echocardiography is cheap and the disease itself, or its therapy, such as ventilation or supplemental oxygen, would interfere with the accuracy of screening. That would lead to false-negative screens, as in the case of oxygen therapy for lung disease, which masks low saturation from some heart lesions, or resulting in false positives, as in the case of an infant with lung disease who would have low oxygen saturation falsely attributed to heart disease (8). Therefore, the screening would have to be performed when the infants had recovered from their disease. As diseases can take different courses, this would make it difficult to decide screening timings. To address the problem, the simple rule would be to test all eligible infants 24–48 hours before hospital discharge; otherwise, the diagnosis for critical CHD would be delayed. Manja et al. (5) reported that they performed screening 24–48 hours before discharge along with other screening tests, such as hearing, and believed that such a screen could be conducted earlier. In the current study, we performed screening within 24 hours of admission. Although the false-positive rate increased significantly, no critical case of CHD was missed and they were detected quickly. As we already known, critical CHD interventions are typically performed in the first weeks of life to optimise haemodynamics and prevent the end-organ injury associated with delayed diagnosis. Because timely recognition of critical CHD could improve outcomes, it is important to identify and evaluate strategies to enhance early detection.

CONCLUSION

Pulse oximetry still plays an important role in screening critical CHD in NICUs. Based on clinical evaluation, pulse oximetry screening can significantly enhance the early detection rate of critical CHD. This suggests that POX plus clinical evaluation should be applied as a screening protocol for critical CHD in NICUs.

FUNDING

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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