BUKTI KORESPONDENSI

ARTIKEL JURNAL INTERNASIONAL BEREPUTASI

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(26 Januari 2022)

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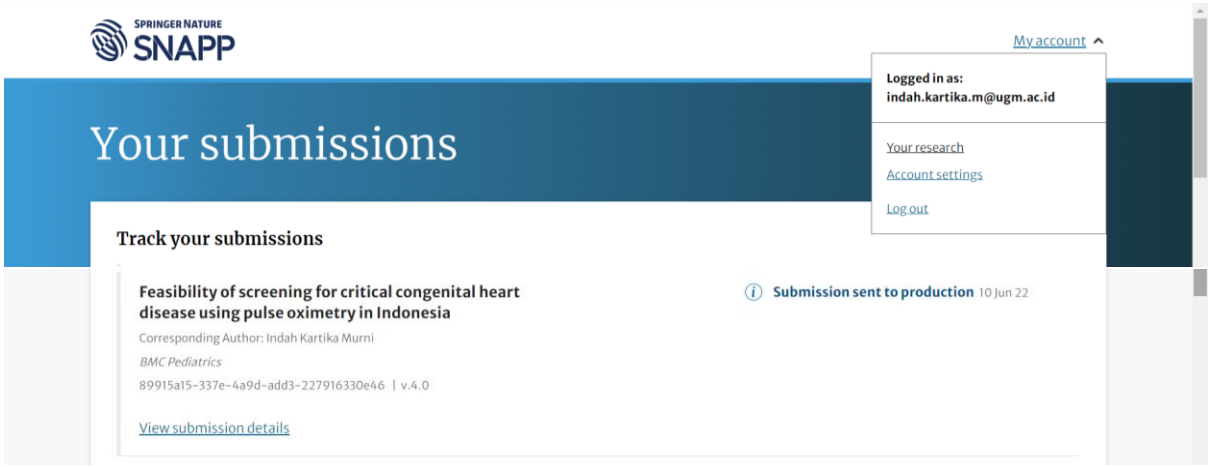
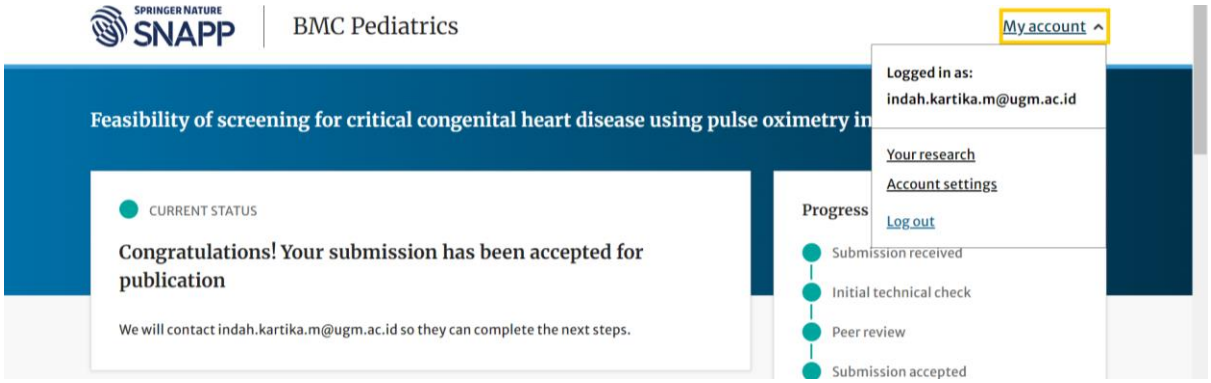
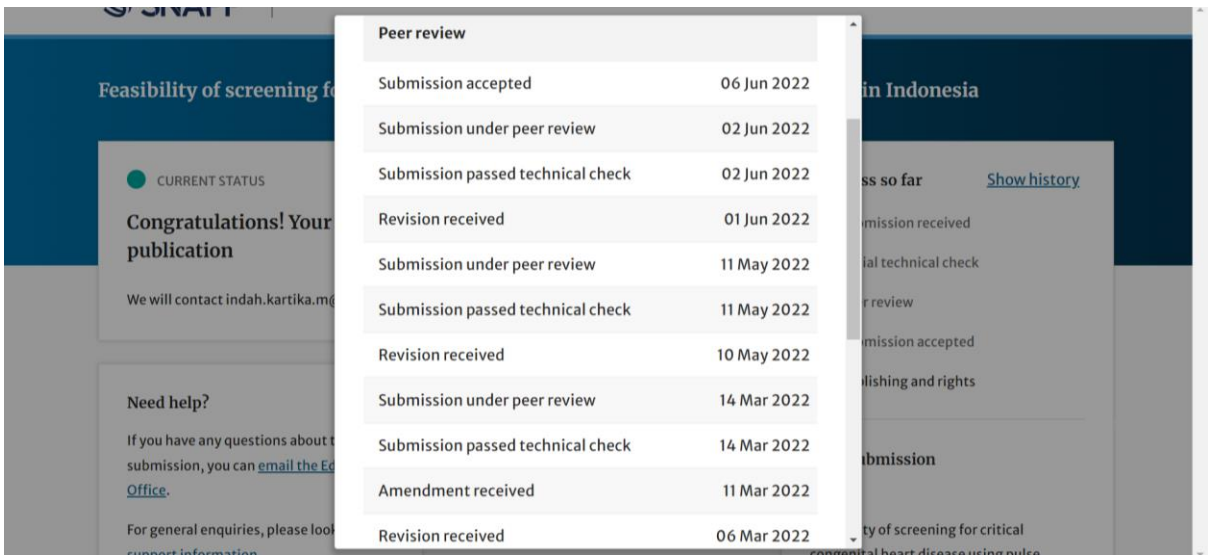
Seluruh dokumen, revisi dan respon kepada reviewer jurnal BMC Pediatric dengan judul artikel *"Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia"* diunggah oleh penulis korespondensi (Indah Kartika Murni) melalui website resmi jurnal BMC Pediatric melalui alamat https://submission.springernature.com/ dengan akun Indah.kartika.m@ugm.ac.id







TITLE PAGE

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Keywords: congenital heart disease, pulse oximetry screening, Indonesia, critical congenital heart disease

Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia

Abstract

Background: Screening of critical congenital heart disease (CCHD) using pulse oximetry has been a routine procedure in many countries, but not in Indonesia. We aimed to evaluate the feasibility of implementing CCHD screening with pulse oximetry for newborns in Yogyakarta, Indonesia.

Methods: A cross-sectional study was conducted in four hospitals in Yogyakarta, Indonesia. Newborns aged 24-48 hours who met inclusion criteria were screened using pulse oximetry on the right hand and left or right foot. Positive results indicated by SpO_2 <90% in one extremity, (2) SpO_2 90-94% in both right hand or forearm on three measurement between 1 hour, and (3) a saturation difference >3% between the upper and lower extremity on three measurements between 1 hour were confirmed with echocardiography.

Results: Of 1,452 newborns eligible for screening, 10 had positive results and referred for echocardiography evaluation. Of those, 8 (6 per 1000 live birth, 8/1,452) had CCHD. The obstacles found during screening process were associated with regulation, equipment, lack of healthcare and newborn condition.

Conclusion: Pulse oximetry screening is feasible to be implemented in the setting to the routine newborn care for detection of CCHD in Indonesia.

BACKGROUND

Congenital heart disease (CHD) is the most common congenital abnormality in newborns [1] with the incidence reported from 4 to 50 per 1,000 live births [2,3]. Approximately 25% of CHD were classified as critical congenital heart disease (CCHD), that are often lethal and required immediate transcatheter or surgical intervention in the first year of life [4]. CHD is responsible for over 260,000 deaths annually worldwide [5]. The mortality rate of CHD was 81 cases per 100,000 live births with mortality associated with CCHD at 64.7% [6]. Challenges remains with early detection of CCHD since some CCHD newborns may appear healthy at first and sent home before diagnosis with greater challenges showed in resource limited settings.

In Indonesia, approximately 2.5 per 1,000 live births born with CHD [7]. Six in 10 of CHD had significant delayed in diagnosis and often presented with severe complications [8]. One-third of the newborns with CCHD were not detected before discharge [9]. Screening for CCHD using pulse oximetry has been recommended and widely implemented in many countries followed by a significant reduction of mortality among newborns with CCHD. Further, the cost related to complications of late diagnosis CCHD can be avoided [10]. Despite the importance of immediate detection of CCHD, no screening program in newborns has been implemented in Indonesia and cases often present late in the tertiary hospital in terminal condition. This study aimed to evaluate the feasibility of CCHD screening using pulse oximetry and provide local evidence for policymakers in implementing pulse oximetry screening program in Yogyakarta, Indonesia.

METHODS

A cross-sectional study was conducted in four hospitals in Yogyakarta, Indonesia from August 1, 2021 to November 30, 2021. Dr. Sardjito Hospital is a class A, tertiary referral hospital; JIH

Hospital is a class B, general hospital; Sadewa and Sakina Idaman Hospitals are class C of specialty hospitals for maternal and neonatal care. All apparently healthy newborns were included. Neonates who were born at <35 weeks' gestation, had prenatal diagnosis of CHD, dysmorphic features and signs of cardiovascular problems such as cyanosis, cardiac murmur or abnormal vital signs were excluded [11].

Pulse oximetry screening was performed using the standard of American Academy of Pediatrics (AAP) algorithm by measuring oxygen saturation of the right hand and the left or right foot between 24-48 hours of age or before 24 hours of age if the baby is discharged early [12]. The screening was performed by the healthcare workers such as doctor, nurse, or midwife in charge. Training was performed prior to the study conduct.

Screening for critical CHD was considered negative or passed if $SpO_2 \geq 95\%$ for both right hand and right or left foot and the difference in saturation of the foot and right hand is <3%. No further cardiac evaluation was done in these babies unless indicated by subsequent clinical condition. Screening was considered positive or failed if at least one the following: (1) SpO_2 <90% in one extremity, (2) SpO_2 90-94% in both right hand or forearm on three measurement between 1 hour, and (3) a saturation difference >3% between the upper and lower extremity on three measurements between 1 hour [12]. If failing the screening, the newborns were referred to Dr. Sardjito Hospital for echocardiographic evaluation.

Since not all hospitals have the same type of pulse oximetry available, we did an inter-rater agreement correlation before the recruitment using three types of pulse oximetry: Massimo (Massimo corporation, Irvine, CA, USA), Mindray (Mindray Cooperation, Nanshan, Shenzhen, China) and fingertip.

Data were analyzed using STATA version 12.1 (StataCorp, College Station, Texas, USA) and presented as appropriate. Descriptive statistics were presented as number and percentage, mean or median.

We also did a survey for the screening performer on the obstacles they found during the screening process. The qualitative data were reviewed, defined and presented thematically based of the common obstacles.

The Medical and Health Research Ethics Committee, of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia approved this study (230/UN.1/FKKMK.3/IKA.2/TU/PT.01.04/2021). The approval did not require individual patient consent, but all parents were informed of this study.

RESULTS

During the study period, there were 2,631 newborns at the four selected hospitals. There were 118 newborns who were ineligible: 89 newborns were <35-week gestation age, 10 died, 14 confirmed CHD and 5 had dysmorphic features. Of 2,513 eligible subject, 1,452 (57.7%) newborns were screened (Figure 1). Of those, 10 had positive results and referred for echocardiography evaluation and 8 (0.6%) had CCHD. The screening was performed ≤24 hours in 855 cases (59%) and 597 (41%) subjects were screened after 24 hours of age.

Most newborns screening used a standardized pulse oximetry (Massimo). The inter-rater agreement among Massimo and Fingertip pulse oximetry was 0.815, while the inter-rater agreement among Massimo and Mindray pulse oximetry was 0.943.

The echocardiography performed in the 10 newborns who had the positive screening test showed the following results:

- 8 CCHD: 2 cases of Ebstein Anomaly; 1 case of pulmonary atresia with ventricle septal defect (VSD) and vertical patent ductus arteriosus (PDA); 1 case of tricuspid atresia with pulmonary atresia, small secundum atrial septal defect (ASD); 1 case of mitral atresia with transposition of the great arteries (TGA), severe pulmonary stenosis, and single ventricle with hypoplastic left ventricle; 1 case of tricuspid atresia, inlet VSD, moderate secundum

ASD, small right ventricle and pulmonary stenosis; 1 case of double outlet right ventricle (DORV) with TGA, VSD; and 1 case of unbalanced atrioventricular septal defect (AVSD) with moderate PDA.

- 2 non-critical CHD: 1 case of small secundum ASD and 1 case of patent foramen ovale (PFO).

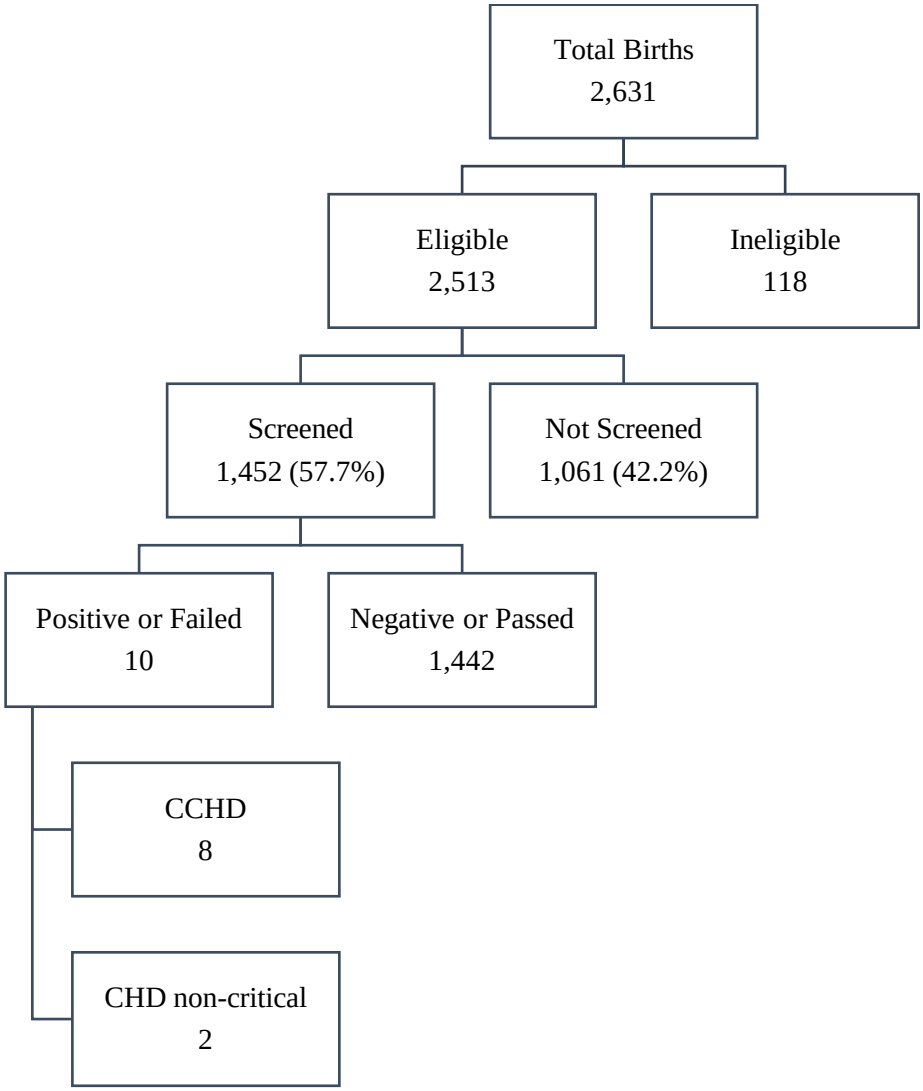

Figure 1. Distribution of the newborns enrolled in the study.

The baseline characteristics of the eligible newborns are presented in Table 1.

Table 1. Baseline characteristics of screened newborns

Characteristics	Newborns n=1,452 (%)
Sex, n (%)	
Male	769 (53)
Female	683 (47)
Birth weight in gram, median (min-max)	3,045.4 (1,360-4,532)
<2,500	154 (10.6)
2,500-4,000	1,279 (88.1)
>4,000	19 (1.3)
Gestational of age in week, n (%)	
<37	81 (5.6)
37-42	1,367 (94.1)
>42	4 (0.3)
Type of delivery, n (%)	
Caesarean section	859 (59.2)
Vacuum extraction	29 (2)
Normal	564 (38.8)
Type of pulse oximetry, n (%)	
Massimo	1,067 (73.5)
Fingertip	18 (1.2)
Mindray	367 (25.3)

Main obstacles during performing pulse oximetry screening are shown in Table 2.

Table 2. Obstacles during screening process

Type of obstacles	Details
Regulation	The hospital regulation of the length of postnatal stay at hospital is relatively short, and therefore, most of the newborns were screened before 24 hours.
	The pulse oximetry measurement is not yet part of standard of care of the healthy newborns before discharge therefore some of healthcare (especially nurses and midwives) checks were not routinely done even though this research has been conducted.
	Among newborns who had positive result of screening, they did not immediately undergo an echocardiography examination because the echocardiography was performed only in the general and tertiary hospital while they still have to become inpatients.
Equipment	The lack of pulse oximetry device in the wards, with pulse oximetry only available in the neonatal ICU.
	Sensors with tape are not widely available, which is easier and faster to use than fingertip-type pulse oximetry.
	Adult probe for newborns was also used due to the limited sources in the ward.
Healthcare personnel	The healthcare workers were busy with other clinical duties and forgot to do screening.
Condition of the baby	Some newborns who were constantly crying or moving made oximetry application was difficult to use.

DISCUSSION

The prevalence of CCHD in our study was 6 of 1,000 live birth showing the positive CCHD screens occurred in 8/1,452 (0.6%) of newborns. This positive rate was larger than previously reported in India 0.16% (3/1,855) [13], Turkey 0.12% (12/10,200) [14], Morocco 0.06% (5/8,013) [15], Netherland 0.02% (5/23,959) [16], New Zealand 0.02% (3/16,644) [17], United States 0.01% (1/6,745) [11]. However, the sensitivity and specificity of pulse oximetry screening could not be calculated due to there was no further follow up visit for infants who passed the test and not all of the infants were screened.

Pulse oximetry screening has been successfully implemented in high-income countries and has led to a significant reduction in CCHD related deaths. A study showed that an evaluation 6 years (2007-2013) after implementation of this program across the United States found a 33.4% (95% CI: 10.6%-50.3%) reduction in CCHD deaths per 100,000 births and has a potential reduction of 120 infant deaths per year from CCHD [19].

Several countries such as the United States, China, the Netherlands, and the United Kingdom that have conducted CCHD screening programs with pulse oximetry showed that screening for CCHD using clinical assessment and oximetry is beneficial and cost-effective [10]. Because of this program, the cost of treating complications of CCHD due to late diagnosis can be avoided. A US study reported that a screening program were reported to save 20 infant lives annually at a cost of $40 385 per life-year gained under base case assumptions with additional screening cost of $6.28 per newborn [20].

Meanwhile, low- and middle-income countries still have to face some barriers to execute the pulse oximetry screening program. One study in Morocco revealed several barriers such as tendency to discharge healthy newborns before 24 hours and the investigation of positive screening is also difficult because not all hospital has echocardiography [15]. Other reported challenges in implementing pulse oximetry screening includes the acceptance of

program, the timing of screening and significance of false positives rate, and response to positive screen [21].

In our study, we classified obstacles found during screening process into four elements. The first one concerns regulations. According to the AAP recommendations, the screening process should be done within 24-48 hours of age. But, most of infants in our study were screened before 24 hours due to the hospital regulation of the length of postnatal stay at hospital which is relatively short. The timing of screening should be considered since it will influence the screening results. A previous study revealed that the measurement of saturation before age 24 hours will increase the false positive or negative rate [16]. The transition from fetal to neonatal circulation and stabilization of systemic oxygen saturation levels might explain this. Study in New Zealand revealed that midwifery-led maternity setting, characterized with early discharge, was influencing the time of testing and it can also influence saturation levels [17].

Other obstacles involved undersupply of standardized neonatal pulse oximetry. These were available in neonatal intensive care units or observation rooms for monitoring of sick newborns, but not routinely available in the postnatal wards. The pulse oximeters were sometimes sensors with tape which are easier to use than finger-type. The pulses tend to be difficult to detect and take longer time to read. The type of probe can affect the effectiveness of examination results. Due to the limited sources, some of hospitals were using adult probes for newborns. Food and Drugs Administrator (FDA) US stated three recommendations in using pulse oximetry. First, aware the factors that can affect the accuracy of a pulse oximeter reading, understand a particular brand and sensor by refering the device labelling or manufactures's website, and always considered the accuracy limitations when using the pulse oximeter to assist in diagnosis and treatment decision. Knowing this recommendation is important for understanding the risk of inaccuracy measurement and providing highest outcomes [22]. Nevertheless, one recent study revealed that accuracy a pulse oximetry device could provide

good accuracy in ruling out hypoxemia compared to saturation reading by arterial blood gas sample [23].

The condition of the baby also can become obstacle. In our study, some of the newborns who were unsettled with constantly crying or moving challenge the application and assessment of pulse oximetry. When the screening is being performed, it is recommended that the infants should be awake and settled. Deep sleep may result in hypoventilation and a low saturation documentation [24]. Previous study in New Zealand showed that newborns that are asleep or unsettled at the time of screening were less likely to have positive results than the newborns who were awake and settled [17].

The last obstacles include the lack of healthcare in the postnatal ward. The healthcare providers were busy with other clinical duties and sometimes forgot about the screening protocol. Some of them did not consider the pulse oximetry measurement to be in the scope of their practice. Studies in New Zealand stated that most of midwives were sure that pulse oximetry screening was worthwhile to do, but their workload was heavy enough and staff to do this screening were under-resourced. This was one of their concerns about implementing it as a universal screening program [25].

Indonesia has a large number of annual live birth rates; it is about 5 million per year with 62.7% deliveries which were commonly attended by midwives, but Indonesia still has yet to have any national program for screening CCHD [7, 8]. Pulse oximetry fulfils the criteria for mass screening. It is very effective, low cost and can significantly reduce morbidities and mortality by providing earlier detection of CHD. However, to achieve these goals optimally in the setting of limited resources is challenging, but it is not impossible. These goals require extensive standardized training for healthcare providers who work directly in newborn care (midwives, nurse, general practitioner), and the protocols need formal regulations and the

involvement of policy makers such as health ministries and pediatric cardiology society for making pulse oximetry screening as recommendation in the standard of care of the newborns.

The major limitation of our study is the high proportion of newborns who were not screened over the study period due to the many aforementioned reasons. Despite the limitation, our study is among the first reports of the feasibility of CCHD screening using pulse oximetry in limited resource settings and provides the local evidence of barrier perspectives from healthcare workers during the screening process. The findings can be used as available local evidence for policymakers before recommending needed changes to the national screening program.

CONCLUSIONS

Pulse oximetry screening is feasible to be implemented to the routine newborn care for detection of CCHD in Indonesia.

List of Abbreviations

AAP: American Academy of Pediatric

ASD: Atrial Septal Defect

CHD: Congenital Heart Disease

CCHD: Critical Congenital Heart Disease

DORV: Double Outlet Right Ventricle

PDA: Patent Ductus Arteriosus

PFO: Patent Foramen Ovale

TGA: Transposition of the Great Aorta

VSD: Ventricle Septal Defect

Declarations

Ethics approval and consent to participate

The Medical and Health Research Ethics Committee (MHREC) of Universitas Gadjah Mada approved this study (230/UN.1/FKKMK.3/IKA.2/TU/PT.01.04/2021). The ethics committee did not require individual patient consent, but all parents were informed of this study.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests

Funding

None

Authors' contributions

IKM, DP, LP were major contributors in writing the manuscript and the study design. DP collected the data. IKM, DP, LP analyzed and interpreted the data. All authors read, critically revised and approved the final manuscript.

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2. Bukti konfirmasi review dan hasil review pertama

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Dear Dr Murni,

Re: "Feasibility of screening for critical congenital heart disease using pulse oximetry Indonesia"

We are pleased to let you know that your manuscript has now passed through the review stage and is ready for revision. Many manuscripts require a round of revisions, so this is a normal but important stage of the editorial process.

Editor comments
This is a study reporting the feasibility of CCHD screening using pulse oximetry in limited resource settings and provides the local evidence of barrier perspectives from healthcare workers during the screening process.There are some minor linguistic mistakes. Also a patent foramen ovale cannot be considered a congenital heart defect. I agree with the comments of the reviewers which should be addressed before the paper can be considered suitable for publication

To ensure the Editor and Reviewers will be able to recommend that your revised manuscript is accepted, please pay careful attention to each of the comments that have been pasted underneath this email. This way we can avoid future rounds of clarifications and revisions, moving swiftly to a decision.

Once you have addressed each comment and completed each step listed below, please log in here with the same email you used to submit your manuscript to upload the revised submission and final file:

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Alternatively, please visit https://researcher.nature.com/your-submissions to upload your revised submission and to track progress of any other submissions you might have.

CHECKLIST FOR SUBMITTING YOUR REVISION

1. Please upload a point-by-point response to the comments, including a description of any additional experiments that were carried out and a detailed rebuttal of any criticisms or requested revisions that you disagreed with. This must be uploaded as a 'Point-by-point response to reviewers' file.

Please note that we operate a transparent peer review process, where we publish reviewers' reports with the article, together with any responses that you make to reviewers or the handling Editor.

2. Please highlight all the amends on your manuscript or indicate them by using tracked changes.

3. Check the format for revised manuscripts in our submission guidelines, making sure you pay particular attention to the figure resolution requirements:

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Finally, if you have been asked to improve the language or presentation of your manuscript and would like the assistance of paid editing services, we can recommend our affiliates, Nature Research Editing Service: https://authorservices.springernature.com/language-editing/ and American Journal Experts: https://www.aje.com/go/springernature

Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our resources page: https://www.springernature.com/gp/researchers/campaigns/english-language-forauthors

To support the continuity of the peer review process, we recommend returning your manuscript to us within 14 days. If you think you will need additional time, please let us know and we will aim to respond within 48 hours.

Kind regards,

Aleliki Karatza
Editorial Board Member
BMC Pediatrics

Reviewer Comments:

Reviewer 1
Pulse oximetry screening is a simple examination that is very well suited for the early detection of critical congenital heart defects.
The prerequisite is that the method is applied at the right time and methodologically correctly.
The authors have well analyzed the reasons why pulse oximetry screening is unsuccessful.

Reviewer 2
Thank you for the opportunity to review this important feasibility study conducted over three months in four hospitals in Indonesia. This manuscript was well organized and provides insights and results from CCHD screening using pulse oximetry in a resource limited setting. In addition to the identification of critical congenital heart disease, the authors provide needed awareness of the challenges associated with screening from a survey conducted on barriers to screening. This can be helpful to other teams interested in implementing CCHD screening in low resource settings as well as to those who are looking to improve process and protocol adherence.
Importantly, this study adds additional evidence that CCHD screening using PO is valuable in low resource settings, and that these regions may have a higher yield than in developed countries where the number of infants identified with CCHD is higher per 1,000 infants screened. In this study, infants were being identified even with a not insignificant prenatal detection rate of 14 infants out of 2,513. All of the infants who failed screening were found to have either CCHD or CHD, which is unusual as several large studies from various countries have shown that secondary non-cardiac targets are identified as frequently or more frequently than CCHD. It would be helpful for the research team to address whether non-cardiac causes of low oxygen readings were addressed or assessed for in the infants who failed.
Mortality for CCHD is stated as 67% from a somewhat obscure 2018 study conducted in Brazil (reference 6). Would be more helpful to include a more current study examining at the global regional and national mortality from CCHD and/or provide context as to how this can vary based on the availability and access to cardiac interventions including surgery and catheterization. Or, in the alternative, please provide context as to why Brazil may be the best approximation for CCHD mortality in Indonesia. Some of the references were not the most current, for example, updating the Holy Cross feasibility study to referencing the 2020 Holy Cross 8 year outcomes published in Pediatrics (Schwartz Pediatrics 2020).
There were several limitations with this study which are addressed by the authors including the use of three different types of pulse oximeters from three different manufacturers as well as the use of an adult sensor on a newborn. It is interesting to note that some screens were conducted on the infants right forearm rather than the right hand which may decrease the ability to obtain an accurate pulse oximetry reading.
There were very minor issues with grammar and English language which could be easily corrected. For example, “challenges remain” instead of “challenges remains.” Please clarify whether “between 1 hour” means the re-screens were conducted 1 hour apart. “Regulation” might be more appropriately categorized as “work flow” or “hospital procedure.”
Overall, I would recommend this manuscript for publication as it provides important evidence of the feasibility and potential value of CCHD screening in resource limited settings.

Title: Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia

Version: 3 **Date:** 22 Feb 2022

Reviewer's report:

Thank you for the opportunity to review this important feasibility study conducted over three months in four hospitals in Indonesia. This manuscript was well organized and provides insights and results from CCHD screening using pulse oximetry in a resource limited setting. In addition to the identification of critical congenital heart disease, the authors provide needed awareness of the challenges associated with screening from a survey conducted on barriers to screening. This can be helpful to other teams interested in implementing CCHD screening in low resource settings as well as to those who are looking to improve process and protocol adherence.

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Title: Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia

Version: 3 **Date:** 21 Feb 2022

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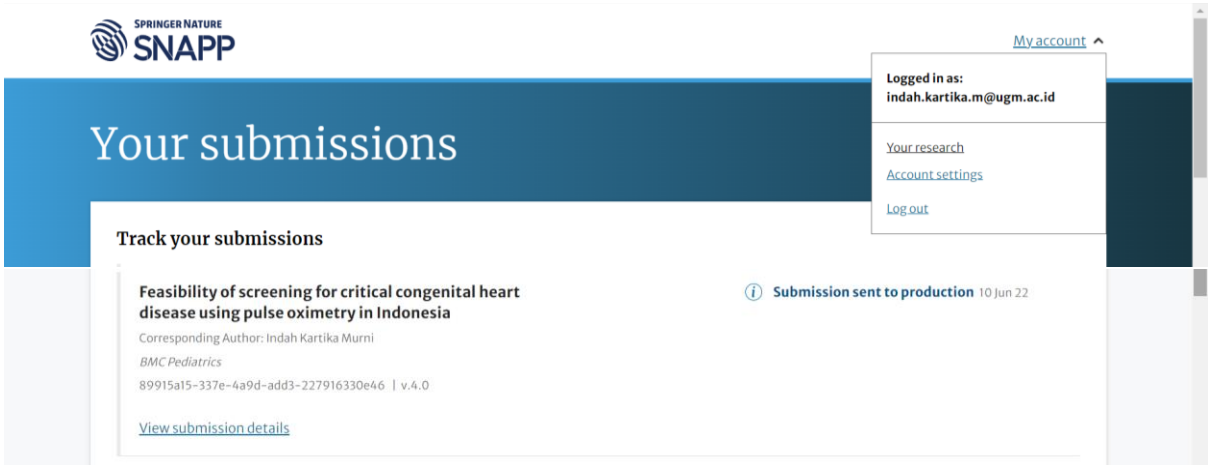
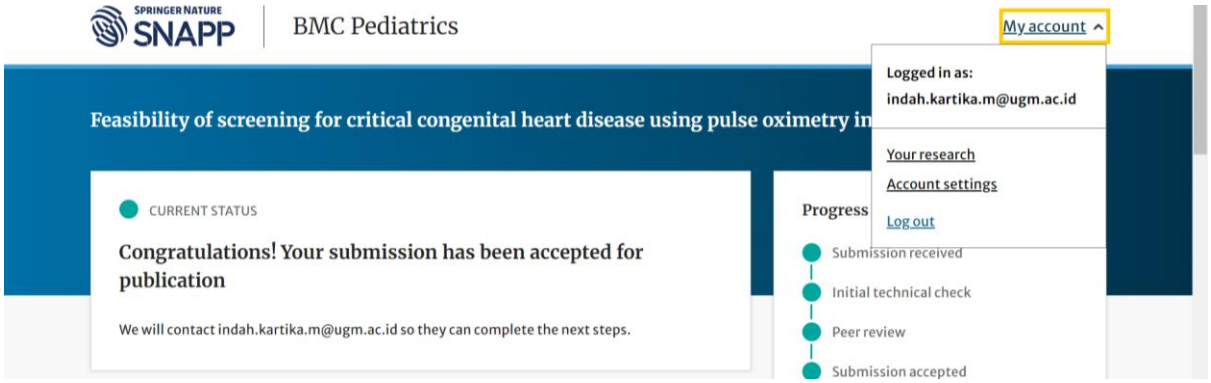
The authors have well analyzed the reasons why pulse oximetry screening is unsuccessful.

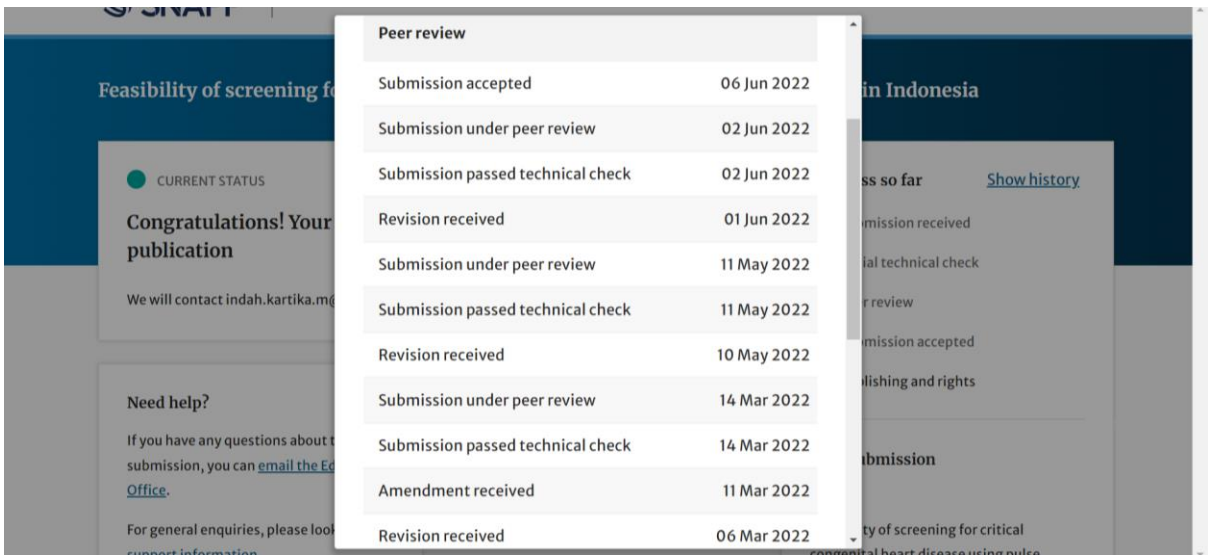
3. Bukti konfirmasi submit revisi pertama, respon kepada reviewer dan artikel yang disubmit

(6 Maret 2022)

Seluruh dokumen, revisi dan respon kepada reviewer jurnal BMC Pediatric dengan judul artikel *"Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia"* diunggah oleh penulis korespondensi (Indah Kartika Murni) melalui website resmi jurnal BMC Pediatric melalui alamat https://submission.springernature.com/ dengan akun Indah.kartika.m@ugm.ac.id







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Response to Reviewer's comment:
We thank you very much for the positive comments and interest in the paper.

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Thank you for the opportunity to review this important feasibility study conducted over three months in four hospitals in Indonesia. This manuscript was well organized and provides insights and results from CCHD screening using pulse oximetry in a resource limited setting. In addition to the identification of critical congenital heart disease, the authors provide needed awareness of the challenges associated with screening from a survey conducted on barriers to screening. This can be helpful to other teams interested in implementing CCHD screening in low resource settings as well as to those who are looking to improve process and protocol adherence.

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Response to Reviewer's comment:
We thank you very much for raising this.
In daily practice, when the baby getting bluish or desaturated or respiratory distress, the doctors or nurses were directly administered oxygen supplementation for the babies. These frequently occurred soon after birth (less than 24 hours) and most commonly causes were asphyxia, pulmonary hypertension of the newborn, or other pulmonary problems. The healthcare workers did not include these neonates for screening.
We have included these sentences in the Results section.

Mortality for CCHD is stated as 67% from a somewhat obscure 2018 study conducted in Brazil (reference 6). Would be more helpful to include a more current

study examining at the global regional and national mortality from CCHD and/or provide context as to how this can vary based on the availability and access to cardiac interventions including surgery and catheterization. Or, in the alternative, please provide context as to why Brazil may be the best approximation for CCHD mortality in Indonesia.

Response to Reviewer's comment:
We thank you very much for raising this. We have removed this reference and changed to the study from a developing country (Malaysia) revealing the mortality associated with CCHD was 34.8%, which is quite similar to ours.
In 2012 to 2019, among 104 neonates with critical CHD, 37 died (35.6%) at the Dr Sardjito Hospital in Yogyakarta, Indonesia (unpublished study).
We have also modified the sentence the more accurately reflect the body of evidence in this area.

Some of the references were not the most current, for example, updating the Holy Cross feasibility study to referencing the 2020 Holy Cross 8 year outcomes published in Pediatrics (Schwartz Pediatrics 2020).

Response to Reviewer's comment:
We thank you very much for providing this information, we have updated the reference as suggested.

There were several limitations with this study which are addressed by the authors including the use of three different types of pulse oximeters from three different manufacturers as well as the use of an adult sensor on a newborn. It is interesting to note that some screens were conducted on the infants right forearm rather than the right hand which may decrease the ability to obtain an accurate pulse oximetry reading.

Response to Reviewer's comment:
We thank you very much for raising this. We actually used right hand not the forearm, we have revised the sentence.
We have also added limitation on the use of three different types of pulse oximeters.

There were very minor issues with grammar and English language which could be easily corrected. For example, “challenges remain” instead of “challenges remains.” Please clarify whether “between 1 hour” means the re-screens were conducted 1 hour apart. “Regulation” might be more appropriately categorized as “work flow” or “hospital procedure.”
Overall, I would recommend this manuscript for publication as it provides important evidence of the feasibility and potential value of CCHD screening in resource limited settings.

Response to Reviewer's comment:
We thank you very much for the advice. We have revised as suggested.
We also have consulted to a native English speaker, who is:

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Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada
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We have carefully revised the manuscript to address the errors and grammatical mistakes throughout the paper.

TITLE PAGE

Type of article: Original Article

Title of the article: Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia

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Word counts:

- Abstract: 188 words
- Main text: 2175 words

Keywords: congenital heart disease, pulse oximetry screening, Indonesia, critical congenital heart disease

Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia

Indah K Murni, Tunjung Wibowo, Nadya Arafuri, Vicka Oktaria, Lucia K Dinarti, Dicky Panditatwa, Linda Patmasari, Noormanto Noormanto, Sasmito Nugroho

Abstract

Background: Screening of critical congenital heart disease (CCHD) using pulse oximetry has been a routine procedure in many countries, but not in Indonesia. We aimed to evaluate the feasibility of implementing CCHD screening with pulse oximetry for newborns in Yogyakarta, Indonesia.

Methods: A cross-sectional study was conducted in four hospitals in Yogyakarta, Indonesia. Newborns aged 24-48 hours who met inclusion criteria were screened using pulse oximetry on the right hand and left or right foot. Positive results indicated by SpO_2 <90% in one extremity, (2) SpO_2 90-94% in both right hand or foot on three measurement conducted 1 hour apart, and (3) a saturation difference >3% between the upper and lower extremity on three measurements conducted 1 hour apart were confirmed with echocardiography.

Results: Of 1,452 newborns eligible for screening, 10 had positive results and referred for echocardiography evaluation. Of those, 8 (6 per 1000 live birth, 8/1,452) had CCHD. The obstacles found during screening process were associated with hospital procedure, equipment, lack of healthcare, and newborn condition.

Conclusion: Pulse oximetry screening is feasible to be implemented in the setting to the routine newborn care for detection of CCHD in Indonesia.

BACKGROUND

Congenital heart disease (CHD) is the most common congenital abnormality in newborns [1] with the incidence reported from 4 to 50 per 1,000 live births [2,3]. Approximately 25% of CHD were classified as critical congenital heart disease (CCHD), that are often lethal and required immediate transcatheter or surgical intervention in the first year of life [4]. CHD is responsible for over 260,000 deaths annually worldwide [5]. The mortality associated with CCHD was 34.8% in a developing country [6]. Challenges remain with early detection of CCHD since some CCHD newborns may appear healthy at first and sent home before diagnosis with greater challenges showed in resource limited settings.

In Indonesia, approximately 2.5 per 1,000 live births born with CHD [7]. Six in 10 of CHD had significant delayed in diagnosis and often presented with severe complications [8]. One-third of the newborns with CCHD were not detected before discharge [9]. Screening for CCHD using pulse oximetry has been recommended and widely implemented in many countries followed by a significant reduction of mortality among newborns with CCHD. Further, the cost related to complications of late diagnosis CCHD can be avoided [10]. Despite the importance of immediate detection of CCHD, no screening program in newborns has been implemented in Indonesia and cases often present late in the tertiary hospital in terminal condition. This study aimed to evaluate the feasibility of CCHD screening using pulse oximetry and provide local evidence for policymakers in implementing pulse oximetry screening program in Yogyakarta, Indonesia.

METHODS

A cross-sectional study was conducted in four hospitals in Yogyakarta, Indonesia from August 1, 2021 to November 30, 2021. Dr. Sardjito Hospital is a class A, tertiary referral hospital; JIH Hospital is a class B, general hospital; Sadewa and Sakina Idaman Hospitals are class C of

specialty hospitals for maternal and neonatal care. All apparently healthy newborns were included. Neonates who were born at <35 weeks' gestation, had prenatal diagnosis of CHD, dysmorphic features and signs of cardiovascular problems such as cyanosis, cardiac murmur or abnormal vital signs were excluded [11,12].

Pulse oximetry screening was performed using the standard of American Academy of Pediatrics (AAP) algorithm by measuring oxygen saturation of the right hand and the left or right foot between 24-48 hours of age or before 24 hours of age if the baby is discharged early [13]. The screening was performed by the healthcare workers such as doctor, nurse, or midwife in charge. Training was performed prior to the study conduct.

Screening for critical CHD was considered negative or passed if SpO_2 ≥95% for both right hand and right or left foot and the difference in saturation of the foot and right hand is <3%. No further cardiac evaluation was done in these babies unless indicated by subsequent clinical condition. Screening was considered positive or failed if at least one the following: (1) SpO_2 <90% in one extremity, (2) SpO_2 90-94% in both right hand on three measurement conducted 1 hour apart, and (3) a saturation difference >3% between the upper and lower extremity on three measurements conducted 1 hour apart [13]. If failing the screening, the newborns were referred to Dr. Sardjito Hospital for echocardiographic evaluation.

Since not all hospitals have the same type of pulse oximetry available, we did an inter-rater agreement correlation before the recruitment using three types of pulse oximetry: Massimo (Massimo corporation, Irvine, CA, USA), Mindray (Mindray Cooperation, Nanshan, Shenzhen, China) and fingertip.

Data were analyzed using STATA version 12.1 (StataCorp, College Station, Texas, USA) and presented as appropriate. Descriptive statistics were presented as number and percentage, mean or median.

We also did a survey for the screening performer on the obstacles they found during the screening process. The qualitative data were reviewed, defined and presented thematically based of the common obstacles.

Ethics

The Medical and Health Research Ethics Committee, of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia approved this study (230/UN.1/FKKMK.3/IKA.2/TU/PT.01.04/2021). Informed consent to participate was obtained from the parents of participants.

All the experiment protocol for involving humans was in accordance to guidelines of national/international/institutional or Declaration of Helsinki.

RESULTS

During the study period, there were 2,631 newborns at the four selected hospitals. There were 118 newborns who were ineligible: 89 newborns were <35-week gestation age, 10 died, 14 confirmed CHD and 5 had dysmorphic features. Of 2,513 eligible subject, 1,452 (57.7%) newborns were screened (Figure 1). Of those, 10 had positive results and referred for echocardiography evaluation and 8 (0.6%) had CCHD. The screening was performed ≤24 hours in 855 cases (59%) and 597 (41%) subjects were screened after 24 hours of age.

When the baby getting bluish or desaturated or respiratory distress, the doctors or nurses were directly administered oxygen supplementation for the babies. These frequently occurred soon after birth (less than 24 hours) and most commonly causes were asphyxia, pulmonary hypertension of the newborn, or other pulmonary problems. The healthcare workers did not include these neonates for screening.

Most newborns screening used a standardized pulse oximetry (Massimo). The inter-rater agreement among Massimo and Fingertip pulse oximetry was 0.815, while the inter-rater agreement among Massimo and Mindray pulse oximetry was 0.943.

The echocardiography performed in the 10 newborns who had the positive screening test showed the following results:

- 8 CCHD: 2 cases of Ebstein Anomaly; 1 case of pulmonary atresia with ventricle septal defect (VSD) and vertical patent ductus arteriosus (PDA); 1 case of tricuspid atresia with pulmonary atresia, small secundum atrial septal defect (ASD); 1 case of mitral atresia with transposition of the great arteries (TGA), severe pulmonary stenosis, and single ventricle with hypoplastic left ventricle; 1 case of tricuspid atresia, inlet VSD, moderate secundum ASD, small right ventricle and pulmonary stenosis; 1 case of double outlet right ventricle (DORV) with TGA, VSD; and 1 case of unbalanced atrioventricular septal defect (AVSD) with moderate PDA.
- 1 non-critical CHD: 1 case of small secundum ASD
- 1 case of normal as patent foramen ovale (PFO)

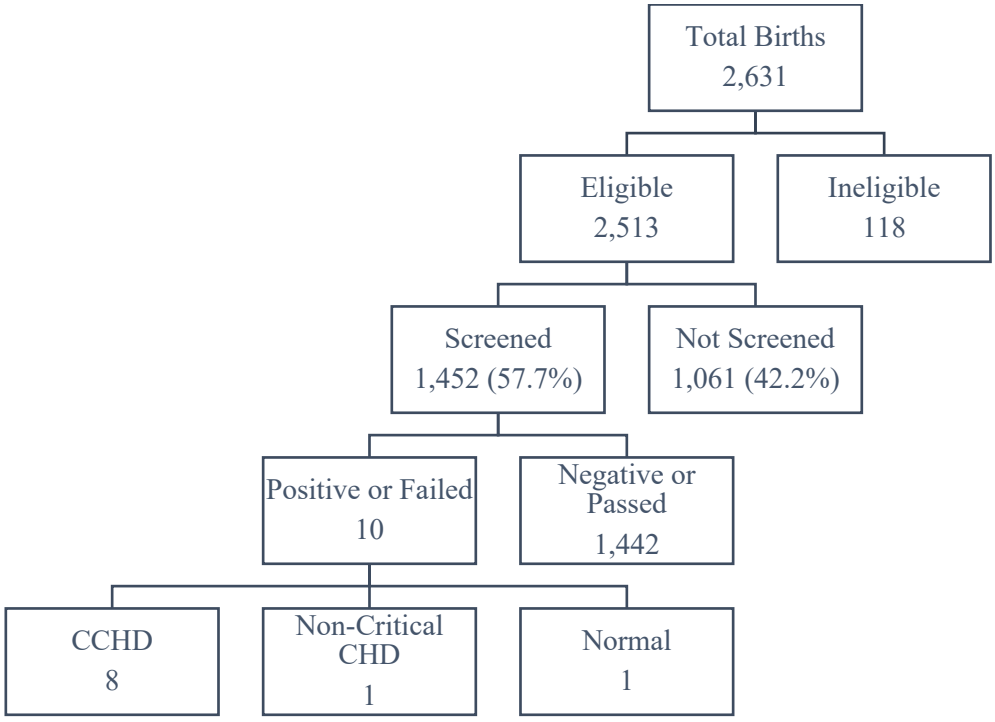

Figure 1. Distribution of the newborns enrolled in the study.

The baseline characteristics of the eligible newborns are presented in Table 1.

Table 1. Baseline characteristics of screened newborns

Characteristics	Newborns n=1,452 (%)
Sex, n (%)	
Male	769 (53)
Female	683 (47)
Birth weight in gram, median (min-max)	3,045.4 (1,360-4,532)
<2,500	154 (10.6)
2,500-4,000	1,279 (88.1)

>4,000	19 (1.3)
Gestational of age in week, n (%)	
<37	81 (5.6)
37-42	1,367 (94.1)
>42	4 (0.3)
Type of delivery, n (%)	
Caesarean section	859 (59.2)
Vacuum extraction	29 (2)
Normal	564 (38.8)
Type of pulse oximetry, n (%)	
Massimo	1,067 (73.5)
Fingertip	18 (1.2)
Mindray	367 (25.3)

Main obstacles during performing pulse oximetry screening are shown in Table 2.

Table 2. Obstacles during screening process

Type of obstacles	Details
Hospital procedure	The hospital procedure of the length of postnatal stay at hospital is relatively short, and therefore, most of the newborns were screened before 24 hours.
	The pulse oximetry measurement is not yet part of standard of care of the healthy newborns before discharge, and therefore, some of healthcare (especially nurses and midwives) checks were not routinely done even though this research has been conducted.

	Among newborns who had positive result of screening, they did not immediately undergo an echocardiography examination because the echocardiography was performed only in the general and tertiary hospital while they still have to become inpatients.
Equipment	The lack of pulse oximetry device in the wards, with pulse oximetry only available in the neonatal ICU.
	Sensors with tape are not widely available, which is easier and faster to use than fingertip-type pulse oximetry.
	Adult probe for newborns was also used due to the limited sources in the ward.
Healthcare personnel	The healthcare workers were busy with other clinical duties and forgot to do screening.
Condition of the baby	Some newborns who were constantly crying or moving made oximetry application was difficult to use.

DISCUSSION

The prevalence of CCHD in our study was 6 of 1,000 live birth showing the positive CCHD screens occurred in 8/1,452 (0.6%) of newborns. This positive rate was larger than previously reported in India 0.16% (3/1,855) [14], Turkey 0.12% (12/10,200) [15], Morocco 0.06% (5/8,013) [16], Netherland 0.02% (5/23,959) [17], New Zealand 0.02% (3/16,644) [18], United States 0.01% (1/6,745) [12].

A meta-analysis with 21 studies and involving 457,202 participants concluded that pulse oximetry is a highly specific and moderately sensitive test for detection of CCHD with very low false-positive rates [19]. The pulse oximetry screening has been successfully implemented in high-income countries and has led to a significant reduction in CCHD related

deaths. A study showed that an evaluation 6 years (2007-2013) after implementation of this program across the United States found a 33.4% (95% CI 10.6%-50.3%) reduction in CCHD deaths per 100,000 births and has a potential reduction of 120 infant deaths per year from CCHD [20].

Several countries such as the United States, China, the Netherlands, and the United Kingdom that have conducted CCHD screening programs with pulse oximetry showed that screening for CCHD using clinical assessment and oximetry is beneficial and cost-effective [10]. Because of this program, the cost of treating complications of CCHD due to late diagnosis can be avoided. A US study reported that a screening program were reported to save 20 infant lives annually at a cost of $40,385 per life-year gained under base case assumptions with additional screening cost of $6.28 per newborn [21].

Meanwhile, low- and middle-income countries still have to face some barriers to execute the pulse oximetry screening program. One study in Morocco revealed several barriers such as tendency to discharge healthy newborns before 24 hours and the investigation of positive screening is also difficult because not all hospital has echocardiography [16]. Other reported challenges in implementing pulse oximetry screening includes the acceptance of program, the timing of screening and significance of false positives rate, and response to positive screen [22].

In our study, we classified obstacles found during screening process into four elements. The first one concerns hospital procedure or workflow. According to the AAP recommendations, the screening process should be done within 24-48 hours of age. But, most of infants in our study were screened before 24 hours due to the hospital procedure of the length of postnatal stay at hospital which is relatively short. The timing of screening should be considered since it will influence the screening results. A previous study revealed that the measurement of saturation before age 24 hours will increase the false positive or negative rate

[17]. The transition from fetal to neonatal circulation and stabilization of systemic oxygen saturation levels might explain this. Study in New Zealand revealed that midwifery-led maternity setting, characterized with early discharge, was influencing the time of testing and it can also influence saturation levels [18].

Other obstacles involved undersupply of standardized neonatal pulse oximetry. These were available in neonatal intensive care units or observation rooms for monitoring of sick newborns, but not routinely available in the postnatal wards. The pulse oximeters were sometimes sensors with tape which are easier to use than finger-type. The pulses tend to be difficult to detect and take longer time to read. The type of probe can affect the effectiveness of examination results. Due to the limited sources, some of hospitals were using adult probes for newborns. Food and Drugs Administrator (FDA) US stated three recommendations in using pulse oximetry. First, aware the factors that can affect the accuracy of a pulse oximeter reading, understand a particular brand and sensor by referring the device labelling or manufacture's website, and always considered the accuracy limitations when using the pulse oximeter to assist in diagnosis and treatment decision. Knowing this recommendation is important for understanding the risk of inaccuracy measurement and providing highest outcomes [23]. Nevertheless, one recent study revealed that accuracy a pulse oximetry device could provide good accuracy in ruling out hypoxemia compared to saturation reading by arterial blood gas sample [24].

The condition of the baby also can become obstacle. In our study, some of the newborns who were unsettled with constantly crying or moving challenge the application and assessment of pulse oximetry. When the screening is being performed, it is recommended that the infants should be awake and settled. Deep sleep may result in hypoventilation and a low saturation documentation [25]. A previous study in New Zealand showed that newborns that are asleep

or unsettled at the time of screening were less likely to have positive results than the newborns who were awake and settled [18].

The last obstacle includes the lack of healthcare in the postnatal ward. The healthcare providers were busy with other clinical duties and sometimes forgot about the screening protocol. Some of them did not consider the pulse oximetry measurement to be in the scope of their practice. Studies in New Zealand stated that most of midwives were sure that pulse oximetry screening was worthwhile to do, but their workload was heavy enough and staff to do this screening were under-resourced. This was one of their concerns about implementing it as a universal screening program [26].

Indonesia has a large number of annual live birth rates; it is about 5 million per year with 62.7% deliveries which were commonly attended by midwives, but Indonesia still has yet to have any national program for screening CCHD [7, 8]. Pulse oximetry fulfils the criteria for mass screening. It is very effective, low cost and can significantly reduce morbidities and mortality by providing earlier detection of CHD. However, to achieve these goals optimally in the setting of limited resources is challenging, but it is not impossible. These goals require extensive standardized training for healthcare providers who work directly in newborn care (midwives, nurse, general practitioner), and the protocols need formal regulations and the involvement of policy makers such as health ministries and pediatric cardiology society for making pulse oximetry screening as recommendation in the standard of care of the newborns.

The major limitation of our study is the high proportion of newborns who were not screened over the study period due to the many aforementioned reasons. This study was also limited by the use of three different types of pulse oximeters from three different manufacturers as well as the use of an adult sensor on a newborn. Despite the limitation, our study is among the first reports of the feasibility of CCHD screening using pulse oximetry in limited resource settings and provides the local evidence of barrier perspectives from healthcare workers during

the screening process. The findings can be used as available local evidence for policymakers before recommending needed changes to the national screening program.

CONCLUSIONS

Pulse oximetry screening is feasible to be implemented to the routine newborn care for detection of CCHD in Indonesia.

List of Abbreviations

AAP: American Academy of Pediatric

ASD: Atrial Septal Defect

CHD: Congenital Heart Disease

CCHD: Critical Congenital Heart Disease

DORV: Double Outlet Right Ventricle

PDA: Patent Ductus Arteriosus

PFO: Patent Foramen Ovale

TGA: Transposition of the Great Aorta

VSD: Ventricle Septal Defect

Declarations

Ethics approval and consent to participate

The Medical and Health Research Ethics Committee (MHREC) of Universitas Gadjah Mada approved this study (230/UN.1/FKKMK.3/IKA.2/TU/PT.01.04/2021). Informed consent to participate was obtained from the parents of participants.

All the experiment protocol for involving humans was in accordance to guidelines of national/international/institutional or Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests

Funding

None

Authors' contributions

IKM, DP, LP were major contributors in writing the manuscript and the study design. DP collected the data. IKM, DP, LP analyzed and interpreted the data. All authors read, critically revised and approved the final manuscript.

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4. Bukti konfirmasi review dan hasil “revision quality check”

(10 Maret 2022)

UGM Mail

Indah Kartika Murni <indah.kartika.m@ugm.ac.id>

BMC Pediatrics: Revision Quality Check "Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia"

Sudhanshu Raj <bmcpediatrics@biomedcentral.com> Thu, Mar 10, 2022 at 12:31 AM
Reply-To: Sudhanshu Raj <bmcpediatrics@biomedcentral.com>
To: indah.kartika.m@ugm.ac.id

Dear Dr. Murni,

Thank you for submitting your revision to BMC. However, in order to process your paper further, we need you to include the following:

1. Please ensure authors listed in the manuscript match those on the system; one author is listed as **"Noormanto"** in the manuscript and "**Noormanto Noormanto**" on our system. Could you please update whichever is incorrect? In addition, please ensure any changes made to the author list are also reflected in the 'Author contribution' statement.

You can access your submission via the following link:

https://submission.nature.com/submission/8eee0911-aa80-416c-a244-d6daac0ced2f
Please make all of the required amendments before selecting the "Submit manuscript" button on the "Review" page.

Meanwhile, if you have any questions please feel free to contact me.

Regards,

Sudhanshu Raj
Editorial Support at BMC

5. Bukti konfirmasi review dan hasil review kedua

(18 April 2022)

Indah Kartika Murni <indah.kartika.m@ugm.ac.id>

BMC Pediatrics: Decision on your manuscript

BMC Pediatrics <bmcpediatrics@biomedcentral.com> Mon, Apr 18, 2022 at 6:59 PM
To: indah.kartika.m@ugm.ac.id

Ref: Submission ID 89915a15-337e-4a9d-add3-227916330e46

Dear Dr Murni,

Re: "Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia"

We are pleased to let you know that your manuscript has now passed through the review stage and is ready for revision. Many manuscripts require a round of revisions, so this is a normal but important stage of the editorial process.

Editor comments
This study reports of the feasibility of CCHD screening using pulse oximetry in limited resource settings and provides the local evidence of barrier perspectives from healthcare workers during the screening process The authors conclude that CCHD screening is very effective, low cost and can significantly reduce morbidities and mortality by providing earlier detection of CHD. However, to achieve these goals optimally in the setting of limited resources is challenging, but it is not impossible. These goals require extensive standardized training for healthcare providers who work directly in newborn care (midwives, nurse, general practitioner), and the protocols need formal regulations and the involvement of policy makers such as health ministries and pediatric cardiology society for making pulse oximetry screening as recommendation in the standard of care of the newborns. The study has much improved after the suggestions of the reviewers and I think that further amendments have to be applied according to the comments of reviewer 2. I suggest revision of the manuscript to meet with the reviewer 2 suggestions

To ensure the Editor and Reviewers will be able to recommend that your revised manuscript is accepted, please pay careful attention to each of the comments that have been pasted underneath this email. This way we can avoid future rounds of clarifications and revisions, moving swiftly to a decision.

Once you have addressed each comment and completed each step listed below, please log in here with the same email you used to submit your manuscript to upload the revised submission and final file:

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Alternatively, please visit https://researcher.nature.com/your-submissions to upload your revised submission and to track progress of any other submissions you might have.

CHECKLIST FOR SUBMITTING YOUR REVISION

1. Please upload a point-by-point response to the comments, including a description of any additional experiments that were carried out and a detailed rebuttal of any criticisms or requested revisions that you disagreed with. This must be uploaded as a 'Point-by-point response to reviewers' file.

Please note that we operate a transparent peer review process, where we publish reviewers' reports with the article, together with any responses that you make to reviewers or the handling Editor.

2. Please highlight all the amends on your manuscript or indicate them by using tracked changes.

3. Check the format for revised manuscripts in our submission guidelines, making sure you pay particular attention to the figure resolution requirements:

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Finally, if you have been asked to improve the language or presentation of your manuscript and would like the assistance of paid editing services, we can recommend our affiliates, Nature Research Editing Service: https://authorservices.springernature.com/language-editing/ and American Journal Experts: https://www.aje.com/go/springernature

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available from our resources page: https://www.springernature.com/gp/researchers/campaigns/english-language-forauthors

To support the continuity of the peer review process, we recommend returning your manuscript to us within 14 days. If you think you will need additional time, please let us know and we will aim to respond within 48 hours.

Kind regards,

Aleliki Karatza
Editorial Board Member
BMC Pediatrics

Reviewer Comments:

Reviewer 2
The authors have addressed all of my concerns and I recommend for publication. There are still a few places that require minor edits by the Journal to correct for grammar/syntax.

Reviewer 3
General

Thank you for the opportunity to review the manuscript “Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia” The authors are commended for undertaking this study in a location where POS does not form part of current standard care. The early identification of asymptomatic newborns with CCHD remains important so as to reduce mortality and facilitate early appropriate intervention to improve outcomes.

I do however find the manuscript provides a quite superficial report by comparison to some studies previously conducted in other low-to middle income countries. As a result, I am questioning whether the study really contributes any new knowledge on the feasibility, practicability and clinical utility of pulse oximetry screening in identifying CCHD in low-to-middle income contexts. It does provide a snapshot of some of the location specific barriers to implementing pulse oximetry screening in Yogyakarta, Indonesia.

The manuscript would benefit from professional language editing to improve readability.

Abstract: No mention on how feasibility was determined.

Background and Introduction

The tile is aligned with the stated aim of the study: “to evaluate the feasibility of CCHD screening using pulse oximetry and provide local evidence for recommendation to local policymakers for the implementing pulse oximetry screening programme in Yogyakarta, Indonesia.” However, the background, methods and results also speak to the accuracy of POS in identifying CCHD in asymptomatic newborns in a low-to-middle income setting prior to hospital discharge. If this forms part of the scope of the current manuscript, this should be reflected in the title and the statement of purpose (aim).

Information on the incidence/ prevalence of CCHD should be included in the background.

The authors refer to CCHD as being a cardiac condition requiring immediate surgical or percutaneous cardiac catheterization interventions and then later refer to the need for intervention in the first year of life. The definition of CCHD is variable and the authors should clarify which definition that have adopted for the use in the current study. The intervention timeframe should align with the definition adopted.

For context, it may be important to indicate that according to the Global Burden of Disease study (2017) LMICs have higher prevalence of CHD due to higher fertility rates, and thereby an increased the burden of disease. Globally, CHD causes over 260,000 deaths annually, and the majority of those deaths occurred in infants younger than one year and in LMICs. Most (90%) of children born with CHD live in locations where there is little to no access to cardiac services and where mortality remains high. Young children with severe CHD in LMICs are more likely to be diagnosed late, not have access to cardiac services and are more likely to die before their fifth birthday than are those children in high income countries.

Not much information is provided in the background on what is known on feasibility, practicability and clinical utility of POS in low-to-middle income setting. Several studies have been conducted in LMICS on this including in South Africa, India, Sri Lanka and Brazil. The background and introduction should be better aligned with the scope and purpose of the study and provide insights into what is currently known on the topic.

Methodology

The methods sections should be written with more detail and clarity to enhance the reader's understanding of the process undertaken. Providing the methods in a logical sequence may also assist the reader in better following the

research steps.

It appears that there are three objectives, but this is not well delineated in the methods i.e., objective i (i) determining the diagnostic accuracy of POS in identify asymptomatic newborns with CCHD and (ii) Provide feedback on the feasibility of POS in the study setting (iii) provide recommendations to present to policy makers. The methods related to each objective should be clearly described.

The POS procedure is unclear. It may be beneficial to supplement the narrative with a figure explaining the exact screening process.

The authors speak of inter-rater agreement correlation for the different types of pulse oximeters devices used. Interrater reliability refers to the extent to which two or more examiners agree when using same measurement tool. As described here the point of interest is not the interrater reliability but rather the accuracy and consistency of the oxygen saturation reading when taken by the three different types of pulse oximeters used in the study. Unclear in the methods how this was tested. E.g. were readings taken on same newborn with all three brands of pulse oximeters and compared. Please provide clarity. Were all the pulse oximeters used in the current study standardised?

The methodology provides no information on how and by by whom the POS data was captured e.g. electronic data base, electronic record.

A more detailed description of the data analysis should be provided. AS stated in the manuscript only basic descriptive statistics calculated when looking at the accuracy of POS in identifying CCHD correctly. no mention is made of additional analyses being conducted to calculate e.g. screening rates, predictive values, sensitivity and specificity.

For objective ii it indicates that a survey was conducted to gather qualitative information on feasibility. Unclear if the survey was paper-based or administered as a semi-structed interview. It is stated that the feasibility study was a qualitative design, but no qualitative methodology is provided.. No information is provided on the method s used for the analysis of the qualitative data. The reporting style is also not consistent with qualitative research. From the table presented in results it seems to be a brief superficial quantitative summary- by comparison qualitative findings are richly descriptive.

Results

Only 57.7% of the eligible newborns were screened prior to hospital discharge. Why was the screening rate of eligible newborns so low? This would be important information to report on and would be an important consideration when establishing the feasibility of POS in asymptomatic newborns prior to hospital discharge in the study setting.

The AAP algorithm includes up to two retests if oxygen saturations do not meet passing criteria. Clinical assessment of the newborn is not required until after the second retest. No information is provided how many children has a positive screen on the first screen and how many had to have a second and third screen with a clinical examination screen. Only noted that 10 newborns had a positive screen. Multiple screens and the need for additional clinical examination would increase the work of the healthcare professionals who are already overworked and understaffed in LMIC settings. This could be important to consider when looking at the required staffing and equipment's requirements to make it feasible.

Table 1
I am looking for more detailed information e.g. Time point/ age of screening? Earliest and latest age point for screen prior discharge?What was the average hospital length stays for an asymptomatic newborns?
Please include units of measure where applicable in the table.
Gestational age < 37 weeks. Unclear is this data being reported here for newborns with a gestational age > 35 weeks but < 37 weeks as newborns with gestational age < 35 weeks were excluded?
Unclear why is meant by type of pulse oximetry – do mean type/brand of pulse oximeter used? Clarify.

“When the baby presented with cyanosis, …….The healthcare workers did not include these neonates for screening.” Unclear why this paragraph is included in the results as all symptomatic newborns were excluded based on the exclusion criteria set.

What proportion failed first and then second screen – requiring follow-up screening? Reason for follow-up screens?

“Most (include 73%) newborns screening used a standardized pulse oximeter (Massimo). The inter-rater agreement among Massimo and Fingertip pulse oximetry was 0.815, while the inter-rater agreement among Massimo and Mindray pulse oximetry was 0.943”. Again, the interrater agreement here is unclear are comparing the oxygen saturation reading on the same newborn with different brand devices or comparing overall values for saturation across devices. Please clarify. Provide reference values and descriptors for how the stated values here should be interpreted.

"The echocardiography performed in the 10 newborns who had the positive screening test showed the following

results" I would suggest that the authors rather present this information in the demographic results tables for ease of reading. Bulleted reporting of results is not recommended.

Figure 1 does not depict how many infants failed the first screen and had to be screened a second time and a third time etc. Provide more detailed information.

Eight out of 10 positive screens subsequently resulted in the identification of CCCHD, yet no information provided in the results on the specificity and sensitivity of the study? Diagnostic odds? Percentage correctly diagnosed etc.

Table 2 Obstacles (I would suggest using the word barriers or challenges) identified by clinicians during screening process.
No information is provided on the number of clinicians that provided the feedback represented in Table 2 and their occupational categories. Feedback may differ according to occupational class, and this may be important to consider when making recommendations.

It may be worth noting the proportion of respondents that identified specific challenges as this may assist the authors in priority ranking the challenges/ barriers to POS. This will assist in identifying key barriers which will need to be addressed in order to implement a successful screening programme.

The findings presented in table 2 does not seem to be consistent with qualitative reporting style and seems to only provide a superficial quantitative summary. Information provided on barriers/ challenges is quite vague.
Were there any technical issues e.g. difficulty with probe placement, probe, or machine malfunction.
Where there any protocol application and interpretation errors?
"Among newborns who had positive result, they did not immediately undergo an echocardiography examination because the echocardiography was performed only in the general and tertiary hospital while they still have to become inpatients." Revise this statement as it does not make sense. Explain more clearly what the barriers were to a newborn with a positive screen receiving echocardiography. This would be important to report as these would be considerations when making recommendations and when considering the value and success of POS for identifying CCHD.

Discussion

At the start if the discussion perhaps again highlight the purpose of the study for the reader and the key findings.

The screen positivity rate was higher than previously reported by other studies. Can the authors offer any explanation for this? How do the diagnoses of CCHD made in the current study relate to the model created for Sensitivity of Pulse Oximetry for Detection of CCHD Screening Targets [Martin et al. 2020 in Updated Strategies for Pulse Oximetry Screening for Critical Congenital Heart Disease]?

The discussion at times reads like a literature review, rather than a critical discussion of the results of the current study in relation previous findings, especially those in developing countries. A more critical discussion would add value to the manuscript.

"In our study, we classified obstacles found during screening process into four elements. Unclear are these themes that emerged from the thematic analysis of the qualitative data collected or where the stated categories predetermined by the authors.

According to the AAP recommendations, the screening process should be done within 24-48 hours of age." More recent guidance on POS for the identification of CCHD in newborns has recommended that screening in newborns younger than 24 hours should be considered acceptable, recognising that early discharge of asymptomatic newborns often occurs. Although it is recognised that CCHD screening false positive rate is higher if screening occurs within the first 24 hours, a further consideration should be that many s with CCHDs present within the first 24 hours with relatively mild symptoms at first and others with rapid cardiovascular collapse or even death. The purpose POS to identify CCHD is to identify these children before such events take place.

"The last obstacle includes the lack of healthcare in the postnatal ward." The authors should clarify what is meant by this statement.

"Some of them did not consider the pulse oximetry measurement to be in the scope of their practice." This does not make sense as the methods state the staff were provided with appropriate education and training prior to the commencement of the study. Who did not view this as within their scope of practice after this and why?

"Indonesia has a large number of annual live birth rates; around 5 million per year with 62.7% deliveries which were commonly attended by midwives, g CCHD" Where do these births take place in community clinics, at home? Provide more information on the context. In case of home births POS is likely to be unfeasible.

In principle pulse oximetry is quite simple, relatively inexpensive, and easy to implement. Screening is just one step in a lifelong continuum of management for the child diagnosed with CCHD and their family. Should a child have a

positive screen for CCHD they require immediate access to definitive diagnosis, safe transportation, and surgical and interventional cardiology services. Newborn screening cannot save as many lives as it should if high quality cardiac services are not available to the child and family following a positive screen. It will help detect cases, but many will not survive or will live a life with serious disability. What is, the study locations downstream cardiac service delivery capacity nd quality as this will have and impact on the success of pulse oximetry screening?

“However, to achieve these goals optimally in the setting of limited resources is challenging, but it is not impossible”. If feasible provide comments on how barriers / challenges could be overcome in resource and human constrained environments in LMICs. Are challenges consistent across LMICs or situation or location specific? What lessons have been learnt and recommendations been put forward by other LMICS?

“Despite the limitation, our study is among the first reports of the feasibility of CCHD screening using pulse oximetry in limited resources “ there are several other LMIC studies. May be first in this specific location.

Recommendations- none provided despite it being stated that part of the purpose of the study was to make recommendations to policy makers.

Limitations no report provided on parent’s acceptance of- and uptake of the pulse oximetry screening for CCHD. This may be an important consideration when looking at feasibility.

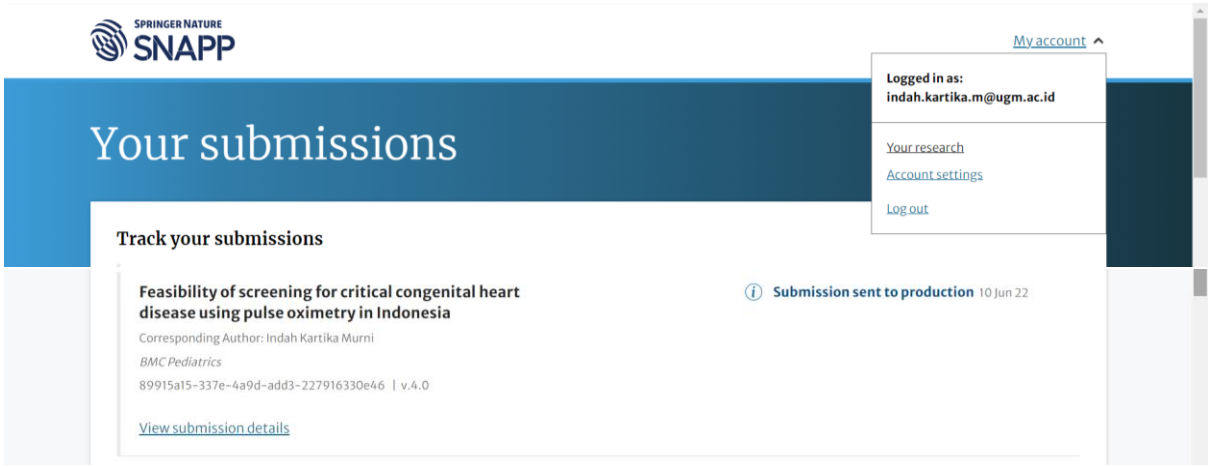
Conclusions

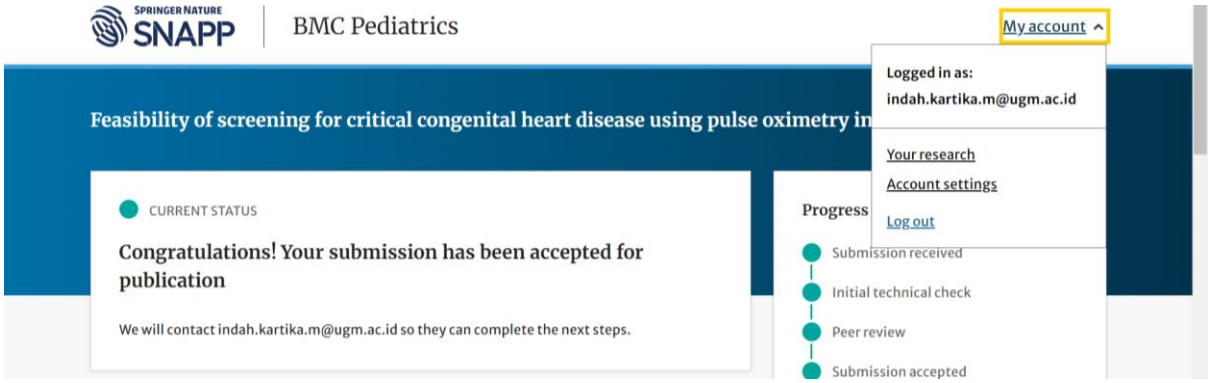
“Pulse oximetry screening is feasible to be implemented to the routine newborn care for detection of CCHD in Indonesia.”
I do not find that the conclusion drawn, is consistent with the study findings. It may be of value e but not necessarily feasible to be implemented on a large scale in the presence of noted t barriers e.g. just more than half of eligible newborns were screened, there are considerable shortage of pulse oximeters, staff forget or appear resistant to conducting screening, delays in access to echocardiography in case of positive screens. The barriers will first need to be addressed before POS to identify CCHD can be widely and successfully implemented in Indonesia.

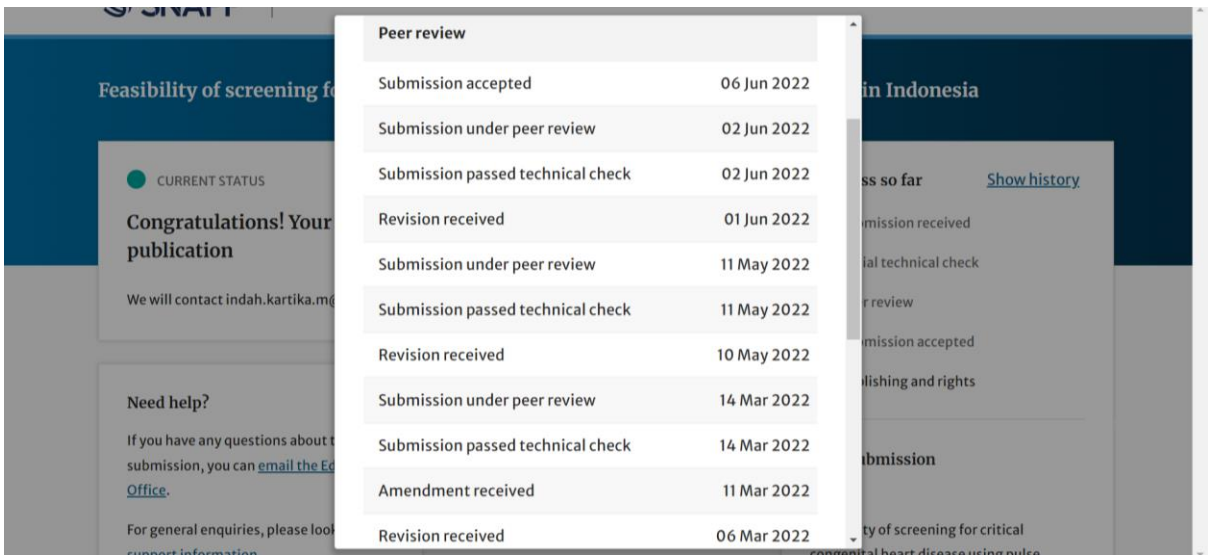
6. Bukti konfirmasi submit revisi kedua, respon kepada reviewer dan artikel yang disubmit

(10 Mei 2022)

Seluruh dokumen, revisi dan respon kepada reviewer jurnal BMC Pediatric dengan judul artikel *"Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia"* diunggah oleh penulis korespondensi (Indah Kartika Murni) melalui website resmi jurnal BMC Pediatric melalui alamat https://submission.springernature.com/ dengan akun Indah.kartika.m@ugm.ac.id







Ref: Submission ID 89915a15-337e-4a9d-add3-227916330e46

"Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia"

Editor comments
This study reports of the feasibility of CCHD screening using pulse oximetry in limited resource settings and provides the local evidence of barrier perspectives from healthcare workers during the screening process The authors conclude that CCHD screening is very effective, low cost and can significantly reduce morbidities and mortality by providing earlier detection of CHD. However, to achieve these goals optimally in the setting of limited resources is challenging, but it is not impossible. These goals require extensive standardized training for healthcare providers who work directly in newborn care (midwives, nurse, general practitioner), and the protocols need formal regulations and the involvement of policy makers such as health ministries and pediatric cardiology society for making pulse oximetry screening as recommendation in the standard of care of the newborns. The study has much improved after the suggestions of the reviewers and I think that further amendments have to be applied according to the comments of reviewer 2. I suggest revision of the manuscript to meet with the reviewer 2 suggestions

Response to Editor:
We thank you very much for the positive comment and interest to our paper. We have revised the manuscript to correct for grammar/syntax as suggested by Reviewer 2.

Reviewer Comments:

Reviewer 2
The authors have addressed all of my concerns and I recommend for publication. There are still a few places that require minor edits by the Journal to correct for grammar/syntax.

Response to Reviewer:
We thank you very much for the positive comment and interest to our paper. We have revised the manuscript to correct for grammar/syntax as suggested.

Reviewer 3
General

Thank you for the opportunity to review the manuscript “Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia” The authors are commended for undertaking this study in a location where POS does not form part of current standard care. The early identification of asymptomatic newborns with CCHD remains important so as to reduce mortality and facilitate early appropriate intervention to improve outcomes.

I do however find the manuscript provides a quite superficial report by comparison to some studies previously conducted in other low-to middle income countries. As a result, I am

questioning whether the study really contributes any new knowledge on the feasibility, practicability and clinical utility of pulse oximetry screening in identifying CCHD in low-to-middle income contexts. It does provide a snapshot of some of the location specific barriers to implementing pulse oximetry screening in Yogyakarta, Indonesia.

The manuscript would benefit from professional language editing to improve readability.

Response to Editor:
We thank you very much for the positive comment and interest to our paper. We have revised the manuscript to correct for grammar/syntax as suggested.

Abstract: No mention on how feasibility was determined.

Response to Reviewer:
Thank you very much for raising on how the feasibility was determined. We have mentioned in the Method section of abstract that a cross-sectional study was conducted at four hospitals in Yogyakarta, Indonesia to evaluate the feasibility of implementing CCHD screening. Newborns aged 24-48 hours who met the inclusion criteria were screened on the right hand and left or right foot using a pulse oximeter.

Background and Introduction

The tile is aligned with the stated aim of the study: “to evaluate the feasibility of CCHD screening using pulse oximetry and provide local evidence for recommendation to local policymakers for the implementing pulse oximetry screening programme in Yogyakarta, Indonesia.” However, the background, methods and results also speak to the accuracy of POS in identifying CCHD in asymptomatic newborns in a low-to-middle income setting prior to hospital discharge. If this forms part of the scope of the current manuscript, this should be reflected in the title and the statement of purpose (aim).

Response to Reviewer:
Thank you very much for raising this. We have revised the manuscript not to include the accuracy of POS in the body of manuscript.

Information on the incidence/ prevalence of CCHD should be included in the background.

Response to Reviewer:
Thank you very much for raising this. We have included this sentence in the Introduction: "Congenital heart disease (CHD) is the most common congenital abnormality in newborns [1] with a reported incidence of 4 to 50 per 1,000 live births [2,3]. Approximately 25% of CHD are classified as critical congenital heart disease (CCHD)"

The authors refer to CCHD as being a cardiac condition requiring immediate surgical or percutaneous cardiac catheterization interventions and then later refer to the need for intervention in the first year of life. The definition of CCHD is variable and the authors should clarify which definition that have adopted for the use in the current study. The intervention timeframe should align with the definition adopted.

Response to Reviewer:
Thank you very much for raising this. We have mentioned the definition of CCHD in the Introduction:
"Critical congenital heart diseases are congenital heart diseases that require immediate transcatheter or surgical intervention in the first year of life".

For context, it may be important to indicate that according to the Global Burden of Disease study (2017) LMICs have higher prevalence of CHD due to higher fertility rates, and thereby an increased the burden of disease. Globally, CHD causes over 260,000 deaths annually, and the majority of those deaths occurred in infants younger than one year and in LMICs. Most (90%) of children born with CHD live in locations where there is little to no access to cardiac services and where mortality remains high. Young children with severe CHD in LMICs are more likely to be diagnosed late, not have access to cardiac services and are more likely to die before their fifth birthday than are those children in high income countries.

Not much information is provided in the background on what is known on feasibility, practicability and clinical utility of POS in low-to-middle income setting. Several studies have been conducted in LMICS on this including in South Africa, India, Sri Lanka and Brazil. The background and introduction should be better aligned with the scope and purpose of the study and provide insights into what is currently known on the topic.

Response to Reviewer:
Thank you very much for the feedback. We have added this sentence in the Introduction:
"Studies on the feasibility of pulse oximetry screening to detect CCHD had been conducted in low- and middle-income country setting including South Africa [11], India [12], Sri Lanka [13] and Brazil [14]".

The methods sections should be written with more detail and clarity to enhance the reader's understanding of the process undertaken. Providing the methods in a logical sequence may also assist the reader in better following the research steps.

Response to Reviewer:
Thank you very much for the feedback. We have added the algorithm of study was presented in figure 1.

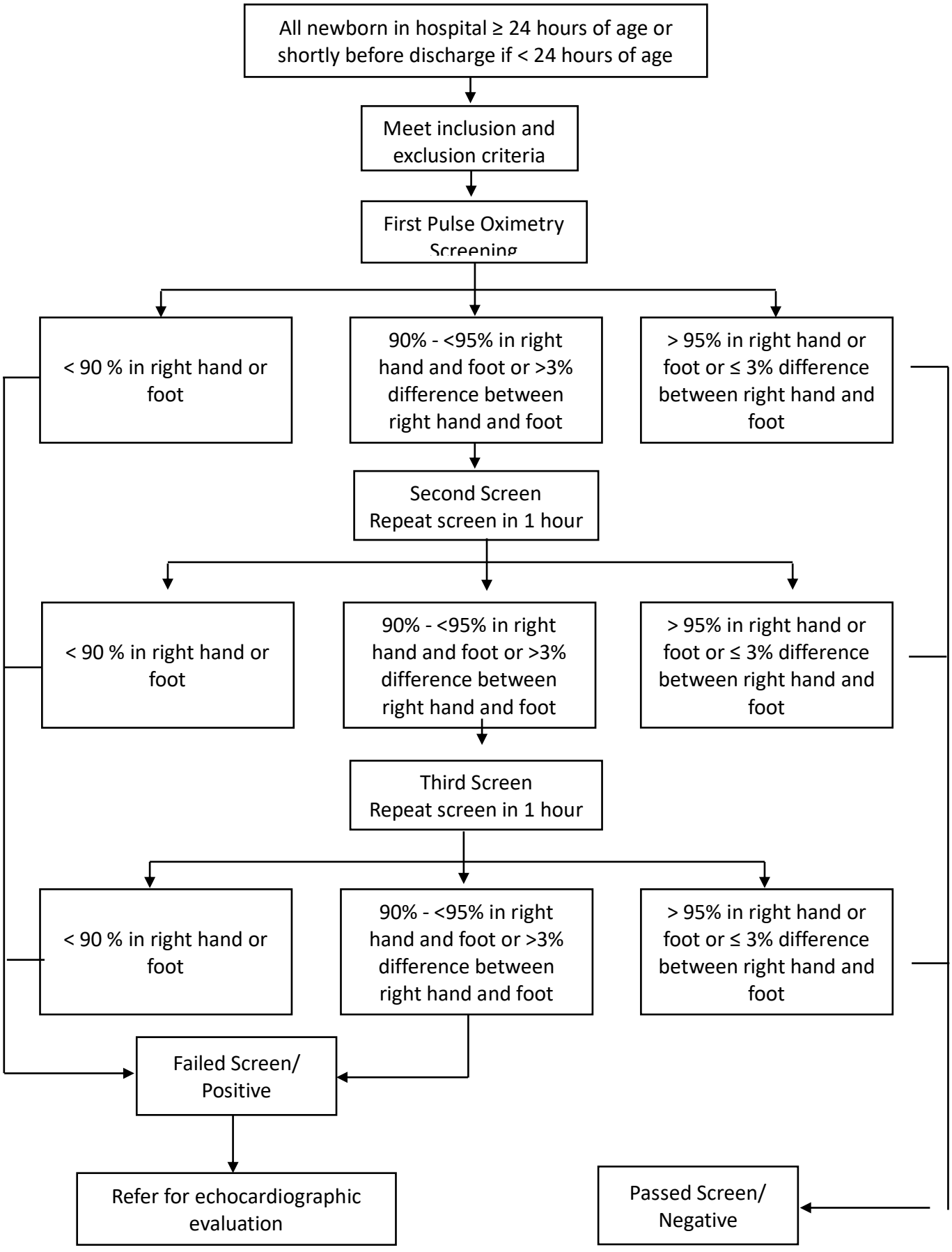
It appears that there are three objectives, but this is not well delineated in the methods i.e., objective i (i) determining the diagnostic accuracy of POS in identify asymptomatic newborns with CCHD and (ii) Provide feedback on the feasibility of POS in the study setting (iii) provide recommendations to present to policy makers. The methods related to each objective should be clearly described.

Response to Reviewer:
Thank you very much for the feedback. We did not conduct the diagnostic accuracy of POS. We have revised the manuscript for clarity.

The POS procedure is unclear. It may be beneficial to supplement the narrative with a figure explaining the exact screening process.

Response to Reviewer:
Thank you very much for the feedback. We have added the algorithm of study was presented in figure 1.

Figure 1. Algorithm of study protocol (Adapted from the protocol in Ewer et al [17])



The authors speak of inter-rater agreement correlation for the different types of pulse oximeters devices used. Interrater reliability refers to the extent to which two or more examiners agree when using same measurement tool. As described here the point of interest is not the interrater reliability but rather the accuracy and consistency of the oxygen saturation reading when taken by the three different types of pulse oximeters used in the study. Unclear in the methods how this was tested. E.g. were readings taken on same newborn with all three brands of pulse oximeters and compared. Please provide clarity. Were all the pulse oximeters used in the current study standardised?

Response to Reviewer:
Thank you very much for raising this concern and positive feedback. Because the pulse oximetry available varies in the hospitals and therefore to compensate for the variability of available oximeter types among hospitals, we performed an agreement correlation before recruitment using three types of pulse oximeters: Massimo (Massimo corporation, Irvine, CA, USA), Mindray (Mindray Cooperation, Nanshan, Shenzhen, China) and fingertip. We considered that this could standardised the available pulse oximetry by comparing with the standard POS of Massimo (Massimo corporation, Irvine, CA, USA). Since the agreement among Massimo and Fingertip pulse oximetry was 0.815 and the agreement among Massimo and Mindray pulse oximetry was 0.943, the Fingertip and Mindray POS were considered to be accurate as compared with standardised Massimo POS.

The methodology provides no information on how and by whom the POS data was captured e.g. electronic data base, electronic record.

Response to Reviewer:
Thank you very much for raising this concern and positive feedback. We have included these sentences in the Method section:
"Screening was performed by a healthcare worker, which included either a doctor, nurse, or midwife in charge. The measurement was written manually in case report form. Training of healthcare workers was conducted prior to the study to avoid variability in screening procedures".

A more detailed description of the data analysis should be provided. AS stated in the manuscript only basic descriptive statistics calculated when looking at the accuracy of POS in identifying CCHD correctly. no mention is made of additional analyses being conducted to calculate e.g. screening rates, predictive values, sensitivity and specificity.

Response to Reviewer:
Thank you very much for the feedback. We did not conduct the diagnostic accuracy of POS. We have revised the manuscript for clarity.

For objective ii it indicates that a survey was conducted to gather qualitative information on feasibility. Unclear if the survey was paper-based or administered as a semi-structed interview. It is stated that the feasibility study was a qualitative design, but no qualitative methodology is provided. No information is provided on the methods used for the analysis

of the qualitative data. The reporting style is also not consistent with qualitative research. From the table presented in results it seems to be a brief superficial quantitative summary- by comparison qualitative findings are richly descriptive.

Response to Reviewer:
Thank you very much for raising this and the feedback. A semi-structured interview on barriers experienced by the medical personnel throughout the screening process was also conducted. The qualitative data were then reviewed, defined and presented thematically based of the common barriers. We have added these sentences in the Method section.

Results

Only 57.7% of the eligible newborns were screened prior to hospital discharge. Why was the screening rate of eligible newborns so low? This would be important information to report on and would be an important consideration when establishing the feasibility of POS in asymptomatic newborns prior to hospital discharge in the study setting.

Response to Reviewer:
Thank you very much for raising this. We have included this concern in the limitation of our study, which is the high proportion of newborns who were not screened over the study period due to the many aforementioned barriers including hospital procedures or workflow, the scarcity of standardized neonatal pulse oximeters, related with the condition of the baby, the lack of healthcare personnel in the postnatal ward, and some did not consider the pulse oximetry measurement to be within the scope of their practice due to lower motivation because no incentive was given.

The AAP algorithm includes up to two retests if oxygen saturations do not meet passing criteria. Clinical assessment of the newborn is not required until after the second retest. No information is provided how many children has a positive screen on the first screen and how many had to have a second and third screen with a clinical examination screen. Only noted that 10 newborns had a positive screen. Multiple screens and the need for additional clinical examination would increase the work of the healthcare professionals who are already overworked and understaffed in LMIC settings. This could be important to consider when looking at the required staffing and equipment's requirements to make it feasible.

Response to Reviewer:
Thank you very much for raising this. We have revised this figure 2 below showing on how many children has a positive screen on the first screen and how many had to have a second and third screen with a clinical examination screen.

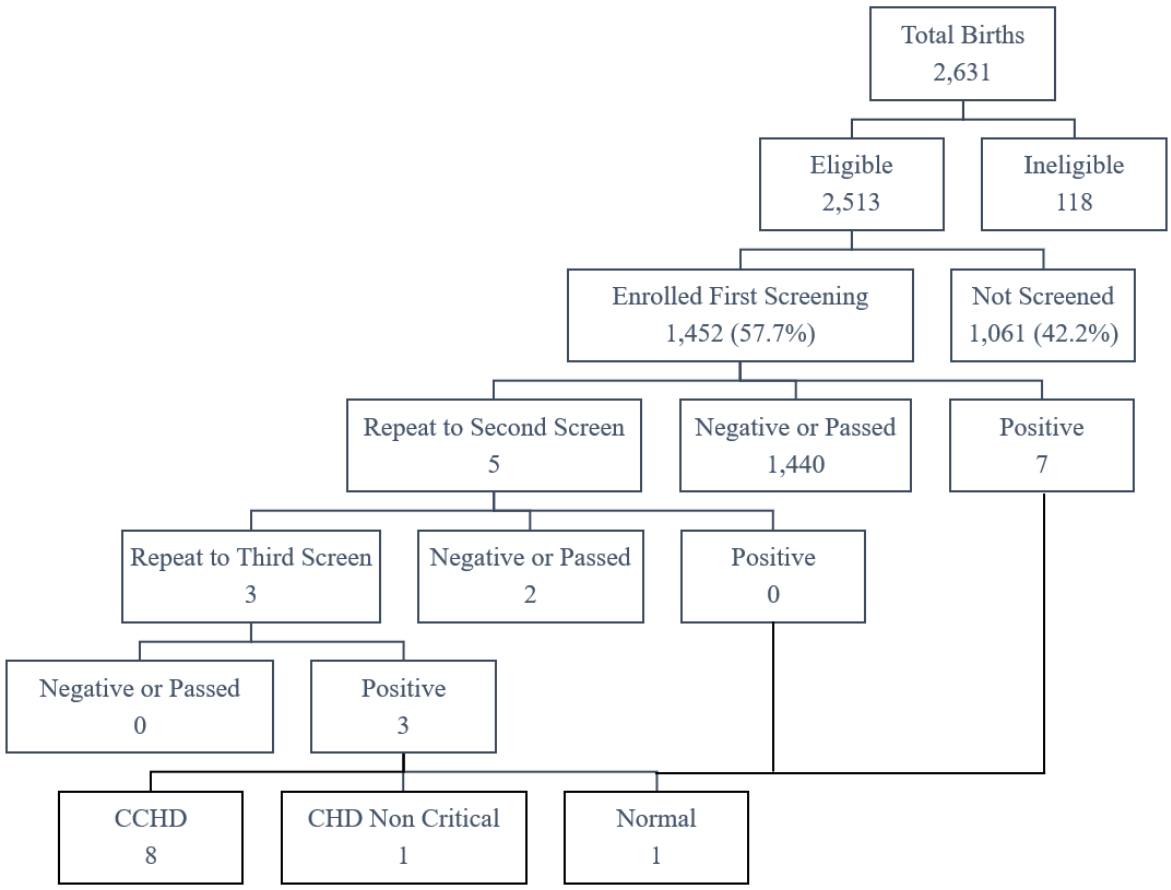


Table 1

I am looking for more detailed information e.g. Time point/ age of screening? Earliest and latest age point for screen prior discharge?What was the average hospital length stays for an asymptomatic newborns?

Please include units of measure where applicable in the table.

Gestational age < 37 weeks. Unclear is this data being reported here for newborns with a gestational age > 35 weeks but < 37 weeks as newborns with gestational age < 35 weeks were excluded?

Unclear why is meant by type of pulse oximetry – do mean type/brand of pulse oximeter used? Clarify.

Response to Reviewer:

Thank you very much for raising this. We have revised the Table 1 as suggested. We included newborns with a gestational age > 35 weeks but < 37 weeks and newborns with gestational age < 35 weeks were excluded.

The earliest age point of screening prior discharge was 6 hours and the latest age point was 78 hours.

"When the baby presented with cyanosis, …….The healthcare workers did not include these neonates for screening." Unclear why this paragraph is included in the results as all symptomatic newborns were excluded based on the exclusion criteria set.

Response to Reviewer's comment:
We thank you very much for the positive comments. As implied by previous Reviewer that this study adds additional evidence that CCHD screening using pulse oximetry is valuable in low resource settings, and that these regions may have a higher yield than in developed countries where the number of infants identified with CCHD is higher per 1,000 infants screened. In this study, infants were being identified even with a not insignificant prenatal detection rate of 14 infants out of 2,513. All of the infants who failed screening were found to have either CCHD or CHD, which is unusual as several large studies from various countries have shown that secondary non-cardiac targets are identified as frequently or more frequently than CCHD. It would be helpful for the us to address whether non-cardiac causes of low oxygen readings were addressed or assessed for in the infants who failed. Therefore, we mentioned that in daily practice, when the baby getting bluish or desaturated or respiratory distress, the doctors or nurses were directly administered oxygen supplementation for the babies. These frequently occurred soon after birth (less than 24 hours) and most commonly causes were asphyxia, pulmonary hypertension of the newborn, or other pulmonary problems. The healthcare workers did not include these neonates for screening.

What proportion failed first and then second screen – requiring follow-up screening? Reason for follow-up screens?

Response to Reviewer's comment:
We thank you for the feedback. As previously mentioned in the flowchart that in the first screening the number of newborns who failed were 7, in the second screening were 3. No follow-up screening was conducted.

“Most (include 73%) newborns screening used a standardized pulse oximeter (Massimo). The inter-rater agreement among Massimo and Fingertip pulse oximetry was 0.815, while the inter-rater agreement among Massimo and Mindray pulse oximetry was 0.943”. Again, the interrater agreement here is unclear are comparing the oxygen saturation reading on the same newborn with different brand devices or comparing overall values for saturation across devices. Please clarify. Provide reference values and descriptors for how the stated values here should be interpreted.

Response to Reviewer's comment:
We thank you very much for the positive comments and feedback. We have revised accordingly as suggested.
Because the pulse oximetry available varies in the hospitals and therefore to compensate for the variability of available oximeter types among hospitals, we performed an agreement correlation before recruitment using three types of pulse oximeters: Massimo (Massimo corporation, Irvine, CA, USA), Mindray (Mindray Cooperation, Nanshan, Shenzhen, China) and fingertip. We considered that this could standardised the available pulse oximetry by comparing with the standard POS of Massimo (Massimo corporation, Irvine, CA, USA). Since the agreement among Massimo and Fingertip pulse oximetry was 0.815 and the agreement

among Massimo and Mindray pulse oximetry was 0.943, the Fingertip and Mindray POS were considered to be accurate as compared with standardised Massimo POS.

"The echocardiography performed in the 10 newborns who had the positive screening test showed the following results" I would suggest that the authors rather present this information in the demographic results tables for ease of reading. Bulleted reporting of results is not recommended.

Response to Reviewer's comment:
We thank you very much for the positive comments and feedback. We have added Table 2 presenting the information on echocardiography results in the 10 newborns who had the positive screening test as suggested.

Figure 1 does not depict how many infants failed the first screen and had to be screened a second time and a third time etc. Provide more detailed information.

Response to Reviewer:
Thank you very much for raising this. We have revised this figure 2 showing on how many children has a positive screen on the first screen and how many had to have a second and third screen with a clinical examination screen.

Eight out of 10 positive screens subsequently resulted in the identification of CCCHD, yet no information provided in the results on the specificity and sensitivity of the study? Diagnostic odds? Percentage correctly diagnosed etc.

Response to Reviewer:
Thank you very much for the feedback. We did not conduct the diagnostic accuracy of POS. We have revised the manuscript for clarity.

Table 2 Obstacles (I would suggest using the word barriers or challenges) identified by clinicians during screening process.
No information is provided on the number of clinicians that provided the feedback represented in Table 2 and their occupational categories. Feedback may differ according to occupational class, and this may be important to consider when making recommendations.

It may be worth noting the proportion of respondents that identified specific challenges as this may assist the authors in priority ranking the challenges/ barriers to POS. This will assist in identifying key barriers which will need to be addressed in order to implement a successful screening programme.

Response to Reviewer's comment:
We thank you very much for the positive comments and feedback.
We have revised obstacles with the word barriers or challenges as suggested.

We have no detailed information on their occupational categories, but the screening was performed by a healthcare worker, which included either a doctor, nurse, or midwife in charge and the training of healthcare workers was conducted prior to the study to avoid variability in screening procedures.

The findings presented in table 2 does not seem to be consistent with qualitative reporting style and seems to only provide a superficial quantitative summary. Information provided on barriers/ challenges is quite vague.
Were there any technical issues e.g. difficulty with probe placement, probe, or machine malfunction.
Where there any protocol application and interpretation errors?
"Among newborns who had positive result, they did not immediately undergo an echocardiography examination because the echocardiography was performed only in the general and tertiary hospital while they still have to become inpatients." Revise this statement as it does not make sense. Explain more clearly what the barriers were to a newborn with a positive screen receiving echocardiography. This would be important to report as these would be considerations when making recommendations and when considering the value and success of POS for identifying CCHD.

Response to Reviewer's comment:
We thank you very much for the positive comments and feedback. We have revised the sentence as suggested:
"Among subjects with positive screening results, echocardiography examinations were not all immediately performed. This was mainly caused by the availability of echocardiographs only at the tertiary and general hospitals, meanwhile some subjects were inpatients at the other two hospitals".

Discussion

At the start if the discussion perhaps again highlight the purpose of the study for the reader and the key findings.

Response to Reviewer's comment:
We thank you very much for the positive comments and feedback. We have added these sentences at the start of the Discussion section:
"This study explored the feasibility of implementing CCHD screening with pulse oximetry for 1,452 newborns in Yogyakarta, Indonesia. The results of the study indicate that pulse oximetry screening is feasible to be implemented within the routine newborn care setting for CCHD in Indonesia".

The screen positivity rate was higher than previously reported by other studies. Can the authors offer any explanation for this? How do the diagnoses of CCHD made in the current study relate to the model created for Sensitivity of Pulse Oximetry for Detection of CCHD Screening Targets [Martin et al. 2020 in Updated Strategies for Pulse Oximetry Screening for Critical Congenital Heart Disease]?

Response to Reviewer:
Thank you very much for the feedback. The screen positivity rate in our study was higher than previously reported by other studies might be because we conducted pulse oximetry screening at the hospitals in the Yogyakarta city and regions in the Province which also have referral patients from other relatively small hospitals and maternity clinics.
We did not conduct the diagnostic accuracy of POS.

The discussion at times reads like a literature review, rather than a critical discussion of the results of the current study in relation previous findings, especially those in developing countries. A more critical discussion would add value to the manuscript.

Response to Reviewer:
Thank you very much for the feedback. We have revised accordingly as suggested.

"In our study, we classified obstacles found during screening process into four elements. Unclear are these themes that emerged from the thematic analysis of the qualitative data collected or where the stated categories predetermined by the authors.

According to the AAP recommendations, the screening process should be done within 24-48 hours of age." More recent guidance on POS for the identification of CCHD in newborns has recommended that screening in newborns younger than 24 hours should be considered acceptable, recognising that early discharge of asymptomatic newborns often occurs. Although it is recognised that CCHD screening false positive rate is higher if screening occurs within the first 24 hours, a further consideration should be that many s with CCHDs present within the first 24 hours with relatively mild symptoms at first and others with rapid cardiovascular collapse or even death. The purpose POS to identify CCHD is to identify these children before such events take place.

"The last obstacle includes the lack of healthcare in the postnatal ward." The authors should clarify what is meant by this statement.

"Some of them did not consider the pulse oximetry measurement to be in the scope of their practice." This does not make sense as the methods state the staff were provided with appropriate education and training prior to the commencement of the study. Who did not view this as within their scope of practice after this and why?

Response to Reviewer:
Thank you very much for the feedback. We have added some more sentences in the Discussion regarding the barriers. Lack of healthcare personnel in the postnatal ward might because the healthcare providers were occupied with other clinical duties and sometimes forgot the screening protocol. Some did not consider the pulse oximetry measurement to be within the scope of their practice due to low motivation because no incentive was given. Studies in South Africa reported that most all nurse involved in that study were satisfied with the purpose and aim of the study. But they do not have enough time to do while their workload were heavy enough before this study was began [11]. Studies in New Zealand

stated that most of midwives agreed that pulse oximetry screening was beneficial, but their already heavy workload prevented them from routinely performing screens. This was one of their concerns regarding the implementation of pulse oximetry as a universal screening program [29].

“Indonesia has a large number of annual live birth rates; around 5 million per year with 62.7% deliveries which were commonly attended by midwives, g CCHD” Where do these births take place in community clinics, at home? Provide more information on the context. In case of home births POS is likely to be unfeasible.

Response to Reviewer:
Thank you very much for the feedback. Most deliveries were commonly attended by midwives and these births take place in community clinics. Seventy nine percent woman gave birth at health care centre, around 16% gave birth at home.
To make it feasible we are planning to conduct extensive standardized training for healthcare providers who work directly in childbirth and newborn care (midwives, nurse, general practitioner), the measurement protocols need formal regulations and the involvement of policy makers such as health ministries and the pediatric cardiology society to make pulse oximetry screening a recommendation in the standard care of newborns.

In principle pulse oximetry is quite simple, relatively inexpensive, and easy to implement. Screening is just one step in a lifelong continuum of management for the child diagnosed with CCHD and their family. Should a child have a positive screen for CCHD they require immediate access to definitive diagnosis, safe transportation, and surgical and interventional cardiology services. Newborn screening cannot save as many lives as it should if high quality cardiac services are not available to the child and family following a positive screen. It will help detect cases, but many will not survive or will live a life with serious disability. What is, the study locations downstream cardiac service delivery capacity and quality as this will have and impact on the success of pulse oximetry screening?

Response to Reviewer:
Thank you very much for the positive feedback and suggestion. We have added these sentence in the Discussion as suggested.

“However, to achieve these goals optimally in the setting of limited resources is challenging, but it is not impossible”. If feasible provide comments on how barriers / challenges could be overcome in resource and human constrained environments in LMICs. Are challenges consistent across LMICs or situation or location specific? What lessons have been learnt and recommendations been put forward by other LMICS?

Response to Reviewer:
Thank you very much for the feedback. The challenges are also consistent across LMICs and also some studies in the high income countries as described in the Discussion section.

"One study in Morocco revealed barriers such as the tendency to discharge healthy newborns before 24 hours, and the difficulty in confirming positive screening results due to

the lack of available echocardiographs in several hospitals [19]. Other reported challenges in implementing pulse oximetry screening includes acceptance of the program, timing of screening and significance of false positives rate, and response to positive screen results [25].

"It is recommended that infants should be fully awake but settled during the screening process. Deep sleep may result in hypoventilation and low saturation results [28]. A previous study in New Zealand showed that newborns that were asleep or unsettled during screening were less likely to have positive results than those who were awake but settled [21].

The healthcare providers were occupied with other clinical duties and sometimes forgot the screening protocol. Some did not consider the pulse oximetry measurement to be within the scope of their practice due to low motivation because no incentive was given. Studies in South Africa reported that most all nurse involved in that study were satisfied with the purpose and aim of the study. But they do not have enough time to do while their workload were heavy enough before this study was began [11]. Studies in New Zealand stated that most of midwives agreed that pulse oximetry screening was beneficial, but their already heavy workload prevented them from routinely performing screens. This was one of their concerns regarding the implementation of pulse oximetry as a universal screening program [29].

“Despite the limitation, our study is among the first reports of the feasibility of CCHD screening using pulse oximetry in limited resources “ there are several other LMIC studies. May be first in this specific location.

Recommendations- none provided despite it being stated that part of the purpose of the study was to make recommendations to policy makers.

Limitations no report provided on parent’s acceptance of- and uptake of the pulse oximetry screening for CCHD. This may be an important consideration when looking at feasibility.

Response to Reviewer:
Thank you very much for the feedback. We have added this sentence in the limitation.

Conclusions

“Pulse oximetry screening is feasible to be implemented to the routine newborn care for detection of CCHD in Indonesia.”
I do not find that the conclusion drawn, is consistent with the study findings. It may be of value e but not necessarily feasible to be implemented on a large scale in the presence of noted t barriers e.g. just more than half of eligible newborns were screened, there are considerable shortage of pulse oximeters, staff forget or appear resistant to conducting screening, delays in access to echocardiography in case of positive screens. The barriers will

first need to be addressed before POS to identify CCHD can be widely and successfully implemented in Indonesia.

Response to Reviewer:
Thank you very much for the feedback.
With all those limitation and barriers, we revised the conclusion revealing pulse oximetry screening might be feasible to be implemented within the routine newborn care for detection of CCHD in Indonesia. In order to successfully implemented POS to identify CCHD in Indonesia, the barriers will need to be addressed.

TITLE PAGE

Type of article: Original Article

Title of the article: Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia

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- Main text: 2175 words

Keywords: congenital heart disease, pulse oximetry screening, Indonesia, critical congenital heart disease

Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia

Indah K Murni, Tunjung Wibowo, Nadya Arafuri, Vicka Oktaria, Lucia K Dinarti, Dicky Panditatwa, Linda Patmasari, Noormanto Noormanto, Sasmito Nugroho

Abstract

Background: Screening of critical congenital heart disease (CCHD) using pulse oximetry is a routine procedure in many countries, but not in Indonesia. We aimed to evaluate the feasibility of implementing CCHD screening with pulse oximetry for newborns in Yogyakarta, Indonesia.

Methods: A cross-sectional study was conducted at four hospitals in Yogyakarta, Indonesia. Newborns aged 24-48 hours who met the inclusion criteria were screened on the right hand and left or right foot using a pulse oximeter. Positive results were indicated by either (1) SpO_2 level <90% in one extremity, (2) SpO_2 level of 90-94% in both right hand and either foot on three measurements conducted 1 hour apart, or (3) a saturation difference >3% between the upper and lower extremity on three measurements conducted 1 hour apart. Positive findings were confirmed by echocardiography.

Results: Of 1,452 newborns eligible for screening, 10 had positive results and were referred for echocardiographic evaluation. Of those, 8 (6 per 1000 live birth, 8/1,452) had CCHD. Barriers found during screening processes were associated with hospital procedures, equipment, healthcare personnel, and condition of the newborn.

Conclusion: Pulse oximetry screening might be feasible to be implemented within the routine newborn care setting for CCHD in Indonesia. In order to successfully implemented pulse oximetry screening to identify CCHD in Indonesia, the barriers will need to be addressed.

BACKGROUND

Congenital heart disease (CHD) is the most common congenital abnormality in newborns [1] with a reported incidence of 4 to 50 per 1,000 live births [2,3]. Approximately 25% of CHD are classified as critical congenital heart disease (CCHD), that are often lethal and require immediate transcatheter or surgical intervention in the first year of life [4]. Furthermore, CHD is responsible for over 260,000 deaths annually worldwide [5] with a CCHD associated mortality count of 34.8% in developing countries [6]. Challenges primary lies in early detection of CCHD, with some CCHD newborns prematurely sent home before diagnosis, as they may appear healthy at first. This challenge is considerably noticeable in resource limited settings.

In Indonesia, approximately 2.5 per 1,000 live births suffer from CHD [7]. A significant delay in CHD diagnosis is seen in 6 out of 10 cases, most with severe complications [8]. Additionally, one-third of the newborns with CCHD were not detected before discharge [9]. Pulse oximetry screening for CCHD has been recommended and widely implemented in many countries, leading to a significant reduction in mortality among newborns with CCHD. What is more, unnecessary costs related to complications due to late diagnosis of CCHD can be avoided [10]. Studies on the feasibility of pulse oximetry screening to detect CCHD had been conducted in low- and middle-income country setting including South Africa [11], India [12], Sri Lanka [13] and Brazil [14]. Despite the importance shown in the immediate detection of CCHD, no screening program has been implemented in Indonesia, causing the often presentation of late and even terminal cases at tertiary hospitals. Therefore, this study aims to evaluate the feasibility of CCHD screening using pulse oximetry and provide relatable evidence for local and national policymakers in implementing pulse oximetry screening program in Indonesia.

METHODS

A cross-sectional study was conducted at four hospitals in Yogyakarta, Indonesia from August 1st, 2021, to November 30th, 2021. The hospitals namely, Dr. Sardjito a class A, tertiary referral hospital; JIH a class B, general hospital; and Sadewa and Sakina Idaman, both class Cs maternal and neonatal care specialty hospitals. All seemingly healthy newborns were included, and those born at <35 weeks' gestation age, prenatally diagnosed with CHD, carrying dysmorphic features or signs of cardiovascular abnormalities such as cyanosis, cardiac murmur or those with abnormal vital signs were excluded [15, 16].

Pulse oximetry screening was performed using the American Academy of Pediatrics (AAP) standardized algorithm by measuring oxygen saturation of the right hand and the left or right foot between 24-48 hours of age or before 24 hours of age if the baby is discharged early. Screening of CCHD was considered negative or passed if measurement of SpO_2 was ≥95% for both the right hand and right or left foot, with a difference of <3% between the right hand and either foot. No further cardiac evaluation was performed in these subjects unless indicated by subsequent clinical condition(s). Screening was considered positive or failed if at least one of the following: (1) SpO2 level <90% in one extremity, (2) SpO2 level of 90-94% in both right hand and either foot on three measurements conducted 1 hour apart, or (3) a saturation difference >3% between the upper and lower extremity on three measurements conducted 1 hour apart [17]. Subjects failing the screening were referred to Dr. Sardjito Hospital for echocardiographic evaluation. The algorithm of study was presented in figure 1.

Screening was performed by a healthcare worker, which included either a doctor, nurse, or midwife in charge. The measurement was written manually in case report form. Training of healthcare workers was conducted prior to the study to avoid variability in screening procedures. To compensate for the variability of available oximeter types among hospitals, we performed an agreement correlation before recruitment using three types of pulse oximeters:

Massimo (Massimo corporation, Irvine, CA, USA), Mindray (Mindray Cooperation, Nanshan, Shenzhen, China) and fingertip.

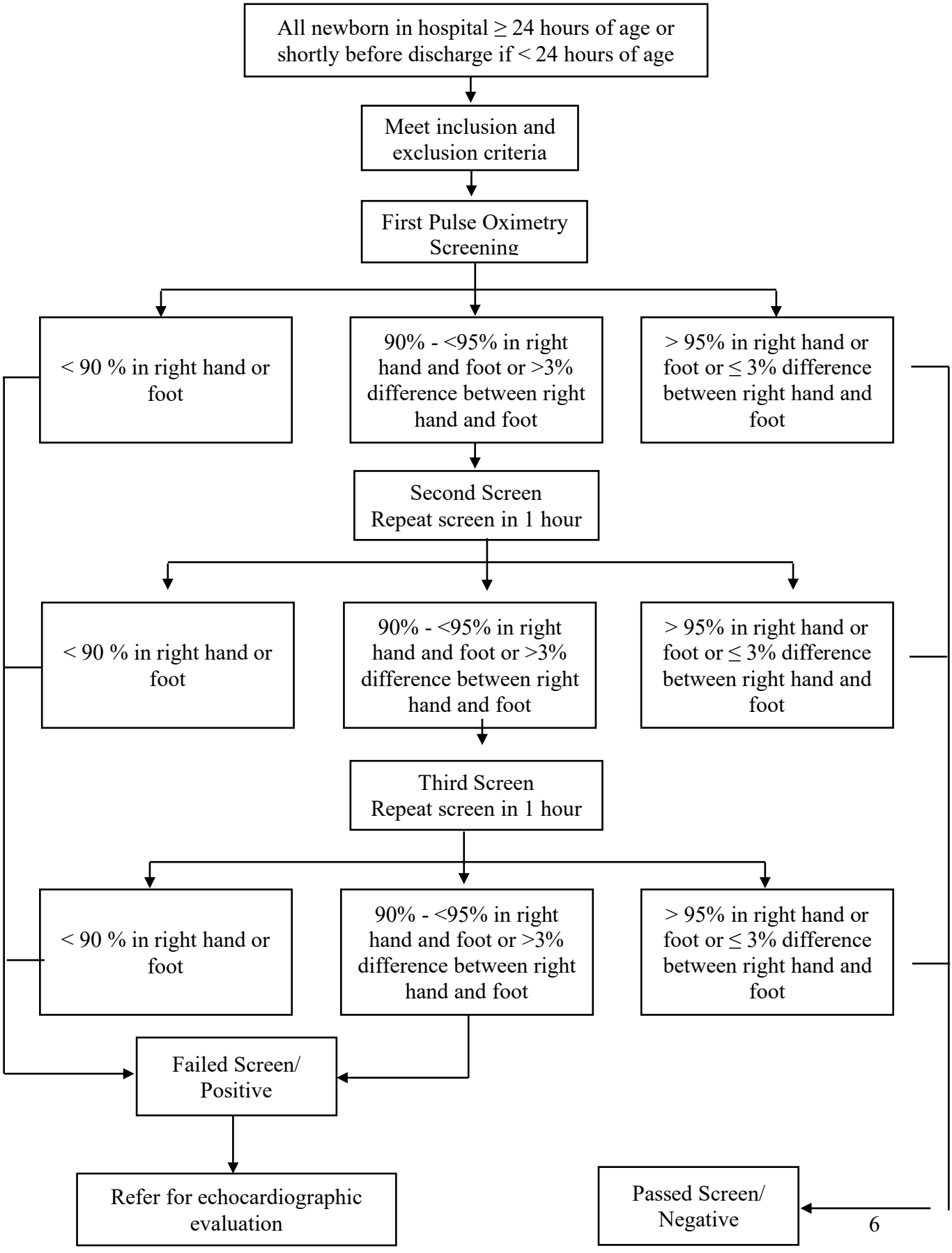

Figure 1. Algorithm of study protocol (Adapted from the protocol in Ewer et al [17])

Data were analyzed using STATA version 12.1 (StataCorp, College Station, Texas, USA) and presented appropriately. Descriptive statistics were presented as numbers and percentages, mean or medians.

A semi-structured interview on barriers experienced by the medical personnel throughout the screening process was also conducted. The qualitative data were then reviewed, defined and presented thematically based of the common barriers.

Ethics

The Medical and Health Research Ethics Committee, of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia has approved this study (230/UN.1/FKKMK.3/IKA.2/TU/PT.01.04/2021). Informed consent to participate in the study was obtained from the parents or legal guardians of participants.

All experiment protocols involving humans was in accordance with national/international/institutional guidelines or the Declaration of Helsinki.

RESULTS

Throughout the study period, there were 2,631 newborns delivered at the four selected hospitals. From 118 newborns who were ineligible: 89 were <35-weeks' gestation age, 10 had passed away, 14 were prenatally confirmed with CHD and 5 had dysmorphic features. A total of 1,452 (57.7%) from the remaining 2,513 eligible newborns were then screened (Figure 2). Of the 1,452 babies screened, seven babies had positive results at first screen and only 5 (0.3%) needed a second screen. Two of the babies were passed the second screen. The third screen were positive to all three babies. Of those, 10 had positive results and were referred for further echocardiography confirmation, finally resulting in 8 (0.6%) subjects with CCHD. The

screening was performed within a period of ≤24 hours after birth in 855 subjects (59%) and after 24 hours in 597 (41%) subjects.

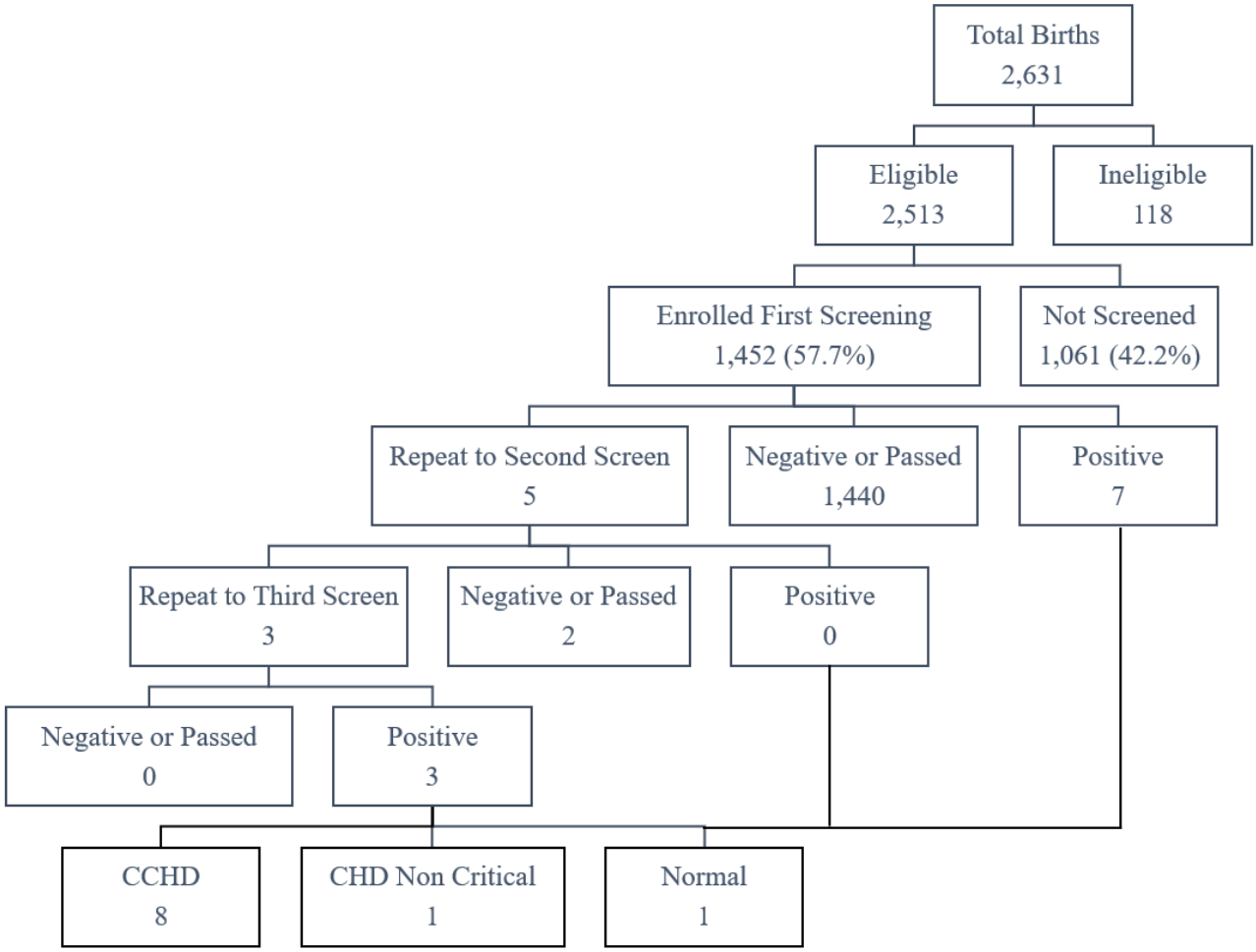

Figure 2. Distribution of the newborns enrolled in the study.

Oxygen supplementation was promptly administered in cases where newborns were visibly bluish or when desaturation of SpO_2 levels or signs of respiratory distress were apparent. These frequently occurred soon after birth (less than 24 hours) and was most commonly caused by asphyxia, pulmonary hypertension of the newborn, or other pulmonary problems. The healthcare workers did not include these neonates for screening.

Most screening was performed using the standardized pulse oximetry (Massimo). The agreement among Massimo and Fingertip pulse oximetry was 0.815, while the agreement among Massimo and Mindray pulse oximetry was 0.943.

The baseline characteristics of the eligible newborns are presented in Table 1. Echocardiography performed in the 10 newborns with positive screening results showed in the Table 2.

Table 1. Baseline characteristics of screened newborns

Characteristics	Newborns n=1,452 (%)
Sex, n (%)	
Male	769 (53)
Female	683 (47)
Birth weight in gram, median (min-max)	3,045.4 (1,360-4,532)
<2,500	154 (10.6)
2,500-4,000	1,279 (88.1)
>4,000	19 (1.3)
Gestational age in weeks, n (%)	
35-<37	81 (5.6)
37-42	1,367 (94.1)
>42	4 (0.3)
Type of delivery, n (%)	
Caesarean section	859 (59.2)
Vacuum extraction	29 (2)
Normal	564 (38.8)

Type of pulse oximetry, n (%)	
Massimo	1,067 (73.5)
Fingertip	18 (1.2)
Mindray	367 (25.3)

Table 2. Echocardiography results of 10 newborns with positive screening pulse oximetry

CCHD (n=8)	Non CCHD (n=2)
2 cases of Ebstein anomaly	1 case of small secundum ASD
1 case of pulmonary atresia with ventricle septal defect (VSD) and vertical patent ductus arteriosus (PDA);	1 case of patent foramen ovale (PFO) (considered normal)
1 case of tricuspid atresia with pulmonary atresia, small secundum atrial septal defect (ASD)	
1 case of mitral atresia with transposition of the great arteries (TGA), severe pulmonary stenosis, and single ventricle with hypoplastic left ventricle	
1 case of tricuspid atresia, inlet VSD, moderate secundum ASD, small right ventricle and pulmonary stenosis	
1 case of double outlet right ventricle (DORV) with TGA, VSD	

1 case of unbalanced atrioventricular septal defect (AVSD) with moderate PDA.	

Main barriers during process of pulse oximetry screening are shown in Table 3.

Table 3. Barriers during screening process

Type of barriers	Details
Hospital procedure	The standard hospital procedure for the length of postnatal stay is relatively short, and therefore, most of the newborns were screened before 24 hours.
	Pulse oximetry measurement has yet to be part of the pre-discharge standard care for healthy newborns, and therefore, several healthcare personnel (especially nurses and midwives) did not routinely conduct measurements despite the ongoing study.
	Among subjects with positive screening results, echocardiography examinations were not all immediately performed. This was mainly caused by the availability of echocardiographs only at the tertiary and general hospitals, meanwhile some subjects were inpatients at the other two hospitals.
Equipment	The lack of pulse oximetry devices in the common wards, with devices only available at the neonatal ICU.
	tightly fixed sensors using Velcro or rubber fasteners were not widely available, despite being easier and faster to use compared to fingertip-type pulse oximetry.

	Adult probes were sometimes utilized due to the limited resources in the ward.
Healthcare personnel	Healthcare personnel were often occupied with other clinical duties causing them to forget to perform the screening.
Condition of the baby	Some newborns were constantly crying or moving, making measurement of SpO_2 difficult to perform using pulse oximetry.

DISCUSSION

This study explored the feasibility of implementing CCHD screening with pulse oximetry for 1,452 newborns in Yogyakarta, Indonesia. The results of the study indicate that pulse oximetry screening might be feasible to be implemented within the routine newborn care setting for CCHD in Indonesia.

The prevalence of CCHD in our study was 6 of 1,000 live births, with positive CCHD screens occurring in 8/1,452 (0.6%) of newborns. This was higher than previously reported in Sri Lanka 0.16% (14/8,718), [13], India 0.16% (3/1,855) [12], Turkey 0.12% (12/10,200) [18], Morocco 0.06% (5/8,013) [19], Netherland 0.02% (5/23,959) [20], New Zealand 0.02% (3/16,644) [21], South Africa 0.01% (1/1,001) [11] and the United States 0.01% (1/6,745) [16].

A meta-analysis of 21 studies involving 457,202 participants concluded that pulse oximetry is a highly specific and moderately sensitive test for detection of CCHD with very low false-positive rates [22]. Pulse oximetry screening has been successfully implemented in high-income countries and has led to a significant reduction in CCHD related deaths. A study showing results from a 6 years evaluation (2007-2013) after implementation of pulse oximetry screenings across the United States found a 33.4% (95% CI 10.6%-50.3%) reduction in CCHD deaths per 100,000 births, with a further potential reduction of 120 infant deaths per year from CCHD [23].

Several countries that have already conducted CCHD screening programs with pulse oximetry such as the United States, China, the Netherlands, and the United Kingdom have showed that the practice combined with clinical assessment is beneficial and cost-effective [10]. Through the program, costs for treating complications due to the late diagnosis of CCHD can be avoided. A US study reported the screening program saves 20 infants annually, with an equivalent cost of $40,385 per life-year gained under base case assumptions that each screening would cost $6.28 per newborn [24].

Meanwhile, low- and middle-income countries still must face several barriers to be able to execute the pulse oximetry screening program. One study in Morocco revealed barriers such as the tendency to discharge healthy newborns before 24 hours, and the difficulty in confirming positive screening results due to the lack of available echocardiographs in several hospitals [19]. Other reported challenges in implementing pulse oximetry screening includes acceptance of the program, timing of screening and significance of false positives rate, and response to positive screen results [25].

In our study, we classified barriers found during screening into four elements. First concerning hospital procedures or workflow. The AAP recommends screenings should be done within 24-48 hours of age. Adversely, most subjects in our study were screened before 24 hours due to the relatively short postnatal length of stay for healthy babies decided in hospital procedures. The timing of screening should be considered since it will influence the screening results. A previous study revealed that the measurement of saturation before 24 hours of age will increase the false positive or false negative rate [20]. The transition from fetal to neonatal circulation and stabilization of systemic oxygen saturation levels might explain this finding. A New Zealand study revealed that a midwifery-led maternity setting characterized by early discharge, influenced the time of testing, effecting saturation levels [21].

The second barriers included the scarcity of standardized neonatal pulse oximeters. With devices readily available in neonatal intensive care units or observation rooms for monitoring sick newborns, but not in postnatal wards. Only some pulse oximeters were equipped with tightly fixed sensors using Velcro or rubber fasteners which are easier to use compared to finger-type devices where the pulses tend to be difficult to detect and take longer to read. Owing to limited sources, some hospitals even resorted to using adult probes for newborns. The type of probe can affect the effectiveness of examinations. The US Food and Drugs Administrator (FDA) stated three recommendations in using a pulse oximeter; (1) be aware to the factors that can affect the accuracy of a pulse oximeter reading, (2) understand the particular brand and sensor by referring to the device labelling or manufacture's website, and (3) always consider accuracy limitations when using a pulse oximeter to assist in diagnosis and treatment. Knowing these recommendations is important in understanding the risk of measurement inaccuracy and providing the highest outcomes [26]. Nevertheless, a recent study revealed that a pulse oximetry device provided good accuracy in ruling out hypoxemia in comparison to saturation reading by arterial blood gas sample [27].

The third barriers correlated with the condition of the baby. During our study, some newborns were constantly crying or moving, posing a challenge in the application and assessment of pulse oximetry. It is recommended that infants should be fully awake but settled during the screening process. Deep sleep may result in hypoventilation and low saturation results [28]. A previous study in New Zealand showed that newborns that were asleep or unsettled during screening were less likely to have positive results than those who were awake but settled [21].

The fourth and last barriers was the lack of healthcare personnel in the postnatal ward. The healthcare providers were occupied with other clinical duties and sometimes forgot the screening protocol. Some did not consider the pulse oximetry measurement to be within the

scope of their practice due to low motivation because no incentive was given. A study in South Africa reported that most all nurses involved in the study were satisfied with the purpose and aim of the study, but they have no enough time to do the screening since their workload were heavy enough [11]. A study in New Zealand stated that most of midwives agreed that pulse oximetry screening was beneficial, but their already heavy workload prevented them from routinely performing screens. This was one of their concerns regarding the implementation of pulse oximetry as a universal screening program [29].

Indonesia has a large annual live birth rate; at 5 million per year with around 62.7% deliveries commonly assisted by midwives. Seventy nine percent woman gave birth at health care center, around 16% gave birth at home [30]. Nevertheless Indonesia still has yet to have any national program for CCHD screening [8]. Pulse oximetry fulfils the criteria for mass screening. It is very effective, low cost and can significantly reduce morbidities and mortality by providing earlier detection of CHD. However, to achieve these goals optimally in a setting where resources are limited is challenging, though not impossible. These goals require extensive standardized training for healthcare providers who work directly in childbirth and newborn care (midwives, nurse, general practitioner), the measurement protocols need formal regulations and the involvement of policy makers such as health ministries and the pediatric cardiology society to make pulse oximetry screening a recommendation in the standard care of newborns.

In order to optimize the impact of pulse oximetry screening in low-middle income countries, Zheleva et al summarize several recommendations to be considered including the assessment of referral CHD health services, assessment of birth delivery centre processes and staff training needs, financial burden and implementation of CCHD screening process as part of the overall patient care continuum [31]. In principle pulse oximetry screening is quite simple, relatively inexpensive, and easy to implement. Screening is just one step in a lifelong

continuum of management for the child diagnosed with CCHD and their family. Should a child have a positive screen for CCHD they require immediate access to definitive diagnosis, safe transportation, and surgical and interventional cardiology services. Newborn screening cannot save as many lives as it should if high quality cardiac services are not available to the child and family following a positive screen. It will help detect cases, but many will not survive or will live a life with serious disability.

The major limitation of our study is the high proportion of newborns who were not screened over the study period due to the many aforementioned reasons and no report provided on parent's acceptance of- and uptake of the pulse oximetry screening for CCHD. This study was also limited by the use of three different types of pulse oximeters from three different manufacturers as well as the use of an adult sensor. Despite the limitation, our study is among the first reports of the feasibility of CCHD screening using pulse oximetry in Indonesia and provides the local evidence of barrier perspectives from healthcare workers during the screening process. The findings can be used as available local evidence for policymakers before recommending needed changes to the national screening program.

CONCLUSIONS

Pulse oximetry screening might be feasible to be implemented within the routine newborn care for detection of CCHD in Indonesia. In order to successfully implemented pulse oximetry screening to identify CCHD in Indonesia, the barriers will need to be addressed.

List of Abbreviations

AAP: American Academy of Pediatric

ASD: Atrial Septal Defect

CHD: Congenital Heart Disease

CCHD: Critical Congenital Heart Disease

DORV: Double Outlet Right Ventricle

PDA: Patent Ductus Arteriosus

PFO: Patent Foramen Ovale

TGA: Transposition of the Great Aorta

VSD: Ventricle Septal Defect

Declarations

Ethics approval and consent to participate

The Medical and Health Research Ethics Committee, of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia has approved this study (230/UN.1/FKKMK.3/IKA.2/TU/PT.01.04/2021). Informed consent to participate in the study was obtained from the parents or legal guardians of participants.

All experiment protocols involving humans was in accordance with national/international/institutional guidelines or the Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests

Funding

None

Authors' contributions

All authors were contributed to conception or the design of the study. IKM, DP, LP were major contributors in writing the manuscript. DP collected the data. IKM, DP, LP analyzed the data. All authors interpreted the data. All authors read, critically revised and approved the final manuscript.

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7. Bukti konfirmasi review dan hasil review ketiga

(23 Mei 2022)

Indah Kartika Murni <indah.kartika.m@ugm.ac.id>

BMC Pediatrics: Decision on your manuscript

1 message

BMC Pediatrics <bmcpediatrics@biomedcentral.com> Mon, May 23, 2022 at 7:15 PM
To: indah.kartika.m@ugm.ac.id

Ref: Submission ID 89915a15-337e-4a9d-add3-227916330e46

Dear Dr Murni,

Re: "Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia"

We are pleased to let you know that your manuscript has now passed through the review stage and is ready for revision. Many manuscripts require a round of revisions, so this is a normal but important stage of the editorial process.

Editor comments
This study explored the feasibility of implementing CCHD screening with pulse oximetry for 1,452 newborns in Yogyakarta, Indonesia. The results of the study indicate that pulse oximetry screening might be feasible to be implemented within the routine newborn care setting for CCHD in Indonesia and provides the local evidence of barrier perspectives from healthcare workers during the screening process. The major limitation of this study is the high proportion of newborns who were not screened over the study period due to the many aforementioned reasons. Also the authors do not comment how home births were screened.
The use of English remains unsatisfactory and the paper requires language polishing. Reviewer 3 was quite demanding but I think that their questions have been promptly replied. I suggest that the manuscript might be reviewed following my minor suggestions and then get accepted for publication

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Kind regards,

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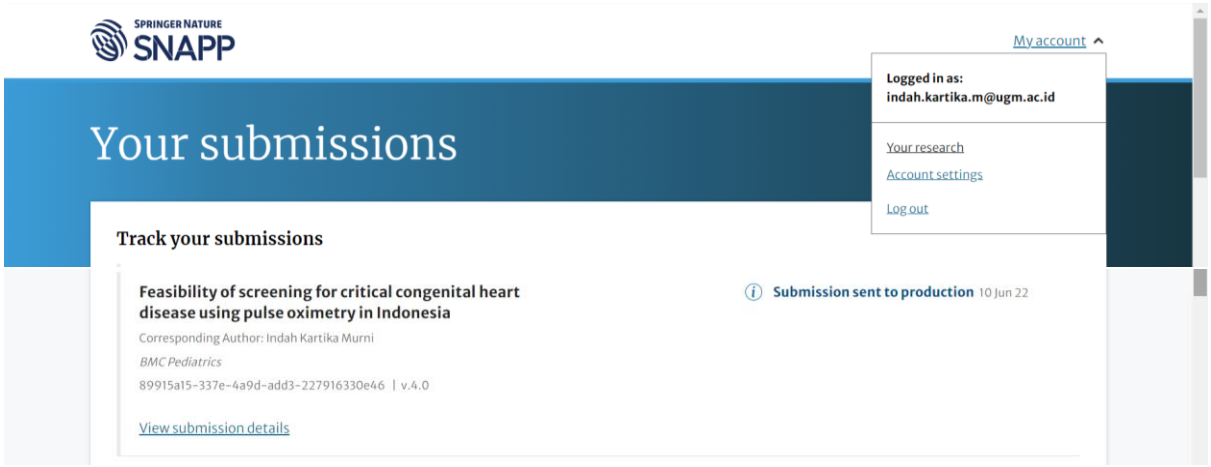
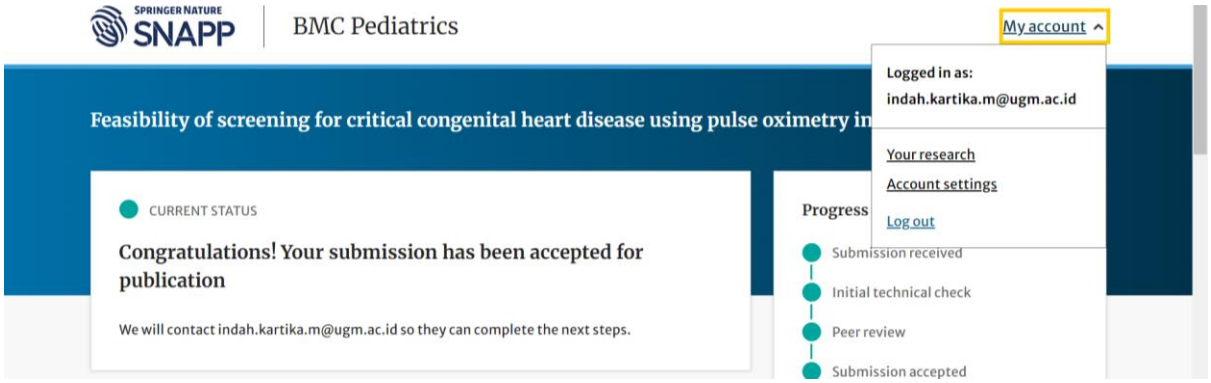
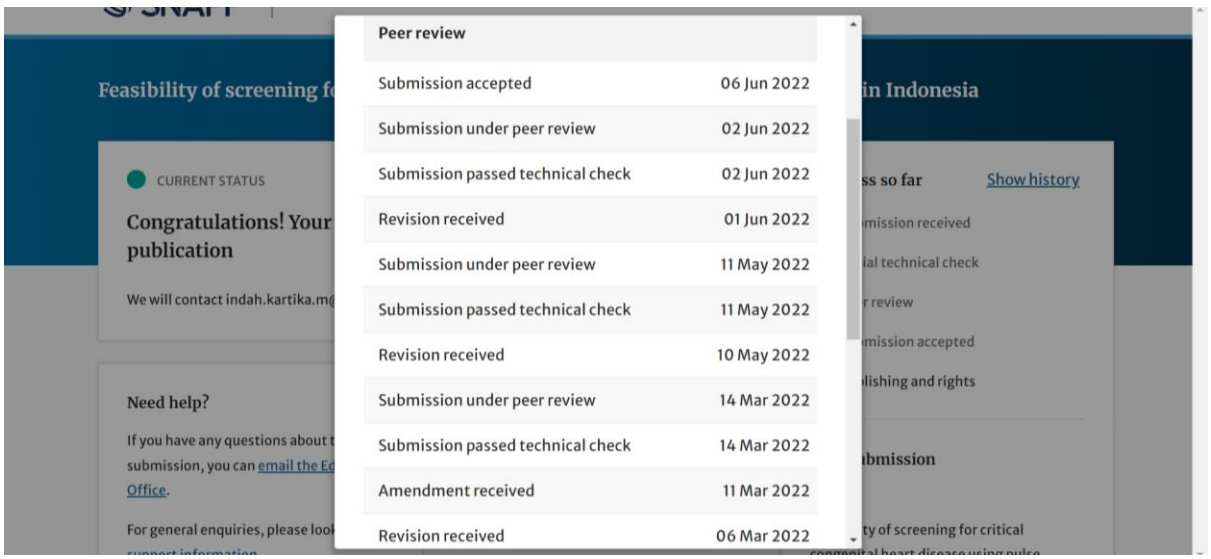
8. Bukti konfirmasi submit artikel dan artikel yang disubmit

(1 Juni 2022)

Seluruh dokumen, revisi dan respon kepada reviewer jurnal BMC Pediatric dengan judul artikel *"Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia"* diunggah oleh penulis korespondensi (Indah Kartika Murni) melalui website resmi jurnal BMC Pediatric melalui alamat https://submission.springernature.com/ dengan akun Indah.kartika.m@ugm.ac.id







Response to the Editor's comments

"Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia"

Editor comments
This study explored the feasibility of implementing CCHD screening with pulse oximetry for 1,452 newborns in Yogyakarta, Indonesia. The results of the study indicate that pulse oximetry screening might be feasible to be implemented within the routine newborn care setting for CCHD in Indonesia and provides the local evidence of barrier perspectives from healthcare workers during the screening process. The major limitation of this study is the high proportion of newborns who were not screened over the study period due to the many aforementioned reasons.
Also the authors do not comment how home births were screened.

Response to Editor:
We thank you very much for the positive comment and interest to our paper.

Most deliveries were commonly attended by midwives and these births take place in community clinics. Seventy nine percent woman gave birth at health care centre, around 16% gave birth at home.
To make the implementation of pulse oximetry screening feasible, an extensive standardized training for healthcare providers who work directly in childbirth and newborn care (midwives, nurse, general practitioner) should be conducted.
In order to develop an appropriate system for home birth, the timing of administration of pulse oximetry might need to be altered. The measurements might be taken >1 hour after birth since a community midwife leaves approximately several hours after an uncomplicated home birth. Extensive training for community midwives and providing each midwife with a handheld pulse oximeter also need to be conducted. However, in order to make this approach works, an appropriate regional system to support the use of pulse oximetry in individual home births should be developed.

The use of English remains unsatisfactory and the paper requires language polishing. Reviewer 3 was quite demanding but I think that their questions have been promptly replied. I suggest that the manuscript might be reviewed following my minor suggestions and then get accepted for publication

Response to Editor:
We have revised the manuscript to correct for grammar/syntax as suggested.
We have re-consulted to a native English speaker, who is:
Erik Christopher Hookom, BA, M.Ed, TEFL.
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Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada
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All attachments have been checked and corrected for proper spelling and grammar using American English. A Certificate of Editing is available from the ORP if needed.

TITLE PAGE

Type of article: Original Article

Title of the article: Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia

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Keywords: congenital heart disease, pulse oximetry screening, Indonesia, critical congenital heart disease

Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia

Indah K Murni, Tunjung Wibowo, Nadya Arafuri, Vicka Oktaria, Lucia K Dinarti, Dicky Panditatwa, Linda Patmasari, Noormanto Noormanto, Sasmito Nugroho

Abstract

Background: Screening of critical congenital heart disease (CCHD) using pulse oximetry is a routine procedure in many countries, but not in Indonesia. This study aimed to evaluate the feasibility of implementing CCHD screening with pulse oximetry for newborns in Yogyakarta, Indonesia.

Methods: A cross-sectional study was conducted at four hospitals in Yogyakarta, Indonesia. Newborns aged 24-48 hours who met the inclusion criteria were screened on the right hand and left or right foot using a pulse oximeter. Positive results were indicated by: either (1) SpO_2 level <90% in one extremity, (2) SpO_2 level of 90-94% in both right hand and either foot on three measurements conducted 1 hour apart, or (3) a saturation difference >3% between the upper and lower extremity on three measurements conducted 1 hour apart. Positive findings were confirmed by echocardiography.

Results: Of 1,452 newborns eligible for screening, 10 had positive results and were referred for echocardiographic evaluation. Of those, 8 (6 per 1,000 live birth, 8/1,452) had CCHD. Barriers found during screening processes were associated with hospital procedures, equipment, healthcare personnel, and condition of the newborn.

Conclusion: Pulse oximetry screening might be feasible to be implemented within the routine newborn care setting for CCHD in Indonesia. In order to successfully implement pulse oximetry screening to identify CCHD in Indonesia, the barriers will need to be addressed.

BACKGROUND

Congenital heart disease (CHD) is the most common congenital abnormality in newborns [1] with a reported incidence of 4 to 50 per 1,000 live births [2,3]. Approximately 25% of CHD are classified as critical congenital heart disease (CCHD), that are often lethal and require immediate transcatheter or surgical intervention in the first year of life [4]. Furthermore, CHD is responsible for over 260,000 deaths annually worldwide [5] with a CCHD associated mortality count of 34.8% in developing countries [6]. Challenges primarily exist in early detection of CCHD, with some CCHD newborns prematurely sent home before diagnosis, since they may appear healthy at first. This challenge is considerably noticeable in resource limited settings.

In Indonesia, approximately 2.5 per 1,000 live births suffer from CHD [7]. A significant delay in CHD diagnosis is seen in 6 out of 10 cases, most with severe complications [8]. Additionally, one-third of the newborns with CCHD were not detected before discharge [9]. Pulse oximetry screening for CCHD has been recommended and widely implemented in many countries, leading to a significant reduction in mortality among newborns with CCHD. Furthermore, unnecessary costs related to complications due to late diagnosis of CCHD can be avoided [10]. Studies on the feasibility of pulse oximetry screening to detect CCHD have been conducted in low- and middle-income country setting including South Africa [11], India [12], Sri Lanka [13] and Brazil [14]. Despite the importance shown in the immediate detection of CCHD, no screening program has been implemented in Indonesia, contributing to the often presentation of late and even terminal cases at tertiary hospitals. Therefore, this study aimed to evaluate the feasibility of CCHD screening using pulse oximetry and provide relatable evidence for local and national policymakers in implementing pulse oximetry screening program in Indonesia.

METHODS

A cross-sectional study was conducted at four hospitals in Yogyakarta, Indonesia from August 1st, 2021, to November 30th, 2021. The hospitals were: Dr. Sardjito a class A, tertiary referral hospital; JIH a class B, general hospital; and Sadewa and Sakina Idaman, both class Cs maternal and neonatal care specialty hospitals. All seemingly healthy newborns were included, and those born at <35 weeks' gestation age, prenatally diagnosed with CHD, carrying dysmorphic features or signs of cardiovascular abnormalities such as cyanosis, cardiac murmur or those with abnormal vital signs were excluded [15, 16].

Pulse oximetry screening was performed using the American Academy of Pediatrics (AAP) standardized algorithm by measuring oxygen saturation of the right hand and the left or right foot between 24-48 hours of age or before 24 hours of age if the baby is discharged early. Screening of CCHD was considered negative or passed if measurement of SpO_2 was ≥95% for both the right hand and right or left foot, with a difference of <3% between the right hand and either foot. No further cardiac evaluation was performed in these subjects unless indicated by subsequent clinical condition(s). Screening was considered positive or failed if at least one of the following: (1) SpO_2 level <90% in one extremity, (2) SpO_2 level of 90-94% in both right hand and either foot on three measurements conducted 1 hour apart, or (3) a saturation difference >3% between the upper and lower extremity on three measurements conducted 1 hour apart [17]. Subjects failing the screening were referred to Dr. Sardjito Hospital for echocardiographic evaluation. The algorithm of study is presented in Figure 1.

Screening was performed by a healthcare worker, which included either a doctor, nurse, or midwife in charge. The measurement was written manually in case report form. Training of healthcare workers was conducted prior to the study to avoid variability in screening procedures. To compensate for the variability of available oximeter types among hospitals, we performed an agreement correlation before recruitment using three types of pulse oximeters:

Massimo (Massimo Corporation, Irvine, CA, USA), Mindray (Mindray Cooperation, Nanshan, Shenzhen, China) and fingertip.

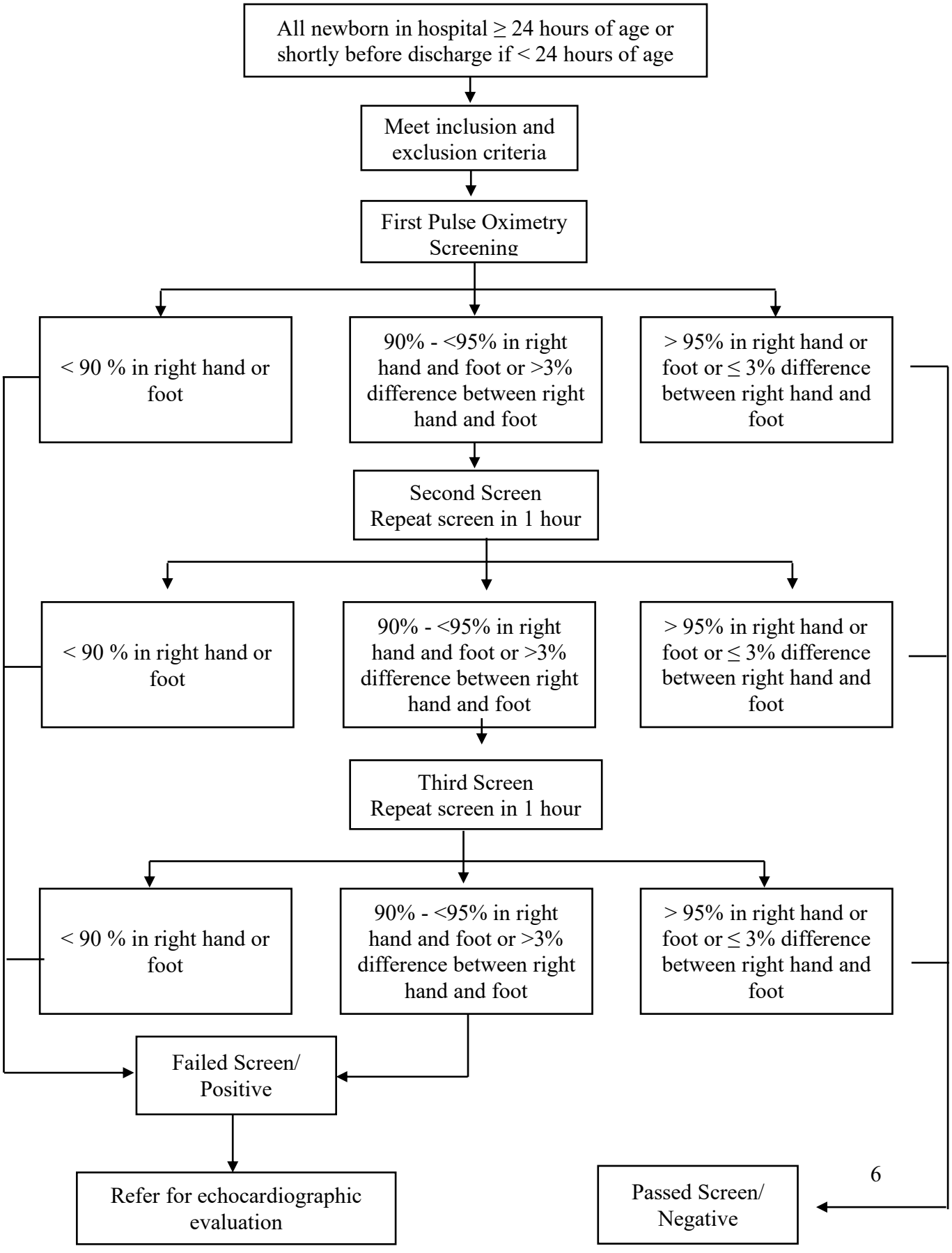

Figure 1. Algorithm of study protocol (Adapted from the protocol in Ewer et al. [17]).

Data were analyzed using STATA version 12.1 (StataCorp, College Station, Texas, USA) and presented appropriately. Descriptive statistics were presented as numbers and percentages, mean or medians.

A semi-structured interview on barriers experienced by the medical personnel throughout the screening process was also conducted. The qualitative data were then reviewed, defined and presented thematically based on the common barriers.

Ethics

The Medical and Health Research Ethics Committee, of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia has approved this study (230/UN.1/FKKMK.3/IKA.2/TU/PT.01.04/2021). Informed consent to participate in the study was obtained from the parents or legal guardians of participants.

All experiment protocols involving humans were in accordance with national/international/institutional guidelines or the Declaration of Helsinki.

RESULTS

Throughout the study period, there were 2,631 newborns delivered at the four selected hospitals. From 118 newborns who were ineligible, 89 were <35-weeks' gestation age, 10 passed away, 14 were prenatally confirmed with CHD and 5 had dysmorphic features. A total of 1,452 (57.7%) from the remaining 2,513 eligible newborns were then screened (Figure 2). Of the 1,452 babies screened, 7 babies had positive results at the first screening and only 5 (0.3%) needed a second screening. Two of the babies passed the second screening. The third screening results were positive for all of the remaining three babies. Of those, 10 had positive results and were referred for further echocardiography confirmation, finally resulting in 8

(0.6%) subjects with CCHD. The screening was performed within a period of ≤24 hours after birth in 855 subjects (59%) and after 24 hours in 597 (41%) subjects.

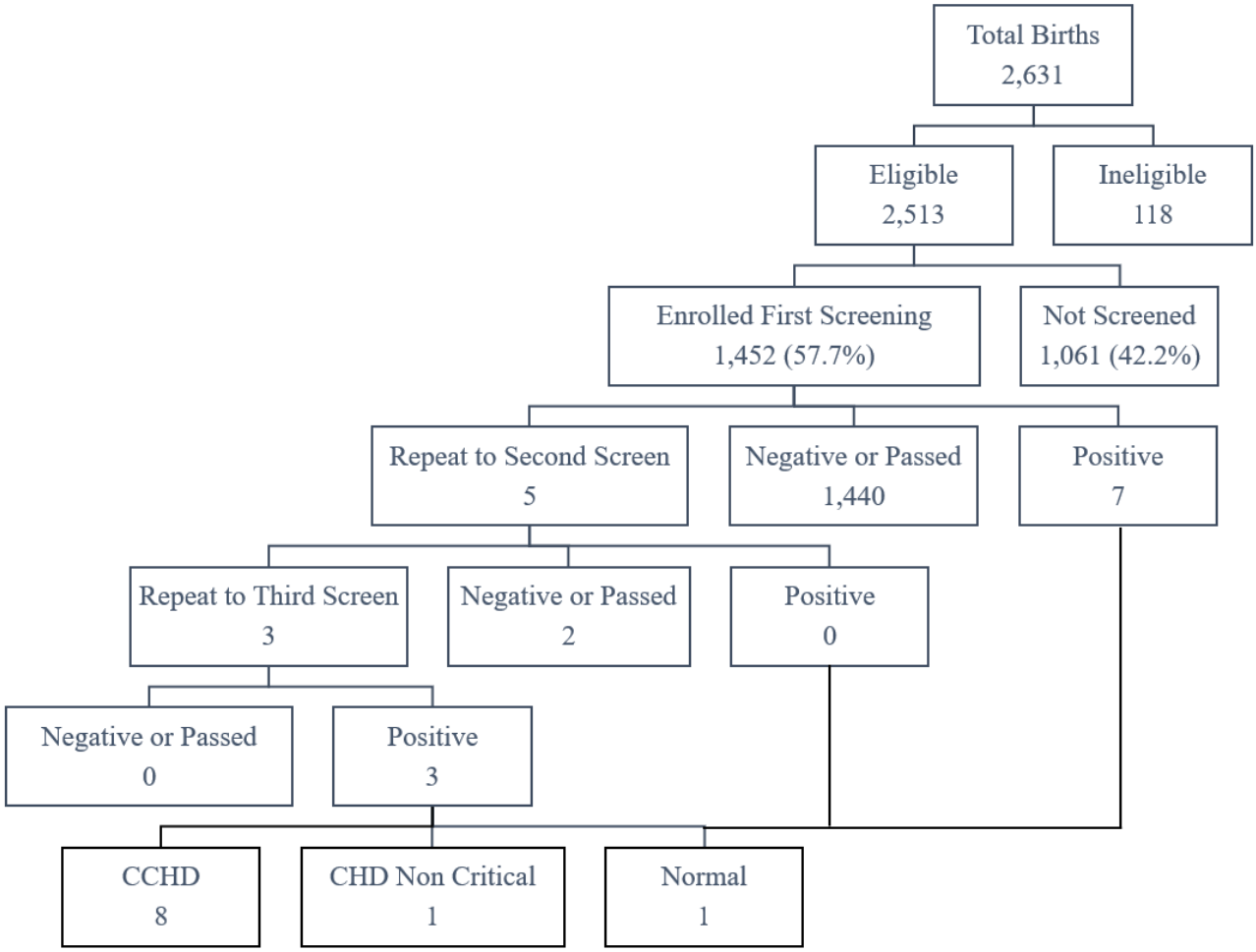

Figure 2. Distribution of the newborns enrolled in the study.

Oxygen supplementation was promptly administered in cases where newborns were visibly bluish or when desaturation of SpO_2 levels or signs of respiratory distress were apparent. These frequently occurred soon after birth (less than 24 hours) and was most commonly caused by asphyxia, pulmonary hypertension of the newborn, or other pulmonary problems. The healthcare workers did not include these neonates for screening.

Most screening was performed using the standardized pulse oximetry (Massimo). The agreement among Massimo and Fingertip pulse oximetry was 0.815, while the agreement among Massimo and Mindray pulse oximetry was 0.943.

The baseline characteristics of the eligible newborns are presented in Table 1. Echocardiography results performed in the 10 newborns with positive screening are shown in the Table 2.

Table 1. Baseline characteristics of screened newborns

Characteristics	Newborns n=1,452 (%)
Sex, n (%)	
Male	769 (53)
Female	683 (47)
Birth weight in gram, median (min-max)	3,045.4 (1,360-4,532)
<2,500	154 (10.6)
2,500-4,000	1,279 (88.1)
>4,000	19 (1.3)
Gestational age in weeks, n (%)	
35-<37	81 (5.6)
37-42	1,367 (94.1)
>42	4 (0.3)
Type of delivery, n (%)	
Caesarean section	859 (59.2)
Vacuum extraction	29 (2)
Normal	564 (38.8)

Type of pulse oximetry, n (%)	
Massimo	1,067 (73.5)
Fingertip	18 (1.2)
Mindray	367 (25.3)

Table 2. Echocardiography results of 10 newborns with positive screening by pulse oximetry

CCHD (n=8)	Non CCHD (n=2)
2 cases of Ebstein anomaly	1 case of small secundum ASD
1 case of pulmonary atresia with ventricle septal defect (VSD) and vertical patent ductus arteriosus (PDA);	1 case of patent foramen ovale (PFO) (considered normal)
1 case of tricuspid atresia with pulmonary atresia, small secundum atrial septal defect (ASD)	
1 case of mitral atresia with transposition of the great arteries (TGA), severe pulmonary stenosis, and single ventricle with hypoplastic left ventricle	
1 case of tricuspid atresia, inlet VSD, moderate secundum ASD, small right ventricle and pulmonary stenosis	
1 case of double outlet right ventricle (DORV) with TGA, VSD	

1 case of unbalanced atrioventricular septal defect (AVSD) with moderate PDA.	

Main barriers during process of pulse oximetry screening are shown in Table 3.

Table 3. Barriers during screening process

Type of barriers	Details
Hospital procedure	The standard hospital procedure for the length of postnatal stay is relatively short, and therefore, most of the newborns were screened before 24 hours.
	Pulse oximetry measurement has yet to be part of the pre-discharge standard care for healthy newborns, and therefore, several healthcare personnel (especially nurses and midwives) did not routinely conduct measurements despite the ongoing study.
	Among subjects with positive screening results, echocardiography examinations were not all immediately performed. This was mainly caused by the availability of echocardiographs only at the tertiary and general hospitals, while some subjects were inpatients at the other two hospitals.
Equipment	The lack of pulse oximetry devices in the common wards, with devices only available at the neonatal ICU.
	Tightly fixed sensors using Velcro or rubber fasteners were not widely available, despite being easier and faster to use compared to fingertip-type pulse oximetry.

	Adult probes were sometimes utilized due to the limited resources in the ward.
Healthcare personnel	Healthcare personnel were often occupied with other clinical duties causing them to forget to perform the screening.
Condition of the baby	Some newborns were constantly crying or moving, making measurement of SpO_2 difficult to perform using pulse oximetry.

DISCUSSION

This study explored the feasibility of implementing CCHD screening with pulse oximetry for 1,452 newborns in Yogyakarta, Indonesia. The results of the study indicate that pulse oximetry screening might be feasible to be implemented within the routine newborn care setting for CCHD in Indonesia.

The prevalence of CCHD in our study was 6 of 1,000 live births, with positive CCHD screens occurring in 8/1,452 (0.6%) of newborns. This was higher than previously reported in Sri Lanka 0.16% (14/8,718), [13], India 0.16% (3/1,855) [12], Turkey 0.12% (12/10,200) [18], Morocco 0.06% (5/8,013) [19], the Netherlands 0.02% (5/23,959) [20], New Zealand 0.02% (3/16,644) [21], South Africa 0.01% (1/1,001) [11] and the United States (US) 0.01% (1/6,745) [16].

A meta-analysis of 21 studies involving 457,202 participants concluded that pulse oximetry is a highly specific and moderately sensitive test for detection of CCHD with very low false-positive rates [22]. Pulse oximetry screening has been successfully implemented in high-income countries and has led to a significant reduction in CCHD related deaths. A study showing results from a 6 years evaluation (2007-2013) after implementation of pulse oximetry screenings across the United States found a 33.4% (95% CI: 10.6%-50.3%) reduction in CCHD

deaths per 100,000 births, with a further potential reduction of 120 infant deaths per year from CCHD [23].

Several countries that have already conducted CCHD screening programs with pulse oximetry such as the US, China, the Netherlands, and the United Kingdom have indicated the practice combined with clinical assessment is beneficial and cost-effective [10]. Through the program, costs for treating complications due to the late diagnosis of CCHD can be avoided. A US study reported the screening program saves 20 infants annually, with an equivalent cost of $40,385 per life-year gained under base case assumptions that each screening would cost $6.28 per newborn [24].

Meanwhile, low- and middle-income countries still must face several barriers to be able to execute the pulse oximetry screening program. One study in Morocco revealed barriers such as the tendency to discharge healthy newborns before 24 hours, and the difficulty in confirming positive screening results due to the lack of available echocardiographs in several hospitals [19]. Other reported challenges in implementing pulse oximetry screening include acceptance of the program, timing of screening and significance of false positives rate, and response to positive screen results [25].

In our study, we classified barriers found during screening into four concerns. The first concerns involve hospital procedures or workflow. The AAP recommends screenings should be done within 24-48 hours of age. Adversely, most subjects in our study were screened before 24 hours due to the relatively short postnatal length of stay for healthy babies decided in hospital procedures. The timing of screening should be considered since it will influence the screening results. A previous study revealed that the measurement of saturation before 24 hours of age will increase the false positive or false negative rate [20]. The transition from fetal to neonatal circulation and stabilization of systemic oxygen saturation levels might explain this

finding. A New Zealand study revealed that a midwifery-led maternity setting characterized by early discharge, influenced the time of testing, effecting saturation levels [21].

The second barrier involves the scarcity of standardized neonatal pulse oximeters, with devices readily available in neonatal intensive care units or observation rooms for monitoring sick newborns, but not in postnatal wards. Only some pulse oximeters were equipped with tightly fixed sensors using Velcro or rubber fasteners which are easier to use compared to finger-type devices where the pulses tend to be difficult to detect and take longer to read. Owing to limited sources, some hospitals even resorted to using adult probes for newborns. The type of probe can affect the effectiveness of examinations. The US Food and Drugs Administrator (FDA) stated three recommendations in using a pulse oximeter: (1) be aware to the factors that can affect the accuracy of a pulse oximeter reading, (2) understand the particular brand and sensor by referring to the device labelling or manufacture's website, and (3) always consider accuracy limitations when using a pulse oximeter to assist in diagnosis and treatment. Knowing these recommendations is important in understanding the risk of measurement inaccuracy and providing the highest outcomes [26]. Nevertheless, a recent study revealed that a pulse oximetry device provided good accuracy in ruling out hypoxemia in comparison to saturation reading by arterial blood gas sample [27].

The third barrier is related with the condition of the baby. During our study, some newborns were constantly crying or moving, posing a challenge in the application and assessment of pulse oximetry. It is recommended that infants should be fully awake but settled during the screening process, since deep sleep may result in hypoventilation and low saturation results [28]. A previous study in New Zealand showed that newborns that were asleep or unsettled during screening were less likely to have positive results than those who were awake but settled [21].

The fourth and last of the barriers is the lack of healthcare personnel in the postnatal ward. The healthcare providers were occupied with other clinical duties and sometimes forgot the screening protocol. Some did not consider the pulse oximetry measurement to be within the scope of their practice due to low motivation because no incentive was given. A study in South Africa reported that most of the nurses involved in the study were satisfied with the purpose and aim of the study, but they do not have enough time to do the screening since their workloads were already heavy [11]. A study in New Zealand stated that most of midwives agreed that pulse oximetry screening was beneficial, but their already heavy workload prevented them from routinely performing screens. This was one of their concerns regarding the implementation of pulse oximetry as a universal screening program [29].

Indonesia has a large annual live birth rate, at 5 million per year with around 62.7% deliveries commonly assisted by midwives. As many as 79% of women gave birth at health care centers, with around 16% giving birth at home [30]. Nevertheless, Indonesia still lacks any national program for CCHD screening [8]. Pulse oximetry fulfils the criteria for mass screening. It is very effective, low cost and can significantly reduce morbidities and mortality by providing earlier detection of CHD. However, to achieve these goals optimally in a setting where resources are limited is challenging, though not impossible. These goals require extensive standardized training for healthcare providers who work directly in childbirth and newborn care (midwives, nurse, and general practitioner), the measurement protocols need formal regulations and the involvement of policy makers such as health ministries and the pediatric cardiology society to make pulse oximetry screening a recommendation in the standard care of newborns. Further, in order to develop an appropriate system for home birth, the timing of administration of pulse oximetry might need to be altered since a community midwife leaves approximately several hours after an uncomplicated home birth. Extensive training for community midwives and providing each midwife with a handheld pulse oximeter

also need to be conducted. However, in order to make this approach works, an appropriate regional system to support the use of pulse oximetry in individual home births should be developed.

In order to optimize the impact of pulse oximetry screening in low-middle income countries, Zheleva et al. summarized several recommendations to be considered including the assessment of referral CHD health services, assessment of birth delivery center processes and staff training needs, financial burden and implementation of CCHD screening process as part of the overall patient care continuum [31]. In principle and practice, pulse oximetry screening is relatively simple, inexpensive, and easy to implement. However, screening is just one step in a lifelong continuum of management for the child diagnosed with CCHD and their family. If a child has a positive screening for CCHD, they require immediate access to definitive diagnosis, safe transportation, and surgical and interventional cardiology services. Newborn screening cannot save as many lives as it should if high quality cardiac services are not available to the child and family following a positive screen. It will help detect cases, but many will not survive or will live a life with serious disability.

The major limitations of our study involve the high proportion of newborns who were not screened over the study period due to the many aforementioned reasons and there was no report provided on parent's acceptance of and uptake of the pulse oximetry screening for CCHD. This study was also limited by the use of three different types of pulse oximeters from three different manufacturers as well as the use of an adult sensor. Despite the limitations, our study is among the first reports of the feasibility of CCHD screening using pulse oximetry in Indonesia and provides the local evidence of barrier perspectives from healthcare workers during the screening process. The findings can be used as available local evidence for policymakers before recommending needed changes to the national screening program.

CONCLUSIONS

Pulse oximetry screening might be feasible to be implemented within the routine newborn care for detection of CCHD in Indonesia. In order to successfully implement pulse oximetry screening to identify CCHD in Indonesia, the barriers will need to be addressed.

List of Abbreviations

AAP: American Academy of Pediatric

ASD: Atrial Septal Defect

CHD: Congenital Heart Disease

CCHD: Critical Congenital Heart Disease

DORV: Double Outlet Right Ventricle

PDA: Patent Ductus Arteriosus

PFO: Patent Foramen Ovale

TGA: Transposition of the Great Aorta

VSD: Ventricle Septal Defect

Declarations

Ethics approval and consent to participate

The Medical and Health Research Ethics Committee, of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia has approved this study (230/UN.1/FKKMK.3/IKA.2/TU/PT.01.04/2021). Informed consent to participate in the study was obtained from the parents or legal guardians of participants.

All experiment protocols involving humans was in accordance with national/international/institutional guidelines or the Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

Funding

None

Authors' contributions

All authors contributed to the conception or the design of the study. IKM, DP, LP were major contributors in writing the manuscript. DP collected the data. IKM, DP, LP analyzed the data. All authors interpreted the data. All authors read, critically revised and approved the final manuscript.

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9. Bukti konfirmasi artikel accepted

(6 Juni 2022)

Indah Kartika Murni <indah.kartika.m@ugm.ac.id>

BMC Pediatrics: Decision on your manuscript

1 message

BMC Pediatrics <bmcpediatrics@biomedcentral.com> Mon, Jun 6, 2022 at 4:42 PM
To: indah.kartika.m@ugm.ac.id

Ref: Submission ID 89915a15-337e-4a9d-add3-227916330e46

Dear Dr Murni,

Re: "Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia"

We're delighted to let you know that your manuscript has been accepted for publication in BMC Pediatrics.

Editor comments
This is a study aiming to evaluate the feasibility of CCHD screening using pulse oximetry and provide relatable evidence for local and national policymakers in implementing pulse oximetry screening program in Indonesia. To compensate for the variability of available oximeter types among hospitals, the authors performed an agreement correlation before recruitment using three types of pulse oximeters: Massimo (Massimo Corporation, Irvine, CA, USA), Mindray (Mindray Cooperation, Nanshan, Shenzhen, China) and fingertip. A semi-structured interview on barriers experienced by the medical personnel throughout the screening process was also conducted. A total of 1,452 (57.7%) from the 2,513 eligible newborns were screened. Several barriers during the process of pulse oximetry screening were documented.. Most subjects in the study were screened before 24 hours due to the relatively short postnatal length of stay for healthy babies decided in hospital procedures. The timing of screening should be considered since it will influence the screening results. There was also scarcity of standardized neonatal pulse oximeters. Owing to limited sources, some hospitals even resorted to using adult probes for newborns. The type of probe can affect the effectiveness of examinations. During the study, some newborns were constantly crying or moving, posing a challenge in the application and assessment of pulse oximetry. It is recommended that infants should be fully awake but settled during the screening process. The 4th barrier was the lack of healthcare personnel in the postnatal ward. Some did not consider the pulse oximetry measurement to be within the scope of their practice due to low motivation because no incentive was given. Also 16% of women gave birth at home which represents another barrier to pulse oximetry screening. Despite these limitations the authors report that pulse oximetry screening might be feasible to be implemented within the routine newborn care setting for CCHD in Indonesia and propose policies to improve the implementation of this simple but valuable process. The most interesting part of the study is the report of the implementation of a supposed easy test in a low income country. The identification of 8 babies with CCHD over 1,452 checked is important and I think that the paper is suitable for publication in the journal. The language has improved but in the manuscript the words are very often stack together with no gap between them. This minor issue needs to be fixed.

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Andrew Wervone Aguilar <andrew.wervoneaguilar@springer-sbm.com> Tue, Jun 14, 2022 at 9:13 AM
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Cc: Alvin Costas <alvin.costas@springernature.com>

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3 attachments

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Feasibility of screening for critical congenital heart disease using pulse oximetry in Indonesia

Indah K. Murni[1,2*], Tunjung Wibowo[1], Nadya Arafuri[1], Vicka Oktaria[2,3], Lucia K. Dinarti[4], Dicky Panditatwa[1], Linda Patmasari[1], Noormanto Noormanto[1] and Sasmito Nugroho[1]

Abstract

Background: Screening of critical congenital heart disease (CCHD) using pulse oximetry is a routine procedure in many countries, but not in Indonesia. This study aimed to evaluate the feasibility of implementing CCHD screening with pulse oximetry for newborns in Yogyakarta, Indonesia.

Methods: A cross-sectional study was conducted at four hospitals in Yogyakarta, Indonesia. Newborns aged 24–48 hours who met the inclusion criteria were screened on the right hand and left or right foot using a pulse oximeter. Positive results were indicated by: either (1) SpO_2 level < 90% in one extremity, (2) SpO_2 level of 90–94% in both right hand and either foot on three measurements conducted 1 hour apart, or (3) a saturation difference > 3% between the upper and lower extremity on three measurements conducted 1 hour apart. Positive findings were confirmed by echocardiography.

Results: Of 1452 newborns eligible for screening, 10 had positive results and were referred for echocardiographic evaluation. Of those, 8 (6 per 1000 live birth, 8/1452) had CCHD. Barriers found during screening processes were associated with hospital procedures, equipment, healthcare personnel, and condition of the newborn.

Conclusion: Pulse oximetry screening might be feasible to be implemented within the routine newborn care setting for CCHD in Indonesia. In order to successfully implement pulse oximetry screening to identify CCHD in Indonesia, the barriers will need to be addressed.

Keywords: Congenital heart disease, Pulse oximetry screening, Indonesia, Critical congenital heart disease

Background

Congenital heart disease (CHD) is the most common congenital abnormality in newborns [1] with a reported incidence of 4 to 50 per 1000 live births [2, 3]. Approximately 25% of CHD are classified as critical congenital heart disease (CCHD), that are often lethal and require immediate transcatheter or surgical intervention in the first year of life [4]. Furthermore, CHD is responsible for over 260,000 deaths annually worldwide [5] with a CCHD associated mortality count of 34.8% in developing countries [6]. Challenges primarily exist in early detection of CCHD, with some CCHD newborns prematurely sent home before diagnosis, since they may appear healthy at first. This challenge is considerably noticeable in resource limited settings.

In Indonesia, approximately 2.5 per 1000 live births suffer from CHD [7]. A significant delay in CHD diagnosis is seen in 6 out of 10 cases, most with severe complications [8]. Additionally, one-third of the newborns with CCHD were not detected before discharge [9]. Pulse oximetry screening for CCHD has been recommended and widely implemented in many countries, leading to a significant reduction in mortality among newborns with CCHD.

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Full list of author information is available at the end of the article

Furthermore, unnecessary costs related to complications due to late diagnosis of CCHD can be avoided [10]. Studies on the feasibility of pulse oximetry screening to detect CCHD have been conducted in low- and middle-income country setting including South Africa [11], India [12], Sri Lanka [13] and Brazil [14]. Despite the importance shown in the immediate detection of CCHD, no screening program has been implemented in Indonesia, contributing to the often presentation of late and even terminal cases at tertiary hospitals. Therefore, this study aimed to evaluate the feasibility of CCHD screening using pulse oximetry and provide relatable evidence for local and national policymakers in implementing pulse oximetry screening program in Indonesia.

Methods

A cross-sectional study was conducted at four hospitals in Yogyakarta, Indonesia from August 1st, 2021, to November 30th, 2021. The hospitals were: Dr. Sardjito a class A, tertiary referral hospital; JIH a class B, general hospital; and Sadewa and Sakina Idaman, both class Cs maternal and neonatal care specialty hospitals. All seemingly healthy newborns were included, and those born at < 35 weeks' gestation age, prenatally diagnosed with CHD, carrying dysmorphic features or signs of cardiovascular abnormalities such as cyanosis, cardiac murmur or those with abnormal vital signs were excluded [15, 16].

Pulse oximetry screening was performed using the American Academy of Pediatrics (AAP) standardized algorithm by measuring oxygen saturation of the right hand and the left or right foot between 24 and 48 hours of age or before 24 hours of age if the baby is discharged early. Screening of CCHD was considered negative or passed if measurement of SpO_2 was ≥ 95% for both the right hand and right or left foot, with a difference of < 3% between the right hand and either foot. No further cardiac evaluation was performed in these subjects unless indicated by subsequent clinical condition(s). Screening was considered positive or failed if at least one of the following: (1) SpO_2 level < 90% in one extremity, (2) SpO_2 level of 90–94% in both right hand and either foot on three measurements conducted 1 hour apart, or (3) a saturation difference > 3% between the upper and lower extremity on three measurements conducted 1 hour apart [17]. Subjects failing the screening were referred to Dr. Sardjito Hospital for echocardiographic evaluation. The algorithm of study is presented in Fig. 1.

Screening was performed by a healthcare worker, which included either a doctor, nurse, or midwife in charge. The measurement was written manually in case report form. Training of healthcare workers was conducted prior to the study to avoid variability in screening procedures. To compensate for the variability of available oximeter types among hospitals, we performed an agreement correlation before recruitment using three types of pulse oximeters: Massimo (Massimo Corporation, Irvine, CA, USA), Mindray (Mindray Cooperation, Nanshan, Shenzhen, China) and fingertip.

Data were analyzed using STATA version 12.1 (StataCorp, College Station, Texas, USA) and presented appropriately. Descriptive statistics were presented as numbers and percentages, mean or medians.

A semi-structured interview on barriers experienced by the medical personnel throughout the screening process was also conducted. The qualitative data were then reviewed, defined and presented thematically based on the common barriers.

Ethics

The Medical and Health Research Ethics Committee, of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia has approved this study (230/UN.1/FKKMK.3/IKA.2/TU/PT.01.04/2021). Informed consent to participate in the study was obtained from the parents or legal guardians of participants.

All experiment protocols involving humans were in accordance with national/international/institutional guidelines or the Declaration of Helsinki.

Results

Throughout the study period, there were 2631 newborns delivered at the four selected hospitals. From 118 newborns who were ineligible, 89 were < 35-weeks' gestation age, 10 passed away, 14 were prenatally confirmed with CHD and 5 had dysmorphic features. A total of 1452 (57.7%) from the remaining 2513 eligible newborns were then screened (Fig. 2). Of the 1452 babies screened, 7 babies had positive results at the first screening and only 5 (0.3%) needed a second screening. Two of the babies passed the second screening. The third screening results were positive for all of the remaining three babies. Of those, 10 had positive results and were referred for further echocardiography confirmation, finally resulting in 8 (0.6%) subjects with CCHD. The screening was performed within a period of ≤24 hours after birth in 855 subjects (59%) and after 24 hours in 597 (41%) subjects.

Oxygen supplementation was promptly administered in cases where newborns were visibly bluish or when desaturation of SpO_2 levels or signs of respiratory distress were apparent. These frequently occurred soon after birth (less than 24 hours) and was most commonly caused by asphyxia, pulmonary hypertension of the newborn, or other pulmonary problems. The healthcare workers did not include these neonates for screening.

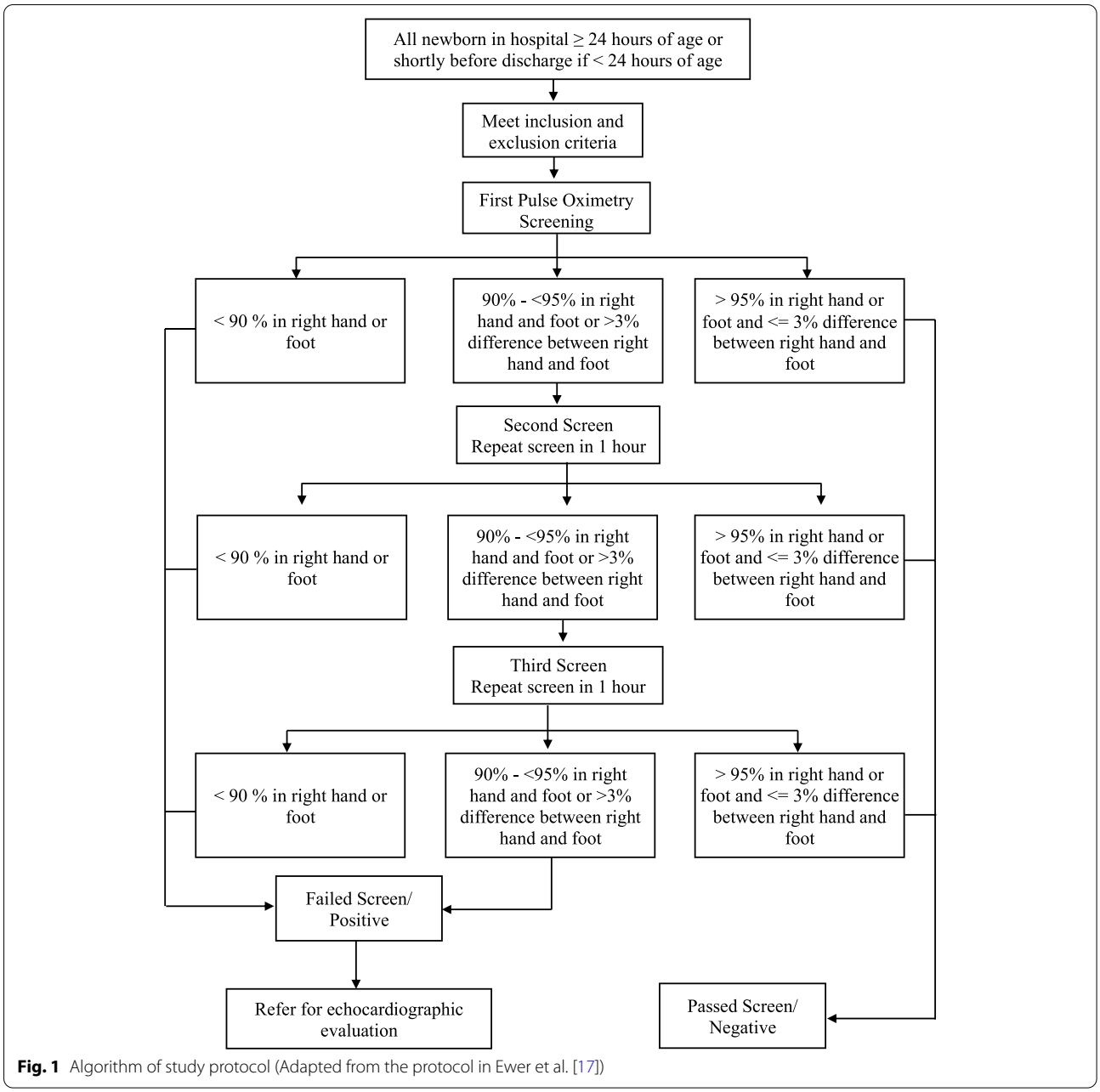

Fig. 1 Algorithm of study protocol (Adapted from the protocol in Ewer et al. [17])

Most screening was performed using the standardized pulse oximetry (Massimo). The agreement among Massimo and Fingertip pulse oximetry was 0.815, while the agreement among Massimo and Mindray pulse oximetry was 0.943.

The baseline characteristics of the eligible newborns are presented in Table 1. Echocardiography results performed in the 10 newborns with positive screening are shown in the Table 2.

Main barriers during process of pulse oximetry screening are shown in Table 3.

Discussion

This study explored the feasibility of implementing CCHD screening with pulse oximetry for 1452 newborns in Yogyakarta, Indonesia. The results of the study indicate that pulse oximetry screening might be feasible to be implemented within the routine newborn care setting for CCHD in Indonesia.

The prevalence of CCHD in our study was 6 of 1000 live births, with positive CCHD screens occurring in 8/1452 (0.6%) of newborns. This was higher than previously reported in Sri Lanka 0.16% (14/8718), [13], India

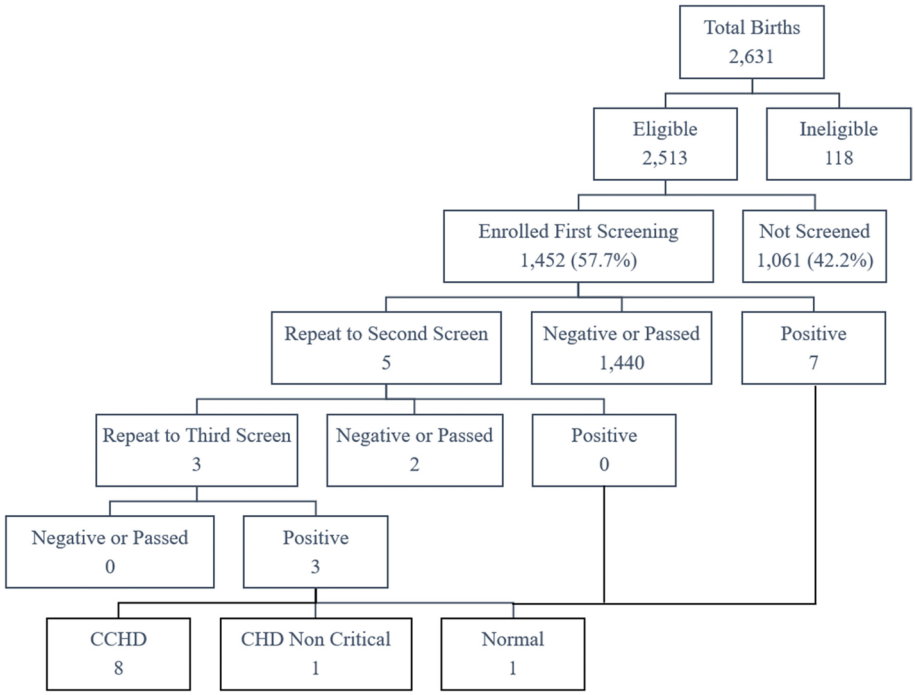

Fig. 2 Distribution of the newborns enrolled in the study

Table 1 Baseline characteristics of screened newborns

Characteristics	Newborns *n* = 1452 (%)
Sex, n (%)	
Male	769 (53)
Female	683 (47)
Birth weight in gram, median (min-max)	3045.4 (1360-4532)
< 2500	154 (10.6)
2500–4000	1279 (88.1)
> 4000	19 (1.3)
Gestational age in weeks, n (%)	
35- < 37	81 (5.6)
37–42	1367 (94.1)
> 42	4 (0.3)
Type of delivery, n (%)	
Caesarean section	859 (59.2)
Vacuum extraction	29 (2)
Normal	564 (38.8)
Type of pulse oximetry, n (%)	
Massimo	1067 (73.5)
Fingertip	18 (1.2)
Mindray	367 (25.3)

0.16% (3/1855) [12], Turkey 0.12% (12/10,200) [18], Morocco 0.06% (5/8013) [19], the Netherlands 0.02% (5/23,959) [20], New Zealand 0.02% (3/16,644) [21], South Africa 0.01% (1/1001) [11] and the United States (US) 0.01% (1/6745) [16].

A meta-analysis of 21 studies involving 457,202 participants concluded that pulse oximetry is a highly specific and moderately sensitive test for detection of CCHD with very low false-positive rates [22]. Pulse oximetry screening has been successfully implemented in high-income countries and has led to a significant reduction in CCHD related deaths. A study showing results from a 6 years evaluation (2007–2013) after implementation of pulse oximetry screenings across the United States found a 33.4% (95% CI: 10.6–50.3%) reduction in CCHD deaths per 100,000 births, with a further potential reduction of 120 infant deaths per year from CCHD [23].

Several countries that have already conducted CCHD screening programs with pulse oximetry such as the US, China, the Netherlands, and the United Kingdom have indicated the practice combined with clinical assessment is beneficial and cost-effective [10]. Through the program, costs for treating complications due to the late diagnosis of CCHD can be avoided. A US study reported the screening program saves 20 infants annually, with an equivalent cost of $40,385 per life-year gained under base case assumptions that each screening would cost $6.28 per newborn [24].

Meanwhile, low- and middle-income countries still must face several barriers to be able to execute the pulse

Table 2 Echocardiography results of 10 newborns with positive screening by pulse oximetry

CCHD ($n=8$)	Non CCHD ($n=2$)
2 cases of Ebstein anomaly	1 case of small secundum ASD
1 case of pulmonary atresia with ventricle septal defect (VSD) and vertical patent ductus arteriosus (PDA);	1 case of patent foramen ovale (PFO) (considered normal)
1 case of tricuspid atresia with pulmonary atresia, small secundum atrial septal defect (ASD)	
1 case of mitral atresia with transposition of the great arteries (TGA), severe pulmonary stenosis, and single ventricle with hypoplastic left ventricle	
1 case of tricuspid atresia, inlet VSD, moderate secundum ASD, small right ventricle and pulmonary stenosis	
1 case of double outlet right ventricle (DORV) with TGA, VSD	
1 case of unbalanced atrioventricular septal defect (AVSD) with moderate PDA.	

Table 3 Barriers during screening process

Type of barriers	Details
Hospital procedure	The standard hospital procedure for the length of postnatal stay is relatively short, and therefore, most of the newborns were screened before 24 hours.
	Pulse oximetry measurement has yet to be part of the pre-discharge standard care for healthy newborns, and therefore, several healthcare personnel (especially nurses and midwives) did not routinely conduct measurements despite the ongoing study.
	Among subjects with positive screening results, echocardiography examinations were not all immediately performed. This was mainly caused by the availability of echocardiographs only at the tertiary and general hospitals, while some subjects were inpatients at the other two hospitals.
Equipment	The lack of pulse oximetry devices in the common wards, with devices only available at the neonatal ICU.
	Tightly fixed sensors using Velcro or rubber fasteners were not widely available, despite being easier and faster to use compared to fingertip-type pulse oximetry.
	Adult probes were sometimes utilized due to the limited resources in the ward.
Healthcare personnel	Healthcare personnel were often occupied with other clinical duties causing them to forget to perform the screening.
Condition of the baby	Some newborns were constantly crying or moving, making measurement of SpO_2 difficult to perform using pulse oximetry.

oximetry screening program. One study in Morocco revealed barriers such as the tendency to discharge healthy newborns before 24 hours, and the difficulty in confirming positive screening results due to the lack of available echocardiographs in several hospitals [19]. Other reported challenges in implementing pulse oximetry screening include acceptance of the program, timing of screening and significance of false positives rate, and response to positive screen results [25].

In our study, we classified barriers found during screening into four concerns. The first concerns involve hospital procedures or workflow. The AAP recommends screenings should be done within 24–48 hours of age. Adversely, most subjects in our study were screened before 24 hours due to the relatively short postnatal length of stay for healthy babies decided in hospital procedures. The timing of screening should be considered since it will influence the screening results. A previous study revealed that the measurement of saturation before 24 hours of age will increase the false positive or false negative rate [20]. The transition from fetal to neonatal circulation and stabilization of systemic oxygen saturation levels might explain this finding. A New Zealand study revealed that a midwifery-led maternity setting characterized by early discharge, influenced the time of testing, effecting saturation levels [21].

The second barrier involves the scarcity of standardized neonatal pulse oximeters, with devices readily available in neonatal intensive care units or observation rooms for monitoring sick newborns, but not in postnatal wards. Only some pulse oximeters were equipped with tightly fixed sensors using Velcro or rubber fasteners which are easier to use compared to finger-type devices where the pulses tend to be difficult to detect and take longer to read. Owing to limited sources, some hospitals even resorted to using adult probes for newborns. The type of probe can affect the effectiveness of examinations. The US Food and Drugs Administrator (FDA) stated three recommendations in using a pulse oximeter: (1) be aware to the factors that can affect the accuracy of a pulse oximeter reading, (2) understand the particular brand and sensor by referring to the device labelling or manufacture's website, and (3) always consider accuracy limitations when using a pulse oximeter to assist in

diagnosis and treatment. Knowing these recommendations is important in understanding the risk of measurement inaccuracy and providing the highest outcomes [26]. Nevertheless, a recent study revealed that a pulse oximetry device provided good accuracy in ruling out hypoxemia in comparison to saturation reading by arterial blood gas sample [27].

The third barrier is related with the condition of the baby. During our study, some newborns were constantly crying or moving, posing a challenge in the application and assessment of pulse oximetry. It is recommended that infants should be fully awake but settled during the screening process, since deep sleep may result in hypoventilation and low saturation results [28]. A previous study in New Zealand showed that newborns that were asleep or unsettled during screening were less likely to have positive results than those who were awake but settled [21].

The fourth and last of the barriers is the lack of healthcare personnel in the postnatal ward. The healthcare providers were occupied with other clinical duties and sometimes forgot the screening protocol. Some did not consider the pulse oximetry measurement to be within the scope of their practice due to low motivation because no incentive was given. A study in South Africa reported that most of the nurses involved in the study were satisfied with the purpose and aim of the study, but they do not have enough time to do the screening since their workloads were already heavy [11]. A study in New Zealand stated that most of midwives agreed that pulse oximetry screening was beneficial, but their already heavy workload prevented them from routinely performing screens. This was one of their concerns regarding the implementation of pulse oximetry as a universal screening program [29].

Indonesia has a large annual live birth rate, at 5 million per year with around 62.7% deliveries commonly assisted by midwives. As many as 79% of women gave birth at health care centers, with around 16% giving birth at home [30]. Nevertheless, Indonesia still lacks any national program for CCHD screening [8]. Pulse oximetry fulfils the criteria for mass screening. It is very effective, low cost and can significantly reduce morbidities and mortality by providing earlier detection of CHD. However, to achieve these goals optimally in a setting where resources are limited is challenging, though not impossible. These goals require extensive standardized training for healthcare providers who work directly in childbirth and newborn care (midwives, nurse, and general practitioner), the measurement protocols need formal regulations and the involvement of policy makers such as health ministries and the pediatric cardiology society to make pulse oximetry screening a recommendation in the standard care of newborns. Further, in order to develop an appropriate system for home birth, the timing of administration of pulse oximetry might need to be altered since a community midwife leaves approximately several hours after an uncomplicated home birth. Extensive training for community midwives and providing each midwife with a handheld pulse oximeter also need to be conducted. However, in order to make this approach works, an appropriate regional system to support the use of pulse oximetry in individual home births should be developed.

In order to optimize the impact of pulse oximetry screening in low-middle income countries, Zheleva et al. summarized several recommendations to be considered including the assessment of referral CHD health services, assessment of birth delivery center processes and staff training needs, financial burden and implementation of CCHD screening process as part of the overall patient care continuum [31]. In principle and practice, pulse oximetry screening is relatively simple, inexpensive, and easy to implement. However, screening is just one step in a lifelong continuum of management for the child diagnosed with CCHD and their family. If a child has a positive screening for CCHD, they require immediate access to definitive diagnosis, safe transportation, and surgical and interventional cardiology services. Newborn screening cannot save as many lives as it should if high quality cardiac services are not available to the child and family following a positive screen. It will help detect cases, but many will not survive or will live a life with serious disability.

The major limitations of our study involve the high proportion of newborns who were not screened over the study period due to the many aforementioned reasons and there was no report provided on parent's acceptance of and uptake of the pulse oximetry screening for CCHD. This study was also limited by the use of three different types of pulse oximeters from three different manufacturers as well as the use of an adult sensor. Despite the limitations, our study is among the first reports of the feasibility of CCHD screening using pulse oximetry in Indonesia and provides the local evidence of barrier perspectives from healthcare workers during the screening process. The findings can be used as available local evidence for policymakers before recommending needed changes to the national screening program.

Conclusions

Pulse oximetry screening might be feasible to be implemented within the routine newborn care for detection of CCHD in Indonesia. In order to successfully implement pulse oximetry screening to identify CCHD in Indonesia, the barriers will need to be addressed.

Abbreviations
AAP: American Academy of Pediatric; ASD: Atrial Septal Defect; CHD: Congenital Heart Disease; CCHD: Critical Congenital Heart Disease; DORV: Double Outlet Right Ventricle; PDA: Patent Ductus Arteriosus; PFO: Patent Foramen Ovale; TGA: Transposition of the Great Aorta; VSD: Ventricle Septal Defect.

Supplementary Information

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Additional file 1.

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Authors' contributions
All authors contributed to the conception or the design of the study. IKM, DP, LP were major contributors in writing the manuscript. DP collected the data. IKM, DP, LP analyzed the data. All authors interpreted the data. All authors read, critically revised and approved the final manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
The Medical and Health Research Ethics Committee, of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia has approved this study (230/UN.1/FKKMK.3/IKA.2/TU/PT.01.04/2021). Informed consent to participate in the study was obtained from the parents or legal guardians of participants.
All experiment protocols involving humans was in accordance with national/international/institutional guidelines or the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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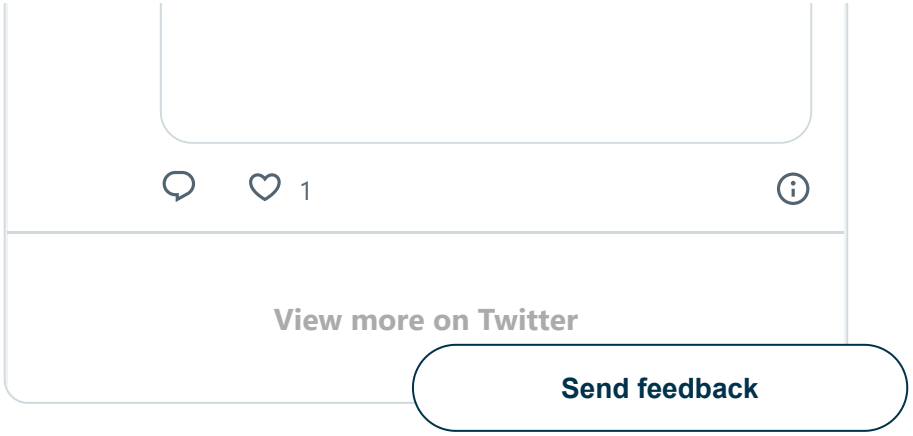

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