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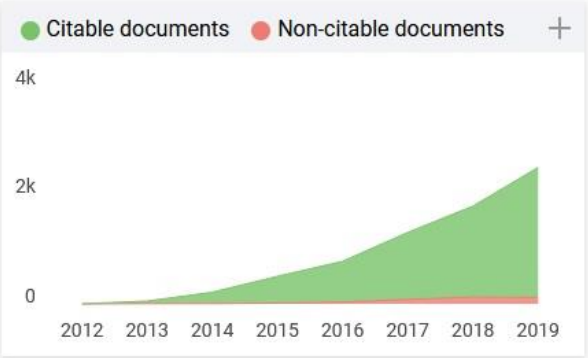

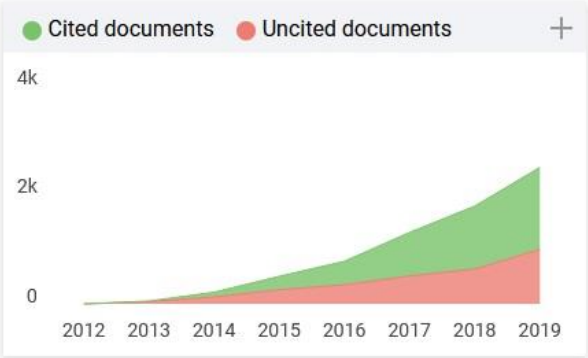

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RESEARCH ARTICLE

Transcutaneous bilirubin level to predict hyperbilirubinemia in preterm neonates [version 1; peer review: 2 approved with reservations]

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Abstract

Background: Hyperbilirubinemia is common in neonates, with higher prevalence among preterm neonates, which can lead to severe hyperbilirubinemia. Assessment of total serum bilirubin (TSB) and use of a transcutaneous bilirubinometer (TcB) are existing methods to identify and predict hyperbilirubinemia. This study aimed to determine TcB cut-off values during the first day for preterm neonates to predict hyperbilirubinemia at 48 and 72 hours.
Methods: A total of 90 neonates born ≤35 weeks were included in the study. They were divided into two groups (Group I: 1000-1500 grams; Group II: 1501-2000 grams). The bilirubin level was measured on the sternum using TcB at the ages of 12, 24, and 72 h. TSB measurements were taken on the third day or if TcB level reached ± 1.24 mg/dL phototherapy threshold and if TcB showed abnormal results (Group I: 5.76-8.24 mg/dL; Group II: 8.76-11.24 mg/dL). Hyperbilirubinemia was defined as TSB ≥7 mg/dL for group I and >10 mg/dL for group II.
Results: In total, 38 group I neonates and 48 group II neonates were observed. Almost half of neonates in group I (44.7%) were suffering from hyperbilirubinemia at the age of 48 hours, with 45.8% of group II at the age of 72 hours. To predict hyperbilirubinemia at the age of 48 hours, the best 24-hour-age TcB cut-off values were calculated to be 4.5 mg/dL for group I and 5.8 mg/dL for group II. To predict hyperbilirubinemia at the age of 72 hours, we determined 24-hour-age TcB value of 5.15 mg/dL for group II.
Conclusion: TcB values in the early days of life can be used as hyperbilirubinemia predictors on the following days for preterm neonates. Close monitoring should be managed for those with TcB values higher than the calculated cut-off values.

Keywords

transcutaneous bilirubin, preterm neonates, predict, hyperbilirubinemia

Open Peer Review

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Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Hyperbilirubinemia is a common condition occurring in neonatal periods[1], with a prevalence of around 60% in term neonates and 80% in preterm neonates. Preterm neonates have greater risk of severe hyperbilirubinemia, which can lead to encephalopathy[2]. This condition is preventable if early detection and prompt treatment can be arranged and managed properly[1,3,4].

Visual assessment is not reliable especially in the first 24–48 hours, since only 80% of jaundiced babies can be recognized visually if the bilirubin level reaches > 6 mg/dL[5–8]. High bilirubin levels can be dangerous, since preterm neonates have a greater risk of low bilirubin kernicterus[2].

Total serum bilirubin (TSB) measurement remains the gold standard for diagnosing hyperbilirubinemia. The drawbacks of this procedure, however, are that it is painful, causes stress to the neonates, has a greater risk of infection, and needs a couple of hours to get the results[9–11].

Trancutaneous bilirubinometry (TcB) is a non-invasive procedure to identify hyperbilirubinemia. A number of studies have been conducted to validate TcB to assess whether it can be used safely. These found that TcB has good correlations with TSB. The use of TcB can also reduce the need for blooding sampling by 41–73%[10,12,13].

Due to the burdens of an occurrence of hyperbilirubinemia, its early detection and prediction are crucial. TSB or TcB is recommended to predict neonatal hyperbilirubinemia for neonates with >35 weeks of gestation[13–15]. Some studies using TcB to predict hyperbilirubinemia have already been conducted, but all of them recruited only late preterm and term neonates[5,16]. For preterm neonates, one study was already conducted using TSB measurement at the age of 6 until 24 hours to predict hyperbilirubinemia in the following hours or days[4]. As far as the researchers know, there has been no previous study using TcB to predict hyperbilirubinemia for preterm neonates. Therefore, the aim of this study was to use TcB to predict hyperbilirubinemia in preterm neonates to prevent complications since visual assessment is no longer reliable.

Methods

Study background and ethical approval

This was a cohort study conducted in the Neonatal Intensive Care Unit (NICU) at Dr Soetomo General Hospital for 5 months (September 2018–January 2019). This study was approved by Dr. Soetomo General Hospital Surabaya Ethics Committee (No. 0586/KEPK/Ix/2018). An informed consent was signed by parents after they understood the information for consent. Study size retrieved in this research used purposive sampling with inclusion and exclusion criteria (a flow diagram is available as *Extended data*)[17,18] during the research period. The sample size that we retrieved was estimated by applying Hulley *et al.*[19] formulation of which confidence interval was at 95%, coefficient correlation at 0.84 and standard deviation of 1.8[4]. Therefore, we applied minimum sample of 20 samples for each group, classified by infants' body weight in certain ranges. While staying in accord with the minimum sample size, we expanded our samples up to 45 infants for each group with total sample of 90 infants. Yet, we had excluded four data due to missing TSB measurement.

Race and thickness of melanin layer of skin tissue were taken into account as confounding variables, and as variables able to modify and differ the outcomes of others. Therefore, to control for study bias, the subjects addressed for this study were those subjects which had similar ethnic backgrounds, which were Malay Mongoloid.

Participant eligibility

The inclusion criteria were: 1) born at ≤35 weeks of gestational age and with a birth weight of <2000 g, and 2) parental consent by signing a form. The exclusion criteria were: 1) being diagnosed as hyperbilirubinemia at the age of 12 hours, 2) having any major congenital anomaly, 3) being discharged from hospital at an age of less than 3 days. Neonates who received phototherapy before the observation was done, missed TSB, or voluntarily resigned from this study were excluded from the study. The subjects recruited were divided into two groups, neonates with birth weights of 1001–1500 g (Group I) and 1501–2000 g (Group II).

Variables

The bilirubin level of each neonate was measured on the sternum by TcB (Dräger® Jaundice Meter 105) at the age of 12 hours, 24 hours, and 72 hours with ±3 hours tolerance (the TcB measurement could be taken within 3 hours before/after the exact time). The TSB measurement was taken for each neonate at the age of 3 days or if the TcB bilirubin level was ≥5.76 mg/dl for group I and TcB ≥8.76 mg/dl for group II and it had to be taken within 6 hours before/after the TcB measurement. The TSB measurement also had to be taken if the TcB measurement showed abnormal results. Hyperbilirubinemia was defined as TSB ≥7 mg/dl for preterm neonates with birth weights of 1000–1500 g and TSB >10 mg/dl for preterm neonates with birth weights of 1501–2000 g.

Statistical analysis

The data was analysis by Microsoft Office Excel, IBM SPSS Statistics Version 21. We performed receiver operating characteristic (ROC) curve analysis to determined cut off point of TcB level to predict hyperbilirubinemia at the age of 48 and 72 hours. We calculated the specificity, sensitivity, positive predicted value (PPV), negative predicted value (NPV), and likelihood ratio.

Results

There were 90 preterm neonates recruited for this study, 40 of whom weighed 1000–1500 grams (Group I) and 50 of whom weighed 1501–2000 grams (Group II). Only 38 neonates of group I and 48 neonates of group II were observed until the end of the study. Four neonates were excluded from the study due to missing TSB results.

Maternal and neonatal characteristics are shown in Table 1. For group I, the mean gestational age of group I was 32.29 ± 1.84 weeks, with a mean birth weight of 1273.68 ± 177.34 grams. Meanwhile for group II the mean gestational age was 33.69 ± 1.26 weeks and a mean birth weight of 1792.70 ± 145.86 grams. Based on risk factors of ABO-incompatibility, one subject of group I who suffered hyperbilirubinemia at the age of 48 hours. Meanwhile, two subjects in group II suffered hyperbilirubinemia at the age of 48 hours and another two subjects at the age of 72 hours at the end of observation, the maximum bilirubin level was 15.2 mg/dl for group I and 16.33 mg/dL for group II. Most neonates of group I (44.7%) suffered hyperbilirubinemia at the age of 48 hours, while most neonates of group II (45.8%) at the age of 72 hours (Figure 1). We found the TSB mean in group I at the age of 24, 48, and 72 hours to be 7.9 mg/dL, 9.16 mg/dL, and 9.3 mg/dL respectively, and 11.01 mg/dL, 10.23 mg/dL, and 11.04 mg/dL respectively, in group II.

TcB bilirubin level to predict hyperbilirubinemia at the age of 48 hours in group I preterm neonates

A ROC curve was constructed to determine a hyperbilirubinemia threshold based on the data collected. We found that the AUC (area under curve) of the TcB bilirubin level at the age of 12 hours to predict hyperbilirubinemia at the age of 48 hours for group I was 0.804 (p 0.002) with a cut-off point of 2.35 mg/dL (sensitivity 79.20% and specificity 71.40%). For the TcB bilirubin level at the age of 24 hours to predict hyperbilirubinemia at the age of 48 hours, we found an AUC 0.771 (p 0.06), with a cut-off point of 4.50mg/dl (sensitivity 87.50% and specificity 64.26%) (Figure 2a, Figure 2b, Table 2).

TcB bilirubin level to predict hyperbilirubinemia at the age of 48 hours in group II preterm neonates

We found the AUC of TcB bilirubin levels at the age of 12 hours to predict hyperbilirubinemia at the age of 48 hours for group II was 0.658 (p = 0.083), with a cut-off point of 3.05 mg/dL (sensitivity 66.7% and specificity 66.7%). The AUC of TcB bilirubin level at the age of 24 hours was 0.732 (p = 0.011), with a cut-off point of 5.80 mg/dL (sensitivity 80% and specificity 63.6%). (Figure 2c, Figure 2d and Table 3).

TcB bilirubin level to predict hyperbilirubinemia at the age of 72 hours in Group I preterm neonates

The TcB bilirubin level of group I at the age of 12 hours, 24 hours, and 48 hours to predict hyperbilirubinemia at the age of 72 hours showed a very weak AUC, which were 0.243 (p = 0.386); 0.297 (p = 0.494); 0.500 (p = 1.000) respectively, therefore no cut-off point could be determined.

TcB bilirubin level to predict hyperbilirubinemia at the age of 72 hours in Group II preterm neonates

The TcB bilirubin level of group II at the age of 12 hours to predict hyperbilirubinemia at the age of 72 hours showed a weak

Table 1. Maternal and neonatal characteristics of subjects.

Maternal characteristics	Group I (n=38) n(%)	Group II (n=48) n(%)
Gestational Age (weeks) (mean ±SD)	32.29 ± 1.84	33.69 ± 1.26
Mode of delivery		
- spontaneous	11(29)	9(19)
- c-section	26(68)	38(80)
- vacuum	1(3)	1(1)
Maternal Blood Type		
A	7(18.4)	12(25)
B	14(36.80)	10(20.80)
O	16(42.10)	19(39.60)
AB	1(2.70)	7(14.60)
Neonatal characteristics	**Group I (n=38) n (%)**	**Group II (n=48) n (%)**
Birth Weight (g) (mean ±SD)	1273.68 ± 177.34	1792.70 ± 145.86
Hematocrit (%) (mean ±SD)	48.04 ± 10.47	46.99± 8.48
Gender		
Male	19 (50)	30(62.50)
Female	19 (50)	18(37.50)
Neonatal blood-type		
A	4(10.50)	9(18.8)
B	11(28.90)	10(20.8)
O	21(55.30)	24(50)
AB	2(5.30)	5(10.4)

*Descriptive analysis was used.

Maternal and neonatal rhesus were positive.

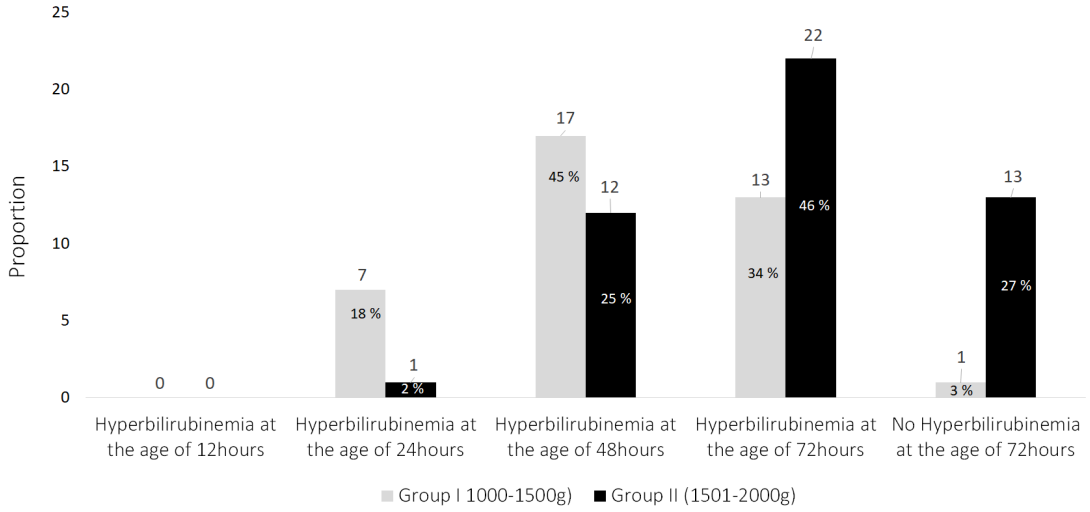

Figure 1. Incidence of hyperbilirubinemia in preterm neonates.

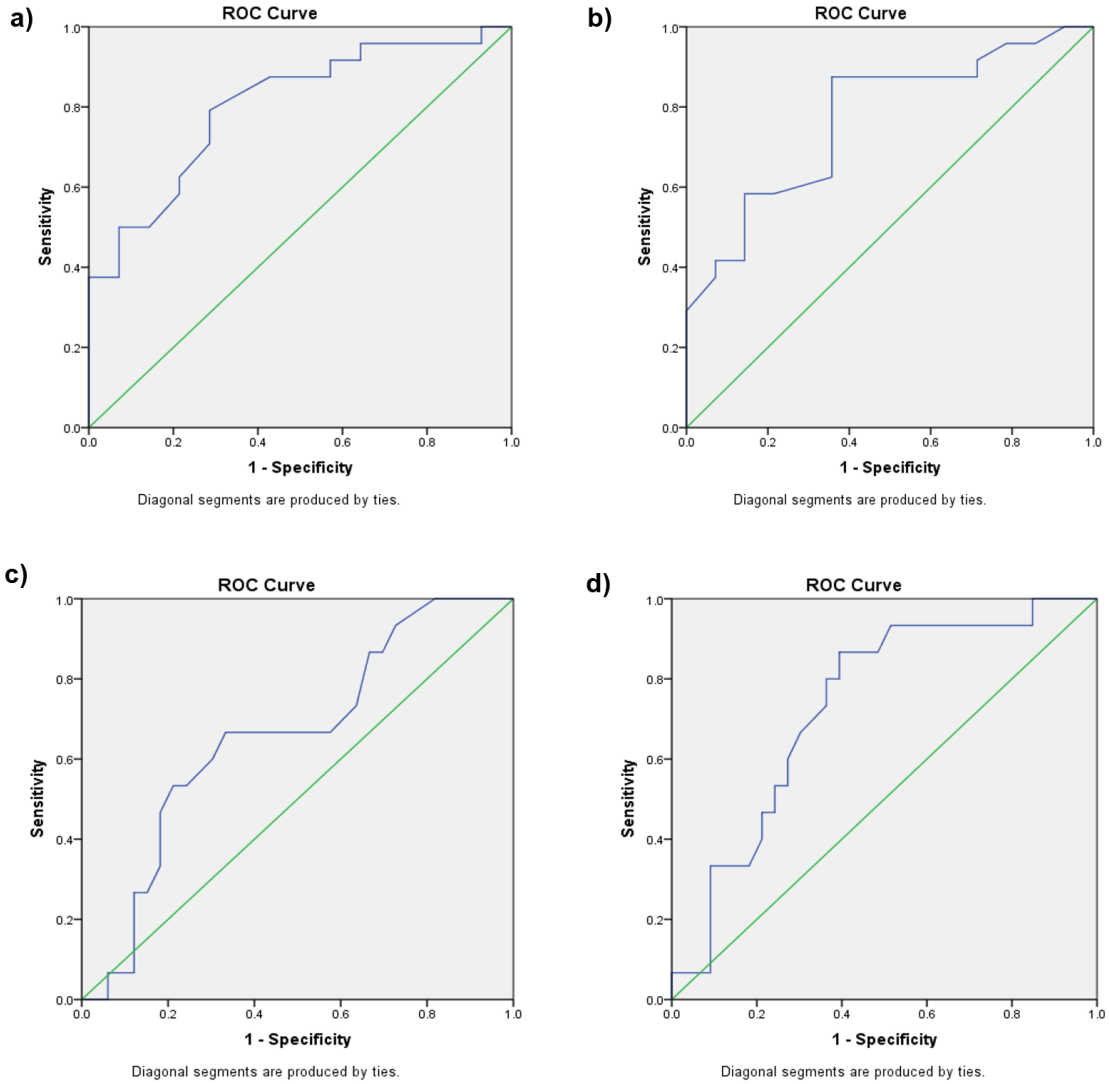

Figure 2. Transcutaneous bilirubinometer (TcB) level to predict hyperbilirubinemia at the age of 48 hours. (**a**) Receiver operating characteristic (ROC) curve for TcB at the age of 12 hours to predict hyperbilirubinemia at the age of 48 hours for group I. (**b**) ROC curve for TcB at the age of 24 hours to predict hyperbilirubinemia at the age of 48 hours for group I. (**c**) ROC curve for TcB at the age of 12 hours to predict hyperbilirubinemia at the age of 48 hours for group II. (**d**) ROC curve for TcB at the age of 24 hours to predict hyperbilirubinemia at the age of 48 hours for group II.

Table 2. Transcutaneous bilirubinometer (TcB) bilirubin level cut-off point to predict hyperbilirubinemia at the age of 48 hours for group I.

TcB level Cut-off (mg/dl)		Group I				
		Sn (%)	Sp (%)	PPV (%)	NPV (%)	LR
12 hours old	2.35	79.2	71.4	82.60	66.67	2.78
24 hours old	4.5	87.5	64.3	80.77	64.26	2.45

†Receiver operative characteristic curve analysis was used. Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio.

Table 3. TcB Bilirubin Level Cut-off Point to Predict Hyperbilirubinemia at the age of 48 hours for Group II.

TcB level Cut-off (mg/dl)		Group II				
		Sn (%)	Sp (%)	PPV (%)	NPV (%)	LR
12 hours old	3.05	66.7	66.7	47.62	81.48	2.00
24 hours old	5.85	80	63.6	50.00	87.50	2.19

†Receiver operative characteristic curve analysis was used. Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio.

AUC (0.499; p = 0.991) with a cut-off point of 2.65 mg/dL (sensitivity 60% and specificity 46%). At the age of 24 hours, we found TcB AUC 0.751 (p = 0.008), with a cut-off point of 5.15 mg/dL (sensitivity 74.3% and specificity 76.9%). Meanwhile, at the age of 48 hours the TcB AUC was 0.731 (p = 0.015), with a cut-off point 8.65 mg/dL (sensitivity 67.6% and specificity 61%) (Figure 3a–c and Table 4).

Discussion

This study has determined a TcB cut-off value of 4.5 mg/dL at the age of 24 hours in group I (1000–1500 grams) and 5.8 mg/dL in group II (1501–2000 grams) as predictive of hyperbilirubinemia at the age of 48 hours. To predict hyperbilirubinemia at the age of 72 hours, this study could not determine any TcB cut-off value for group I (1000–1500 gram) as a result of very weak correlation. The TcB cut-off value of 5.15 mg/dL at the age of 24 hours was determined as the best predictor for hyperbilirubinemia at the age of 72 hours in group II (1501–2000 grams). This cut-off level was established with a sensitivity value ranging from 74.3% to 87.5% at 24 hours after birth. Similar studies have already been conducted, but those studies recruited only late preterm neonates. Lavanya *et al.* found that TcB values measured in the first 24–48 hours of life can predict hyperbilirubinemia at an age of more than 48 hours[20]. Bansal *et al.* determined that TcB values of >4.6 mg/dl at the age of 12–24 hours (sensitivity 83.09%; specificity 87.37%; PPV 90.4% and NPV 78.3%) and >7.4 mg/dl at the age of 24–48 hours (sensitivity 93.55%; specificity 82.11%; PPV 81.69% and NPV 95.35%) are predictors for hyperbilirubinemia in the first 48 hours of life[5]. Other studies conducted used TSB values to predict hyperbilirubinemia in the following days. Mayer recruited preterm neonates weighing 1000–1500 grams and determined a capillary TSB value of 3.55 mg/dl at the age of 12 hours as the best predictor of significant hyperbilirubinemia (sensitivity 94.4%, PPV 98.1%, and NPV 40%)[4].

Most neonates recruited in this study suffered hyperbilirubinemia before the age of 72 hours old. This study also showed that smaller babies suffered peak incidence earlier (at 48 hours) than larger babies (at 72 hours). Hyperbilirubinemia is more prevalent in preterm neonates[4,5,20]) and is usually more severe and has longer duration compared to that in term neonates[4]. This is caused by increased bilirubin production, decreased bilirubin excretion, increased enterohepatic circulation, lower albumin level and a weak albumin-bilirubin bond[11,21]. Early detection of hyperbilirubinemia will decrease its mortality and morbidity. The need for reliable methods to predict hyperbilirubinemia is important. The use of a noninvasive procedure, like TcB, in the first 6–24 hours of life is recommended as a marker of bilirubin production[22] and it can decrease the need for blood sampling[23].

In group I at the ages of 24, 48, and 72 hours, we found TSB mean values of 7.9, 9.16, and 9.3 mg/dL, respectively; in group II, these values were 11.01, 10.23, and 11.04 mg/dL, respectively. This is similar to previous study which found that TSB mean values in the first 5 days of the lives of preterm neonates were 10–12 mg/dL[24]. However, this study found there were preterm neonates who reached a TSB value >15 mg/dL in the first 72 hours. However, it is possible for preterm neonates to have high bilirubin levels in the first days of life, which can lead to hyperbilirubinemia complications if not recognized and treated properly. The previous study conducted by Bhutani *et al.* also indicated that neonates who suffer from hyperbilirubinemia in the following days had higher percentiles on the first day of life[25]. Therefore, the American Academy of Pediatrics (AAP) recommends routine checks of TSB or TcB along with risk factor assessments in the first days of life[14].

To the knowledge of the researchers, this was the first study conducted to predict hyperbilirubinemia in preterm neonates weighing 1000–2000 grams using TcB. One limitation of the study was that it could not determine TcB cut-off values to predict hyperbilirubinemia at the age of 72 hours for preterm neonates weighing 1000–1500 grams due to a lack of subjects able to complete the study, since most had already developed significant hyperbilirubinemia by this time. This, it is hoped that future similar studies will be able to recruit larger populations.

Conclusion

TcB values in the early days of life can be used as a predictor of hyperbilirubinemia in the following days for preterm neonates. It is possible for preterm neonates to have high bilirubin levels in the first few days of their lives. Therefore, daily measurement of TcB is important for early identification of hyperbilirubinemia, especially in order to prevent complications in certain more vulnerable preterm neonates. Close monitoring should be arranged for those who have TcB values higher than the cut-off values.

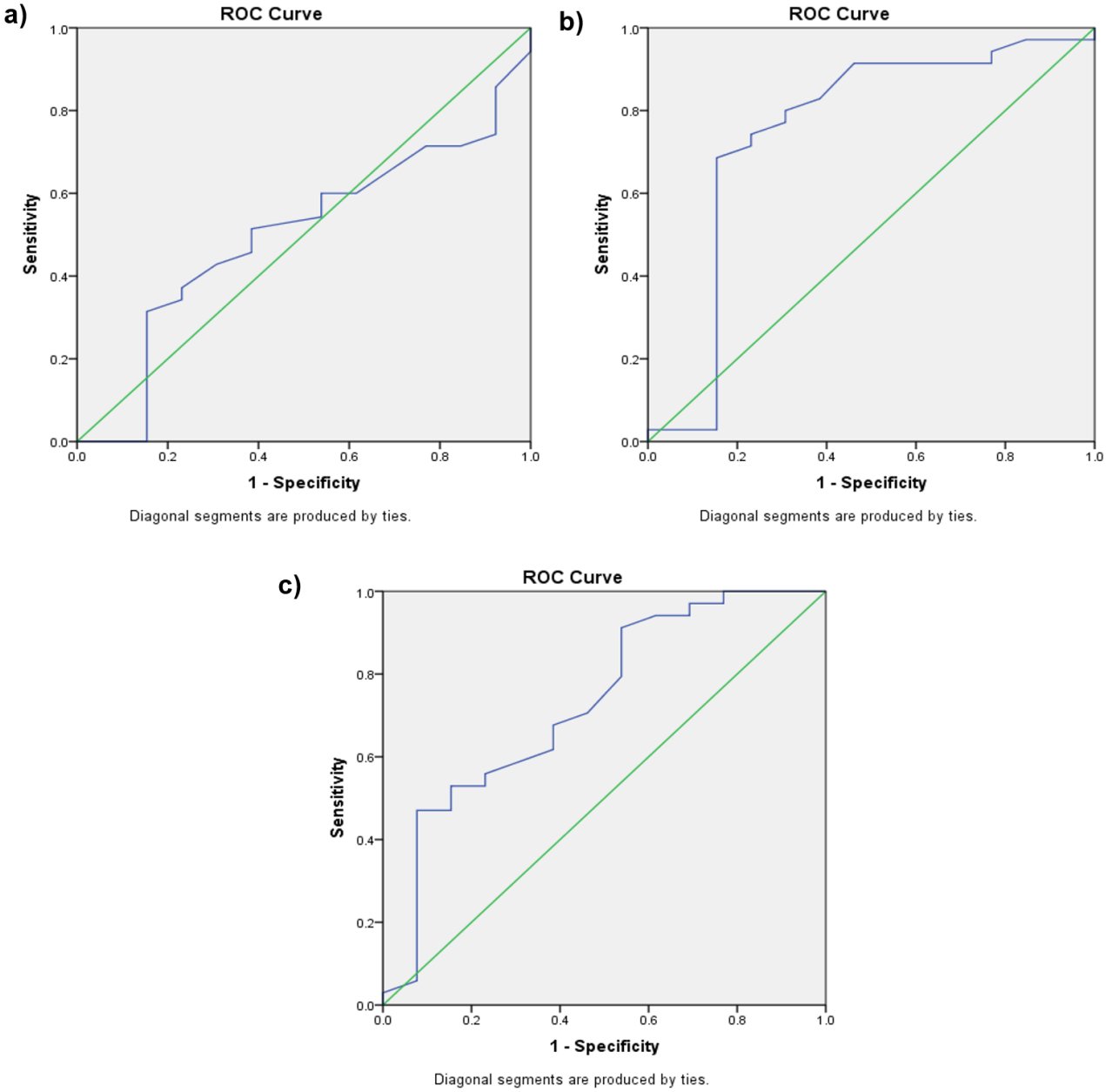

Figure 3. Transcutaneous bilirubinometer (TcB) level to predict hyperbilirubinemia at the age of 72 hours. (**a**) Receiver operating characteristic (ROC) curve for TcB at the age of 12 hours to predict hyperbilirubinemia at the age of 72 hours for group II. (**b**) ROC curve for TcB at the age of 24 hours to predict hyperbilirubinemia at the age of 72 hours for group II. (**c**) ROC curve for TcB at the age of 48 hours to predict hyperbilirubinemia at the age of 72 hours for group II.

Table 4. TcB Bilirubin Level Cut off Point to Predict Hyperbilirubinemia at the age of 72 hours for Group II.

TcB level Cut-off (mg/dl)		Group II				
		Sn (%)	Sp (%)	PPV (%)	NPV (%)	LR
12 hours old	2.65	60	46	75.00	30.00	1.11
24 hours old	5.15	74.3	76.9	89.66	52.63	3.22
48 hours old	8.65	67.6	61	82.75	42.10	1.78

†Receiver operative characteristic curve analysis was used. Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio.

Data availability

Underlying data

Figshare: Datasheet TcB and TSB - Group 1. https://doi.org/10.6084/m9.figshare.11948490.v1[26].

This project contains data gathered for neonates in group 1 (those 1000–1500 grams).

Figshare: TcB Level and TSB-MTA - Group 2. https://doi.org/10.6084/m9.figshare.11948529.v1[27].

This project contains data gathered for neonates in group 2 (those 1500–2000 grams).

Extended data

Figshare: Supplemental File - Flow Chart Study of TcB and TSB. https://doi.org/10.6084/m9.figshare.12017586.v1[18].

This project contains a study flow diagram.

Reporting guidelines

Figshare: STROBE checklist for 'Transcutaneous bilirubin level to predict hyperbilirubinemia in preterm neonates'. https://doi.org/10.6084/m9.figshare.11991672.v2[17].

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Open Peer Review

Current Peer Review Status: ? ?

Version 1

Reviewer Report 21 May 2020

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Tina M. Slusher
Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA

This study is an interesting study looking at the correlation between transcutaneous bilirubin (TcB) and serum bilirubin and the predictive value of subsequent clinically significant hyperbilirubinemia in neonates. However, there are some problems with the study that need to be addressed.

1. They authors state that TcB has not been used in premature infants with the exception of late preterms. However, in a systematic review by Nager *et al.* most of the 22 articles they mention include very preterm infants. Perhaps the authors need to mean to say in their population but this needs to be clarified.

2. Each country does indeed need to develop their own criteria for diagnosis and treatment levels of hyperbilirubinemia based on risk in their environment, treatments available and other specifics related to their own country. However, authors do need to tell us where there cutoffs for each group came from---are the in country normal, standard cutoffs for their hospital or region or how were they selected.

3. Numbers too small to extrapolate widely to Indonesia or beyond.

4. Rhesus of mothers and infants missing; G6PD status missing if not done state that.

5. Although not a major problem or limitation this article could be improved by having a native English speaker read and make minor edits throughout.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pediatric Global Health, Neonatal Hyperbilirubinemia, Pediatric Critical Care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 11 May 2020

https://doi.org/10.5256/f1000research.24559.r62844

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Claudio Tiribelli
Italian Liver Foundation, Trieste, Italy

This is an interesting study investigating in preterm neonates (PTNs) the predictive value of the bilirubin level assessed by transcutaneous technique (TcB) for hyperbilirubinemia (HB). 90 PTNs were and divided into two groups according to the weight (1500 g as diving value). Bilirubin was prospectively measured at different time points (12, 24, 48, and 72 h). Bilirubin level was confirmed by serum bilirubin measurement (TSB) if the TcB was “increased”. ROC curves were used to assess a 24 h TcB value predicting 48 and 72 h HB. Although the data may be of interest, the study suffers several intrinsic weaknesses what must be addressed before being considered further.

Major Critiques:

1. The indication when TSB was measured is unclear and confusing. In the abstract it is stated that TSB was assessed before 72 h if TcB showed “abnormal results”. What does this mean? Detailed numerical values must be provided to allow to understand why TSB was performed.

2. On what basis the TSB value of ≥ 7 mg/dL in group 1 and > 10 mg/dL HB in group 2 was selected? This needs to be scientifically substantiated. At what time this level was measured?

3. How TSB was measured? Were the lab values confirmed by internal calibration? This must be clarified.

4. Fig 1 shows that the time course of HB is different in the 2 groups being the bilirubin peak reached 24 h later in group 2. This difference accounts for the different TcB cutoff values. This needs to be considered and addressed in the discussion.

5. How was the correlation between TcB and TSB at 72h? This information is important to assess the reliability of the two techniques (see also point #3).

6. The abstract is inaccurate as data reported are different from those indicated in the text (see for example the lack of 48H values).

Is the work clearly and accurately presented and does it cite the current literature?
No

Is the study design appropriate and is the work technically sound?
No

Are sufficient details of methods and analysis provided to allow replication by others?
No

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Bilirubin, Jaundice

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.