ACCURACY OF TRANSCUTANEOUS BILIRUBIN DETERMINATION IN NEONATAL HYPERBILIRUBINEMIA: A META-ANALYSIS

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ABSTRACT

BACKGROUND: Timely initiation of therapy for neonatal hyperbilirubinemia is routinely made based on total serum bilirubin levels. However, serial samplings by invasive needle pricks are needed for laboratory analyses. Studies comparing the correlation between serum bilirubin and transcutaneous bilirubin have yielded diverse results. A meta- analysis was done to find out the relationship between transcutaneous bilirubin measurements and serum bilirubin values.

OBJECTIVE: This study aims to analyze scientific articles regarding the accuracy of transcutaneous bilirubin measurements among healthy neonates as an alternative screening for hyperbilirubinemia.

STUDY DESIGN: Diagnostic Accuracy meta- analysis

METHODS: Studies on the accuracy of transcutaneous bilirubin measurements were identified through intensive literature search. Local studies were confirmed thru personal communication.

RESULTS: Three hundred eighteen studies were identified through literature search. Ten studies met the eligibility criteria. Eight of the ten studies reported results as correlation coefficients. The pooled estimates of correlation coefficients is high at r = 0.85 (95% CI = 0.84 to 0.857). Five studies reported results with data for diagnostic accuracy. The pooled analysis for sensitivity and specificity are high at 0.84 (95% CI 0.8-0.88) and 0.79 (95% CI 0.77-0.81) respectively. The pooled likelihood ratio has a significant difference with a pooled positive LR of 4.19 (95% CI 2.98-5.9, P<0.01) while the negative likelihood ratio is 0.23 (95% CI: 0.17 to 0.29). The AUC for transcutaneous bilirubinometry is 0.89.

CONCLUSIONS: Transcutaneous bilirubin measurement can be an alternative in monitoring the risk of healthy neonates for hyperbilirubinemia based on the pooled analysis of correlation coefficient and diagnostic accuracy.

KEYWORDS: Transcutaneous bilirubin, Term and late preterm, serum bilirubin, hyperbilirubinemia

INTRODUCTION

Jaundice is one of the most common conditions needing medical care during the first two weeks of life. It is a relatively prevalent disease that affects approximately 2.4-15% of newborns. Sixty percent of term and 80% of preterm neonates develop jaundice in their first week of life. Ten percent of breastfed neonates are persistently jaundiced requiring readmissions

Neonatal jaundice is categorized into physiologic and pathologic hyperbilirubinemia. Physiologic hyperbilirubinemia conotes to an immaturity of neonates to metabolize increased bilirubin production. It usually appears after 24 hours of age and bilirubin level peaks up to 12-15mg/dl and resolves spontaneously. Pathologic hyperbilirubinemia is jaundice in the first 24 hours of life with increasing bilirubin concentration for more than 5mg/dl in 24 hours. It also requires intervention for its resolution.

Considering the overall socioeconomic burden associated with hyperbilirubinemia, the American Academy of Pediatrics in 2004 issued guidelines for the management of hyperbilirubinemia in term or near-term newborn. It recommends serum bilirubin measurement in all jaundiced infants in the first 24 hours of life and for infants appearing with disproportionate jaundice for the infant's age.

Serum samples are obtained by an invasive capillary puncture or venipuncture giving neonates and parents an additional burden. Another method was generated using a device that measures the intensity of specific wavelength when directed into the skin may alleviate apprehension of most parents from an invasive procedure.

The purpose of this meta-analysis is to determine the impact of non-invasive transcutaneous bilirubin determination by its sensitivity and nearness to serum bilirubin determination. The usefulness of transcutaneous bilirubinometry to decrease the need for blood sampling compared to serum total bilirubin in the management of jaundiced healthy neonates. Thus the research question is: "How accurate is transcutaneous bilirubin determination as screening tool to serum bilirubin in determining level of bilirubin in neonates?"

METHODOLOGY

Electronic search was done through a systematic review of all English articles using MEDLINE (Ovid, PubMed), WHO search portal, Herdin and the Cochrane Controlled Trials Register from January 1990 to October 2017 and EMBASE from January 1990 to October 2017. Additional studies were identified thru personal communication with specialist, researcher, institution and organization. Manual search of reference lists and abstracts were searched from different specialty society conferences scientific program. Manual search for relevant studies was conducted for researches of residents or consultants from different hospitals and institution.

Medical subject heading terms used were cross-sectional studies, neonates, term and late preterm neonates, newborn, transcutaneous bilirubinometer, transcutaneous bilirubin determination, transcutaneous bilinometry, hyperbilirubinemia and serum bilirubin determination.

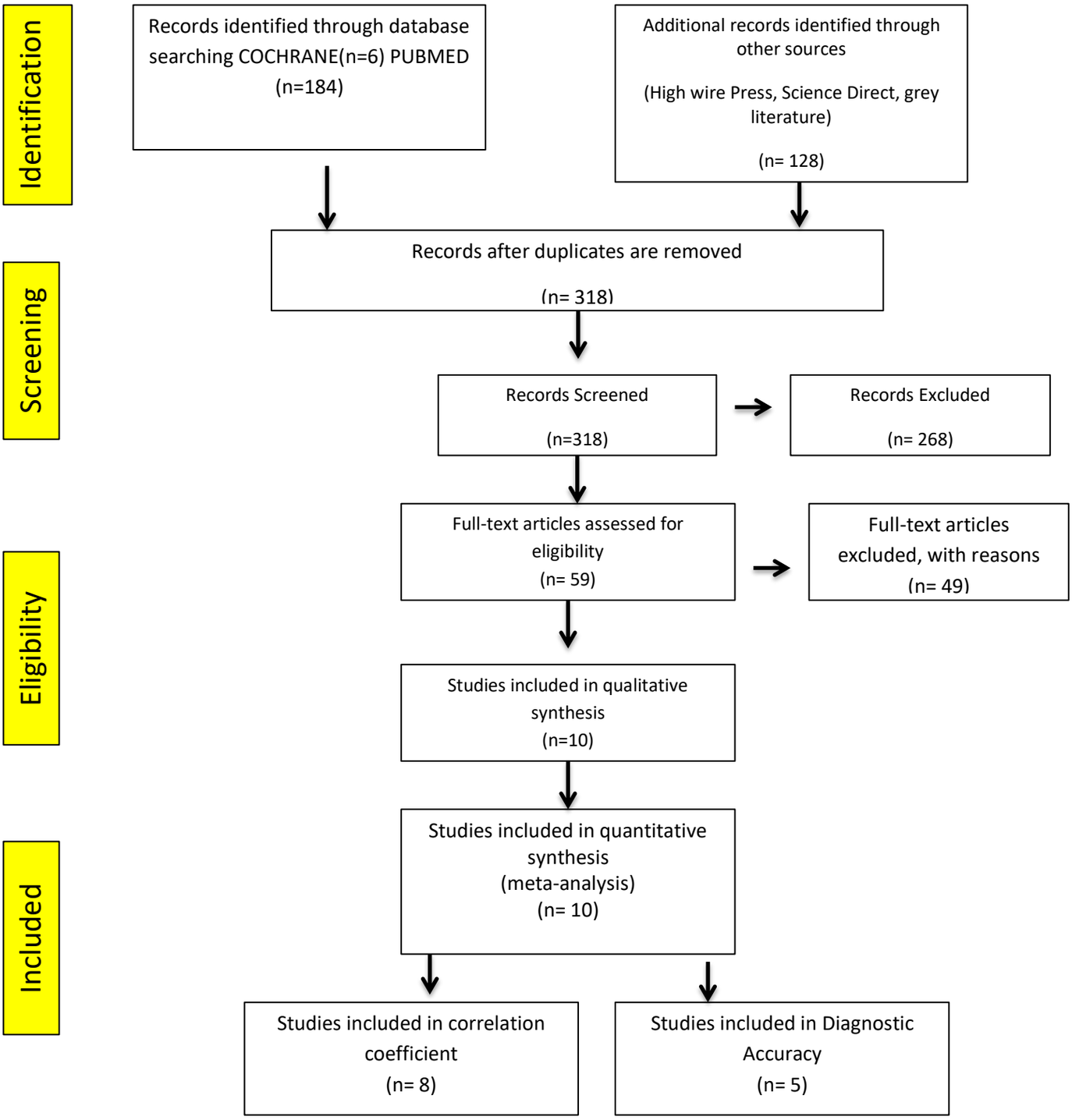
Diagnostic accuracy studies comparing transcutaneous bilirubin determination and serum bilirubin determination for neonatal hyperbilirubinemia were searched and appraised for validity. This meta-analysis included all cross-sectional studies evaluating the use of transcutaneous bilirubin and subsequently with serum bilirubin levels. The participants of the included studies are neonates, term or late preterm neonates age 35 to 37 weeks, which require bilirubin measurement as a universal screening test or for monitoring the risk for hyperbilirubinemia.

Two independent researchers conducted a literature review in accordance to PRISMA standards for selecting qualified studies for meta-analysis. Full texts of identified studies were reviewed for its significance separately by the investigators. Issues and discrepancies in the selection of studies were discussed and resolved. A third party was recruited as mediator if there are any unresolvable issues encountered in the article selections.

We included researches that studies any type of hyperbilirubinemia determined by transcutaneous bilirubin compared to serum bilirubin determination. We required that the authors had state in their methodology section the sensitivity and specificity for both transcutaneus and serum bilirubin levels among neonates. Researches that studied accuracy of transcutaneous bilirubinometry in the diagnosis of hyperbilirubinemia having correlation coefficients as there data were also included to further optimize the quality of the research. The studies not meeting the eligibility criteria and abstracts for which complete results were not available were not examined in the analysis.

We excluded basic research and animal studies. We also excluded from our primary analysis studies that focused on patients with unstable health states, such as those following acute hospitalization and needing interventions such as phototherapy or exchange transfusions.

Fig. 1 Data Extraction And Evaluation Of Studies



A meta-analysis was performed on the available data from the correlation coefficients between measurements of TcB and TSB. All correlations were first converted to Fisher z scores before being pooled. The resulting pooled Fisher z scores were then transformed back into standard correlation coefficients for ease of interpretation. Data was analyzed using StatsDirect 3.1.11 to generate forest plot for the primary outcome

Data on the sensitivity, specificity, and positive and negative predictive values were pooled together and presented in a forrest plot. Summary Receiver Operating Characteritics, (SROC) with analysis of the area under the curve (AUC) were also obtained. Data was analyzed using Meta-Disc v.1.4.

RESULTS

The literature search generated a total of 318 studies with potential relevant citations. A total of 268 articles were excluded for non-fulfillment of eligibility criteria. Fifty- nine studies were reviewed and assessed for eligibility. Forty-nine studies were excluded. Reasons vary, but mostly, it did not state in their methodology section the sensitivity and specificity for both transcutaneus and serum bilirubin levels among neonates.

A trial of ten cross- sectional studies appraised was considered eligible for further analysis. These full articles were reviewed. However, the lack of information from four (4) of the published manuscripts, most prominently the lack of values of true positives, true negatives, false positive and false negatives needed to construct the aforementioned 2x2 table. In order to optimize the significance of the study, an additional study was pooled for the correlation coefficient and was analyzed. A total of 5 prospective cross- sectional studies were included in the final meta-analysis of diagnostic accuracy, while eight cross-sectional studies were included in the meta-analysis of correlation coefficient.

As shown in table 1, the characteristics of the included studies where identified providing 5,948-paired measurements of TcB and TSB in 5, 310 patients who fulfilled the inclusion criteria. All have comparable baseline characteristics. However, included studies varied according to gestational age of the participants being either term or late preterm; site of transcutaneous bilirubin measurement (forehead: 8 studies; sternum: 4 studies); transcutaneous bilirubin device used (BiliCheck: 10 studies; JM-103: 2 studies; VanHou: 1 study); and agreement statistic used for comparison (correlation co- efficient: 1 study; and sensitivity and specificity: 5 studies. There are 7 studies reporting results by both correlation coefficient and Bland- Altman method. Studies conducted transcutaneous and serum bilirubin estimations within a short interval of time ranging either simultaneously to an hour.

Table 2 showed the results for risk of bias assessments on the I ncluded studies. Using the QUADAS tool, the majority of the included studies were assessed as low risk for bias with respect to patient selection, index test, reference standard, and flow and timing.

Table 1. Characteristics of the ten Included Studies in the Meta-analysis

Author, Year	Population, Characteristics, Ethnicity	Measurements/ Sample	TcB Site	TcB Device	Comparison Method	TsB Method	Maximum Interval Between tests, min	Comments
Alsaedi 2006	Healthy term neonates	631/631	Forehead	BiliCheck®	r, BA Sn, Sp	Heel prick	10 mins	jaundiced gestational age of 37-42 weeks
Bhutani 2000	Well-baby nurseries of pennsylvania	1788/490	Skin	BiliCheck®	r, BA	Heel prick	10 mins	Some measurements were done earlier due to the staff's discretion for clinical jaundice
Olusanya 2016	Healthy late and term preterm	1553/2107	Sternum	BiliCheck® or JM-103	r, BA	Heel prick	1 hour	Gestational age ≥35 weeks or birth weight ≥2.2 kg

Author, Year	Population, Characteristics, Ethnicity	Measurements/ Sample	TcB Site	TcB Device	Comparison Method	TsB Method	Maximum Interval Between tests, min	Comments
Boo 2007	Healthy Malaysian Term with hyperbilirubinemia	345/ 288	Forehead and Sternum	BiliCheck®	r, BA	Venous puncture	30 mins	Indian and chinese Jaundiced neonates
Holland 2009	Term neonates	70/343	Forehead and Sternum	BiliCheck®	r	Heel prick	10 mins	More than 3 weeks between 1-5 dyas old
Kolman 2007	Hispanic healthy infants	192/198	Forehead	BiliCheck®	r, BA Sn, Sp	Venous puncture	30 mins	Has not had TSB level before
Mohamed 2014	Healthy neonates	347/141	Forehead or sternum	BiliCheck®	Sn, Sp	Venous puncture	simultaneous	>/= 35 to 37 weeks; weigs more than 2000g
Romagnoli 2013	Healthy term and late preterm neonates	298/298	Forehead	BiliCheck® or JM-103	Sn, Sp	Heel prick	Soon after TcB determination	> 35 weeks visually jaundiced &or / prior to discharged
Srinivas 2015	Healthy term neonates	552/ 512	Forehead	BiliCheck®	r, BA Sn, Sp	Heel prick	Obtained serum samples when TcB is greater than the 95th percentile only	Retrospective study
Zhan 2016	Healthy term neonates	172/302	Forehead	Bilicheck ® and VanHou	r, BA	Radial artery puncture	With serum sample for bilirubin in 24 hours	Must have to have bilirubin sample prior to inclusion to studies

Table 2. Risk of Bias Assessments of the Included Studies

Author, Year	Risk of Bias				Applicability Criteria		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Alsaedi 2016	✓	✓	✓	✓	?	✓	✓
Bhutani 2000	✓	✓	✓	?	✓	✓	?
Olusanya 2016	✓	✓	✓	✓	✓	✓	✓
Boo 2007	✓	✓	✓	✓	?	✓	✓
Holland 2009	✓	✓	✓	✓	✓	✓	✓
Kolman 2007	✓	✓	✓	✓	✓	✓	✓
Mohamed 2014	✓	✓	✓	✓	✓	✓	✓
Romagnoli 2013	✓	✓	✓	✓	✓	✓	✓
Svinas 2015	✓	✓	✓	?	✓	✓	✓
Zhan 2016	✓	✓	✓	?	✓	✓	✓

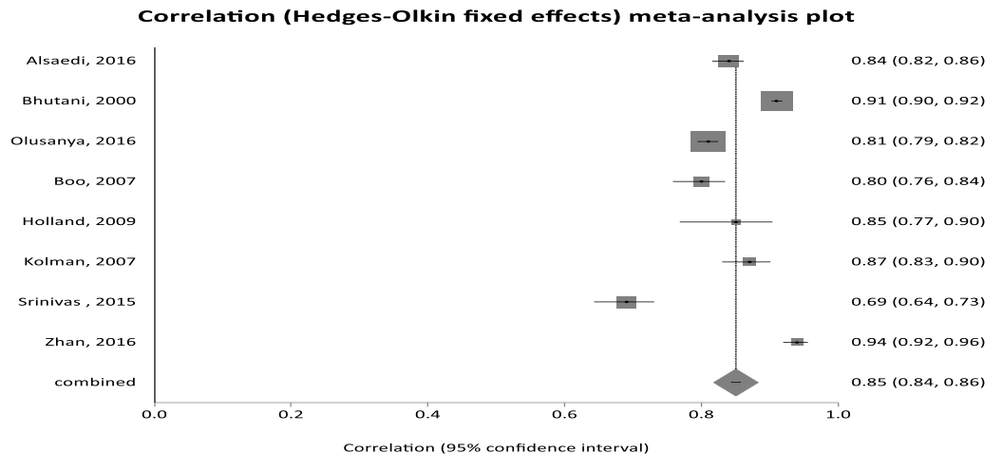
✓, low risk; X, high risk; ? unclea

Pooled Analysis of Correlation Coefficients

Eight studies reported results as correlation coefficients. Figure 2 illustrates eight studies, which provided results for correlation coefficients. The pooled estimates of correlation coefficient r = 0.85 (95% CI = 0.84 to 0.857). All results of TcB regardless of the site of measurement have a positive correlation with the true value of serum bilirubin.

However, the classical measure of heterogeneity, Cochran's Q at 307.62 is high indicating significant heterogeneity among the pooled studies. I^2 statistic is the percentage of variation across studies that is due to heterogeneity rather than chance. I^2 was 97.7%. The high level of heterogeneity may be explained by the differences among hospitals where the studies were conducted in terms of their method, device and site of determination.

Figure 2. Pooled estimates of correlation coefficients according to the site of TcB measurement



Pooled Tests for Diagnostic Accuracy

Figure 3 and 4 demonstrates the analysis of the pooled data for the sensitivity and specificity of the studies. Five studies were included in the study, and results of the studies measuring the sensitivity of TcB do not significantly differ. Overall sensitivity of TcB based on the pooled analysis is high at 0.84 (95% CI 0.8-0.88, P=0.22). This further demonstrates that TcB determination generally has a high sensitivity thereby strengthening its utility for neonates. As illustrated in figure 4, the results of these studies measuring the specificity of TcB significantly differ. Specificity holds the fraction of those with the disease correctly identified as negative by the test. Overall specificity of TcB based on the pooled analysis is high at 0.79 (95% CI 0.77-0.81, P<0.01).

Figure 3. Forest plot evaluating Sensitivity

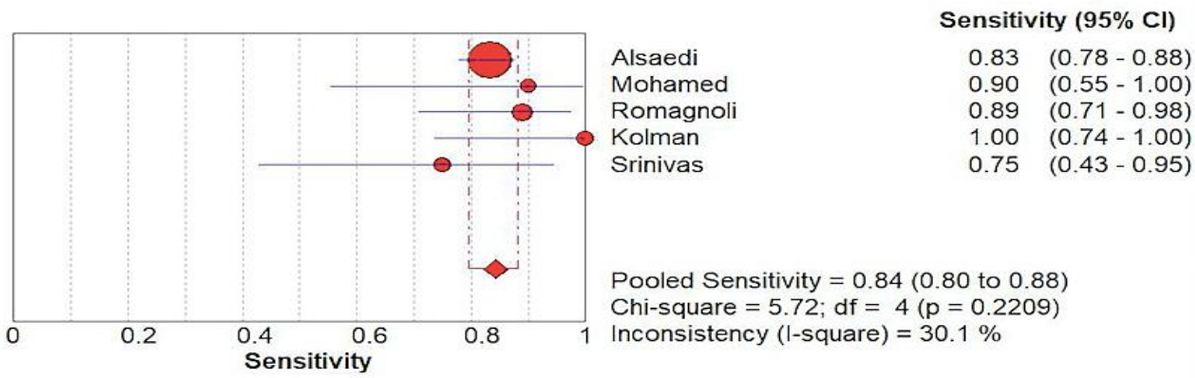
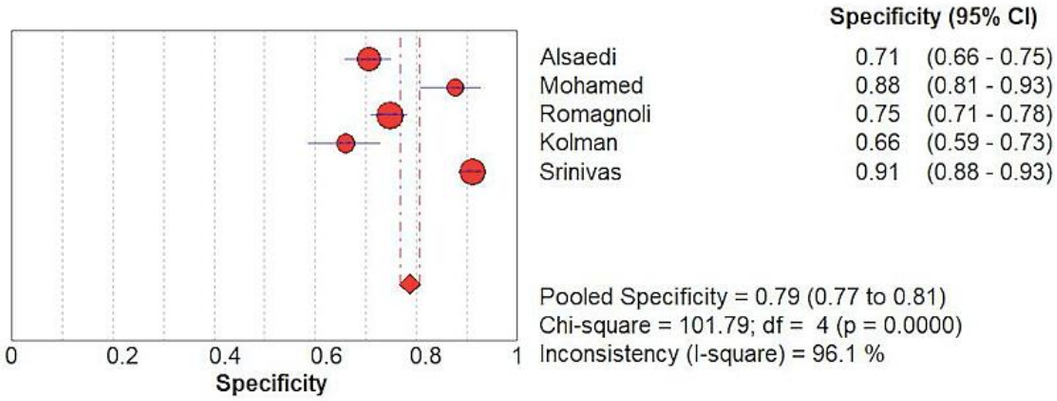


Figure 4. Forest plot evaluating Specificity



The pooled positive likelihood ratio tells us the increase in the probability of disease if the test is positive. This shows a significant difference with a pooled positive LR at 4.19 (95% CI 2.98-5.9, P<0.01) while the negative likelihood ratio is 0.23 (95% CI: 0.17 to 0.29). These represent that if the result of transcutaneous bilirubin measurement is positive, the probability of having the disease is high, but having a negative result would not mean that the patient has no disease. Clinical correlation is still warranted.

Figure 5. Forest plot evaluating Positive Likelihood Ratio

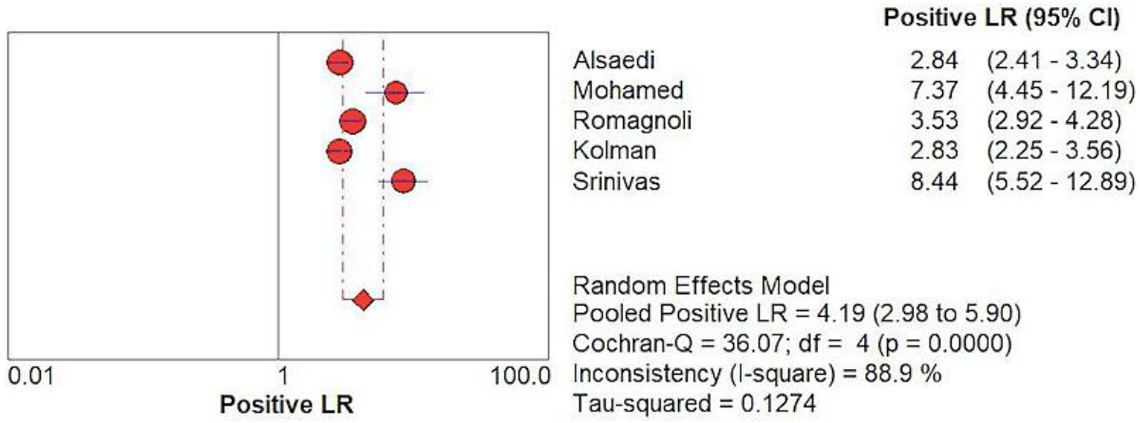
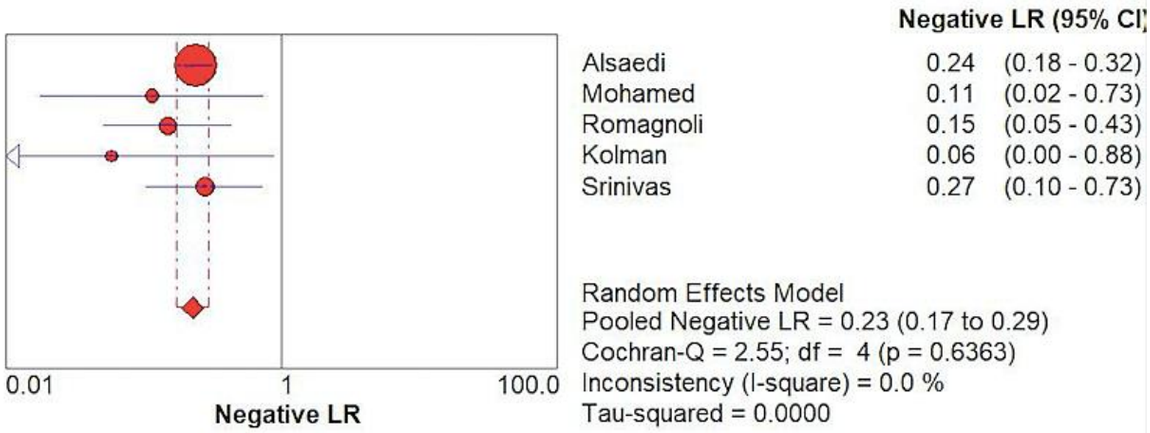
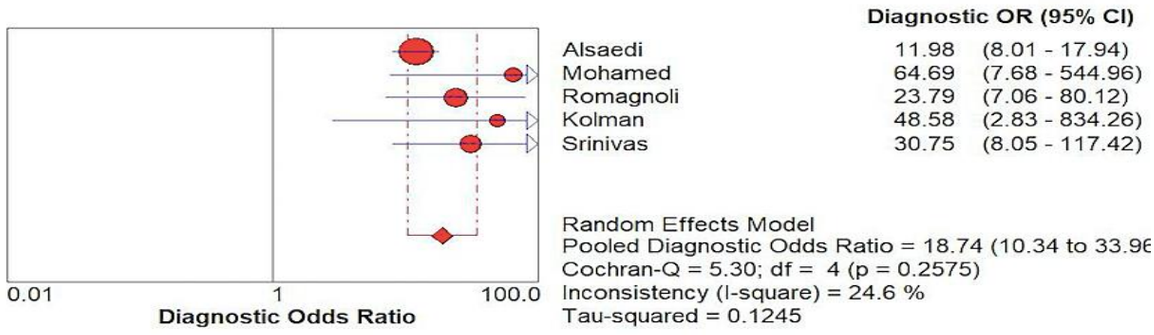


Figure 6. Forest plot evaluating Negative Likelihood Ratio



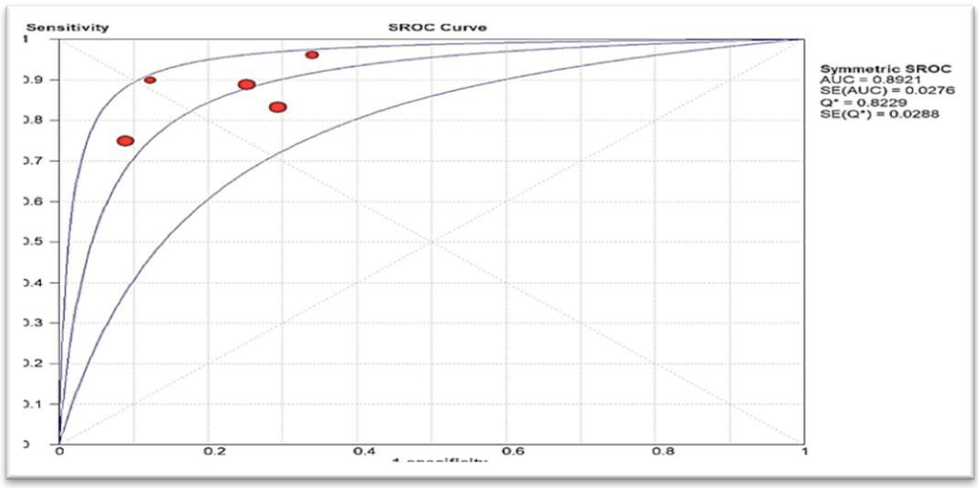
The diagnostic odds ratio (DOR) is a measure of the effectiveness of the diagnostic test: the ratio of the odds of a positive test result among the diseased to the odds of a positive test result among the non-diseased. It is used to discriminate subjects with the disease from subjects without the disease. The diagnostic odds ratio ranges from zero to infinity, with higher DOR indicative of better test performance. In this study, the pooled diagnostic odds ratio is 18.74 (95% CI: 10.34 to 33.96).

Figure 7. Forest plot evaluating Diagnostic Odds Ratio



The summary receiver operating characteristics curve (SROC) was analyzed in order to overcome data pooling difficulties. The AUC for transcutaneous bilirubinometry is 0.89, which is a reasonably good value compared to a perfect AUC value of one (1.0).

Figure 8. ROC Curve



DISCUSSION

Universal screening for neonatal hyperbilirubinemia is controversial, although neonatal jaundice is common and benign in term and near preterm neonates. However, bilirubin encephalopathy or kernicterus may occur and may cause potential long-term impairments and poor outcomes from the initially well infant. Hence, the American Academy of Pediatrics (AAP) recommends universal screening with bilirubin levels or targeted screening based on risk factors. However, the U.S. Preventive Services Task Force and the American Academy of Family Physicians found insufficient evidence that screening improves outcomes.[i] Moreover, universal screening may increase the use of phototherapy, sometimes inappropriately. Several studies supporting the use of transcutaneous bilirubin determination as a near

alternative to serum bilirubin determination, its use for the detection and screening of hyperbilirubinemia in neonates is now accepted worldwide. This review supports the guidelines of AAP[11] that transcutaneous bilirubin determination is suitable to monitor probability of hyperbilirubinemia in neonates, within certain limits.

This study pooled all available data and those who met the criteria to confirm the accuracy of transcutaneous bilirubinometry to further guide practitioners in implementing its use. The identified studies evaluating the diagnostic accuracy of various transcutaneous bilirubin devices in a healthy term and near preterm population found that transcutaneous bilirubin measurements correlate reasonably well with the serum bilirubin estimation in healthy neonates, principally for the two commonly used transcutaneous bilirubin devices in practice, BiliCheck® and JM-103. The accuracy of these two devices was similar for the measurement at the forehead site but noted to be more accurate over the sternum in some studies as illustrated by Mohamed, Holland and Boo. However, according to the study done by Olusanya, increased pigmentation of the skin can affect the bilirubin result done transcutaneously as compared with serum. This can be explained by how transcutaneous bilirubin devices measures bilirubin using reflectance of light in the multi-wavelength spectral reflectance technique, which allows the device to determine the optical densities attributed to bilirubin, dermal thickness, heme and melanin in the epidermal and dermal layers in the infant skin.

The analysis of absolute transcutaneous – serum bilirubin measurement difference plots revealed minimal to no bias in measurements, irrespective of the site and type of device. Looking at the diagnostic accuracy of transcutaneous bilirubin devices in term and near preterm population, we presented a pooled data for bias and precision estimates along with the more commonly used measure of the correlation coefficient. The latter typically describes the strength of a relation between 2 variables rather than agreement between them. Thus, the clinical utility of correlation coefficient data is limited because they intuitively do not provide information regarding expected differences between the measurements conducted on a given patient by 2 separate tests.

The results of this study showed that transcutaneous bilirubin determination has a sensitivity of 84%, showing that 84% of patients with elevated serum bilirubin will also have an elevated bilirubin result transcutaneously. A specificity of 79% will mean that the patient without hyperbilirubinemia will have low levels of bilirubin transcutaneously.

An area under the curve showed an 89% accuracy for transcutaneous bilirubin indicating a good alternative to serum bilirubin as supported by all studies included in the meta analysis. While the odds ratio of 18.74 indicates that transcutaneous bilirubin determination will 18.74 times more likely to reflect the actual serum bilirubin level.

The likelihood ratio indicates that there is 4 times more likely that the patient is positive for the disease, a negative result would not mean that the patient has no disease due to a low negative likelihood ratio of 0.23. Hence, Clinical correlation is still warranted. Regardless of the site of measurement, there was a significant heterogeneity noted in the pooled estimates from the different studies with a correlation coefficient of 0.85. Hence, determination of bilirubin via transcutaneous bilirubin determination will not differ regardless of the site of determination.

According to Nagar, the pooled estimates of bias are comparable in the use of these devices as a result in a marked decrease in blood sampling for assessment of neonatal jaundice. It may yield the nearest estimate of the tests accuracy, and may still provide clinicians with helpful information on the utility of transcutaneous bilirubinometry[ii]. However, there is a lower threshold for the initiation of phototherapy for near preterm infant, with certain guidelines providing specific cutoffs for each gestational week according to the postnatal age. Thus, the information from this meta-analysis should be incorporated in clinical practice, taking into consideration the thresholds for phototherapy in high-risk infants. Similarly, a transcutaneous reading above the phototherapy threshold may be sufficient grounds to initiate phototherapy without the invasive test in most situations. The latter recommendation is made

despite knowing that some of these infants may be classified as below the phototherapy threshold based on serum bilirubin results because those infants are still likely to be reasonably close to the threshold.

Moreover, our analysis has several limitations. First, as mentioned above, there is presence of heterogeneity among the study categories and variables- both clinical and statistical, that were used for establishing hyperbilirubinemia. Some factors that may not be comparable in the trial might have affected the clinical outcomes derived. The high level of heterogeneity seen from the comparison on the incidence of transcutaneousmay be attributed to differences among the local hospital set-up, their practices, and the way the bilirubin levels are obtained. These differences may explain the statistical heterogeneity in some of the secondary outcomes investigated. Second, although we have pooled similar data across all trials, the number of participants per trial may be not sufficient to exclude significant clinical benefit. Thirdly, the setting of most trials was done only in single hospital centers and may have inherent bias related to their local practice habits. Finally, a possibility of publication bias based on funnel plot may discount our extensive search for relevant studies using multiple search items and removing language restriction.

Finally, although initial results seem to be promising for the use of transcutaneous bilirubin determination to early detect hyperbilirubinemia, there is still insufficient evidence to conclude to pediatricians that its use is comparable with the accuracy of the serum due to the pooled studies high heterogeneity. In addition, studies that investigate transcutaneous bilirubin determination device which has more benefit including superiority in terms of ease of use, durability, accuracy and route, are still lacking. These are areas that are yet to be ventured when it comes to evaluation of hyperbilirubinemia in large-scale randomized controlled trials or cross sectional studies for hyperbilirubinemia.

CONCLUSION

The use of transcutaneous bilirubin determination was associated with statistically significant reduction in the incidence of hyperbilirubinemia in high-risk infants. This further strengthened the use of transcutaneous bilirubin devices, particularly JM-103 and BiliCheck®, measure serum bilirubin values in term healthy neonates with rational accuracy. Incorporating the use of transcutaneous bilirubin devices in clinical practice could help reduce the need for blood sampling for the management of high-risk infants or those at risk for hyperbilirubinemia.

The investigators suggest that an analysis of subgroups be done in order to add valuable evidence in the analysis of the diagnostic accuracy of transcutaneous bilirubinometry. A larger and well designed, randomized control trial are needed to determine whether the gestational age, post-natal age, body weight, race, and site of TcB measurement have any influence on the accuracy of transcutaneous bilirubin measurement for hyperbilirubinemia.

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