International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

Original Research Article.

Correlation of Transcutaneous Bilirubin with Serum Bilirubin in Term and Preterm Neonates with Jaundice

Mohammad Masudur Rahaman Khan[1*], Md. Tariqul Islam[2], Shahjadi Nasreen Sultana[3], Mohammed Shaheen[4], Mohammad Neamat Hossain[5], Sanjoy Kumer Dey[6], M A Mannan[7], Mohammod Shahidullah[8]

[1]Assistant Professor, Dept. of Neonatology, Chattogram Medical College, Chattogram, Bangladesh.
[2]Assistant Professor, Dept. of Neonatology, Sir Salimullah Medical College and Mitford Hospital, Dhaka, Bangladesh.
[3]Assistant Professor, Dept. of Neonatology, Mugda Medical College, Dhaka, Bangladesh.
[4]Assistant Professor, Dept. of Neonatology, Chattogram Medical College, Chattogram, Bangladesh.
[5]Assistant Professor, Dept. of Neonatology, Faridpur Medical College, Faridpur, Bangladesh.
[6]Associate Professor, Dept. of Neonatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
[7]Professor, Dept. of Neonatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
[8]Professor and Chairman, Dept. of Neonatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

ABSTRACT

Background: Jaundice is a very common neonatal problem and contributes a lot to the admission into neonatal care units and hospitals. Early estimation of TcB may help identifying neonates with significant jaundice requiring serum bilirubin estimation. This may help avoiding unnecessary estimation of serum bilirubin by invasive method in preterm and term neonates. TcB has been practised mostly in the white population and studies in the nonwhite population is relatively scarce. In Bangladesh, estimation of TcB is a very new approach and not in practice in most of the centres; and involves only term and near-term neonates sparing preterm ones.

Objective: To evaluate the correlation of transcutaneous bilirubin with serum bilirubin in term and preterm neonates with jaundice.

Methods: This cross sectional study was conducted in the department of Neonatology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from September 2015 to August 2016. Jaundiced neonates ranging from 28 to 42 weeks of gestation were studied. JM-103 device and Dichlorophenyl Diazonium method were used to measure TcB and TSB respectively. TcB measurements were obtained over the sternum 30 minutes prior or after blood sampling for TSB. Pearson's correlation coefficient and linear regression analysis were used to determine the correlation between TcB and TSB. Bland-Altman plot was used to analyse the agreement between TcB and TSB. ROC curve was constructed both for term and preterm infants to determine the best cut-off values with their sensitivity and specificity.

Results: A total of 148 paired TcB-TSB readings for 102 jaundiced term and preterm infants were obtained. Correlation coefficient in total population, term and preterm neonates were 0.83, 0.92 and 0.69 respectively. Bland-Altman plot showed reasonable agreement in term newborns but not in preterm babies. Overall best sensitivity and specificity of TcB in term neonates was 90% and 73%, and in preterm neonates 65% and 60% respectively. Area under the curve for TcB was 86% in term neonates, whereas it was 63% in preterm neonates.

Keywords: Jaundice, Transcutaneous Bilirubin, Serum Bilirubin, Term and Preterm Infants.

***Correspondence to:**
Dr. Mohammad Masudur Rahaman Khan,
Assistant Professor,
Dept. of Neonatology,
Chattogram Medical College, Chattogram, Bangladesh.

Article History:
Received: 22-11-2019, **Revised:** 18-12-2019, **Accepted:** 12-01-2020

Access this article online	
Website: www.ijmrp.com	Quick Response code
DOI: 10.21276/ijmrp.2020.6.1.017	

INTRODUCTION

Neonatal jaundice is the clinical condition of neonates caused by high levels of serum bilirubin. This neonatal hyperbilirubinemia incidence is around 60% in term babies. On the contrary, the incidence in preterm babies is around 80-100%.[1]

Preterm are more vulnerable for developing kernicterus at lower bilirubin values.[2] Assessment and management of hyperbilirubinemia require clinical examination and estimation of serum bilirubin. Visual assessment of bilirubin of the skin or sclera has been shown to correlate poorly with serum bilirubin levels.[3] The American Academy of Paediatrics (AAP) guideline recommends both transcutaneous bilirubin (TcB) and total serum bilirubin (TSB) measurements as acceptable methods for estimation of bilirubin accurately.[4] Between them TSB is the gold standard though it is invasive, painful, time-consuming and costly . Significant blood loss is anticipated due to repeated sampling especially in preterms. On the contrary, TcB can overcome the problem as it is a noninvasive method.[5] TcB measurement has been practiced mostly in the white population and studies in the non-white population is relatively scarce. But variation in melanin pigmentation from race to race may have significant impact on measurement of transcutaneous bilirubin.

In Bangladesh, estimation of TcB is a very new approach and involves only term and near-term neonates sparing the preterm ones according to the guidelines of American Academy of Pediatrics. Whereas, jaundice in preterm neonates often assume a more severe and protracted course than in term and near-term neonates. Although the existing guidelines allow use of TcB devices only for the evaluation of jaundice in term and near-term neonates, current meta-analysis study found reasonably well correlation of TcB measurements with TSB in preterm infants.[6] This study was intended to evaluate the correlation of transcutaneous bilirubin with serum bilirubin both in jaundiced term and preterm neonates in the non-white population set-up.

MATERIALS AND METHODS

This study was conducted on 148 patients at the Department of Neonatology in Bangabandhu Sheikh Mujib Medical University from September 2015 to August 2016. All term and preterm neonates diagnosed with clinical jaundice were included in the study. Preterm <28 weeks were excluded from the study. Neonates having previous exposure to phototherapy, neonates with severe sepsis, severe asphyxia and shock as well as neonates requiring exchange transfusion and having congenital malformations were also excluded.

After obtaining informed written consent detailed history was recorded and thorough clinical examination was performed. Gestational age of neonates was determined by LMP date and New Ballard Score of neonates <96 hours of age and LMP alone for neonates >96 hours of age. In case of unavailability of LMP date, EDD date from antenatal USG in first trimester was considered.

Serum bilirubin estimation and TcB readings were taken as soon as a baby with jaundice got admitted or as soon as clinically significant jaundice appeared in an already hospitalized baby or newborn attending outpatient department presented with jaundice. Decision for blood sampling was taken according to clinical judgement and AAP guidelines. Blood samples were drawn from a peripheral vein and TSB was done from the department of Biochemistry, BSMMU by Dichlorophenyl Diazonium method using semi-automated biochemical analyzer. TcB measurement was performed within 30 minutes of blood collection for TSB assay. All TcB measurements were performed by one investigator and only one transcutaneous bilirubin measurement device was used throughout the study period. For TcB measurements, using Drager Jaundice Meter 103 (manufactured by Dräger Medical Canada, Inc., Richmond Hill, ON), five readings at mid sternum were taken in a quiet child, placing the measuring probe vertically on the sternum and then applying gentle pressure until the probe clicks. When the remaining number of measurements was completed, the average of the measured values appeared in the display in mg/dl. The transcutaneous bilirubinometer was standardized according to the manufacturer's guidelines. The probe was disinfected with 70% isopropyl alcohol before and after using it on each baby.

Mean and standard deviation were determined for quantitative data whereas frequency and percentage were presented for qualitative data. Correlation between TcB and TSB were presented through correlation Coefficients (r), Coefficient of determination (R^2) and linear regression analysis. Bland-Altman method was used to assess the bias and agreement between TSB and TcB. The differences between TSB and TcB were compared with mean of TSB and TcB and were palced in Bland-Altman plot. Receiver operating characteristics (ROC) curves were constructed to analyse the diagnostic performance of TcB and cut off values were obtained to determine sensitivity and specificity of TcB in both term and preterm neonates.

Table 1: Baseline characteristics of the study population (n=102)

Variables	n (%)	Mean ± SD (Range)
Sex		
Male	57 (55.88)	
Female	45 (45.12)	
Gestational age (weeks)		
< 37 weeks	53 (51.97)	34.6 ± 3.01
≥37 weeks	49 (49.03)	(28 – 40 weeks)
Age at enrollment		
< 3 days	54 (62.74)	2.98 ± 1.23
≥ 3 days	48 (37.25)	(1-7 days)
Birth weight (gm)		
≥ 2500 gm	40 (39.21)	34.60 ± 3.01
< 2500 gm	62 (60.79)	(960 - 4150 gm)

Numerical data are presented as mean ± SD and categorical data as percentage (%)

Table 2: Distribution of paired bilirubin measurements of TcB and TSB in studied samples (n=148)

Variables	n	Mean TcB (Range)	Mean TSB (Range)
Term	72	14.28 ± 2.07 (SD)	13.61 ± 2.57 (SD)
(≥ 37 weeks)		(8.5 – 10.8)	(9.4 – 18.7)
Preterm	76	12.50 ± 2.27(SD)	10.65 ± 2.62 (SD)
(28 - <37 weeks)		(7.5 – 17.4)	(9.0 – 19.6)

Table 3: Correlation of TcB and TSB by various factors

Variables	r-value	p-value
Gestational age		
Term	0.92	<0.0001
Preterm	0.69	<0.0001
Sex		
Male	0.85	<0.0001
Female	0.81	<0.0001
Birth weight		
≥2500 gm	0.92	<0.0001
<2500 gm	0.77	<0.0001
Postnatal age		
≥3 days	0.849	<0.0001
<3 days	0.76	<0.0001

Statistical test: Pearson's correlation, r = correlation coefficients

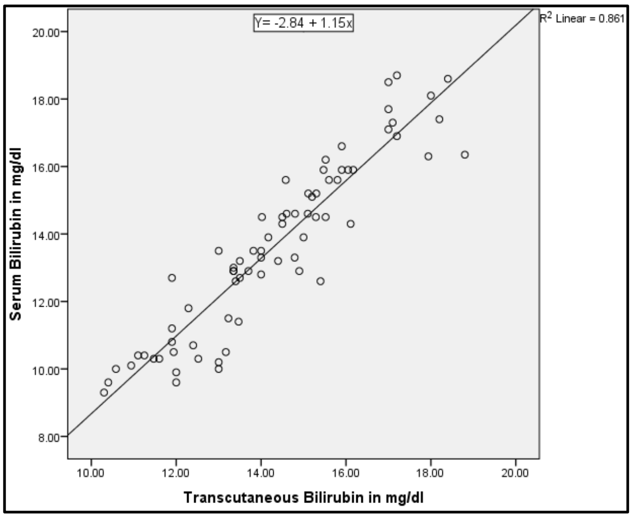

Fig 1: Linear regression plot showing correlation between TcB and TSB measurements in term infants.

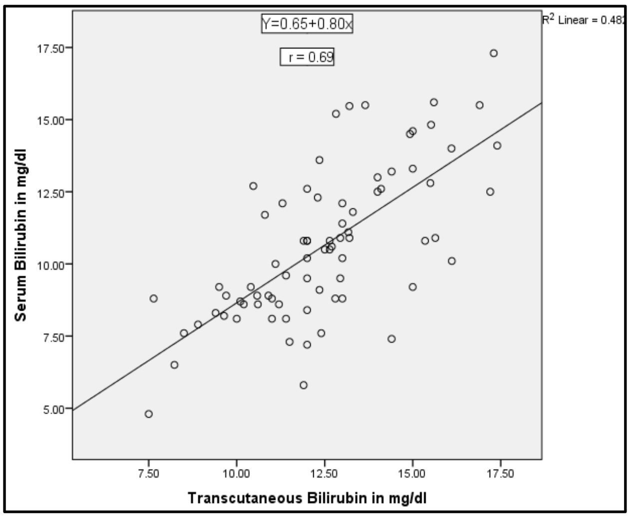

Fig 2: Linear regression plot showing correlation between TcB and TSB measurements in preterm infants.

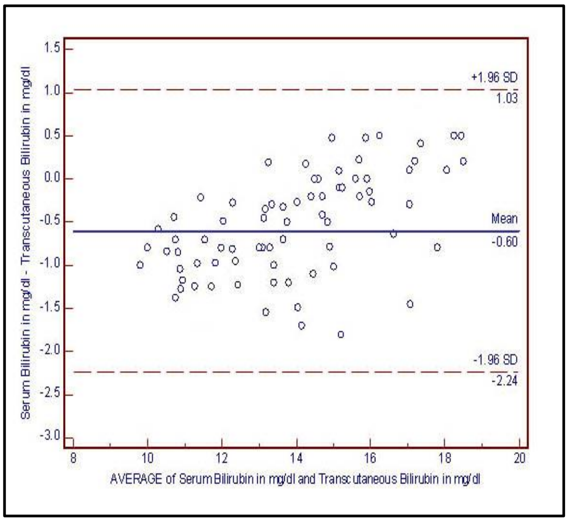

Fig 3: Bland-Altman plot for TcB and TSB in term neonates.

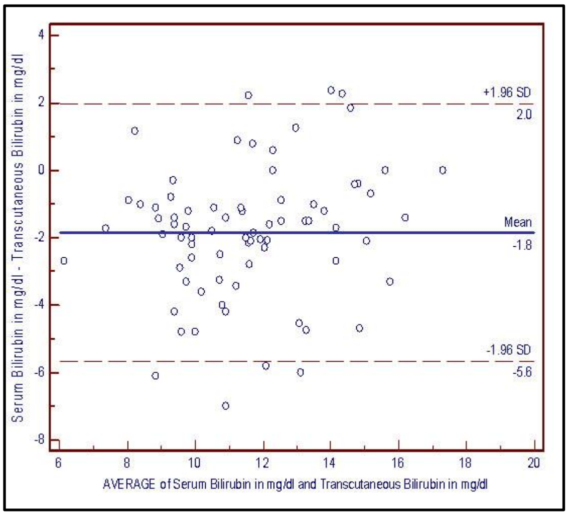

Fig 4: Bland-Altman plot fot TcB and TSB in Preterm neonates.

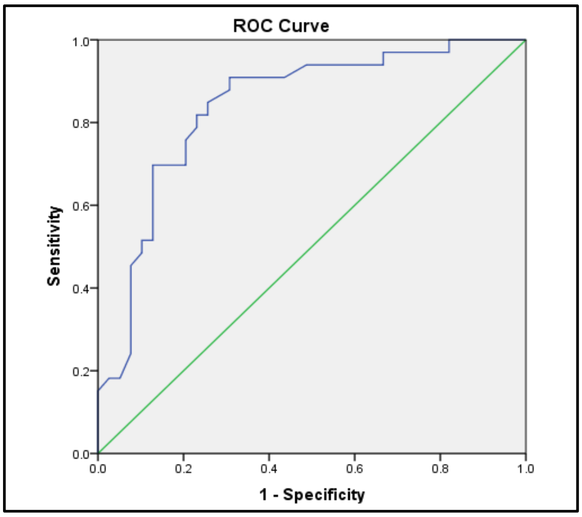

Fig 5: Receiver operator characteristic curves of TcB and TSB in Term infants.

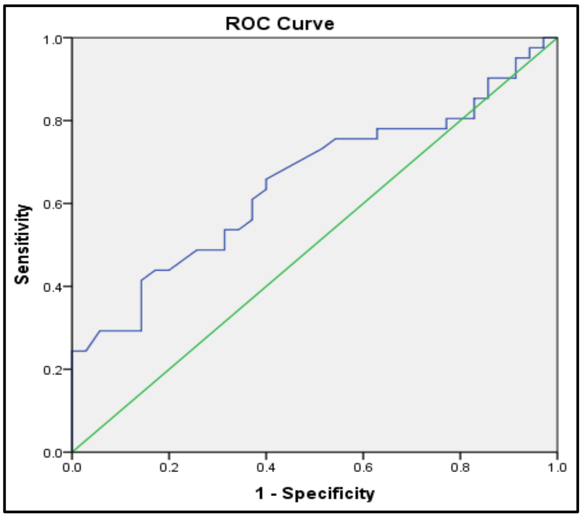

Fig 6: Receiver operator characteristic curves of TcB and TSB in Preterm infants.

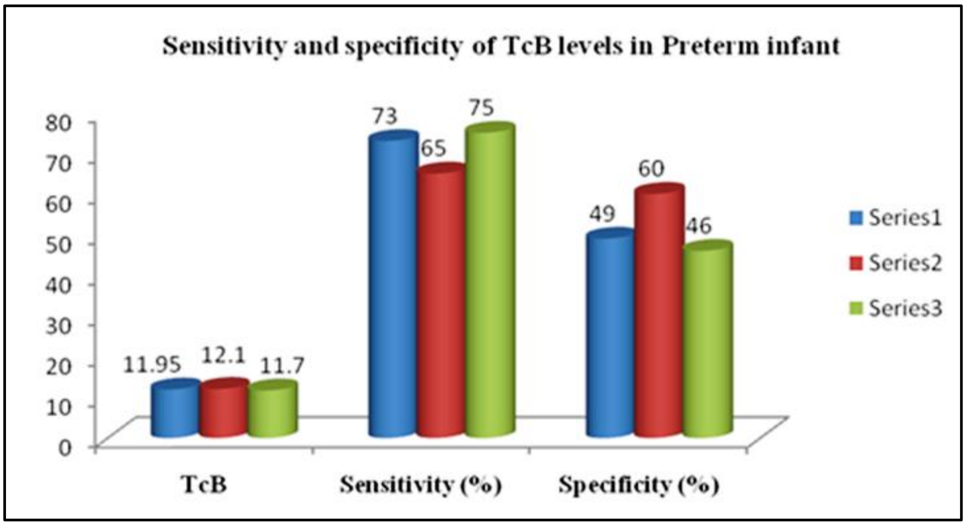

Fig 7: Sensitivity and specificity of TcB levels in Term infant

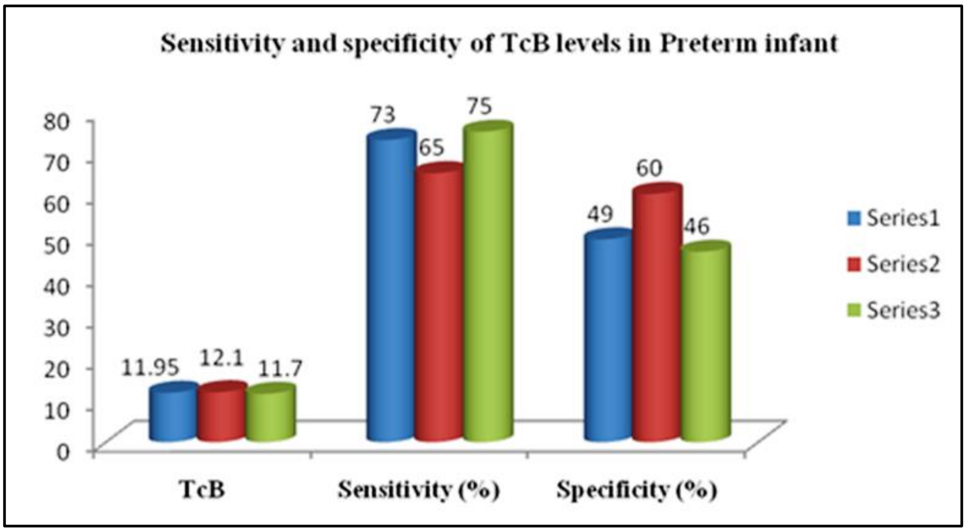

Fig 8: Sensitivity and specificity of TcB levels in Preterm infant

RESULTS

Table-2 shows the distribution of paired bilirubin measurements of enrolled infants. There was higher mean value of two methods of bilirubin measurement in term group. Table-3 shows that in term babies, the value of correlation coefficients, r= 0.92, which implies that there was a strong positive association between the variables, TcB and TSB. Here p - value is <0.0001. In preterm neonates, r=0.69, which reveals a moderate but less TcB-TSB correlation than in term neonates. In male babies, the value of correlation coefficients, r= 0.85, which implies that there was a strong positive association between the variables, TcB and TSB. Here p - value is <0.0001. In female neonates, r=0.81, which also reveals a strong

TcB-TSB correlation. In babies with ≥ 2500 gm birth weight, the value of correlation coefficients, r= 0.92, which implies that there was a strong positive association between the variables, TcB and TSB. Here p - value is < 0.0001. In babies with birth weight <2500 gm, r=0.77, which also reveals a good but less TcB-TSB correlation than in babies with ≥ 2500 gm birth weight. In babies with ≥ 3 days of age, the value of correlation coefficients, r= 0.849, which implies that there was a strong positive association between the variables, TcB and TSB. Here p -value is < 0.0001. In babies with birth weight <2500 gm, r=0.76, which also reveals a good but less TcB-TSB correlation than in babies with ≥ 3 days of age.

Figure 1 and 2 shows correlation between TcB and TSB of preterm and term infants. In term group: R2 = 0.86; r=0.92, p < 0.001 and in preterm group, R2 = 0.48; r=0.69, p < 0.001. There was a good correlation between TcB and TSB in both groups but there was higher correlation with increasing gestational age. Regression equation showed a positive and linear relation between TcB and TSB and TcB value tended to be more than TSB value both in term and preterm groups.

Bland and Altman plot showed the mean difference (bias) in term neonates was -0.6 mg/dl. The 95% limits of agreement were in between -2.24 – 1.30 mg/dl. All the values lied within the limits of agreement.

Bland and Altman plot showed the mean difference (bias) in preterm neonates was -1.8 mg/dl which was more as compared to term neonates. The 95% limits of agreement were in between -5.6 – 2.0 mg/dl. As the figure showed, less than 95% values lied within the limits of agreement.

Receiver Operating Characteristic (ROC) curves was constructed to determine the cut-off value of TcB level in term infants which indicates the need for total serum bilirubin estimation (figure 5). If the cut off value of TcB was set at 13.76 mg/dl, then an over-all best sensitivity of 90% and a specificity of 73% were obtained. TcB value ≤ 13.76 mg/dl showed good predictive value and above which level TSB should be done. The area under the ROC curve was 0.86 for TcB, indicating very good predictive probability.

Receiver Operating Characteristic (ROC) curves was constructed to determine the cut-off value of TcB level in preterm infants which indicates the need for total serum bilirubin estimation (figure 6). If the cut off value of TcB was set at 12.10 mg/dl, then an over-all best sensitivity of 65% and a specificity of 60% were obtained. The area under the ROC curve was 0.63 for TcB, indicating poor predictive probability. In Term infants for TcB levels at 13.91 and 13.60 the sensitivity was 87% and 90 %; the specificity was 73% and 70% respectively. But in case of TcB levels at 13.76 both sensitivity and specificity was found to be a little higher.

In preterm infants the sensitivity and specificity was found to be lower at a high TcB levels of 12.10

DISCUSSION

Blood sample can be collected routinely from neonates to study serum bilirubin. Unfortunately, it is aggressive, painful, might cause local infection as well as anemia in case of frequent sampling. These episodes of complications are more frequently observed in case of premature neonates. There complications increase morbidity of patients as well as anxiety of parents. TSB method of estimation of bilirubin is the gold standard approach for detecting and determining hyperbilirubinemia. This study revealed a significant correlation between TcB and TSB levels measured in term and preterm neonates in terms of correlation co-efficient. The correlation coefficient in term newborns in this study (r=0.92, p< 0.0001) was comparable to those obtained by Bhutani et al.[7] (r=0.91), Sanpavat et al.[8] (r=0.8, p<0.001), Panburana et al.[9] (r=0.81, p <0.001), Kolman et al.[10] (r=0.87), Hemanti and kiyani[11] (r = 0.969), Raimondi et al.[12] (r = 0.85), Engle et al.[13] (r=0.84), Janjindamai et al.[14] (r=0.950) and Akahira-Azuma et al.[15] (r= 0.88). Whereas, in contrast, Neocleous et al.[16] ((r=0.43) demonstrated poor correlation between TcB and TSB measurements in term neonates. As Pearson's coefficient is less reliable in estimating the agreement between two diagnostic tests, we employed Bland-Altman plot which revealed a reasonable agreement in term neonates. Mean difference was -0.6 and all the observations were within the 95% limits of agreement.

The factors that interfere with the accuracy of transcutaneous bilirubinometer measurements were reported to be race, gestational age and body weight. This study revealed that TcB-TSB correlation derived by JM 103 was not affected by gestational age, sex, birth weight, postnatal age. However, the correlation was inversely proportional to gestational age, birth weight and postnatal age .These reports were in line to the findings of previous studies who showed that TcB values were not influenced by gestational age.[11,14] On the contrary, a different study showed the only variable that exhibited a small statistical difference (P=0.003) was postnatal age of less than three days, with the transcutaneous measurements being higher than the blood based one.[15] The effect of postnatal age is ascribed to maturation and thickening of skin and change in the amount of albumin binding. Similar findings were shown by Luca et al.[17] as opposed to the finding of Badiee et al.[18] and our study. Ebbesen et al.[19] reported that female infants had TcB on the forehead greater than their male counterparts (p = 0.003). On the contrary, detected significantly higher TcB value in male babies than female ones. Whereas in this study TcB readings were not affected by sex.

Mahajan et al.[20] conducted a study that comprised of neonates ranging from 28-42 weeks of gestation, like our study, showed a strong TcB-TSB correlation (r=0.90) before phototherapy. Shah et al.[21] studied 410 neonates including neonates from 28-41 weeks GA and found a strong correlation (r=0.85) in term group whereas poor correlation in two other preterm groups (r=0.45, r=0.34, p>0.001). Our study showed strong TcB-TSB correlation in term infants (r=0.92, p<0.001) but moderate correlation in preterm group (r=0.69). This study revealed lower correlation coefficient (0.69) in preterm infants than in term infants (0.92). Regression analysis showed a linear and strong correlation between TcB and TSB in term infants (r=86, P<0.001). These results are consistent with other previous studies where the values of r were 0.788, 0.94 and 0.73 respectively.[11,12,18]

Preterm babies too showed a linear but moderate TcB-TSB correlation. But Bland-Altman plot showed less agreement between TcB and TSB in preterm neonates. Mean difference was -1.8; less than 95% values were within the limits of agreement. Both in term and preterm neonates TcB levels were higher than TSB levels and the difference tended to be more with increasing bilirubin levels as is obvious from regression equation and Bland-Altman plot. The discrepancy in findings of different studies may be attributed to variation in sample size and use of various generations of transcutaneous bilirubinometer.

The most important feature of a screening tool for neonatal jaundice is its capability to detect significant hyperbilirubinemia with high sensitivity and missing a case of severe hyperbilirubinemia with resultant kernicterus is totally unacceptable. The device must also have a reasonable level of specificity because over diagnosis leads to unnecessary admissions and work up. The study assessed the sensitivity and specificity at different TcB cut-off values. In this study, Receiver Operating Characteristic (ROC) curve was constructed separately both for term and preterm newborns to determine the cut-off values of TcB level which indicate the need for total serum bilirubin estimation. If, for the term neonates, the cut off value of TcB was set at 13.76 mg/dl, then the over-all best sensitivity of 90% and a specificity of 73% were obtained. Above this level TSB would be necessary to determine whether therapeutic measures need to be taken. The area under the ROC curve (AUC) was 0.86 ($p < 0.0001$) for TcB , indicating a good predictive probability. Ho et al.[19] showed that TcB cut-off value of 15 mg/dl had highest sensitivity and specificity and AUC were more than 0.9.

The AUC for TcB in preterm neonates in this study was 0.65 rendering a poor diagnostic performance. At TcB cut-off value 12.10 mg/dl, it showed the best over-all sensitivity of 65% and specificity of 60%. Ahmed et al.[20] showed an AUC of 0.77 for TcB in preterm infants <35 weeks GA

CONCLUSION

This study reveals the validity of transcutaneous bilirubin as a screening tool for neonatal jaundice in term neonates, as it demonstrated a significantly high correlation and predictive accuracy in term neonates. Transcutaneous bilirubinometry in preterm neonates is less accurate than in term neonates.

REFERENCES

1. Singh M. Jaundice. In: Singh M. Care of the newborn. 8th ed. 2016:323-48.
2. Pendse A, Jasani B, Nanavati R, Kabra N. Comparison of Transcutaneous Bilirubin Measurement With Total Serum Bilirubin Levels in Preterm Neonates Receiving Phototherapy. Indian Pediatrics 2017; 54: 641-3.
3. Karen T, Bucher HU, fauchere JC. Comparison of a new transcutaneous bilirubinometer (Bilimed) with serum bilirubin measurements in preterm and full-term infants. BMC Pediatrics 2009; 70(9): 1-7.
4. Ip S, Chung M, Kulig J, O'Brien R, Sege R, Glicken S, et al. An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics 2004;114(1):130- 53.
5. Tanja K, Hans Ulrich B, Jean- Claude F. Comparison of a new transcutaneous bilirubinometer (Bilimed) with serum bilirubin measurements in preterm and full-term infants. BMC Pediatrics 2009; 9:70.
6. Nagar G, Vandermeer B, Campbell S, Kumar M . Reliability of Transcutaneous Devices in Preterm Infants: A Systematic Review. Pediatrics 2013; 132(5): 871-81.
7. Bhutani VK, Johnson L and Sivieri EM. Predictive ability a predischargehour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics 1999; 103: 6-14.
8. Sanpavat S and Nuchprayoon I. Noninvasive Transcutaneous Bilirubin as a Screening Test to Identify the Need for Serum Bilirubin Assesment. J Med Assoc Thai 2004; 87(10):1193-8.
9. Panburana J, Boonkasidach S, Rearkyai S. Accuracy of Transcutaneous Bilirubinometry Compared to Total Serum Bilirubin Measurement. J Med Assoc Thai 2010; 93(2): 81- 6.
10. Kolman KB, Matheison KM, Frias C. A Comparison of Transcutaneous and Total Serum Bilirubin in Newborn Hispanic infants at 35 or more weeks of gestation. JABFM 2007; 20(3):266-71.
11. Hemmanti F and Kiyani RN. The Value of Bilicheck as a Screening Tool for Neonatal Jaundice in the South Iran. Iran J Med Sci 2013; 38(2): 122-4.
12. Raimondi F, Lama S et al, 2012. Measuring transcutaneous bilirubin: a comparative analysis of three devices on a multiracial population. BMC pediatrics 2012;70(12) :1-5.
13. Engle WD, Jackson GL, Sendelbach D, Manning D, Frawley WH. Assessment of a Transcutaneous Device in the Assessment of Neonatal hyperbilirubinemia in a Primarily Hispanic Population. Pediatrics 2002; 110(1): 61-7.
14. Janjindamani W and Transantiwong T. Accuracy of Transcutaneous Bilirubinometer Estimates Using Bilicheck in Thai Neonates. J Med Assoc Thai 2005;88(2) :187-90.
15. Akahira-Azuma M, Yonemoto N et al. Validation of a transcutaneous bilirubin meter in Mongolian neonates: comparison with total serum bilirubin. BMC Pediatrics 2013; 151(13): 1-7.
16. Neocleous C, Adramerina A et al. A Comparison between Transcutaneous and Total Serum Bilirubin in Healthy-term Greek Neonate with Clinical Jaundice. Prague Medical Report 2014; 115(2):33-42.
17. Luca D, Romagnoli C, Tiberi E, Zuppa AA, Zecca E. Skin bilirubin nomogram for the first 96 h of life in a European normal healthy newborn population, obtained with multiwavelength transcutaneous bilirubinometry.ActaPaediatrica2008;97(2):146-50.
18. Badiee Z, Mohammadizadeh M and Shamee M. Diagnostic Usefulness of Transcutaneous Bilirubinometry in Very Preterm Newborn. International Journal of Preventive Medicine 2012; 3(4): 262-5.
19. Ebbesen F, Rasmussen LM and Wimberley PD. A new transcutaneous bilirubinometer, Bilicheck, used in the neonatal intensive care unit and the maternity ward. Acta Paediatrica 2002; 91: 203-11.
20. Mahajan G, Kaushal RK, Sankhyan N, Sharma, RL, Nakra M. Transcutaneous Bilirubinometer in Assessment of Neonatal Jaundice in Northen India. Indian Pediatrics 2004; 42.
21. Shah B, Gossai D, Prajapati J. Comparison Study between Serum and Transcutaneous Bilirubin Measurementy with Special Referrence to Gestational Age. International Journal of Science and Research 2003 ;4(1): 2250-3.

Source of Support: Nil. **Conflict of Interest:** None Declared.

Cite this article as: Mohammad Masudur Rahaman Khan, Md. Tariqul Islam, Shahjadi Nasreen Sultana, Mohammed Shaheen, Mohammad Neamat Hossain, Sanjoy Kumer Dey, M A Mannan, Mohammod Shahidullah. Correlation of Transcutaneous Bilirubin with Serum Bilirubin in Term and Preterm Neonates with Jaundice. Int J Med Res Prof. 2020 Jan; 6(1): 58-63.
DOI:10.21276/ijmrp.2020.6.1.017