

Validity of Bilirubin Measured by Biliscan (Smartphone Application) in Neonatal Jaundice – An Observational study

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ABSTRACT

Introduction: Bilirubin is a frequently ordered investigation in neonatal intensive care units and out-patient practice during follow-up. The gold standard for its estimation is serum bilirubin which is invasive resulting in parenteral apprehension, pain, discomfort and iatrogenic anaemia in a neonate, while the non-invasive measurement by transcutaneous bilirubinometer is not available in all the centres because of its cost. Biliscan is a smartphone application that uses a phone's inbuilt camera and a colour calibration card to detect neonatal jaundice. We compared bilirubin measured by Biliscan with reference to serum bilirubin among neonates admitted to a tertiary care centre.

Methods: We conducted an observational study from June-2019 to September-2019 at a tertiary care centre in Hyderabad, India. Inborn neonates (greater than > 35 weeks gestational age at birth, and less than a week old) who required bilirubin estimation, underwent both invasive serum sampling and non-invasive estimation by Biliscan. Photograph of the baby's chest was captured using the colour calibration card of the Biliscan application. Bilirubin values derived from the Biliscan application were compared to those derived from blood samples.

Results: A total of 143 neonates were enrolled. The mean bilirubin value estimated by serum sampling was 11.9 g/dl against 13.1 g/dl of that derived from smartphone application. Biliscan and serum bilirubin showed moderate agreement with a correlation coefficient of 0.6. Bland-Altman plot constructed showed bias of 1.1 with the limits of agreement ranging from -3 to +5.3. Biliscan had a good sensitivity of 90% in identifying high levels of serum bilirubin (> 95th percentile on Bhutani nomogram).

Conclusion: Biliscan application is a non-invasive, real-time, inexpensive and an easily available method that cannot replace serum bilirubin, however can complement and has the potential to help in screening neonates thus facilitating recognition of jaundice early and minimising the number of invasive pricks.

Keywords: Bilirubin; Bhutani's normogram; Biliscan; phototherapy; Smartphone; Transcutaneous bilirubinometer



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INTRODUCTION

Neonatal jaundice is a common problem encountered in 80% of newborn babies.^{1,2} Global estimates show 1.1 million babies develop severe jaundice every year.³ Pathological jaundice can be easily managed with phototherapy with near-zero morbidity. However if left unattended, hyperbilirubinemia may lead to seizures, encephalopathy, hearing impairment and kernicterus. Hence early detection and timely monitoring are the cornerstones to prevent bilirubin induced brain damage.

Conventionally, bilirubin quantification is done by measuring serum bilirubin by the Diazo method. This is considered to be the gold standard for bilirubin estimation. Being an invasive approach, it has concerns like pain, parenteral apprehension, discomfort to the neonates, increasing the probability of infection and iatrogenic anaemia due to frequent sampling. Another challenge faced is in the outpatient setting, where the visual assessment of jaundice could be deceiving and invasive approach may be impractical, cumbersome and time-consuming. To address the above concerns noninvasive bilirubin monitoring by transcutaneous bilirubinometer came into limelight. Though transcutaneous bilirubinometer showed good correlation in Indian population, it is not available in all the centres, due to high cost.^{4,5} It also has its limitations like, not being reliable in preterm neonates, in babies with high levels of bilirubin and post phototherapy. So there is a need for a non-invasive, real-time, inexpensive, easily available and a reliable method for estimating serum bilirubin.

With the advancement in technology, there is increased development of smartphone applications for usage in the medical field. Many applications help us to get vitals like heart rate and even point of care diagnostics like ultrasonography.⁶⁻⁸ One such application is Biliscan which helps to estimate bilirubin by using the phone's camera and a colour calibration card. Easy availability and portability endow such smartphone applications with good potential for clinical use. Before incorporating in clinical practice, validity of these applications need

to be established. Amidst the paucity of literature, this study of ours intends to assess the validity of the smartphone application Biliscan for estimating bilirubin in comparison to the gold standard serum bilirubin in Indian population.

METHODS

We conducted an observational study from June 2019 to September 2019 at the Department of Neonatology in a tertiary care centre in Hyderabad, India. Inborn healthy neonates greater than 35 weeks of completed gestation and developing jaundice (assessed clinically) within seven days of birth were enrolled in the study after obtaining consent from the parents. The following neonates were excluded from the study – a) Neonates who received phototherapy earlier, b) Sick neonates and c) Neonates whose parents did not consent for the study d) Out-born neonates. The primary objective was to study the relationship between serum bilirubin and bilirubin estimated by Biliscan using scatter plot and Bland Altman analysis. Secondary objective was to assess the sensitivity of Biliscan bilirubin in identifying neonates with high TSB values.

Neonates, who satisfied the eligibility criteria, underwent both invasive serum sampling and non-invasive assessment by Biliscan application before starting phototherapy. Apple smartphone iPhone 6s with the Biliscan application installed was used for the study. Photograph of the baby's chest was captured using the colour calibration card of the Biliscan application. The population (> 35 weeks neonates) and the sternum as the site of assessment were selected keeping in mind the functionality and limitations of already validated and time tested non-invasive transcutaneous bilirubinometry. Serum bilirubin was estimated from venous blood sample (collected within an hour of capturing a photograph by Biliscan) using Diazo method. Bilirubin values derived from the Biliscan application algorithm were compared to those derived from blood samples.

Operating the smartphone application was easy with self-explanatory instructions. A colour calibration card was used with a purpose to balance the skin colour with different lighting conditions.

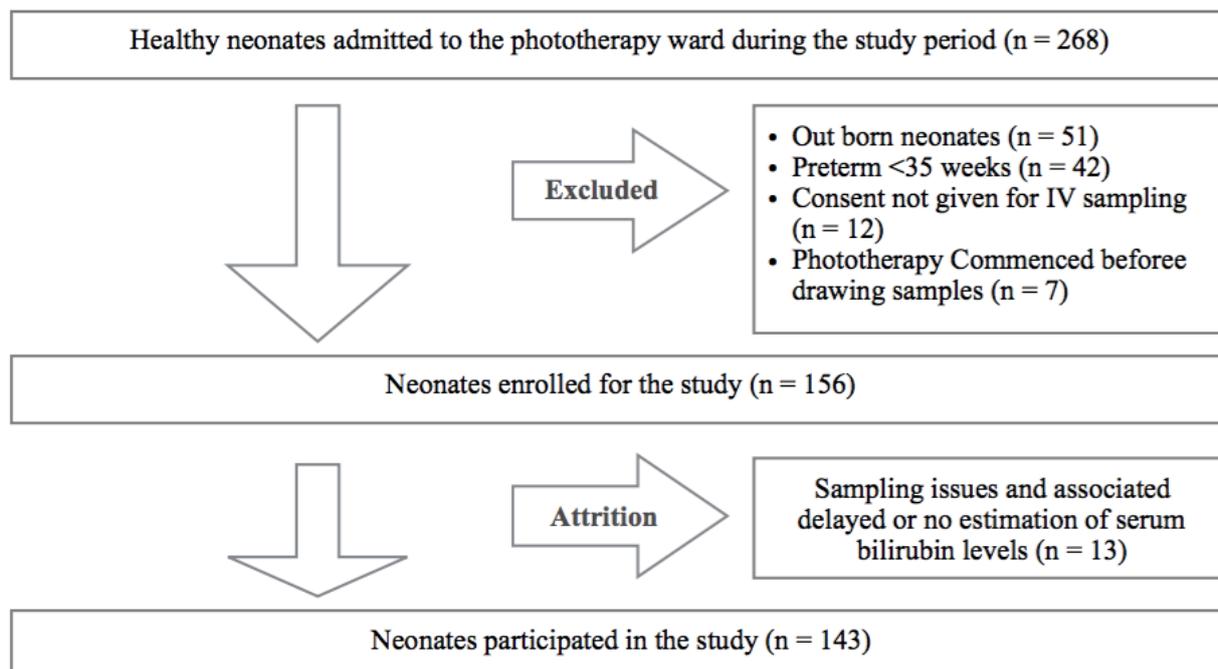


Figure 1. Flow diagram of the study population

The images captured underwent image segmentation and feature extraction. Then various algorithms and regressions are applied by the software to process and yield a final value of bilirubin. Data was collected in a proforma designed for the study and analysed using software SPSS version 21. Continuous variables were summarised using mean and standard deviation. Categorical variables were summarised using percentages. Pearson's correlation coefficient and Bland-Altman plot were used to identify the relationship between serum bilirubin values and Biliscan measurement values. To assess the utility of the Biliscan application as a screening tool, bilirubin values derived from serum and Biliscan application were plotted on the Bhutani nomogram. A positive test result was considered when Biliscan bilirubin was $\geq 75^{\text{th}}$ percentile (in the high-intermediate or high-risk zone), and a serum bilirubin value $\geq 95^{\text{th}}$ percentile (high-risk zone).⁹

RESULTS

A total of 143 neonates were enrolled in the study. Flow diagram of the neonates participated in the study is depicted in Figure 1. The baseline characteristics of the study population are shown in

Table 1. The median birth weight and mean gestational age of the study population were 2.6 kg and 37 weeks respectively. Majority (86.7%) of the neonates presented with hyperbilirubinemia between two to four days of life. The mean bilirubin value estimated by serum sampling was 11.9 g/dl against 13.1 g/dl of that derived from smartphone application. Scatter plot between the two modes of measurement is depicted in Figure 2. Biliscan bilirubin and serum bilirubin measurements showed a moderate agreement with a Pearson's correlation coefficient of 0.6. Bland-Altman plot (Figure 3) constructed showed a bias of 1.1 with the limits of agreement ranging from -3 to +5.3. Biliscan bilirubin value $\geq 75^{\text{th}}$ percentile had a sensitivity of 90% (Table 2) in predicting a serum bilirubin value $\geq 95^{\text{th}}$ centile with only two false-negative predictions in the entire population.

DISCUSSION

Various studies on application of smartphones for estimating jaundice have been published; however, there exists a paucity of literature in the Asian and Indian population.⁹⁻¹¹ To the best of our knowledge,

Table 1. Baseline characteristics of the study population

Characteristics	n = 143
Birth weight – n (%)	
a) < 2500 gm	45 (31.5%)
b) ≥ 2500 gm	98 (68.5%)
Birth weight - Median (IQR)	2.6 (2.4 – 2.9)
Gestational age – n (%)	
a) < 37 weeks	24 (16.8%)
b) ≥ 37 weeks	119 (83.2%)
Gestational age (Mean ± SD)	37.7 ± 1.4
Post natal day of measurement - n (%)	
a) ≤ 1 day	2 (1.4%)
b) 2 – 4 days	124 (86.7%)
c) 5 – 7 days	17 (11.9%)
Gender n (%)	
a) Male	67 (46.9%)
b) Female	76 (53.1%)
Bilirubin (Mean ± SD)	
a) Serum Bilirubin	11.9 ± 2.4
b) Biliscan Bilirubin	13.1 ± 2.3

there is only one study to date in Indian neonates. We, therefore studied the use of a smartphone application ‘Biliscan’ for estimating bilirubin in Indian neonates.

The Pearson correlation coefficient between Biliscan bilirubin and TSB in the present study was 0.6 which only showed a moderate correlation. A similar result with a correlation of 0.6 was observed in a previous study on Indian neonates.¹² In a study done by Taylor JA et al. using a similar smartphone

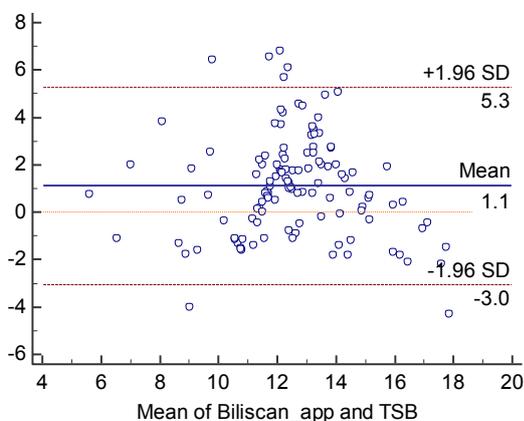


Table 3. Bland – Altman Plot

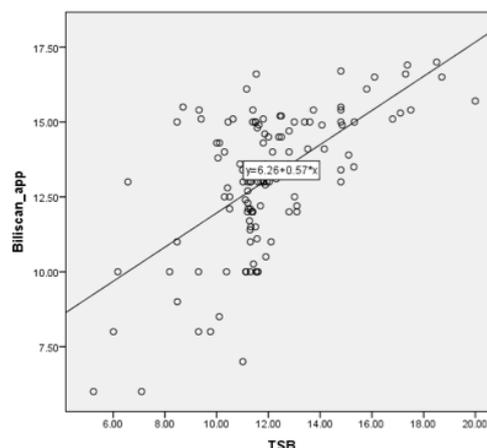


Figure 2. Scatter plot between serum bilirubin values (X-axis) and those derived from Biliscan application

application "Biliscan" yielded an overall correlation of 0.91 (entire population) and 0.88 in neonates with Asian-American background.⁹ This difference could probably be attributed to the difference in ethnicity among the population. Various studies that compared the visual assessment of jaundice with TSB levels had correlation coefficients ranging from 0.36 to 0.75 and a study on transcutaneous bilirubinometry in Indian population, showed a remarkable correlation of 0.9.^{4,5,13-18} So the accuracy of Biliscan bilirubin is better than visual assessment but not as good as the transcutaneous bilirubinometry.

In our study, Bland-Altman plot analysis showed a bias of 1.1 mg/dl, while the imprecision was ± 4.2 mg/dL, which was slightly higher than the finding in the study by Taylor JA et al., where the limits of the agreement were ± 3.6.⁹

In the current study, the mean bilirubin value estimated by the Biliscan application was higher than that derived from serum sampling. A similar observation was also observed in the study on

Table 2. Utility of Biliscan application as a screening tool to identify neonates with high TSB values (≥ 95th centile on Bhutani normogram)

Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
90	33	18	95

Indian neonates by Swarna S et al.¹² Many studies support that even transcutaneous bilirubinometry also tend to overestimate serum bilirubin values in dark-skinned neonates.¹⁹⁻²² Practical implication of this observation is that, if used as a sole criterion for decision making, there would probably be an increase in the rate of intervention (phototherapy).

In the present study, Biliscan application had a sensitivity of 90% and a negative predictive value of 95% for identifying neonates with TSB in the high-risk zone on the Bhutani nomogram. Data from various studies showed that the sensitivity of smartphone applications, in identifying high TSB level was good and well comparable to that of transcutaneous bilirubinometry.^{4,5,9,10} Hence, these smartphone applications can be reliably used for screening hyperbilirubinemia and avoid unnecessary sampling in newborns. They have potential to be used in postnatal wards, outpatient department, at home by parents as screening devices.

However, our study has its own limitation of having a very small sample size. Ours is a single centric study which could cover only a geographically small region. Thus, our results may not be generalised to the entire population. We excluded preterm neonates less than 35 weeks of gestational age, which could be substantial population to have significant hyperbilirubinemia. Concomitant bilirubin estimation by transcutaneous bilirubinometry would have added a better strength to our study. As neonates with clinical icterus were included, the specificity of the test which helps in ruling out hyperbilirubinemia was not assessed.

Using such smartphone applications on different phones with different camera specifications and varied image quality will be a challenge and scope for further research.

CONCLUSIONS

Bilirubin estimated by the Biliscan application showed only moderate correlation with total serum bilirubin values in healthy Indian neonates greater than 35 weeks of gestational age. However, the test tends to overestimate serum bilirubin and has a good sensitivity making it a reliable screening tool. Therefore Biliscan application is a non-invasive, real-time, inexpensive and easily available method that cannot replace serum sampling, but can complement and has potential to help in screening neonates. We look forward to similar applications with a better correlation in Asian population. It would be revolutionary to test and validate such applications in a diverse population (preterm neonates, multi-centric study with different geographic distribution) and on phones with different make and brand. Future awaits such research.

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