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Original Article

Image-Based Neonatal Hyperbilirubinemia Screening after Hospital Discharge

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Abstract

Background: Newborn infants who are risk for severe hyperbilirubinemia and cared at home should be monitored for progression of jaundice. We aimed to verify if a smart phone application (BiliScan Inc), which uses automated imaging for bilirubin (AIB), can be used to estimate total serum bilirubin (TSB) levels at home.

Methods: A convenience sample of 1038 "healthy" infants in China were prospectively enrolled to a single-center study in 2016. Correlations between AIB and TcB measurements were correlated to TB measurements. Bias and imprecision of AIB measurements were determined using Bland-Altman analysis. The diagnostic value of AIB was compared by the area-under-curve (AUC) values of receiver operator characteristic (ROC) curves.

Results: The best correlation and AUC for AIB were at the sternum, both with values of 0.76. We truncated performances to 369 TB values >5 and <15 mg/dL, and sternal AIB showed the best correlation to TB (r =0.5, *P*<0.0001). The AUC for this range was 0.54. However, from a subset of 200 AIB values >13.5 mg/dL (n=369 babies), the sensitivity and negative predictive value (NPV) were 100% with a specificity of 50%. Furthermore, Bland-Altman analyses showed a bias and imprecision of AIB and TcB when TB was >13.5 and <15 mg/dL.

Conclusion: The use of AIB may be a potentially useful screening device for neonatal jaundice. Its performance requires additional improvements for accurate measurements across wider ranges of TB levels.

Keywords: Jaundice; Hyperbilirubinemia; Postnatal; Automatic image-based

Introduction

Newborn jaundice, regardless of its etiology, is an important medical issue in the newborn. When it is unrecognized or unmonitored and progresses untreated, severe hyperbilirubinemia may develop (1,2). Although most infants have a mild clinical course without neurological morbidity, permanent neurologic sequelae can occur in severe cases (3).

Kernicterus is rare in the United States (4, 5) because current follow-up and treatment guidelines for jaundiced newborns prevent most cases. In China, the management of neonatal jaundice varies depending on the regional economic development level (6). In large and medium urban areas, clinicians now perform a systematic assessment of each newborn's risk of severe hyperbilirubinemia before hospital discharge, but follow-up is poor. Since there is a lack of medical resources in China, newborns must go back to the hospital for follow-up. Many families fail to do so because it is extremely inconvenient. Another relevant issue is the implementation of the second child birth policy in 2016.

The number of newborns has increased greatly, making it more difficult to implement neonatal jaundice follow-up. Therefore, we face the challenge of managing the jaundiced newborn so that we avoid the devastating outcome of kernicterus but minimize testing and treatment in the vast majority of newborns who will do well without intervention. Serum bilirubin (SB) is the current predictive gold standard for screening healthy term neonates with hyperbilirubinemia. However, parents are unable to objectively screen for the progression of jaundice once the baby has been discharged. For this reason, we urgently need a feasible, effective device that can be used by families for monitoring neonatal jaundice after discharge.

In rural areas of China and in some developing countries, kernicterus appears to be much more common (7-9). A quantitative method of measuring bilirubin is not available in most of these areas (10, 11). Thus, the rate of encephalopathy is much higher than it is in Europe, the United States, and other developed countries. There are no recent reports on the epidemiology of bilirubin encephalopathy, but a 2009 study that included 28 hospitals reported 223 cases of neonatal bilirubin encephalopathy or kernicterus during the follow-up of 348 newborns, with 42.2% (94 cases) having severe neurological sequelae (9). The most important thing we can do is to provide a reliable jaundice screening tool to these regions.

BiliScan (BeiShen Healthcare Technology Co., LTD., Shenzhen, China) is a smart-phone based application software developed to screen hyperbilirubinemia and address the problem of neonatal bilirubin follow-up after discharge. It is noninvasive and can be easily used by parents at home.

If this method can be implemented effectively, the problem of neonatal jaundice follow-up could be greatly alleviated. Used as a screening tool in the early postnatal period, it represents a means of providing rural areas in China a reliable jaundice screening tool for use after hospital discharge.

Methods

We conducted a single-center, pivotal, prospective study (from March to August in 2016) at Nanjing Maternity And Child Health Care Hospital, an urban teaching hospital in central China. Based on our institutional policy, stable term infants are housed in the postnatal wards, and stable, preterm ≥35 weeks gestational age (GA), birthweight (BW) ≥2000 g infants are admitted to the high-risk nursery for monitoring purposes.

This study was conducted in postnatal wards and the high-risk nursery and in patients who were readmitted for hyperbilirubinemia. All infants were of Chinese ethnicity. The enrolling criteria included GA and/or BW. We excluded those infants who had been admitted to a higher level of intervention. Other exclusions criteria babies exposed to any phototherapy, neonatal illness or need of specialized care.

The Ethics Committee of the Nanjing Maternity and Child Health Care Hospital of the Nanjing Medical University approved the study. Verbal informed consent was obtained from the neonate's parents or guardians as allowed by institutional policy for low-risk, non-invasive study.

Bilirubin Measurements

If an infant enrolled in the study requires serum drawing as part of routine newborn care (e.g., poor feeding, routine newborn metabolic screening, bilirubin level reaches the standard of phototherapy).

TB

Capillary samples were drawn by heel stick for SB measurement, and all blood samples were analyzed immediately. The blood sample for TB assay was centrifuged at 1,000 rpm for 3 min. After centrifugation, samples were analysed with a direct spectrophotometer (APEL-BIL, China). All TB assays were performed in the nursery laboratory by the same skilled lab technician who was blind for the study. This bilirubinometer is our routine device to assay TB and it analyses serum absorbance at 2 wavelengths (455 and 575 nm),

making automatic subtraction of absorbance due to haemoglobin. Its coefficient of variation (CV) is declared to be 1% by the manufacturer.

TcB

TcB levels were obtained by JM-103 (Konica Minolta, Inc., Japan) device. TcB were measured on the infant's forehead, cheek and mid-sternum, avoiding areas with hair, bruises, or other skin anomalies.

AIB

The BiliScan is a smartphone software application designed for the caregiver (e.g., parent) to assess baby's bilirubin level. The user puts a special hollow color calibration card on the baby's skin (forehead, cheek, and sternum). The user then starts the app, which provides brief instructions on obtaining usable images, including a blue frame to provide guidance to optimal positioning of the camera. When lighting is adequate and the blue square is properly aligned with the color calibration card, the app automatically takes a snapshot using the smartphone camera. The image app allows the user to know when the image has been uploaded successfully. Skin and color calibration card image snapshot by smart phone is uploaded via internet to the specific cloud server with an algorithm that is used to estimate a bilirubin value to provide an individualized predicted bilirubin index within two seconds. Key features of the BiliScan include notifications to caregivers about bilirubin assessment and guides caregivers to correct technique and usable image for analysis.

AIB operational features

AIB and TcB were obtained within 1 hour of blood collection. Both AIB and TcB were measured on the infant's forehead, cheek and mid-sternum, avoiding areas with hair, bruises, nevi or other skin anomalies. In our study, BiliScan was installed on iPhone6 (Apple Inc., Cupertino, USA). Data were archived for repeat TB/TcB levels. Capillary samples were drawn by heel stick for TB measurement, and all blood samples were analyzed by point-of-care testing.

Statistical Evaluation of AIB Performance

The predictive value of near-concurrent determinants was assessed at three sites each for AIB and TcB. Both AIB and TcB were measured on forehead, cheek, and mid-sternum. Linear regression analyses were used to determine correlations between all measurements. Bias and imprecision of AIB measurements compared with TB levels using Bland-Altman analyses. Bland-Altman calculations were performed over select intervals to assess the best tradeoff between bias and variance. We assessed the diagnostic value of TcB and AIB by comparing the area-under-curve (AUC) values of receiver operating characteristic (ROC) curves for each cohort. TB values were the designated as the referent and age-specific TB values ≥95th percentile (high-risk zone) on the nomogram was used to classify babies as abnormal for the ROC analysis. We also assessed the predictive value of TcB and AIB using contingency tables. In the analysis, infants with age-specific TB values ≥95th percentile on the nomogram were designated to be at high risk. Infants with age-specific TcB or AIB values ≥75th percentile on the nomogram were considered to have a positive reading from these devices. The ability of TcB and AIB to detect high-risk infants was expressed as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Data were analyzed using GraphPad 7.0d (Prism, La Jolla, CA) and Jupyter Python Notebooks using the Pandas, Matplotlib, and Seaborn libraries. A *P*-value of 0.05 was considered statistically significant.

Results

We recruited 1038 infants. Of these 329 babies were excluded a) 284 tested under or after phototherapy; b) data from those infants with no recordable sternal values (2 babies) and who were >191 hours old (n=45). For the remainder, 709 babies constituted the convenience study cohort. Clinical risk factors for these 709 babies and are shown in Table 1.

Table 1: Demographics and clinical risk factors

Clinical Risk Factors	*n (% or range)*
Total Subjects	1038
Birthweight (BW)	3194 g (1690 to 5290 g)
Newborns with BW >3.5 kg	285 (27.5%)
Gestational age (GA)	Mean±SD = 38.6±1.7
GA <37 weeks	117 (28.5%)
Exclusive breast feed	72.6%
Cesarean section	34.6%
Assisted Instrumented Births	1.7%

* Highlighted data not in spreadsheet given to Stanford University Bilirubin Data Center

Infants enrolled in the study were of Chinese Asian origin. Of the infants, 54.7% were male and 16.5% were born premature at <37 weeks. Mean ± SD GA and BW are 95.0±55.3h and 3101±471g with a range of 0-190h and 1690–4540g, respectively. Median age at the time of AIB, TcB/TB measurements were at 96.0h with an interquartile range (IQR) of 46.0–142.0h. TB levels ranged from zero to 22.8 mg/dL, with a mean ± SD of 11.9±5.2 mg/dL. Sternal AIB, assessed using ROC, was the most optimal of the three sites (forehead: 0.71, cheek: 0.73, and sternum: 0.76). Of these, 369 newborns with TB range >5 mg/dL to <15 mg/dL were used to compare the performance of AIB to TcB and TB.

Sternal AIB significantly correlated with TB in the 369 newborns (r=0.50, r^2=0.25, P <0.001) by linear regression. In 6 of 132 (4.5%) of the study population infants who were in the 24- to 72-hour age range, the predischarge TB values designated them to be at or above the 95th percentile track on the hour-specific nomogram. Sternal TB and TcB correlated to each other (r = 0.77, r^2=0.59, P< 0.0001) as did sternal TcB to AIB (r= 0.58, r^2=0.34, P < 0.0001). Sternal AIB yielded an AUC of 0.54 while sternal TcB yielded an AUC of 0.61 (Fig. 1 and Table 2).

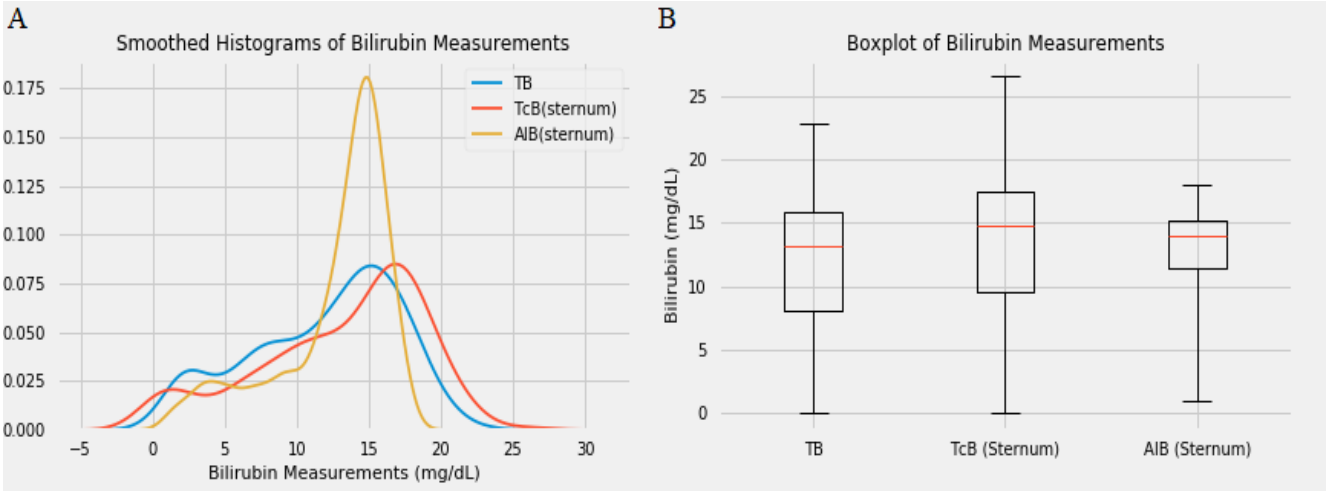

Fig. 1: Number of babies distributed with concurrent bilirubin measurements (n=709 healthy Chinese newborns (mean ± SD postnatal age 95.0 ± 55.3 hrs).

A. Histogram of TB, TcB, and AIB Measurements from the Sternum.

B. A box-whisker plot of simultaneous measures of TB, TcB and AIB in 709 Healthy Chinese Newborns

Table 2: TB measurements data of Fig. 1

TB interval (mg/dL)	*Sample size (n=709 total)*	*Mean bias*	*SD*	*-1.96SD*	*+1.96SD*
<5	90	-2.9	2.9	-8.6	2.9
≥5 and <15	372	-2.1	2.9	-7.8	3.5
≥15 and <18	182	1.4	1.8	-2.2	5.0
Exclusions: ≥18	65	4.0	1.8	0.5	7.5

AIB data at the TB cut-off level of ≥10 to <15 mg/dL demonstrated reasonable performance standards. Infants' limits of agreement by contingency table and Bland-Altman analysis showed an unpredictable mean bias for TB >18 mg/dL (Tables 3, 4 and Fig. 2A). The performance of the AIB device in detecting each TB level at specific AIB cut-off levels are shown in Table 5 with corresponding representations of accuracy. AIB cut-off level to detect TB level of at least 13.5 mg/dL provided good sensitivity (100%) and NPV of 100%. However, this cut-off level provided a specificity of only 50% (n=200). Of the sub-cohort of 369 babies with TB >5 and <15 mg/dL, sternal AIB shows reasonable agreement with TB when TB is ≥10 and <15 mg/dL (Fig. 2B). The best agreement between the two methods occurred when TB is between 13.5 and 15 mg/dL.

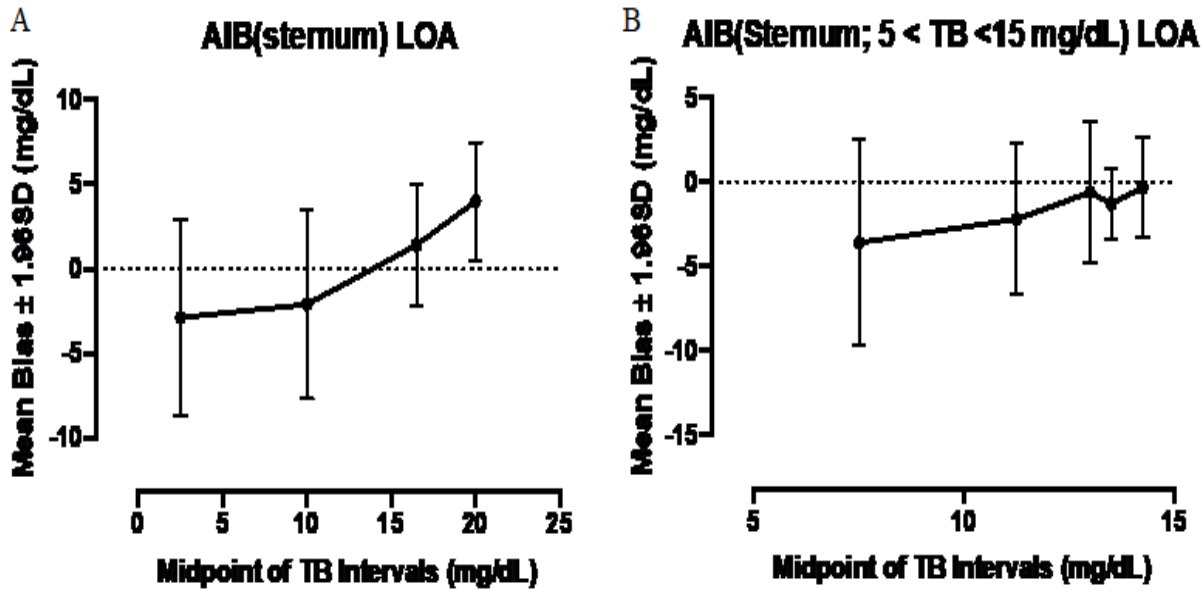

Fig. 2: Bland-Altman analysis of AIB at select intervals

The mean bias and limits of agreement from Bland Altman analysis are represented by the vertical coordinates of a specific TB interval. Each are plotted in the center of the interval. For example, the point representing 0<TB<5 was plotted at 2.5 mg/dL.

A. Plot of limits of agreement (LOA) over the range of all TB levels in the cohort of 709 untreated infants

B. Plot of limits of agreement (LOA) for the sub-cohort of 369 untreated infants with 5 < TB < 15 mg/dL

Table 3: Summary of contingency table analysis of sternal TcB and AIB performance at various TB and AIB cutoffs

Variable	***All TB values (n=709)***			
	Sensitivity	Specificity	PPV	NPV
TcB(sternum)	0.99	0.52	0.30	0.98
AIB(sternum)	0.74	0.61	0.28	0.92
	TB >18 (n=65)			
	Sensitivity	Specificity	PPV	NPV
TcB(sternum)	0.95	0.00	0.92	0.00
AIB(sternum)	0.63	0.60	0.95	0.12

Note: Sternal TcB is compared to sternal AIB for the 709 untreated babies. Neither device perform well at TB > 18 mg/dL

Table 4: TB measurements data of Fig. 2

TB interval (mg/dL)	***Sample size (n=369 total)***	***Mean bias***	***SD***	***-1.96SD***	***+1.96SD***
>5 and <10	146	-3.6	3.1	-9.8	2.5
≥10 and <12.5	90	-2.2	2.3	-6.7	2.4
≥12.5 and <13.5	40	-0.6	2.2	-4.8	3.7
13.5	6	-1.3	1.1	-3.4	0.8
>13.5 and <15	87	-0.3	1.5	-3.3	2.8

Table 5: The performance of the AIB device in detecting each TB level at specific AIB cut-off levels

Variable	***All AIB values (n=369)***			
	Sensitivity	Specificity	PPV	NPV
TcB(sternum)	1.00	0.56	0.06	1.00
AIB(sternum)	0.90	0.60	0.06	1.00
	≥ 10 and <15 (n=225)			
	Sensitivity	Specificity	PPV	NPV
TcB(sternum)	1.00	0.54	0.06	1.00
AIB(sternum)	1.00	0.64	0.07	1.00
	≥10 (n=309)			
	Sensitivity	Specificity	PPV	NPV
TcB(sternum)	1.00	0.52	0.05	1.00
AIB(sternum)	1.00	0.55	0.05	1.00
	≥12.5 (n=253)			
	Sensitivity	Specificity	PPV	NPV
TcB(sternum)	1.00	0.50	0.05	1.00
AIB(sternum)	1.00	0.54	0.06	1.00
	≥13.5 (n=200)			
	Sensitivity	Specificity	PPV	NPV
TcB(sternum)	1.00	0.46	0.06	1.00
AIB(sternum)	1.00	0.50	0.07	1.00
	≥15 (n=84)			
	Sensitivity	Specificity	PPV	NPV
TcB(sternum)	1.00	0.47	0.02	1.00
AIB(sternum)	1.00	0.30	0.02	1.00

Note: Sternal TcB is compared to sternal AIB for the sub-cohort of 369 untreated babies with TB >5 and <15 mg/dL. The 369 babies are filtered by various sternal AIB cutoffs

Discussion

We have validated the clinical utility of a novel smartphone software application, BiliScan (BeiShen Healthcare Technology Co., LTD., Shenzhen, China), to monitor TB levels. This app could be used by both clinicians and parents (caregivers). We validated the accuracy, precision, and performance limitations, of the BiliScan app compared with concurrent TB and TcB values.

AIB significantly correlated with TB. The coefficient of determination varied among the sites but was most optimal at the sternum. Furthermore, the best AUC value was for the sternal AIB (0.76). For TB >5 mg/dL and values <15 mg/dL, sternal AIB showed a correlation of r =0.50, r^2 = 0.25, *P*<0.0001. An AIB values in the range of ≥10 to 15 mg/dL provided a sensitivity of 100% with a specificity of 64%. AIB performance at a cutoff of ≥13.5mg/dL showed a sensitivity of 100% and specificity of 50%. AIB >18 mg/dL were unreliable and unpredictable.

These data confirm the limited and anticipated operating range of its congruence with TB and TcB. The limited number of samples of TB <5 mg/dL and the unreliability of AIB at or >18 mg/dl is associated with high rates of false negative data. Theoretically, 2 to 5% of the entire population would be considered in these groups but are excluded from the device's clinical operational range. A single and preferably serial AIB could be of value in a home or well-baby nursery as a pre-screening for bilirubin tests. For babies with AIB >18, the clinician and parent should be instructed to urgently access the closest NICU alerted by phone. Furthermore, because the device is less precise than the clinically-used JM-103 device, our data suggests that if the AIB value is more than 13 mg/dL, a TcB or a TB measurement is warranted. Clinical risk factors that include frequency of breastfeeding, voiding and stooling as well as progression of jaundice, and signs of illness should all be monitored.

Timely follow-up and effective intervention for hyperbilirubinemia after discharge in neonates is key to prevention of BIND and possibly, kernicterus (12,13). To assess the risk of hyperbilirubinemia after discharge, the American Academy of Pediatrics recommends that all neonates undergo TB or TcB measurements at least once before hospital discharge (1,12,13). However, the implementation of these recommendations could be costly and time-consuming in low and middle-income areas such as China. Xue et al designed a jaundice color card, called the JCard, which can be used by parents to determine the degree of jaundice in newborn infants. They found the AUC using JCard to detect TB levels of at least 13 mg/dL were 0.934 for the forehead, 0.985 for the cheek and 0.966 for the sternum (14). TS Leung et al investigated a screening technique for neonatal jaundice by exploiting the yellow discoloration in the sclera and they the AUC showed that this technique can identify subjects with TB above 12.0 mg/dL with sensitivity of 1.00 and specificity of 0.50, showing its potential as a screening device (15).

Immediate clinical implications of our data serve as key limitations and our data defines the boundaries for safe clinical practice. Unreliable performance of AIB values and non-reliable for values >18 mg/dL have been addressed to alert clinician judgement and the data for TB >18 mg/dL are excluded from data analysis. These babies should have a blood-based bilirubin assayed within 2 to 4 hours and are likely to need phototherapy. Specific instructions could include a) alert consumer (who should have confirmed their understanding of this directive); ii) direct referral for immediate blood test and seamless relay of these results to the clinician; iii) placement of unfettered access to phototherapy (MD guided). These babies could be most at risk for ABE and brain damage if hyperbilirubinemia progresses without intervention. b) Performance below 5 mg/dL are at lower sensitivity. This biologic reasons for these observations are unclear. Sample size of this sub-cohort may be biased. This sub-cohort is least likely to need phototherapy. Thus, for clinical practice, TB values at 10 ± 5 mg/dL suggests a possible "operational range."

Conclusion

The BiliScan can be used to potentially screen neonates at risk for developing hyperbilirubinemia, however its performance at TB levels in the range of requires additional software development. The BiliScan is less precise than the test JM-103 device, our data suggests that if the AIB value is more than 13 mg/dL, a TCB or a TB measurement is warranted and further study should be conducted to verify the safety of this approach.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

Non-declared.

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