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Diagnostic Properties of a Portable Point-of-Care Method to Measure Bilirubin and a Transcutaneous Bilirubinometer

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Keywords
Hyperbilirubinemia · Medical · Point-of-care bilirubin · Bilistick® system (BM-BS 1.0 – FW version 2.0.1) · Transcutaneous bilirubin

Abstract
Background: Recently, the Bilistick®, a point-of-care instrument to measure bilirubin levels, has been developed. It is fast and cheaper than transcutaneous bilirubin (TCB)-measuring devices, but data on diagnostic properties are scarce. ***Objective:*** This study aimed to compare the performance of the Bilistick® (BM-BS 1.0 – FW version 2.0.1) and the JM-105 bilirubinometer for measuring bilirubin. ***Method:*** This is a prospective study in infants born after ≥32 weeks' gestation, and/or a birth weight of ≥1,500 g, and a postnatal age ≤14 days in Surabaya, Indonesia. Bilirubin was measured with the Bilistick® System (BM-BS 1.0 – FW version 2.0.1), transcutaneously (TCB) with the JM-105 bilirubinometer, and in serum (TSB) with a routine laboratory technique. Mean differences and 95% limits of agreement (LOA) and correlations were calculated. ***Result:*** We enrolled 149 neonates and 126 had paired measurements of Bilistick® bilirubin, TCB, and TSB. Bilistick® failed in 16 (10.7%) infants. Mean Bilistick® bilirubin-TSB difference was −11 μmol/L (95% LOA: −101 to 79 μmol/L) and $r = 0.738$ ($p < 0.001$). Mean TCB-TSB difference was 26 μmol/L (95% LOA: −33 to 88) and $r = 0.785$ ($p < 0.001$). The sensitivity, specificity, PPV, and NPV for Bilistick® bilirubin for a TSB above treatment thresholds were 0.74, 0.84, 0.67, and 0.88, respectively, and for TCB 0.92, 0.64, 0.54, and 0.95, respectively. ***Conclusion:*** The Bilistick® System (BM-BS 1.0 – FW version 2.0.1) underestimates TSB, whereas TCB overestimates TSB in jaundiced Indonesian infants. Further improvement of Bilistick®'s diagnostic accuracy with less false-negative readings is essential to increase its use.

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Introduction

Jaundice due to elevated levels of total serum bilirubin (TSB) occurs in up to 80% of all newborn infants in the neonatal period [1]. Severe neonatal hyperbilirubinemia may lead to acute bilirubin encephalopathy or kernicterus spectrum disorder (KSD). Acute bilirubin encephalopathy, KSD, and even bilirubin-associated mortality are commonly reported in low- and middle-income countries (LMICs) where incidence of severe neonatal hyperbilirubinemia is higher compared to high-income countries [2, 3]. KSD is preventable when high bilirubin levels are timely treated [2, 4]. Several methods to detect unconjugated hyperbilirubinemia exist, such as visual assessment with the Kramer score, transcutaneous bilirubinometry (TCB), and measurement of TSB. The Kramer

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score has been used for decades, and many health care professionals still rely on it, despite evidence that hyperbilirubinemia cannot be determined by this method [5]. Kramer's visual assessment detects jaundice but does not reliably differentiate between harmless TSB levels and those requiring treatment [6–8]. In contrast, TCB measurements provide fast and reliable estimations of bilirubin levels that inform whether a TSB should be obtained [9–11]. Measurement of TSB is essential to diagnose hyperbilirubinemia, requiring specialized laboratory equipment [12]. Recently developed low-cost point-of-care (POC) instruments only need a small amount of whole blood to measure total bilirubin. These POC instruments seem promising for LMICs because not all facilities have access to laboratories for timely and accurate TSB measurements [4, 13–16]. POC instruments are also cheaper than TCB devices, and their measurements are reliable during phototherapy (PT). The Bilistick®, a POC instrument, had strong correlations (up to 0.96) with routine laboratory methods, using first-generation devices [13]. A Bilistick® System with updated firmware (BM-BS 1.0 – FW version 2.0.1) should have improved performance, avoiding errors or false-low test results. This study compares diagnostic performance of the Bilistick® and TCB with routine laboratory TSB.

Methods

This was a prospective study conducted in Dr. Soetomo General Hospital, Surabaya, Indonesia, for 7 months (from December 1, 2018, until June 30, 2019). Inclusion criteria consisted of clinical jaundice (any Kramer score >0, assessed by nurses, pediatric residents, and/or neonatologists), a gestational age of ≥32 weeks and/or a birth weight of ≥1,500 g, and a postnatal age ≤14 days. Infants who received PT in the preceding 24 h or with respiratory or circulatory insufficiency were excluded because PT results in bleaching of the skin, and respiratory or circulatory insufficiency may reduce skin perfusion and cause unreliable TCB measurements. Infants with severe congenital abnormalities were excluded because of ethical constraints preventing us from asking for informed consent.

TCB measurements were taken at the sternum using the JM-105 bilirubinometer (Dräger, Lübeck, Germany), repeated 3 times, and then the mean TCB value was used. TCB measurement and heel pricks for whole blood Bilistick® bilirubin measurements were taken simultaneously, while TSB was taken within an hour afterward. The Bilistick® measurement was done with 25 µL blood according to manufacturer's instructions using the Bilistick® System: reader model: BM-BS 1.0; production year: 2017; FW version: 2.0.1 (https://www.bilimetrix.net/bilistick-system). The Bilistick® may identify and display an error, for example, B04, that the serum has not properly entered the NC membrane, or T06, that the NC membrane did not reach optimal saturation within the test time. Measurements resulting in an error message were repeated once before being recorded as an error. TSB was measured using a routine analytical diazo method on the SIEMENS Dimension® (Siemens Healthcare GmbH, Germany). The following patient data were recorded: gender, birth weight, gestational age, postnatal age (in days), and Kramer score.

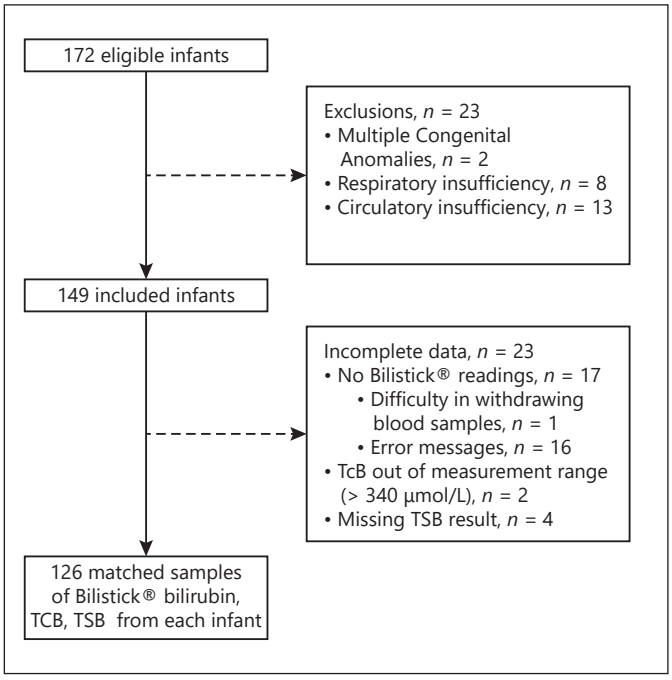

Fig. 1. Sample recruitment. TSB, total serum bilirubin; TCB, transcutaneous bilirubin.

The sample size of our study corresponds with sample sizes of other cross-sectional prospective studies that compared different methods for predicting hyperbilirubinemia requiring treatment [16, 17]. The data were analyzed using IBM SPSS Statistic Version 21.0 and Microsoft Excel (Microsoft 365, version 1911). Pairs of TCB and TSB and pairs of bilirubin obtained by Bilistick® and TSB were analyzed using Spearman correlation and linear regression. Bland-Altman plots were also constructed for each pair to calculate mean differences (MD) and 95% limits of agreement (95% LoA): MD ± 1.96 SDs. We calculated sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios (LH+ and LH−, respectively) to predict significant hyperbilirubinemia, that is, any TSB above treatment thresholds according to the Indonesian Guideline (http://yankes.kemkes.go.id/unduh/fileunduhan_1610349726_94555.pdf/16) [18].

Results

There were 172 eligible infants during the 7-month study period; 23 were excluded (Fig. 1). Twenty-three of the remaining 149 infants had incomplete data (Fig. 1). The Bilistick® showed an error reading in 16 (10.7%) in-

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fants (5 times B04 and 11 times T06, respectively), and for 1 infant, not enough blood was obtained. TCB was too high (i.e., 362 μmol/L and 432 μmol/L, respectively) to be reliably measured in 2 infants. TSB results were missing in 4 infants. A total of 126 neonates had paired measurements of Bilistick® bilirubin, TCB, and TSB. Most of the infants (n = 117) were admitted to our neonatology ward at the time of measurement. Nine infants were included during their visit of the outpatient clinic as routine control after discharge. Table 1 shows that many infants were late preterm with a mean (±SD) birth weight of 2,243 ± 610 g. Most infants presented at the fifth postnatal day with moderate jaundice (73.8% had a Kramer score of 2 or 3). The mean (±SD) POC Bilistick® bilirubin, TCB, and TSB values were 185 (±65) μmol/L, 223 (±42) μmol/L, and 196 (±47) μmol/L, respectively. The relationship between POC Bilistick® bilirubin and TSB is presented in Figure 2a with a correlation coefficient of 0.738 (p < 0.001). The Bland-Altman plot shows 4 extreme outliers; the POC Bilistick® bilirubin values were very low. The POC Bilistick® bilirubin underestimated TSB with an MD (±SD) of −11 (±46) μmol/L with a 95% CI of −19 to −3 μmol/L (Fig. 2b). The 95% LoA were −101 to 79 μmol/L. Figure 2c shows the correlation between TCB and TSB with a correlation coefficient of 0.785 (p < 0.001). TCB tended to overestimate TSB with an MD (±SD) of 26 (±30) μmol/L with a 95% CI of 21–32 μmol/L. The 95% LoA were 33–86 μmol/L (Fig. 2d).

Tables 2 and 3 show data of Bilistick® and TCB versus laboratory TSB for all infants and infants weighing <2,000 g and ≥2,000 g. Table 4 shows diagnostic accuracy parameters of TCB and Bilistick® to predict significant hyperbilirubinemia according to the Indonesian Hyperbilirubinemia Guideline. Diagnostic accuracy of TCB and Bilistick® was higher for infants weighing ≥2,000 than for infants weighing <2,000, except for Sn. Overall, NPVs were 0.88 for Bilistick® and 0.95 for TCB. LH− was the lowest for TCB (0.12) and LH+ was the highest for Bilistick® (4.62). PPVs were 0.67 and 0.54 for Bilistick® and TCB, respectively.

Table 1. Clinical characteristics and bilirubin parameters

Clinical characteristic (n = 126)	Value
Birth weight, g	2,243±610 (1,500–4,500)
Birth weight percentile	28±27 (0–100)
Birth weight, g (%)	
1,500–1,999	53 (42)
≥2,000	73 (58)
Gestational ages, weeks	35.5±2 (32–41)
Gestational ages (%)	
32–37	105 (83.3)
37–42	21 (16.7)
Postnatal age, h	118±68 (34–331)
Gender	
Female	66 (52.4)
Male	60 (47.6)
Hematocrit level, % (n = 104)	47±7 (31–64)
Kramer score	
1	14 (11.1)
2	52 (41.3)
3	41 (32.5)
4	18 (14.3)
5	1 (0.8)
Bilirubin parameters, μmol/L	
TCB	223±42 (106–332)
POC Bilistick®	185±65 (7–330)
TSB	196±47 (61–315)

Data are expressed as mean ± SD (ranges) or n (%). TSB, total serum bilirubin; TCB, transcutaneous bilirubin; POC, point of care.

Discussion

This study demonstrated that both Bilistick® and TCB show a strong and statistically significant correlation with TSB. Bilistick® underestimates TSB with an MD (±SD) of −11 (±46) μmol/L with rather broad LoA of −101 to 79 μmol/L. In contrast, TCB with the JM-105 bilirubinometer tends to overestimate TSB with an MD (±SD) of 26 (±30) μmol/L with corresponding LoA of −33 to 86 μmol/L. Apart from Sn, diagnostic properties of the Bilistick® System (BM-BS 1.0 – FW version 2.0.1) and JM-105 bilirubinometer are slightly better in infants weighing ≥2,000 g. Overall, the Bilistick® has lower Sn and higher negative likelihood ratio when compared with TCB. In contrast, Bilistick® has higher Sp and higher positive likelihood ratio when compared with TCB in all infants. The NPV of the Bilistick® is lower than the NPV of the JM-105 bilirubinometer. If treatment decisions would have been based on the Bilistick®, then 10 out of 39 infants who needed treatment would have been missed. TCB with the JM-105 bilirubinometer would have missed 3 out of 39 infants.

We found a strong correlation between TCB and TSB in accordance with previous studies [10]. Two recent studies from Indonesia and India, respectively, reported higher correlations between TCB and TSB in (late) preterm infants [17, 19]. TCB overestimated TSB with 26 μmol/L at 24 h and 21 μmol/L at 48 h [19]. Greco et al. [16] reported that TCB measured before or during PT

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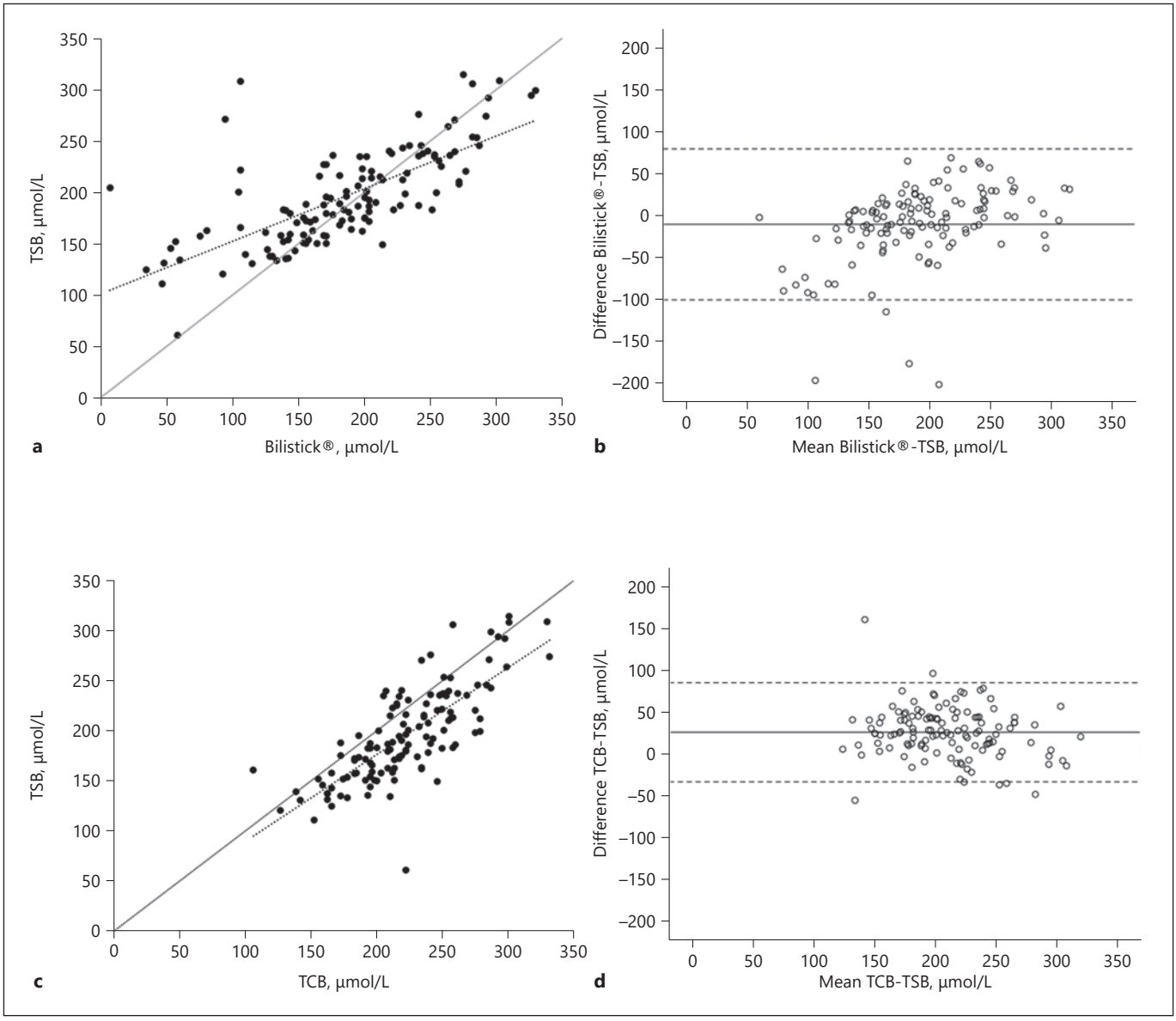

Fig. 2. The correlation of Bilistick® System (BM-BS 1.0 – FW version 2.0.1) and TSB (**a**), the Bland-Altman Plot of Bilistick® and TSB (**b**), the correlation of TCB and TSB (**c**), and the Bland-Altman plot of TCB and TSB (**d**). **a**, **c** The straight line represents the line of identity; the dashed line represents the trend line. **b**, **d** The straight line corresponds with the mean difference; the dashed lines represent the limits of agreement. TSB, total serum bilirubin; TCB, transcutaneous bilirubin.

with the JM-103 overestimated TSB with an MD of 5 (±50) µmol/L and corresponding LoA from −92 to 103 µmol/L. Data on the relationship between TCB and TSB after discontinuation of PT show good correlation after 8 h. TCB is therefore considered a reliable method for early identification of (rebound) hyperbilirubinemia before and after PT. Due to its tendency to overestimate TSB, it is unlikely to miss an infant that should be treated. TCB can also underestimate TSB, so cutoff rules are recommended to correct for falsely low readings [20, 21].

We evaluated whether the problems of the first-generation Bilistick® were overcome after an update of its firmware. In contrast to TCB with the JM-105 bilirubinometer, the Bilistick® System (BM-BS 1.0 – FW version 2.0.1) underestimates TSB, in near-term and preterm infants. Previous data showed that the Bilistick® slightly under-

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Table 2. Bilistick® accuracy to predict significant hyperbilirubinemia based on the Indonesian Hyperbilirubinemia Guideline

N (%)	TSB (+)	TSB (–)	Total
N = 126 (100)			
Bilistick® (+)	29	14	43
Bilistick® (–)	10	73	83
Total	39	87	126
N = 53 (42) <2,000 g			
Bilistick® (+)	15	10	25
Bilistick® (–)	5	23	28
Total	20	33	53
N = 73 (58) ≥2,000 g			
Bilistick® (+)	14	4	18
Bilistick® (–)	5	50	55
Total	19	54	73

(+) indicates hyperbilirubinemia above the treatment threshold of the Indonesian Hyperbilirubinemia Guideline; (–) indicates hyperbilirubinemia that needs no treatment according to the Indonesian Hyperbilirubinemia Guideline. TSB, total serum bilirubin.

Table 3. TCB accuracy to predict significant hyperbilirubinemia based on the Indonesian Hyperbilirubinemia Guideline

N (%)	TSB (+)	TSB (–)	Total
N = 126 (100)			
TCB (+)	36	31	67
TCB (–)	3	56	59
Total	39	87	126
N = 53 (42) BW <2,000 g			
TCB (+)	19	23	42
TCB (–)	1	10	11
Total	20	33	53
N = 73 (58) BW ≥2,000 g			
TCB (+)	17	8	25
TCB (–)	2	46	48
Total	19	54	73

(+) indicates hyperbilirubinemia above the treatment threshold of the Indonesian Hyperbilirubinemia Guideline; (–) indicates hyperbilirubinemia that needs no treatment according to the Indonesian Hyperbilirubinemia Guideline. TSB, total serum bilirubin; TCB, transcutaneous bilirubin.

estimated TSB in 118 near-term newborn infants with an MD of −10 μmol/L. Zabetta et al. [13] concluded that the Bilistick® 1.0 was an effective method to screen bilirubin levels in jaundiced newborns but also to identify infants at risk for kernicterus. It was acknowledged that technical errors may occur when Hct levels are above the threshold maximum Hct of 65% resulting in insufficient saturation of the test strip membrane. Greco et al. [16] excluded 35 (22%) of 161 enrolled infants, 11 (6.8%) due to technical failure of the Bilistick®. The Bilistick® underestimated TSB with an MD (±SD) of −22 (±39) μmol/L, with corresponding LoA from −100 to 56 μmol/L. Falsely low Bilistick® values have been documented in a large study in 4 different countries that analyzed its performance [22]. This study confirmed that Bilistick® values slightly underestimate TSB (−17 μmol/L over a TSB range from 17 to 684 μmol/L). There were 1,230 infants who did not require treatment according to Bilistick® readings, whereas 88 (7.2%) of them reached treatment threshold according to TSB [23]. Thielemans et al. [22] reported error messages in 48.6% of 173 Bilistick® tests. They concluded that Bilistick® 1.0 was not suitable for clinical conditions because of its failure rate and false-negative readings, which would result in undertreatment in 4 out of 5 infants when tested with an Hct value >55% at a humidity ≥75% [22]. Rohsiswatmo et al. [17]compared the first-generation Bilistick® with laboratory TSB in 94 preterm infants in Indonesian climate conditions and found that Bilistick® underestimated TSB; 11 out of 94 infants (12%) would not have received treatment, relying on Bilistick® readings alone. After the 5 studies evaluating the performance of the first version of the Bilistick®, a version with updated firmware was launched. Our study is the first study that has evaluated the performance of the Bilistick® System with updated firmware (BM-BS 1.0 – FW version 2.0.1). We found a lower correlation between TSB and the Bilistick® compared with previous studies [13, 16, 17, 22, 23]. Ten newborns reached the PT threshold as determined by TSB measurement but had low POC Bilistick® bilirubin readings. Solely relying on POC bilirubin measurement with the Bilistick® might have resulted in a de-

Table 4. Accuracy parameters of TCB and Bilistick® based on birth weight

Birth weight, g	Sn	Sp	PPV	NPV	LH (+)	LH (–)
Bilistick®						
<2,000	0.75	0.70	0.60	0.82	2.48	0.36
≥2,000	0.74	0.93	0.78	0.91	9.95	0.28
Overall	0.74	0.84	0.67	0.88	4.62	0.31
TCB						
<2,000	0.95	0.30	0.45	0.91	1.36	0.17
≥2,000	0.89	0.85	0.68	0.96	6.04	0.12
Overall	0.92	0.64	0.54	0.95	2.59	0.12

TCB, transcutaneous bilirubin; Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; LH (+), positive likelihood ratio; LH (–), negative likelihood ratio.

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lay of PT. Around 11% of the measurements resulted in error messages, and in 4 cases, the device showed extremely low values compared to the TSB value up to −203 μmol/L (Fig. 2b). The manual indicates that unpredictable low readings can result from not enough blood on the measurement strip. Unfortunately, in these cases, no error message appears. In line with our findings, Kamineni and colleagues [24] recently called to further improve the accuracy of the Bilistick®. Differences in the comparisons of TCB and Bilistick® System with TSB are not surprising because we compared complete different methodologies. As the Bilistick® System is relatively new when compared to TCB devices, data on its diagnostic performance are essential and should be comparable to or preferably outperform TCB.

We acknowledge several limitations of our study. The current study is composed of a convenient sample size (similar to that of other studies) using a BS 1.0 with the highest firmware version possible. To the best of our knowledge, data from the recently launched, and commercially available, second generation of the Bilistick® System with novel firmware (BS 2.0 – FW version 4.0.36) and test strips are not available yet. The inclusion of newborn infants who were jaundiced may lead to bias as there may be newborns who do not appear jaundiced, but actually do have increased TSB when tested. Current practice in our hospital is that TSB measurement is not routinely done in infants without jaundice. This is in agreement with previous data of Keren and colleagues [7] that 'the complete absence of jaundice had high Sn (95%) for ruling out the development of significant hyperbilirubinemia. As such, we think the risk of bias is small. TSB was measured by a routine laboratory technique. Although used universally to determine bilirubin, there is much variation in TSB measurement by these methods [25]. Among other advanced methods for bilirubin measurement, high-performance reversed-phase liquid chromatography is a more sensitive method but impractical for routine clinical use. Next, blood for laboratory TSB measurement was not taken simultaneously with TCB and Bilistick® measurements, which could have affected calculated diagnostic properties. Laboratory personnel did (venous) blood sampling for laboratory bilirubin measurement, whereas TCB and heel pricks for Bilistick® were done by nurses trained to use the Bilistick®. However, blood for laboratory TSB was taken within 1 h after these measurements to minimize discrepancies. Finally, we did not apply a decision rule for TCB to correct for underestimation of TSB.

Conclusion

TCB is a valuable screening tool for neonatal jaundice in Indonesian newborn infants. The reported overestimation makes it very unlikely to miss an infant with a TSB level that should be treated. The Bilistick® System (BM-BS 1.0 – FW version 2.0.1) underestimates TSB values compared to laboratory measurements. In our study, it also lacked similar diagnostic properties when compared to TCB to serve as a reliable screening instrument for neonatal hyperbilirubinemia. Use of this promising and fast bedside technique has the risk for falsely low readings. Further improvement of Bilistick®'s diagnostic accuracy and validation in a wide variety of populations and settings, not strictly limited to LMICs, is essential.

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Statement of Ethics

The authors have no ethical conflicts to disclose. The study was approved by the Dr. Soetomo General Hospital Surabaya Ethics Committee, No. 0526/KEPK/VIII/2018. Informed consent was obtained from parents or legal guardians.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Mahendra T.A. Sampurna, Pieter J.J. Sauer, Arend F. Bos, Peter H. Dijk, and Christian V. Hulzebos conceived and designed the experiments, analyzed and interpreted the data, and wrote and critically reviewed and revised the manuscript. Siti A.D. Rani performed the experiments, analyzed and interpreted the data, and revised the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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