



## Original Research

# Evaluation of the Relationship Between Transcutaneous Bilirubin Measurement and Total Serum Bilirubin in Neonatal Patients Followed for Jaundice

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### Abstract

**Objectives:** Jaundice is a physiological condition caused by hyperbilirubinemia, which is common in neonatal period. However, severe hyperbilirubinemia can cause kernicterus, which is a serious condition that leads to neurological problems. In this study, we aimed to investigate whether it is safe to use transcutaneous bilirubin (TcB) instead of blood for the evaluation of jaundice by comparing TcB measurement with standard total serum bilirubin (TSB) measurement values.

**Methods:** A total of 105 term and early term infants with gestational ages between 37 and 42 weeks were included in the study. MBJ20 TcB measuring device was used for TcB measurement. TcB was measured from the forehead and sternum. To evaluate the relationship between TcB measurements and TSB measurements, we performed Pearson correlation, Spearman correlation, linear regression analysis, and Bland-Altman analysis in which we evaluated the scatter plot of the differences between the average values of the measurements.

**Results:** There was a positive and statistically significant correlation between TcB forehead and TSB measurements and TcB sternum and TSB measurements ( $p < 0.001$ ). Linear regression analysis showed a positive directional correlation between TcB forehead and TSB measurements ( $R^2 = 0.85$ ) and TcB sternum and TSB measurements ( $R^2 = 0.87$ ). Bland-Altman analysis showed a good consistency between TSB and TcB forehead measurement methods (mean difference:  $0.39 \pm 1.46$ , 95% CI:  $[-2.47] - [3.26]$ ), and between TSB and TcB sternum measurement methods (mean difference:  $0.49 \pm 1.32$ , 95% CI:  $[-2.1] - [3.07]$ ).

**Conclusion:** As a result of our study, we found that TcB measurement can be reliable instead of taking blood for jaundice evaluation.

**Keywords:** Jaundice; neonate; serum bilirubin; transcutaneous bilirubin.

Please cite this article as "Cetinkaya Cat F, Cat A, Cicek T, Geylani G. Evaluation of the Relationship Between Transcutaneous Bilirubin Measurement and Total Serum Bilirubin in Neonatal Patients Followed for Jaundice. Med Bull Sisli Etfal Hosp 2021;55(2):262–267".

Neonatal jaundice is one of the most common conditions in newborns.<sup>[1]</sup> This situation can be seen in approximately 60% of term babies and 80% of preterm babies.<sup>[2]</sup>

Neonatal jaundice is a normal physiological condition that usually occurs in the transition period after birth. It is also not a singular disease, but a physical finding associated

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**Submitted Date:** January 08, 2020 **Accepted Date:** April 13, 2020 **Available Online Date:** July 02, 2021

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with many possible etiologies. Severe neonatal jaundice is considered pathophysiological. Jaundice reflects the accumulation of the yellow-orange pigment bilirubin in the skin, sclera, and other tissues. It does not imply any particular causation. Therefore, preventive and therapeutic approaches to pathophysiological neonatal jaundice or hyperbilirubinemia are typically not specific.<sup>[3]</sup> Management of neonatal jaundice aims to prevent kernicterus that can result from high levels of unconjugated bilirubin. Kernicterus is a serious condition and can cause permanent damage. People with kernicterus typically have dyskinetic tetraplegic cerebral palsy, bilateral sensorineural hearing loss, and often upward gaze restriction.<sup>[4]</sup>

In the 2004 American Academy of Pediatrics Subcommittee on Hyperbilirubinemia guideline, total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) measurement is recommended before discharge from the maternity hospital to evaluate the risk of subsequent severe hyperbilirubinemia in all newborns.<sup>[5]</sup> Although TSB measurement is still the standard in the evaluation of neonatal jaundice, it requires a venous or heel prick blood sampling, which is an invasive and painful procedure.<sup>[6]</sup> Although the risks associated with blood sampling are considered low, the possibilities of complications such as iatrogenic anemia, puncture site infection, bacteremia, and osteomyelitis cannot be excluded in repeated sampling.<sup>[7]</sup> TcB meters estimate total serum or plasma bilirubin using multiwavelength spectral reflection from the skin surface.<sup>[8]</sup>

There are studies showing that the widespread use of TcB or TSB measurements in jaundice screening reduces the rate of newborns with severe hyperbilirubinemia, the rate of hospital readmission for phototherapy, and the number of babies receiving phototherapy.<sup>[9-11]</sup> However, due to the bleaching of the skin, the accuracy of TcB during phototherapy is lower. Therefore, TcB measurement is not reliable in babies receiving phototherapy.<sup>[12-14]</sup> There are significant differences between devices that measure TcB. If TcB will be used instead of TSB measurement in the clinic, the compatibility of the values measured by the new device with the TSB values should be compared, and its accuracy should be ensured.<sup>[15]</sup>

In our study, we aimed to investigate whether it would be safe to use TcB measurement instead of blood collection for jaundice evaluation, by comparing TcB measurement, which is a non-invasive, easy, fast and cheaper method, and TSB measurement values, which is the standard method, in patients with suspected neonatal jaundice.

## Methods

In this study, a total of 105 newborns, including babies born at the University of Health Sciences between Feb-

ruary 1, 2019, and May 1, 2019, and followed up with the mother before discharge and babies who were followed up in the routine newborn outpatient clinic, were included in the study. Verbal and written information was given to the families of each patient included in the study, and verbal and written consents were obtained from each family. This study was approved by the ethics committee. Term and near-term babies with gestational ages between 37 and 42 weeks were included in the study. Newborns who were clinically healthy except for hyperbilirubinemia, with no detectable pathology, no significant intrapartum and postpartum complications, and no ABO and/or Rh hemolytic disease were included in the study. Babies who were older than 15 days postnatally, had skin disease, had received phototherapy before, and received exchange transfusion were not included in the study. MBJ20 TcB measurement device was used for TcB measurement. Three measurements were made from the forehead and sternum in each patient and the average value indicated by the device was taken. TcB measurement was performed during bilirubin measurement of newborns scheduled for postpartum discharge or in cases with clinical jaundice during postpartum follow-up. TcB measurement was made within  $\pm 10$  min of blood collection for TSB measurement. TSB levels were measured with spectrophotometric method in biochemistry autoanalyzer (Beckman Coulter, AU680) from serum samples.

## Statistical Analysis

Statistical analyzes were performed using the Statistical Package for the Social Sciences (version 11, Chicago, IL, USA) software program. Data were given as mean, standard deviation (SD), minimum, maximum, and percentage. Depending on the distribution of correlations between variables, Pearson or Spearman correlation tests were used. Statistical significance limit was  $p < 0.05$  and two sided. Pearson or Spearman correlation tests can be a weak indicator for predicting the relationship between two diagnostic tests. Therefore, we used linear regression and Bland-Altman analysis to evaluate the variability between TSB and TcB measurements. The confidence interval (CI) for the mean difference between measurements was given as a 95% CI. Significance level was accepted as 5%. In the Bland-Altman analysis, the limits of agreement were defined as the mean of the differences  $\pm 1.96$  SDs.

## Results

The study was conducted with a total of 105 newborns (44 [41.9%] females and 61 [58.1%] males). Maternal ages range from 16 to 46, with 26 (24.8%) being primiparous cases and 79 (75.2%) being multiparous cases. The mean

gestational age of the cases was  $38.6 \pm 1$  (range: 37–42 weeks) weeks. The mean birth weight was  $3275 \pm 447$  g (distribution: 2355–4480 g). The number of babies born by spontaneous vaginal delivery was 48 (45.1%), and the number of babies born by cesarean section was 57 (54.3%). The number of cases who were discharged and had their bilirubin measured (coming from home) during outpatient clinic control was 26 (24.8%), and the number of newborns who were followed up after birth in the mother's side was 79 (75.2%).

TcB forehead levels varied between 4.2 and 17.6 mg/dl, with an average value of  $9.16 \pm 2.95$  mg/dl. TcB sternum levels varied between 3.5 and 18.3 mg/dl with an average value of  $9.25 \pm 3.32$  mg/dl. TSB levels varied between 2.2 and 19.2 mg/dl, with an average value of  $8.77 \pm 3.64$  mg/dl (Table 1).

Whether the relationship between the relevant parameters is statistically significant or not was evaluated by the Pearson correlation coefficient, considering each group separately. There was a very strong (92.2%) and statistically significant positive correlation between TSB levels and TcB forehead measurements ( $p < 0.001$ ). There was a very strong positive (93.2%) and statistically significant correlation between TSB levels and TcB sternum measurements ( $p < 0.001$ ). There was a very strong (95.7%) and statistically significant positive correlation between TcB forehead and TcB sternum measurements ( $p < 0.001$ ) (Table 2).

**Table 1.** TcB forehead, TcB sternum, and TSB measurement values of the cases

	Average (mg/dl)	Min–Max	SD
TcB forehead	9.16	4.2–17.6	2.95
TcB sternum	9.25	3.5–18.3	3.32
TSB	8.77	2.2–19.2	3.64

TcB: Transcutaneous bilirubin; TSB: Total serum bilirubin.

**Table 2.** TcB forehead, TcB sternum, and TSB levels correlation

	TcB forehead	TcB sternum	TSB
TcB forehead			
r	1	0.957	0.922
p		0.000	0.000
TcB sternum			
r	0.957	1	0.932
p	0.000		0.000
TSB			
r	0.922	0.932	1
p	0.000	0.000	

r: Pearson correlation coefficient; TcB: Transcutaneous bilirubin; TSB: Total serum bilirubin.

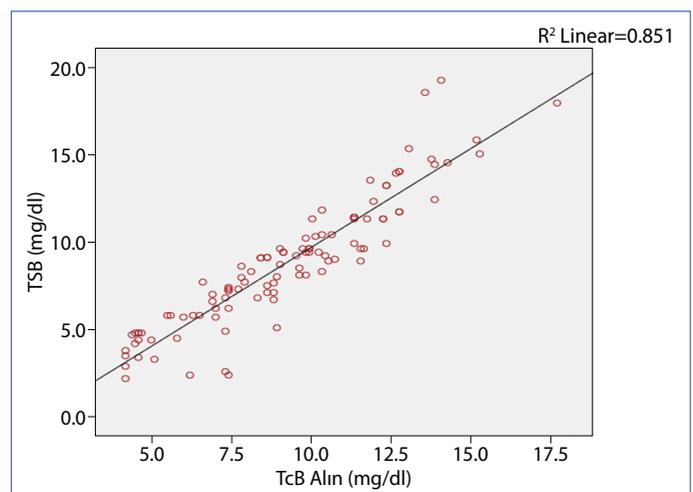
**Table 3.** Correlation of TSB with TcB forehead and TcB sternum measurement intervals

	TSB				
	n	Average (mg/dl)	SD	$r_s$	P
TcB forehead (mg/dl)					
<5	14	4.55	0.81	0.69	0.007
5–10	51	8.30	1.32	0.80	0.001
10–15	37	11.8	1.22	0.78	0.001
>15	3	15.2	1.41	0.50	0.67
TcB sternum (mg/dl)					
<5	12	4.2	0.30	0.96	0.001
5–10	49	7.7	1.46	0.83	0.001
10–15	42	12.4	1.51	0.84	0.001
>15	2	17.1	1.69	1	-

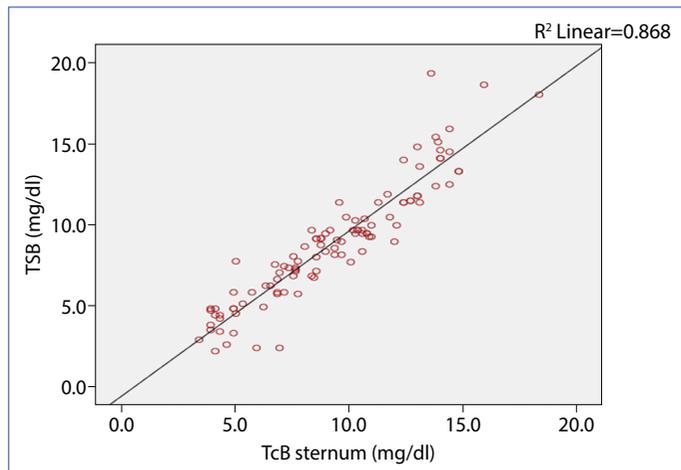
$r_s$ : Spearman correlation coefficient; TcB: Transcutaneous bilirubin; TSB: Total serum bilirubin.

When we compared the TcB forehead and sternum levels with TSB levels separately at the measurement ranges of <5, 5–10, 10–15, and >15 mg/dl, respectively, the values below 15 mg/dl showed a statistically significant correlation with TSB levels ( $p < 0.05$ ). Although the number of patients in the group with TcB forehead level measurement range >15 mg/dl was not sufficient, a statistically significant correlation was not observed ( $p > 0.05$ ). Statistical analysis could not be performed due to the insufficient number of patients in the group with TcB sternum level measurement range >15 mg/dl (Table 3).

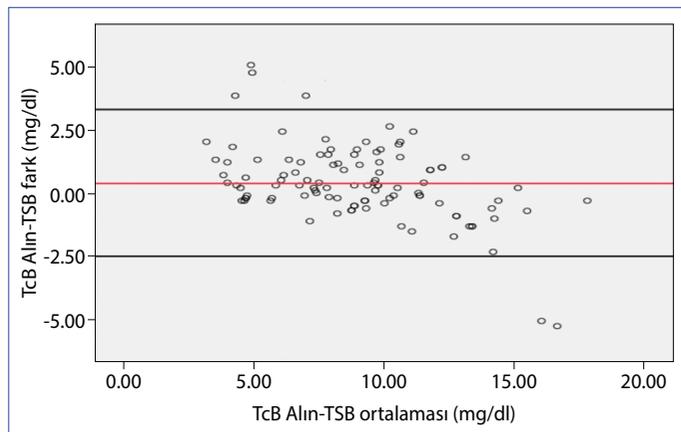
When we evaluated the linear variability between TSB and TcB (forehead and sternum) measurements using linear regression analysis, a positive linear relationship between the methods was found (Figs. 1 and 2).



**Figure 1.** Linear regression analysis between TSB and TcB forehead measurements ( $R^2 = 0.85$ ).



**Figure 2.** Linear regression analysis between TSB and TcB sternum measurements ( $R^2=0.87$ ).

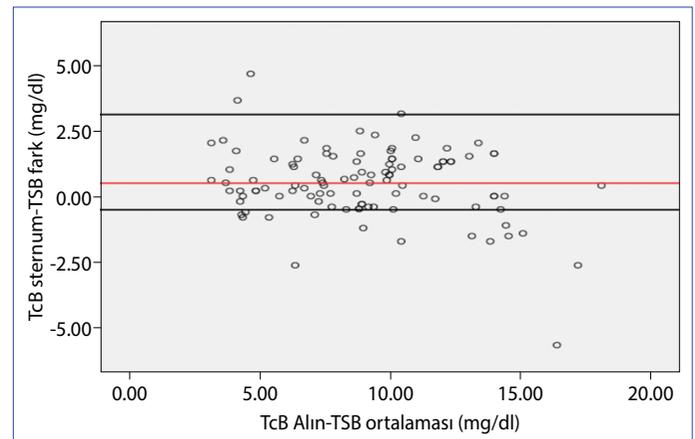


**Figure 3.** Bland-Altman analysis between TSB and TcB forehead measurement methods (average difference:  $0.39 \pm 1.46$ , 95% CI:  $[-2.47]$ – $[3.26]$ , upper limit: 3.26, lower limit:  $-2.47$ ).

In the Bland-Altman analysis, where we evaluated the scatter plots of the differences between the average measurements obtained from the TSB and TcB (forehead and sternum) measurement methods, we found a strong consistency between the two methods (Figs. 3 and 4).

## Discussion

Most of the newborn babies with an age of  $\geq 35$  gestational weeks have some degree of jaundice in the 1st day after birth.<sup>[16]</sup> Neonatal jaundice is generally not harmful and is a self-limiting condition. However, very high levels of bilirubin, a condition called kernicterus, can cause permanent brain damage. Therefore, it is important to diagnose neonatal jaundice and to manage it appropriately.<sup>[17]</sup> TcB measurement is widely used to measure bilirubin levels for screening in newborns. We conducted a prospective correlation study with 105 newborns to examine the correlation of TcB (forehead and sternum), which are non-invasive,



**Figure 4.** Bland-Altman analysis between TSB and TcB sternum measurement methods (average difference:  $0.49 \pm 1.32$ , %95 CI:  $[-2.1]$ – $[3.07]$ , upper limit: 3.07, lower limit:  $-2.1$ ).

easy, fast, and cheaper methods in detecting hyperbilirubinemia, and TSB measurements, and to evaluate its accuracy as a screening tool.

In our study, a positive very high level of statistically significant correlation between TSB levels and TcB forehead measurements was found ( $r=0.92$ ) ( $p<0.001$ ), a positive very high level of correlation between TSB levels and TcB sternum measurements ( $r=0.93$ ) ( $p<0.001$ ), and a positive very high level of correlation between TcB forehead and TcB sternum measurements ( $r=0.95$ ) ( $p<0.001$ ) was found. When we compared TcB (forehead and sternum) levels with TSB levels according to measurement ranges, we found a statistically significant correlation in groups with TcB levels lower than 15 mg/dl ( $p<0.05$ ). In a study conducted by Gunaseelan et al. with 400 newborns whose gestational ages were older than 35 weeks, they compared the TcB sternum measurements with the TSB measurements and found a significant correlation in between ( $p<0.001$ ).<sup>[18]</sup> Likewise, Ho et al. found a significant correlation between TcB measurements and TSB measurements in term or near-term newborns ( $p<0.001$ ).<sup>[19]</sup> In Maisels et al.'s and Rubaltelli et al.'s studies, they stated that there was a decrease in sensitivity and an increase in specificity at higher TcB cutoff measurement levels.<sup>[20,21]</sup> Furthermore, Maisels et al. stated that when the TSB measurement values exceeded 15 mg/dl, the number of false-negative readings increased.<sup>[20]</sup> Likewise, Ho et al. found a significant correlation between TcB measurements and TSB measurements in term or near-term newborns ( $p<0.001$ ).<sup>[19]</sup> In Maisels et al.'s and Rubaltelli et al.'s studies, they stated that there was a decrease in sensitivity and an increase in specificity at higher TcB cutoff measurement levels.<sup>[20,21]</sup> Also, Maisels et al. stated that when the TSB measurement values exceeded 15 mg/dl, the number of false-negative readings

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## Conclusion

Although TSB measurement is standard in the evaluation of neonatal jaundice, it is an invasive, painful procedure that requires a blood sample. In our study, we found a significant correlation between TcB (forehead and sternum) measurements and TSB measurements. We think that TcB measurement is a fast, safe, non-invasive, and low-cost screening test that can help to minimize invasive TSB tests and determine neonatal jaundice. Although devices that measure TcB levels reliably estimate bilirubin levels, none of the original guidelines recommend using TcB measurements as an indicator for phototherapy initiation. It is important to note that TcB is only a screening tool, and verification with TSB should be considered especially in high-risk newborns.

## Disclosures

**Ethics Committee Approval:** This study was approved by Taksim Training and Research Hospital Clinical Research Ethics Committee (10.04.2019/51).

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** The authors have no conflict of interest.

**Authorship Contributions:** Concept – F.C., A.C., T.C.; Design – F.C., A.C., T.C.; Supervision – F.C., A.C., S.G.; Materials – F.C., T.C.; Data collection &/or processing – F.C., T.C.; Analysis and/or interpretation – F.C., A.C., S.G.; Literature search – F.C., A.C., S.G.; Writing – A.C., F.C.; Critical review – A.C., F.C., T.C.

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