Transcutaneous Bilirubin Accuracy Before, During, and After Phototherapy

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Transcutaneous Bilirubin Accuracy Before, During, and After Phototherapy: A Meta-Analysis

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abstract

CONTEXT: Transcutaneous bilirubinometry (TcB) is used as a valid screening to identify neonates requiring measurement of total serum bilirubin (TSB) before phototherapy. Its use during and after phototherapy is not advised yet because of unknown reliability.

OBJECTIVES: To determine the agreement of TcB and TSB measurements before, during, and after phototherapy.

DATA SOURCES: PubMed Medline, Cochrane Library, and references of eligible studies were searched.

STUDY SELECTION: Prospective and retrospective cohort and cross-sectional studies reporting Bland-Altman statistics of paired TcB and TSB measurements in term and preterm newborns.

DATA EXTRACTION: Meta-analysis was performed using the Mantel-Haenszel weighted approach. The agreement between TcB and TSB in μmol/L was described by pooled mean differences (MDs) and limits of agreement (LoA).

RESULTS: Fifty-four studies were included. The pooled MD before phototherapy is 2.5 μmol/L (LoA −38.3 to 43.3). The pooled MD during phototherapy is −0.3 μmol/L (LoA −34.8 to 34.2) on covered skin and −28.6 μmol/L (LoA −105.7 to 48.5) on uncovered skin. The pooled MD after phototherapy is −34.3 μmol/L (LoA −86.7 to 18.1) on covered skin and −21.1 μmol/L (LoA −88.6 to 46.4) on uncovered skin. Subgroup analysis revealed the best agreement at the forehead. We did not find any difference in agreement between term and preterm neonates.

LIMITATIONS: Language restriction.

CONCLUSIONS: TcB measurements before and during phototherapy on covered skin show good agreement compared with TSB in term and preterm newborns. More studies are needed to evaluate the accuracy after phototherapy.

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Dr ten Kate conceptualized and designed the study, collected and extracted data, conducted the initial analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript; Dr van Oorschot conceptualized and designed the study, and collected and extracted data; Dr Woolderink conceptualized and designed the study, and conducted the initial analyses; Dr Teklenburg-Roord reviewed and revised the manuscript; Dr Bekhof conceptualized and designed the study, coordinated and supervised data collection and initial analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

This study is registered at PROSPERO, CRD42022361932. Deidentified data will not be made available. All data, including the calculations concerning the pooling of data, are available upon reasonable request. Please use the contact information below.

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Neonatal jaundice is a common condition occurring in ~60% of term and 80% of preterm infants and is associated with a raised level of unconjugated bilirubin in the circulation called hyperbilirubinaemia.[1] The prevention of severe unconjugated hyperbilirubinemia is important because unconjugated bilirubin can cross the blood–brain barrier and potentially cause neurotoxicity. Visual assessment of the degree of jaundice is known to be unreliable.[2] Measurement of total serum bilirubin (TSB) is considered the golden standard. However, blood sampling for TSB is an invasive, painful, and time-consuming procedure. Transcutaneous bilirubinometry (TcB) is an increasingly applied noninvasive, painless, easily reproducible, and cost-effective point-of-care alternative to estimate TSB.[3–5] TcB measures cutaneous bilirubin by directing light into the skin and measuring the intensity of reflecting specific wavelengths.[6]

TcB measurements are currently advised in several national guidelines for identification of neonates requiring TSB measurements before the application of phototherapy.[1,7] Generally, a safety margin of 50 μmol/L (~3 mg/dL) is applied when TcB is interpreted. Moreover, cautious use of TcB in the higher ranges is warranted because, here, TcB tends to underestimate TSB.[7] The accuracy of TcB in newborns during and after phototherapy is still unclear and therefore not recommended. The use of TcB during and after phototherapy may further reduce blood sampling for TSB measurements and may add to the feasibility of home phototherapy in low-risk newborns.

Until now, 4 systematic reviews have assessed the agreement between TcB and TSB measurements.[8–11] Two included studies before phototherapy,[8,9] and 2 during and after phototherapy.[10,11] One systematic review included term and near-term newborns[11]; the others were restricted to preterm neonates.[8–10] All 4 reviews found strong to very strong correlations between TcB- and TSB-reporting pooled correlations coefficients of 0.82 and 0.83 before phototherapy,[8,9] and respectively, 0.71 and 0.65 during phototherapy on covered and uncovered skin.[11] In 2 of 4 systematic reviews, Bland-Altman analyses were reported in a limited number of studies; however, without pooling data.[9,11]

Bland-Altman analysis is the preferred statistical method for the assessment of the agreement between 2 continuous measurements. The Bland-Altman graph visually depicts the relation of the mean of the 2 paired measurements on the x axis ([TcB + TSB]/2), with the difference between the 2 paired measurements on the y axis (TcB − TSB or TSB − TcB). The agreement is quantified by the mean difference (MD) and limits of agreement (LoA), calculated as the MD ± 1,96 × SD.[12] This provides data that can easily be translated to the clinical practice, which makes it helpful for clinical decision-making. This is in contrast to the correlation coefficient, which indicates the strength of a linear relationship between 2 variables without quantification of the degree of the agreement between these 2 variables.

The aim of this systematic review and meta-analysis was to determine the agreement of TcB and TSB measurements in preterm and term newborns before, during, and after phototherapy, producing a pooled MD with pooled LoA of the Bland-Altman statistics.

METHODS

This systematic review and meta-analysis was registered in PROSPERO, an international prospective register of systematic reviews (CRD42022361932).[13] This study was performed and reported using the reporting guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-analysis of Observational Studies in Epidemiology.[14]

Search Strategy

The literature search was performed in the electronic database PubMed (search string: "[bilirubinometry OR bilirubinometer OR transcutaneous] AND [hyperbilirubinaemie OR hyperbilirubinemia OR jaundice OR bilirubin] AND [neonatal OR newborn]") and Cochrane (search string: hyperbilirubinemia) in December 2021 and the search was updated in July 2022. References of included studies were checked. We restricted our search to studies reported in English, German, and Dutch languages.

Eligibility Criteria

Prospective and retrospective cohort and cross-sectional observational studies evaluating the agreement between paired measurements of TcB and TSB in neonates across all gestational ages ≤28 days postpartum were eligible for inclusion. The following transcutaneous bilirubinometers were assessed as eligible: JM-103/105, BiliChek, Bilicare, MBJ-20, JH20-1C and KJ-8000. Solely studies using Bland-Altman analysis, including a Bland-Altman graph providing an MD of TcB and TSB measurements and SD or LoA, were included.

Two review authors (L.K., T.O.) independently screened all titles and abstracts identified by our search strategy for relevance to this systematic review. Disagreements were solved in consensus. Full-text articles were retrieved and independently assessed by 2 review authors on the above-mentioned predefined eligibility criteria (L.K., T.O.). Disagreements were solved through discussion with a third review author (J.B.).

Data Extraction

Two review authors (L.K., T.O.) extracted data independently from the selected articles: Type of study (prospective, retrospective, cross-sectional); study size; number of paired measurements; gestational age; inclusion and exclusion criteria; the use of phototherapy on covered and/or uncovered skin; type of TcB device and location of measurement; method of TSB measurement; time between

TcB and TSB measurement; MD (TcB − TSB) and SD, whether calculated from the LoA (LoA = MD ± 1,96 x SD). We conversed all data to μmol/L (1 mg/dL = 17.1 μmol/L). Data for meta-analysis were selected if they were clearly defined to the groups before, during, or after the application of phototherapy. After phototherapy was defined as at least 8 hours after discontinuing phototherapy.

Quality Assessment

Quality assessment was performed using the tool Quality Assessment of Diagnostic Accuracy Studies-2 by 2 review authors (L.K., J.B.).[15] We evaluated the studies for patient selection, index test, reference standard, and flow and timing. For reference standard, the well-known TSB methods diazo, direct spectrophotometry, and high-performance liquid chromatography were described as low risk.[16] In the section Flow and Timing, an interval <60 minutes between TcB and TSB measurements was described as appropriate. Uncertainties were solved in consensus.

Statistical Analysis

To obtain a pooled MD and SD, we used the Mantel-Haenszel weighted approach described by Williamson et al: A statistical method for pooling Bland-Altman data that was used before in several systematic reviews assessing the agreement of 2 continuous measurements (Supplemental Fig 3).[17–19] The meta-analysis was executed in Excel. Forest plots were created using R software. We analyzed data before, during (covered and uncovered), and after (covered and uncovered) phototherapy separately. We hypothesized a priori the following sources for clinical heterogeneity and performed subgroup analyses accordingly: Covering of skin during phototherapy, location of TcB measurement, gestational age (<37 weeks and ≥37 weeks), and type of TcB device. We considered an MD between TcB and TSB ≥ ± 50 μmol/L (~3 mg/dL) clinically relevant.[7]

RESULTS

Study Selection

The study selection is illustrated in Fig 1. The literature search identified 550 records, of which 201 studies potentially qualified for inclusion on the basis of screening of titles and abstracts. The 201 full-text records were screened and 67 studies met all inclusion criteria. Of these 67 studies, 54 studies reported results separately to a group before (48 studies),

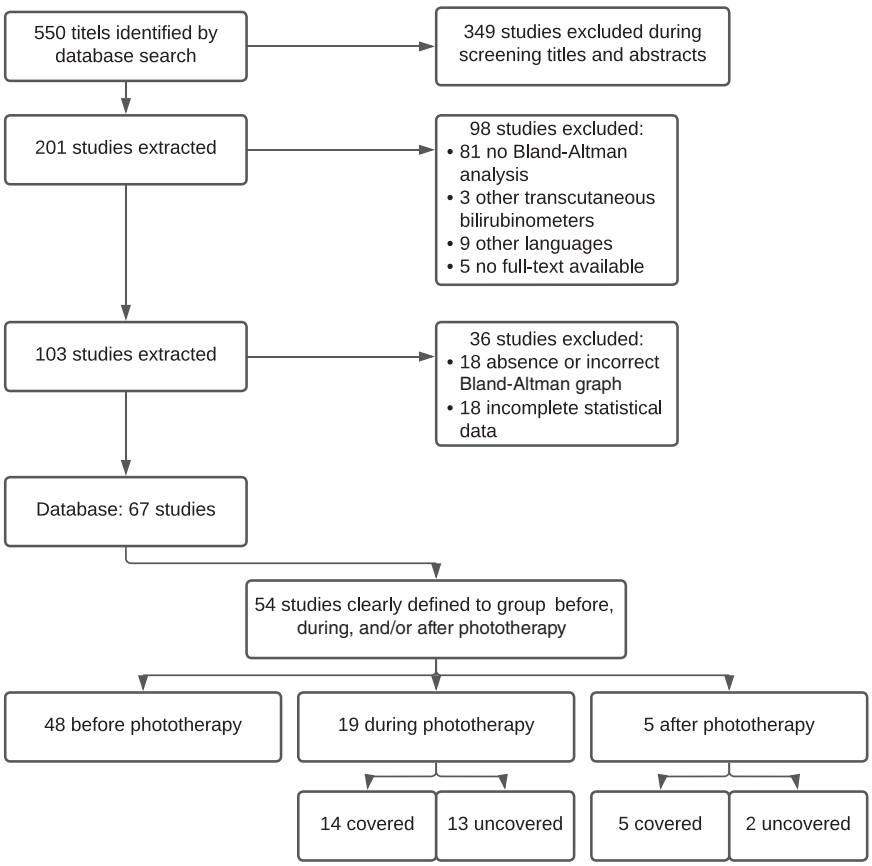


FIGURE 1
Study flow diagram. The 54 studies are not the sum of studies before, during, and after phototherapy because some studies included measurements both before, during, and/or after phototherapy; the same accounts for covered and uncovered in the groups during and after phototherapy.

during (respectively, 14 and 13 studies in covered and uncovered skin), and after phototherapy (respectively, 5 and 2 studies in covered and uncovered skin), and were selected for final inclusion and analysis.

Study Characteristics

The study characteristics of the 54 included studies are reported in Table 1, including a total of 17 236 patients and 23 882 paired measurements. We cannot exclude that this number of paired measurements may not be completely correct because several studies compared >1 TcB measurement; for example, different locations or different kinds of TcB devices to 1 TSB measurement.[20–34] In most studies, TcB was measured on the forehead (37 of 54 studies; 68.5%) or sternum (30 of 54 studies; 55.5%), some in combination with other more caudal locations. In 1 study, only the hipbone was used,[35] in another the ear pinna,[36] and 1 study did not mention the location.[37] Six of 54 studies (11.1%) included only term infants (≥37 weeks of pregnancy) and 13 of 54 studies (24.1%) included only preterm infants. The other studies included both term and preterm neonates (33 of 54 studies; 61.1%) or didn't report gestational age (n = 2). The most frequent reported TcB device was JM-103 (26 of 54 studies, 48.1%) and BiliChek (22 of 54 studies, 40.7%), followed by JM-105 (11 of 54, 20.4%). MBJ-20 and BiliCare were used in 2 studies, and JHC20-1C in 1. Excluded studies with reason for exclusion are presented in Supplemental Table 4.

Quality Assessment

Quality assessment according to Quality Assessment of Diagnostic Accuracy Studies-2 is summarized in Table 2. In general, quality of the included studies was good and risk of bias in most studies was estimated low. We considered consecutive or convenience sampling both as low risk of bias in the domain of patient selection. We assessed retrospective studies as unclear risk (8 of 54; 17.8%) because of the possibility of missing data. None of the studies had risk of bias in the domain of index test. In the domain reference test, 1 study (1.9%) was judged to have high risk of bias because the reference test was not based on 1 of the 3 well-known TSB methods.[38] Four of 54 studies (7.4%) had unclear risk of bias in this domain because the reference method was not mentioned.[22,24,25,39] Concerning flow and timing, 4 of 54 studies (7.4%) had high risk of bias because the time between TcB and TSB measurement was 60 minutes or more.[40–43] In another 4 studies, time between TcB and TSB measurement was not mentioned and risk of bias was therefore unclear.[28,38,44,45]

Meta-Analysis

The pooled MD, pooled SD, and pooled 95% LoA before, during (covered and uncovered), and after (covered and uncovered) phototherapy including subgroup analyses for location of TcB measurement, gestational age, and device of the TcB measurement are listed in Table 3.[17] Figures 2A–E depict the corresponding forest plots.

Before Phototherapy

We identified 48 studies (18 630 paired measurements in 15 544 patients) applicable for meta-analysis before phototherapy, resulting in a pooled MD (TcB − TSB) of 2.5 μmol/L (SD 20.8; LoA −38.3 to 43.3 μmol/L). See Table 3 and Fig 2A.

Subgroup analysis revealed diminished agreement between TcB and TSB measurements, with LoA outside the safety margin of 50 μmol/L when TcB was measured on the sternum (MD 19.7 μmol/L; LoA −32.7 to 72.1 μmol/L) compared with TcB measurements on the forehead (MD −0.4 μmol/L; −45.5 to 44.8 μmol/L). In term infants, the LoA were just outside the 50 μmol/L range (−54.3 to 57.8 μmol/L), whereas in preterm infants, they were within this range (−43.1 to 38.5 μmol/L). Subgroup analyses comparing different TcB devices revealed adequate LoA, except for JM-105 (−39.2 to 65.7 μmol/L), MBJ-20 (−41.9 to 60.8 μmol/L), and JH20-1C (−63.3 to 60.3 μmol/L).

During Phototherapy

We identified 14 studies (2355 paired measurements in 1613 patients) applicable for analysis during phototherapy on covered skin, with a pooled MD of −0.3 μmol/L (SD 17.6 μmol/L; LoA −34.8 to 34.2 μmol/L). The forest plot is presented in Fig 2B.

Subgroup analysis of studies reporting comparisons of TcB and TSB measured during phototherapy on the covered sternum showed LoA outside the 50 μmol/L range (−67.7 to 69.3 μmol/L) compared with LoA well within this range when TcB was measured on the forehead (−21.0 to 32.9 μmol/L). In term infants, the LoA of TcB measurements during phototherapy on covered skin were marginally outside the 50 μmol/L range (−51.4 to 45.9 μmol/L) and within this range in preterm infants (−27.2 to 25.8 μmol/L). Subgroup analysis within the category during phototherapy on covered skin per TcB devices all showed LoA agreement outside the 50 μmol/L (Table 3).

The 13 studies (2796 paired measurements in 1806 patients) applicable for analysis during phototherapy on uncovered skin showed large heterogeneity (Fig 2C). Although strictly pooling should not be done in case of substantial heterogeneity, the calculated pooled MD was −28.6 μmol/L (SD 39.3 μmol/L; LoA −105.7 to 48.5 μmol/L).

All subgroup analyses including TcB measurements during phototherapy on uncovered skin gave LoA outside the 50 μmol/L safety margin (Table 3).

After Phototherapy

We pooled 5 studies (648 paired measurements in 555 patients) applicable for analysis after phototherapy on

TABLE 1 Study Characteristics of Included Studies (54 Studies)

Study (y of Publication)	Study Size/Number of Paired Measurements	Gestational Age (wk)	Phototherapy; Covering (Type of Covering)	Type of Transcutaneous Bilirubinometer; Location	Reference Test Method (Serum Bilirubinometer)	RMaximum Time Between Measurements (min)
Shapiro et al (2022)[44]	251 of 326	26–24	Yes, covered (protective eye covering)	JM-105; forehead	Direct spectrophotometry (Reichert UNISTAT)	N/A
Mohamed et al (2022)[20]	130 of 130	>35	No	JM-105; forehead and sternum	Diazo (Architect C8000, Olympus AU400)	<60
Panda et al (2021)[64]	167 of 167	28–37	No	JM-105; sternum	Diazo (N/A)	Simultaneous; not otherwise specified
Ho et al (2021)[51]	40 of 96	Term and preterm; not otherwise specified	Yes, covered (gauze eye mask) and uncovered	JM-103; forehead and sternum	Direct spectrophotometry (APEL BR-5200P)	<5
Cat et al (2021)[21]	105 of 105	>37	No	MBJ-20; forehead and sternum	Direct spectrophotometry (Beckman Coulter AU680)	<10
Khajehei et al (2021)[22]	78 of 78	>35	No	JM-105 and MBJ-20; forehead and sternum	N of A	<30
Jegathesan et al (2021)[23]	296 of 856	24–36	Yes, uncovered	JM-105; forehead and sternum	Direct spectrophotometry (Beckman Coulter AU680)	<15
Gothwal et al (2021)[52]	100 of 300	<37	Yes, covered (opaque eye protector; Ibis Medical)	BiliCare; forehead	Diazo (N of A)	<10
Lucanova et al (2021)[24]	102 of 102	≥37	No	JM-105; forehead, sternum, and abdomen	N of A	<10
Mendoza-Chuctaya et al (2021)[25]	123 of 123	≥37	No	JM-103; forehead and sternum	N of A	<30
Alptekin et al (2021)[26]	78 of 78	≥35	Yes, covered (eye mask and diaper) and uncovered	BiliChek; forehead, sternum, mons pubis, and left gluteal region	Diazo (Roche Diagnostics GmbH)	<10
Maya-Enero et al (2021)[53]	1359 of 1549	N/A	No	JM-105; sternum	Diazo (COBAS INTEGRA 400 plus)	Simultaneous; not otherwise specified
Jeon et al (2020)[27]	384 of 1084	<32–42; not otherwise specified	Yes, uncovered	JM-103; forehead and sternum	Diazo (COBAS c702)	<60
Ying et al (2020)[40]	787 of 787	≥35	No	JM-103; forehead	Diazo (HITACHI 7600)	<90
Yang et al (2019)[41]	108 of 324	>34	Yes, covered (rectangular-shaped eye patch)	BiliChek; forehead	Direct spectrophotometry (APEL BR-501)	<120
Hulzebos et al (2019)[35]	109 of 856	<32	Yes, covered (diaper)	JM-103; hipbone	Diazo (N/A)	<60
Raba et al (2020)[50]	196 of 470	32–37	Yes, covered (disposable diaper) and uncovered	JM-103 and JM-105; sternum and lower back	Direct spectrophotometry (Architect C8000)	<60
Raba et al (2020)[39]	338 of 231	32–37	No	JM-103 and JM-105; sternum	N/A	<60
Costa-Posada et al (2020)[54]	217 of 328	27–42	Yes, covered (opaque photo-reflective aluminum patch; Ohmeda medical) and uncovered	JM-105; sternum	Diazo (N/A)	Simultaneous; not otherwise specified
Castro et al (2019)[55]	42 of 156	≥32	Yes, covered (oval-shaped photo-opaque patch) and uncovered	JM-103; sternum	Direct spectrophotometry (ABL90 FLEX)	<60

TABLE 1 Continued

Study (y of Publication)	Study Size/Number of Paired Measurements	Gestational Age (wk)	Phototherapy; Covering (Type of Covering)	Type of Transcutaneous Bilirubinometer; Location	Reference Test Method (Serum Bilirubinometer)	RMaximum Time Between Measurements (min)
Lee et al (2019)[42]	790 of 235	≥32	No	JM-105; sternum	Diazo (VITROS 5600)	<120
Rohsiswatmo et al (2018)[38]	94 of 282	≤35	Yes, uncovered	JM-103; sternum	Chemical oxidation method (ADVIA Chemistry Total Bilirubin 2)	N/A
Chokemungmeepisarn et al (2018)[36]	214 of 214	≥35	No	BiliCare; Ear pinna	Diazo (COBAS c111)	<30
Ercan et al (2018)[56]	218 of 271	>35	No	JH20-1C; forehead	Diazo (COBAS c501) and direct spectrophotometry (B-105)	<10
Chimhini et al (2018)[65]	283 of 283	28–42	No	JM-103; forehead and sternum	Diazo (Dimension Xpand Plus, Mindray BS-400)	<30
De Luca et al (2017)[66]	60 of 60	<30	Yes, covered (white thick cotton cap)	BiliChek; forehead	Direct spectrophotometry (ABL800 FLEX)	<10
Katayama et al (2017)[67]	125 of 250	≥37	Yes, uncovered	JM-103; sternum	Direct spectrophotometry (N/A)	<60
Olusanya et al (2017)[37]	1011 of 1011	Term and preterm (≥2.5 kg); not otherwise specified	No	BiliChek and JM-103; location N/A	Direct spectrophotometry (Advanced Bilirubin STAT, Model BR2)	<60
Murli et al (2016)[28]	100 of 400	34–41	Yes, covered (photo-opaque patch; BiliEclipse) and uncovered	BiliChek; sternum	Direct spectrophotometry (APEL BR-5100)	N/A
Olusanya et al (2016)[57]	1553 of 2107	≥35	No	BiliChek and JM-103; sternum	Direct spectrophotometry (Advanced Bilirubin STAT, Model BR2)	<60
Radfar et al (2016)[68]	170 of 340	Term and preterm; not otherwise specified	Yes, covered (photo-opaque patch; BiliEclipse) and uncovered	BiliChek; forehead	Direct spectrophotometry (N/A)	<30
Alsaedi (2016)[69]	665 of 665	37–42	No	BiliChek; forehead	Diazo (Dimension Vista, Dimension Flex)	<10
Rylance et al (2014)[45]	128 of 257	<32–42; not otherwise specified	Yes, uncovered	JM-103; forehead and sternum	Diazo (Beckman Synchron CX5 Pro)	N/A
Chawla et al (2014)[29]	256 of 552	<35	No	BiliChek; forehead, sternum, and abdomen	HPLC (N/A)	<30
Kosarat et al (2013)[30]	257 of 294	≥37	No	JM-103; forehead and sternum	Diazo (HITACHI 902)	<30
Romagnoli et al (2012)[31]	630 of 630	>34	No	BiliChek and JM-103; forehead	Direct spectrophotometry (Microbilimeter Twin Beam Plus)	<10
Campbell et al (2011)[70]	430 of 430	>35	No	BiliChek; forehead	Diazo (Beckman Synchron LX20)	<30

TABLE 1 Continued

Study (y of Publication)	Study Size/Number of Paired Measurements	Gestational Age (wk)	Phototherapy; Covering (Type of Covering)	Type of Transcutaneous Bilirubinometer; Location	Reference Test Method (Serum Bilirubinometer)	RMaximum Time Between Measurements (min)
Wickremasinghe et al (2011)[43]	79 of 296	≥36	No	BiliChek; sternum	Diazo (N/A)	<90
Kaynak-Türkmen et al (2011)[32]	54 of 54	≥30	No	BiliChek; forehead	Direct spectrophotometry (APEL BR 5000N Apel) and Diazo (Architect C8000)	<30
Qualter et al (2010)[71]	84 of 84	≥35	No	BiliChek and JM-103; forehead	Diazo (HITACHI)	<30
Bental et al (2009)[58]	628 of 1091	≥35	No	JM-103; forehead and sternum	Direct spectrophotometry (APEL BR-501)	Immediately; not otherwise specified
Zecca et al (2009)[72]	364 of 364	≥29	Yes, covered (photo-opaque patch; BiliEclipse) and uncovered	BiliChek; forehead	Direct spectrophotometry (Microbilimeter Twin Beam Plus)	<10
Schmidt et al (2009)[59]	90 of 131	≤34	No	JM-103; sternum	Diazo (Olympus AU640)	<45
Jangaard et al (2006)[60]	155 of 204	Term and preterm; not otherwise specified	Yes, covered (N/A)	BiliChek; forehead	Direct spectrophotometry (Vitros)	<60
Rodríguez-Capote et al (2009)[73]	154 of 154	>35	No	BiliChek and JM-103; forehead	Direct spectrophotometry (Vitros 950)	<30
Lam et al (2008)[74]	113 of 113	>35	No	JM-103; forehead and sternum	Direct spectrophotometry (Leica UNISTAT)	<5
Sanpavat et al (2007)[61]	196 of 249	<36	No	JM-103; forehead	Direct spectrophotometry (Leica UNISTAT)	<60
De Luca et al (2007)[75]	340 of 340	30–36	No	BiliChek; forehead	Direct spectrophotometry (Microbilimeter Twin Beam Plus)	<10
Ho et al (2006)[76]	997 of 997	>35	No	JM-103; sternum	Direct spectrophotometry (Reichert UNISTAT)	<30
Sanpavat et al (2005)[33]	134 of 154	≥36	No	BiliChek and JM-103; forehead	Direct spectrophotometry (Leica UNISTAT)	<15
Sanpavat et al (2004)[62]	388 of 460	≥36	No	JM-103; forehead	Direct spectrophotometry (Leica UNISTAT	<15
Slusher et al (2004)[77]	127 of 127	N/A	No	BiliChek; forehead	Direct spectrophotometry (Advanced Bilirubin STAT, Model BR2)	Simultaneously; not otherwise specified
Maisels et al (2004)[34]	849 of 849	≥35	No	BiliChek and JM-103; forehead and sternum	Diazo (Dupont Dimension XL, Beckman Synchron LX20)	<60
Bhutani et al (2000)[63]	490 of 1788	35–42	No	BiliChek; forehead	HPLC (N/A)	<30

HPLC, high-performance liquid chromatography; N/A, not applicable.

TABLE 2 Quality Assessment of Included Studies-2

Study (y of Publication)	Risk of Bias			
	Patient Selection	Index Test	Reference Standard	Flow and Timing
Shapiro et al (2022)[44]	+	+	+	?
Mohamed (2022)	+	+	+	+
Panda et al (2021)[64]	+	+	+	+
Ho et al (2021)[51]	?	+	+	+
Cat et al (2021)[21]	+	+	+	+
Khajehei et al (2021)[22]	+	+	?	+
Jegathesan et al (2021)[23]	+	+	+	+
Gothwal et al (2021)[52]	+	+	+	+
Lucanova et al (2021)[24]	+	+	?	+
Mendoza-Chuctaya et al (2021)[25]	+	+	?	+
Alptekin et al (2021)[26]	?	+	+	+
Maya-Enero et al (2021)[53]	+	+	+	+
Jeon et al (2020)[27]	?	+	+	+
Ying et al (2020)[40]	?	+	+	—
Yang et al (2019)[41]	?	+	+	—
Hulzebos et al (2019)[35]	+	+	+	+
Raba et al (2020)[50]	+	+	+	+
Raba et al (2020)[39]	+	+	?	+
Costa-Posada et al (2020)[54]	+	+	+	+
Castro et al (2019)[55]	+	+	+	+
Lee et al (2019)[42]	+	+	+	—
Rohsiswatmo et al (2018)[38]	+	+	—	?
Chokemungmeepisarn et al (2018)[36]	+	+	+	+
Ercan et al (2018)[56]	+	+	+	+
Chimhini et al (2018)[65]	+	+	+	+
De Luca et al (2017)[66]	+	+	+	+
Katayama et al (2017)[67]	?	+	+	+
Olusanya et al (2017)[37]	?	+	+	+
Murli et al (2016)[28]	+	+	+	?
Olusanya et al (2016)[57]	+	+	+	+
Radfar et al (2016)[68]	+	+	+	+
Alsaedi (2016)[69]	+	+	+	+
Rylance et al (2014)[45]	+	+	+	?
Chawla et al (2014)[29]	+	+	+	+
Kosarat et al (2013)[30]	+	+	+	+
Romagnoli et al (2012)[31]	+	+	+	+
Campbell et al (2011)[70]	+	+	+	+
Wickremasinghe et al (2011)[43]	+	+	+	—
Kaynak-Türkmen et al (2011)[32]	?	+	+	+
Qualter et al (2010)[71]	+	+	+	+
Bental et al (2009)[58]	+	+	+	+
Zecca et al (2009)[72]	?	+	+	+
Schmidt et al (2009)[59]	+	+	+	+
Jangaard et al (2006)[60]	+	+	+	+
Rodríguez-Capote et al (2009)[73]	+	+	+	+
Lam et al (2008)[74]	+	+	+	+
Sanpavat et al (2007)[61]	+	+	+	+
De Luca et al (2007)[75]	+	+	+	+
Ho et al (2006)[76]	?	+	+	+
Sanpavat et al (2005)[33]	+	+	+	+
Sanpavat et al (2004)[62]	+	+	+	+
Slusher et al (2004)[77]	+	+	+	+
Maisels et al (2004)[34]	+	+	+	+
Bhutani et al (2000)[63]	+	+	+	+

+, low risk; ?, unclear risk; —, high risk.

TABLE 3 Pooled MDs, SDs, and LoA Between Transcutaneous Bilirubin and Total Serum Bilirubin Measurements; Unit μmol/L (1 mg/dL = 17.1 μmol/L)

	Before PT	During PT, Covered	During PT, Uncovered	After PT, Covered	After PT, Uncovered
Total					
n studies (M)	48 (22 746)	14 (2511)	13 (3703)	5 (684)	2 (142)
MD	2.5	−0.3	−28.6	−34.3	−21.1
SD	20.8	17.6	39.3	26.7	34.4
95% LoA	−38.3 to 43.3	−34.8 to 34.2	−105.7 to 48.5	−86.7 to 18.1	−88.6 to 46.4
Location					
Forehead					
n studies (M)	28 (9662)	9 (1265)	3 (757)	1 (108)	1 (42)
MD	−0.4	6.0	−45.3	5.1	−18.8
SD	23.1	13.7	44.0	24.9	26.2
95% LoA	−45.5 to 44.8	−21.0 to 32.9	−131.6 to 40.9	−43.7 to 53.9	−71.8 to 32.5
Sternum					
n studies (M)	20 (7703)	4 (755)	9 (1475)	3 (284)	1 (100)
MD	19.7	0.8	−23.4	−6.2	−23.9
SD	26.7	34.9	38.7	31.5	44.5
95% LoA	−32.7 to 72.1	−67.7 to 69.3	−99.3 to 52.4	−68.1 to 55.6	−111.2 to 63.3
Gestational age					
≥37 wk					
n studies (M)	13 (3600)	4 (323)	5 (529)	2 (73)	1 (21)
MD	1.8	−2.8	9.3	2.4	−22.2
SD	28.6	24.8	37.9	23.1	20.9
95% LoA	−54.3 to 57.8	−51.4 to 45.9	−64.9 to 83.5	−42.9 to 47.7	−66.7 to 18.8
<37 wk					
n studies (M)	16 (3837)	8 (1105)	7 (2174)	4 (511)	1 (21)
MD	−2.3	−0.7	−18.0	−41.2	−16.3
SD	20.8	13.5	36.8	26.1	31.9
95% LoA	−43.1 to 38.5	−27.2 to 25.8	−90.2 to 54.2	−92.3 to 10.0	−78.7 to 46.2
TcB device					
BiliChek					
n studies (M)	18 (8191)	7 (1176)	4 (812)	2 (208)	1 (100)
MD	−0.7	−1.0	−57.6	6.5	−23.9
SD	21.0	25.5	45.6	29.0	44.5
95% LoA	−42.0 to 40.5	−51.0 to 49.0	−147.0 to 31.9	−50.2 to 63.3	−111.2 to 63.3
JM-105					
n studies (M)	9 (3338)	2 (333)	2 (1552)	0	0
MD	13.2	20.4	−19.6	—	—
SD	26.8	32.9	38.9	—	—
95% LoA	−39.2 to 65.7	−44.2 to 84.9	−95.8 to 56.6	—	—
JM-103					
n studies (M)	20 (8436)	3 (503)	6 (1030)	2 (334)	1 (42)
MD	1.6	−51.1	−22.7	−54.7	−18.81
SD	19.7	31.2	35.5	24.8	26.17
95% LoA	−37.0 to 40.2	−112.3 to 10.1	−92.4 to 47.0	−103.3 to −6.1	−71.82 to 32.49
BiliCare					
n studies (M)	2 (314)	1 (200)	0	0	0
MD	1.3	—	—	—	—
SD	8.0	—	—	—	—
95% LoA	−14.4 to 17.0	—	—	—	—
MBJ-20					
n studies (M)	2 (366)	0	0	0	0
MD	9.5	—	—	—	—
SD	26.2	—	—	—	—
95% LoA	−41.9 to 60.8	—	—	—	—
JH20-1C					
n studies (M)	1 (271)	0	0	0	0
MD	−1.7	—	—	—	—
SD	31.6	—	—	—	—
95% LoA	−63.3 to 60.3	—	—	—	—

M, number of measurements; PT, phototherapy; —, not applicable.

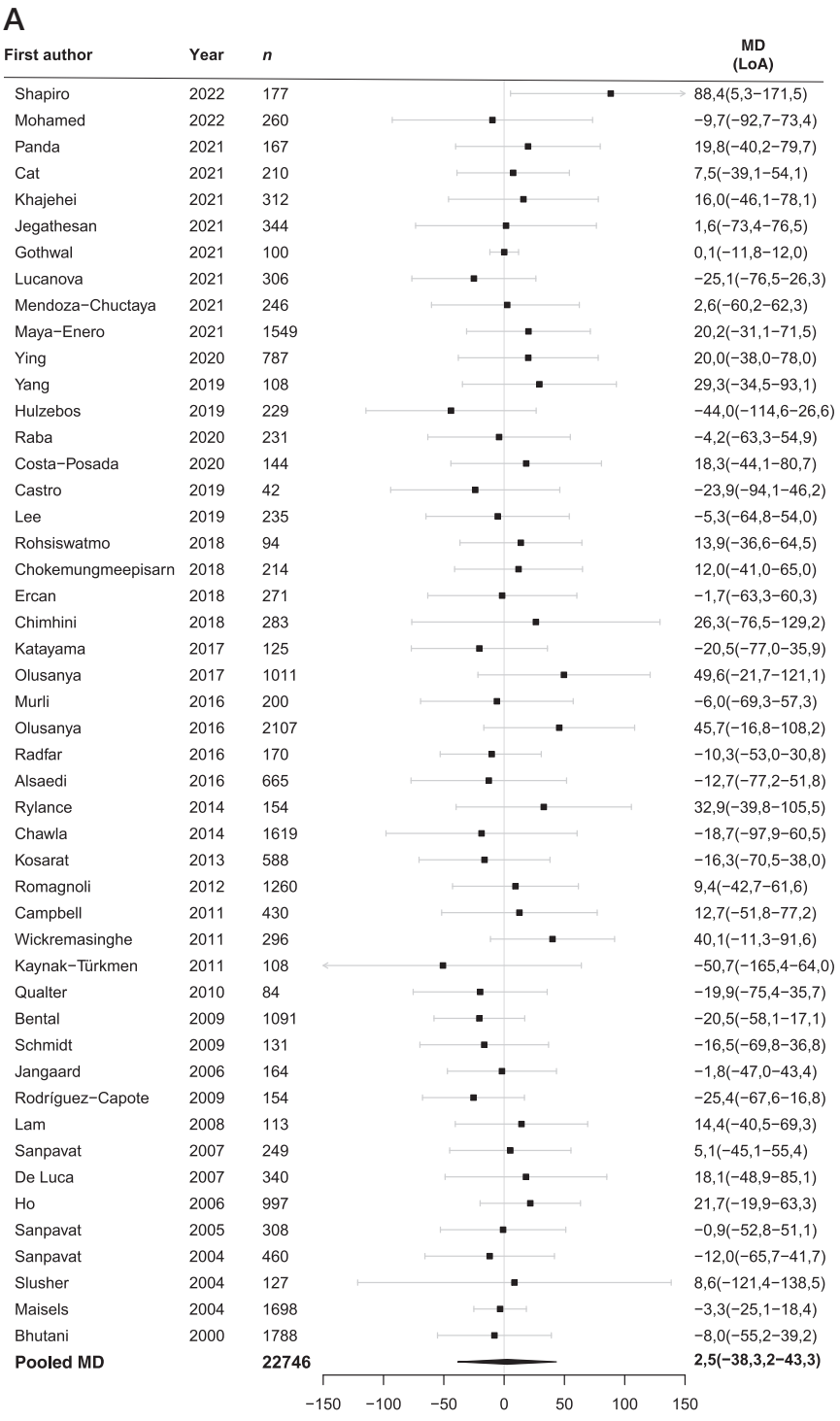
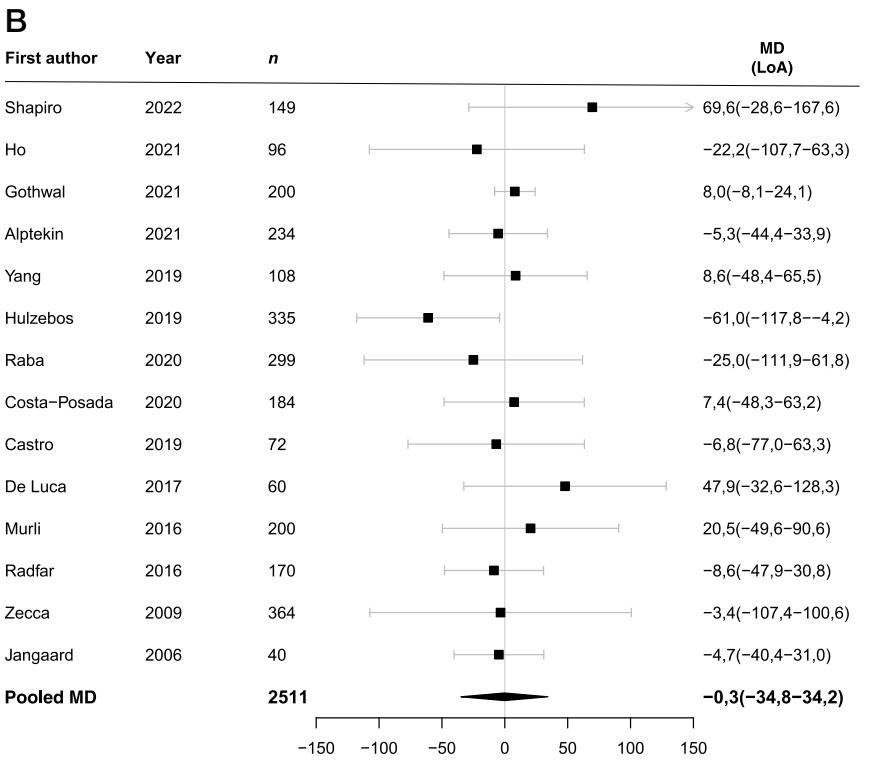


FIGURE 2A

Forest plot before phototherapy. MD TcB − TSB; unit μmol/L (1 mg/dL = 17.1 μmol/L). 2B–C, forest plots during phototherapy on covered skin (B) and during phototherapy on uncovered skin (C). MD TcB − TSB; unit μmol/L (1 mg/dL = 17.1 μmol/L). 2D–E, forest plots after phototherapy on covered skin (D) and after phototherapy on uncovered skin (E). MD TcB − TSB; unit μmol/L (1 mg/dL = 17.1 μmol/L).

covered skin, resulting in a pooled MD of −34.3 μmol/L (SD 26.7 μmol/L; LoA −86.7 to 18.1 μmol/L). In this category, we observed an outlier affecting the results clearly in case of exclusion (MD −1.4 μmol/L; SD 28.7 μmol/L; LoA −54.9 to 57.7 μmol/L).[35] This specific study measured the TcB on the hipbone covered by a diaper.

The 2 studies (142 measurements in 142 patients) applicable for analysis after phototherapy on uncovered



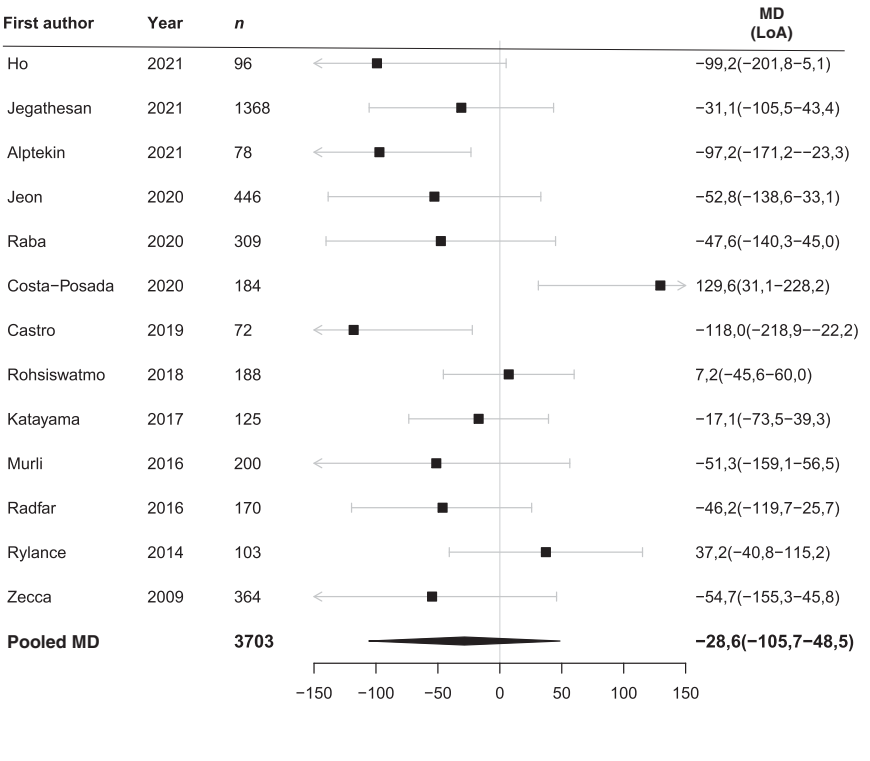


FIGURE 2
Continued

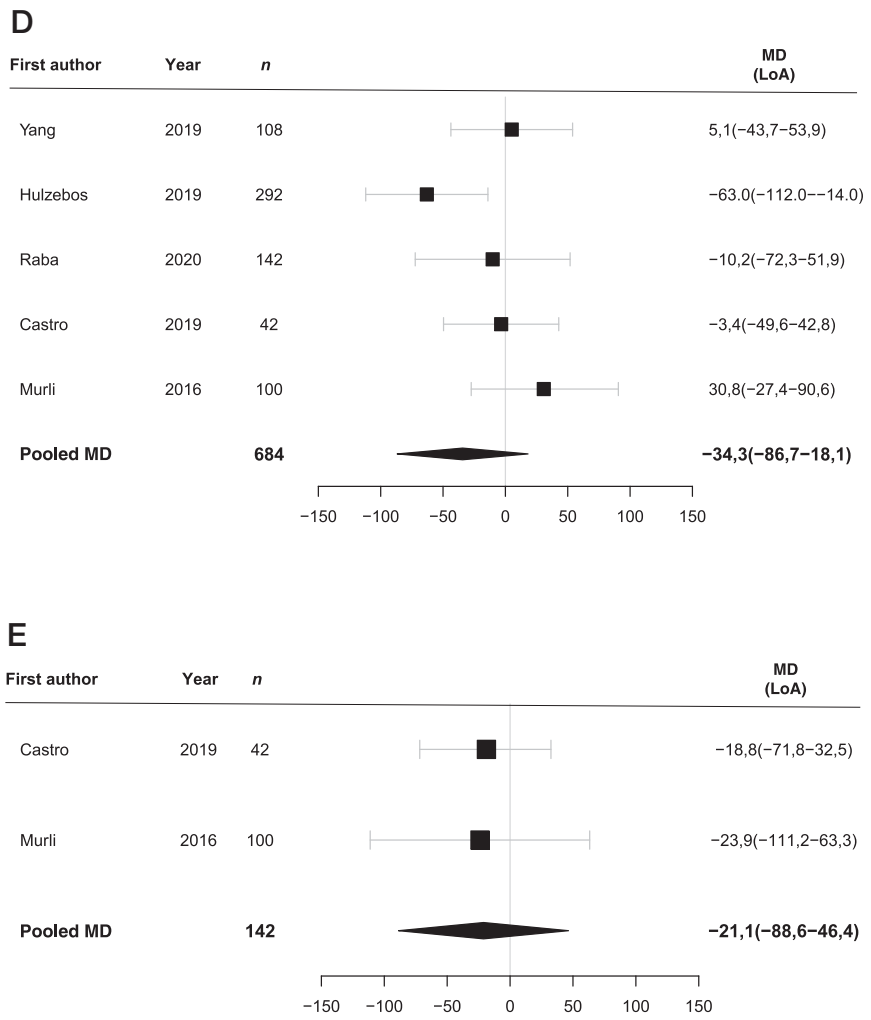


FIGURE 2
Continued

skin revealed a pooled MD of −21.1 μmol/L (SD 34.4 μmol/L; LoA −88.6 to 46.4 μmol/L). All LoA of the different subgroup analyses in this category showed LoA outside the 50 μmol/L margin (Table 3).

All measurements after phototherapy for both covered and uncovered were at least 8 hours after discontinuing phototherapy. Not enough data were available to access the agreement separately for timing after discontinuing phototherapy.

DISCUSSION

This systematic review included 54 studies with >17 000 term and preterm neonates reporting >22 000 paired measurements of TcB and TSB depicted in Bland-Altman plots. The results show good agreement before and during phototherapy, provided that TcB is measured on covered skin. The pooled LoA of ± 40.6 μmol/L, respectively, before and ± 34.5 μmol/L during phototherapy on covered skin are within the safety margin of 50 μmol/L. This safety margin of 50 μmol/L is in accordance with the current guidelines of the American Academy of Pediatrics, where TSB measurements are advised when TcB is within 3 mg/dL (∼50 μmol/L) from the phototherapy threshold.[7]

In contrast, the results after phototherapy on covered skin show that TcB underestimates TSB, with LoA >50 μmol/L. However, the number of studies after phototherapy on covered skin are relatively small, with only 5 studies reporting 648 paired measurements in 555 patients. Sensitivity analysis showed that 1 study acted as outlier with deviating results from the other 4 studies.[35] In this study, TcB was measured on the hipbone, which may explain the lower TcB values compared with measurements on the forehead or sternum because of cephalocaudal progression.[46] The role of the method used for skin covering may also have played a role in the underestimation of TcB in this study in which a diaper was used. We are not aware of studies comparing the effect of different methods of skin covering during

phototherapy on TcB measurements; for example, between a specially designed photo-opaque patch (eg, BiliEclipse) and a diaper. However, Abdulkadir et al researched the irradiance under different kinds of eye protecting during phototherapy and found a difference in shielding from phototherapy with different kinds of material.[47] More studies investigating the agreement between cranial and sternal TcB and TSB measurements using different methods of covering are needed for this purpose. The results during, as well after, phototherapy on uncovered skin show that TcB underestimates TSB. A point to mention is that we did not account for the length of time after discontinuing phototherapy. Time of discontinuing phototherapy may have an influence on the difference between TcB on uncovered skin and TSB measurements. It is assumed that this difference will be negligible after 8 to 18 hours of discontinuing phototherapy.[48–50] Therefore, in several guidelines, the use of TcB measurements after phototherapy is restricted to at least 24 hours after discontinuation phototherapy.[7] Because of lack of studies and original data, we were not able to provide subgroup analysis for this aspect.

Subgroup analysis for location of TcB measurement before phototherapy showed better agreement between TcB and TSB on the forehead compared with the sternum. However, because the sternal TcB measurements tend to overestimate the TSB before phototherapy, the use of sternal TcB measurements is still acceptable and safe at least. We found that TcB is reliable in term, as well as in preterm, infants, with LoA just outside the 50 μmol/L range in term infants and thus better agreement in preterm infants. Concerning the type of TcB device, BiliChek and JM-103 have smaller pooled MDs and SDs compared with JM-105. However, more inclusions are available with BiliChek and JM-103 in comparison with JM-105. For BiliCare, MBJ-20 and JH20-1C, only few studies were available.

Our study represents an up-to-date review of TcB agreements, with TSB using preferred methodology. One of the strengths of this systematic review is the extensive search of studies and the pooling of Bland-Altman statistics. Results of Bland-Altman analysis can easily be translated to the clinical practice and are therefore useful for formulating new policy.

Our study results are difficult to compare with the results of the other already existing systematic reviews of TcB measurements during phototherapy because of different statistical methods used for pooling. As described above, correlation coefficients indicate the strength of a linear relationship and not the agreement of 2 variables. A high correlation does not imply good agreement between 2 variables.

Our systematic review has some limitations. First, our literature search was limited to English, German, and Dutch languages, leading to the exclusions of 9 possible relevant studies. Secondly, several of the included studies have >1 TcB measurement at 1 moment of paired measurement, mostly TcB measurements at different locations or with different kinds of TcB devices compared with 1 serum bilirubin measurement.[20–34] Also, several of the included studies have repeated paired measurements per neonate.[23,28–30,33,35,38,39,44,45,50–63] In earlier literature, it is postulated that TcB values in the higher ranges (above 256 μmol/L [3 mg/dL]) are not reliable.[7] We were not able because of lack of original data to separately assess the agreement in the higher ranges. Furthermore, despite save recommendations in the American Academy of Pediatrics, the influence of the amount of skin melanin and therefore different skin color stays controversial. In our review, we could not address the influence of skin color. Most inclusions were neonates from Caucasic and Asian origin, and most studies with mixed inclusions did not deliver data separately for different skin colors.

In conclusion, this systematic review shows that TcB measurements before and during phototherapy on covered skin show acceptable accuracy compared with TSB measurements in both term and preterm newborns. This suggests that, in addition to the use of TcB for screening of hyperbilirubinemia before the application of phototherapy, the use of TcB may be extended to the use during phototherapy, provided it is measured on covered skin. Evidence of the best method of skin covering does not exist yet, but the use of photo-opaque patches can be recommended. TSB measurements are advised when TcB measurements are above or below but within 50 μmol/L of the phototherapy threshold.[7] The forehead is the preferred location for measurement of TcB; however, the sternum is also safe to use. The use of TcB during phototherapy on uncovered skin is not advised. More studies are needed to evaluate the accuracy of TcB compared with TSB after the application of phototherapy on covered skin.

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ABBREVIATIONS

LoA: limits of agreement
MD: mean difference
TcB: transcutaneous bilirubin
TSB: total serum bilirubin

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