Bilirubin nomograms for identification of neonatal hyperbilirubinemia in healthy term and late-preterm infants: a systematic review and meta-analysis

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Background: **Hyperbilirubinemia occurs in most healthy term and late-preterm infants, and must be monitored to identify those who might develop severe hyperbilirubinemia. Total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) nomograms have been developed and validated to identify neonatal hyperbilirubinemia. This study aimed to review previously published studies and compare the TcB nomograms with the TSB nomogram, and to determine if the former has the same predictive value for significant hyperbilirubinemia as TSB nomogram does.**

Methods: **A predefined search strategy and inclusion criteria were set up. We selected studies assessing the predictive ability of TSB/TcB nomograms to identify significant hyperbilirubinemia in healthy term and late-preterm infants. Two independent reviewers assessed the quality and extracted the data from the included studies. Meta-Disc 1.4 analysis software was used to calculate the pooled sensitivity, specificity, and positive likelihood ratio of TcB/TSB nomograms. A pooled summary of the receiver operating characteristic of the TcB/TSB nomograms was created.**

Results: **After screening 187 publications from electronic database searches and reference lists of eligible articles, we included 14 studies in the systematic review and meta-analysis. Eleven studies were of medium methodological quality. The remaining three studies were of low methodological quality. Seven studies evaluated the TcB nomograms, and seven studies assessed TSB nomograms. There were no differences between the predictive abilities of the TSB and TcB nomograms (the pooled area under curve was 0.819 *vs.* 0.817).**

Conclusions: **This study showed that TcB nomograms had the same predictive value as TSB nomograms, both of which could be used to identify subsequent significant hyperbilirubinemia. But this result should be interpreted cautiously because some methodological limitations of these included studies were identified in this review.**

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Key words: **hyperbilirubinemia;**
newborn;
systematic review;
transcutaneous bilirubin

Review article

Introduction

Hyperbilirubinemia occurs in most healthy newborn infants, and must be monitored and promptly treated to prevent bilirubin encephalopathy.[1] Recently, much attention has been paid to the damage caused by bilirubin encephalopathy which occurs in all countries, even in westernized countries.[2] In developing countries with emerging medical systems, the problem is worsening. In China, 348 cases of bilirubin encephalopathy were reported from 28 hospitals from January to December in 2009.[3] Therefore, identification of newborn infants at risk of developing significant hyperbilirubinemia and prevention of bilirubin encephalopathy remain a high priority among public health institutions.

The American Academy of Pediatrics (AAP) is highly concerned about the continuing appearance of bilirubin encephalopathy. Comprehensive guidelines to screen and identify newborn infants at risk of hyperbilirubinemia, and to treat those who develop hyperbilirubinemia, were implemented by the AAP in 2004.[4] A 2009 update with clarifications of the 2004

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AAP guideline recommended measurement of total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) in a predischarge newborn population to identify severe hyperbilirubinemia.[5] Universal implementation of this strategy in the US has improved outcomes of healthy newborns discharged early, which represents a valuable method to assess the risk of subsequent severe hyperbilirubinemia.[6]

However, measurement of TSB remains an invasive, stressful and time-consuming procedure. Measurements of TcB are less time-consuming and can be used to screen for the need of blood sampling for serum bilirubin level, and reduce the need to measure TSB.[7] The values of TcB after birth have also been plotted on an hour-specific TcB nomogram to predict severe hyperbilirubinemia in term and late-preterm infants.[8] The availability of TcB estimation has made it possible to study the dynamic changes in bilirubin levels noninvasively; thus, TcB nomograms are being used with increasing frequency. Researchers from many countries have developed TcB hour-specific nomograms using their own race/ethnicity data for TcB levels.[9,10] However, it is not clear whether the TcB nomogram is as accurate as the TSB nomogram, which may affect its predictive ability.[11] TSB and TcB nomograms have been developed and validated to identify neonatal hyperbilirubinemia in some studies.[12] This study aimed to review previously published studies and compare the TcB nomogram with the TSB nomogram, and to determine if the former has the same predictive value for significant hyperbilirubinemia as TSB nomogram does.

Methods

Search strategy

An electronic search of Medline, EMBASE, the Chinese Biomedical Literature Database, the Chinese National Knowledge Infrastructure database, and the Cochrane Library for any literature from January 1980 to July 2013 was performed. This search was limited to any study that developed and evaluated an hour-specific (TcB or TSB) bilirubin nomogram to identify significant hyperbilirubinemia in healthy term and late-preterm infants [gestational age (GA) ≥35 weeks]. The search key words were "jaundice" or "hyperbilirubinemia" combined with the terms "transcutaneous bilirubin", "hour-specific bilirubin", "nomogram", "curve" and "prediction", "diagnosis", "sensitivity", "specificity" and "newborn", "near term infant", and "late preterm infant". We used the "related articles" option and consulted the references of evaluated articles. No language restrictions were applied.

Study selection

Two investigators independently screened the results of the electronic searches to select potentially relevant studies. Discrepancies were resolved through consensus, and a third blinded investigator was consulted, when required, to resolve any discrepancies. The inclusion criteria were as follows: 1) the study population was healthy term or late-preterm newborn infants, the study population excluded all sick newborn infants who were admitted to the intensive care unit and those who required phototherapy before discharge; 2) TSB or TcB levels after birth in healthy term and late-preterm neonates were measured and an hour-specific TSB or TcB nomogram was developed; 3) the risk zone to identify neonatal hyperbilirubinemia was classified on the basis of different percentile values of TSB or TcB, four risk zones (high, high-intermediate, low-intermediate, low risk zone); 4) the predictive ability of TcB/TSB nomograms to identify significant hyperbilirubinemia was evaluated, the receiver operating characteristic (ROC) curves were constructed, and the area under the curve (AUC) of diagnostic accuracy could be calculated. The following criteria were applied to exclude inappropriate studies: 1) TcB/TSB nomograms were constructed, but their predictive abilities were not evaluated; 2) the AUC of diagnostic accuracy of the TcB/TSB nomograms could not be calculated; 3) if the same institution reported two or more studies for the same population, the study showing the larger number of patients was included.

Data extraction and assessment of study quality

Two independent reviewers extracted the study designs, total participants and entry criteria, the risk zone of the nomogram, diagnostic criterion for significant hyperbilirubinemia and AUCs from the included studies. A quality assessment scale was adopted, which was based on the criteria proposed by Strengthening the Reporting of Observational Studies in Epidemiology[13] and Tooth et al[14] to assess observational studies. Briefly, we assessed the quality of all included studies in accordance with the following items: study design, representativeness of target population, sample selection, sample size, included proportion of cohort samples, reasons for excluding samples, development and validation of nomograms, diagnostic criteria (significant hyperbilirubinemia), combining TSB/TcB nomograms and clinical risk factors, and follow-up. According to the score achieved (from 0 to 18), studies were classified as high (>14), medium (10-14) or low (<10) quality. Two reviewers independently assessed the quality and resolved differences through discussion. Assessment of multiple systematic reviews (AMSTAR) was used to assess the Kappa (inter-rater reliability),

which measures the methodological quality of a systematic review. A Kappa higher than 0.8 indicated a high inter-rate reliability.[15]

Statistical analysis

The diagnostic sensitivities and specificities for significant hyperbilirubinemia using TcB/TSB nomograms in the 40th, 75th and 95th percentile were extracted. The statistical pooling of sensitivity, specificity, and positive likelihood ratio (PLR) was done with the DerSimonian Laird method (random effects meta-analysis model) using Meta-Disc 1.4 analysis software (Madrid, Spain). Ninety-five percent confidence intervals (95% CIs) were calculated. Additionally, we created a summary ROC of the TcB/TSB nomograms in the 40th, 75th and 95th percentile using Meta-Disc 1.4. If a meta-analysis was inappropriate, data were summarized for each study.

Results

Search and selection results

A total of 187 publications were identified from electronic database searches and reference lists of eligible articles. Upon reviewing the titles and abstracts, 164 publications were excluded because they did not contain data on the predictive ability of TcB/TSB nomograms to identify significant hyperbilirubinemia. Twenty-three full-text articles were reviewed in detail.[8-10,16-35]

Description of the excluded and included studies

Nine studies[8,9,16-22] from seven countries were excluded based on the reasons listed in Fig. 1. The characteristics of the excluded studies are summarized in Table 1. Finally, 14 eligible studies[10,23-35] were included for the systematic review and meta-analysis (Fig. 1). Eight studies[8,9,16-21] had developed the TcB nomogram using the BiliCheck or JM-103 bilirubinometer based on their own race/ethnicity data for TcB levels; only one study[22] validated the previously constructed TSB nomogram by Bhutani. Most of the studies (55.6%) were excluded because the diagnostic accuracy of the constructed TcB nomogram was not assessed.

Table 2 provides descriptive detail for the 14 studies that met the inclusion criteria for the systematic review and meta-analysis.[10,23-35] These studies were from six countries: India, Israel, China, Italy, USA, and Turkey. Seven of these studies evaluated the diagnostic accuracy using the TcB nomogram;[23,25-30] three nomograms were constructed using the JM-103 bilirubinometer,[23,26,28] and four studies[25,27,29,30] used the BiliCheck bilirubinometer. The diagnostic AUC values of the TcB nomograms ranged from 0.720 to 0.971. The remaining seven studies[10,24,31-35] assessed the diagnostic accuracy using the TSB nomogram; the diagnostic AUC values ranged from 0.731 to 0.931 (Table 2).

Quality assessment of the included studies

Twelve included studies[10,23-29,31-34] developed TSB/TcB nomograms based on the values of TSB or TcB at one center, which could not represent the entire national target population. The sample sizes of eight studies[10,25-27,29,31,33,34] were less than 1000 neonates; only three studies[23,28,32] had more than 5000 in the study population. Only five studies[23,30,33-35] developed and validated a nomogram from a different study group using their own race/ethnicity data; the remaining nine studies[10,24-29,31,32] developed and validated a nomogram from the same study group. Only five studies[23,29,32-34] considered that the clinical risk factors that could improve the predictive accuracy of TSB/TcB nomogram. With these limitations, no study scored more than 14, which is necessary to be considered of high methodological quality. Eleven studies[10,23-25,27-30,33-35] received scores between 10 and 14, and were considered to be of medium methodological quality. The remaining three studies[26,31,32] received scores of

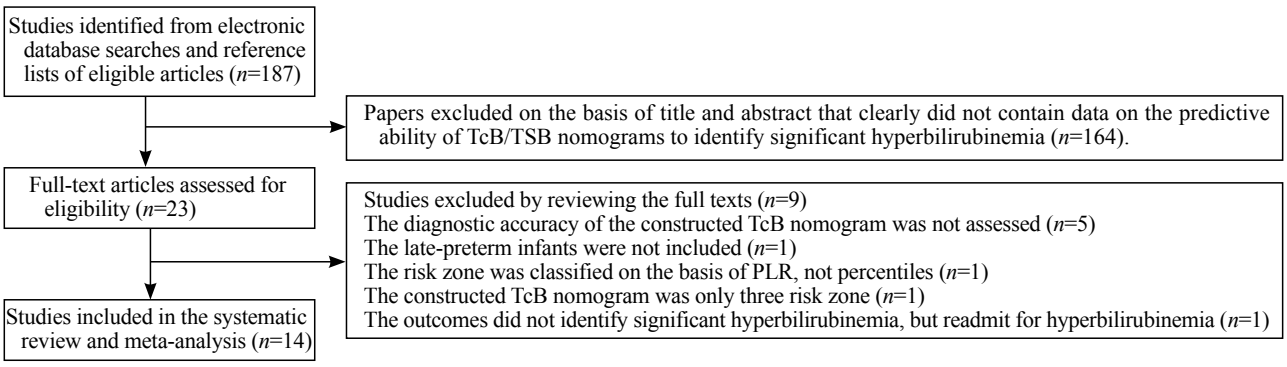

Fig. 1. Flow chart of the article screening and selection process. TcB: transcutaneous bilirubin; TSB: total serum bilirubin; PLR: positive likelihood ratio.

Table 1. Characteristics of the studies excluded from the systematic review

Study	Country	Study design	Total participants and entry criteria	Risk zone of nomogram	Reason for studies excluded from the systematic review
Sanpavat, 2005[16]	Thailand	One center, development and validation of a TcB nomogram using BiliCheck bilirubinometer	392, healthy neonates (GA ≥37 wk)	10th, 25th, 50th, 75th, 85th, 90th, and 95th percentiles	Late preterm infants were not included
Varvarigou, 2009[8]	Greece	One center, development and validation of a TcB nomogram using BiliCheck bilirubinometer	2039, healthy neonates (GA ≥35 wk)	PLR	The risk zone was classified on the basis of PLR, not percentiles
Engle, 2009[17]	USA	One center, development of a TcB nomogram using JM-103 bilirubinometer	2005, healthy neonates (GA ≥35 wk)	5th, 25th, 50th, 75th and 95th percentiles	The diagnostic accuracy of the constructed TcB nomogram was not assessed
Fouzas, 2010[18]	Greece	One center, development of a TcB nomogram using BiliCheck bilirubinometer	793, healthy late preterm neonates (GA ≥35 wk, and <37 wk)	5th, 25th, 50th, 75th and 95th percentiles	The diagnostic accuracy of the constructed TcB nomogram was not assessed
Romagnoli, 2010[19]	Italy	One center, development of a TcB nomogram using BiliCheck bilirubinometer	926, healthy neonates (GA ≥35 wk)	50th, 75th, and 95th percentiles	The diagnostic accuracy of the 50th and 95th percentiles was not assessed
Gonçalves, 2011[20]	Portugal	One center, development of a TcB nomogram using BiliCheck bilirubinometer	463, healthy neonates (GA ≥35 wk)	75th, and 95th percentiles	The constructed TcB nomogram was only three risk zone
Mantagou, 2012[21]	Greece	One center, development of a TcB nomogram using BiliCheck bilirubinometer	419, healthy neonates (GA ≥35 wk)	5th, 10th, 50th, 90th and 95th percentiles	The diagnostic accuracy of the constructed TcB nomogram was not assessed
Bromiker, 2012[22]	Israel	One center, validation of a previously constructed TSB nomogram by Bhutani[1]	25 439, healthy neonates (GA ≥35 wk)	40th, 75th, and 95th percentiles	The outcomes did not identify significant hyperbilirubinemia, but readmit for hyperbilirubinemia
Kuboi, 2013[9]	Japan	One center, development of a TcB nomogram using JM-103 bilirubinometer	181, healthy neonates (GA ≥36 wk)	2.5th, 50th and 97.5th percentiles	The diagnostic accuracy of the constructed TcB nomogram was not assessed

TcB: transcutaneous bilirubin; TSB: total serum bilirubin; GA: gestational age; PLR: positive likelihood ratio.

<10 and were considered to be of low methodological quality. The methodological quality of the systematic review as assessed by AMSTAR, showed a kappa score of 0.82 indicating a high inter-rater reliability.

Meta-analysis

Based on the 40th, 75th, and 95th percentiles values, we pooled the data and assessed the diagnostic accuracy of the TSB/TcB nomograms. The sensitivity, specificity, PLR and AUC values are shown in Table 3. The summary PLR of the TcB nomograms increased gradually (1.67 for the 40th percentile; 3.61 for the 75th percentile; and 8.46 for the 95th percentile). The summary PLR of the TSB nomograms also increased gradually (1.76 for the 40th percentile; 3.34 for the 75th percentile; and 11.46 for the 95th percentile).

The summary AUC that was used to assess the accuracy of the 40th, 75th and 95th percentile is presented in Table 3. The AUC of the TcB nomograms increased gradually (0.512 for the 40th percentile; 0.864 for the 75th percentile; and 0.925 for the 95th percentile). The AUC of the TSB nomograms also increased gradually (0.591 for the 40th percentile; 0.875 for the 75th percentile; and 0.931 for the 95th percentile). Fig. 2 shows the comparison of the summary ROC curves between TcB and TSB nomograms. We found no difference between the predictive ability of summary TSB and summary TcB nomograms (0.819 *vs.* 0.817).

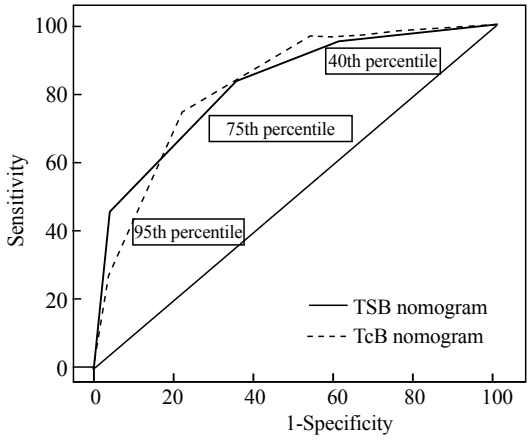

Fig. 2. Summary of the ROC curves for predicting significant hyperbilirubinemia using hour-specific TSB/TcB nomograms from the literature. ROC: receiver operating characteristic; TcB: transcutaneous bilirubin; TSB: total serum bilirubin.

Discussion

The first hour-specific bilirubin nomogram based on TSB of healthy term and late-preterm infants was established by Bhutani et al[24] in 1999. The nomogram could recognize infants at risk of developing significant hyperbilirubinemia. The AUC was 0.931. They found a steady and significant decline in readmission for significant hyperbilirubinemia (0.55%) after initiating the TSB nomogram in 2001 to 2003 compared with that in 1994 (1.4%).[37] The incidence of exchange transfusion following failure of intensive phototherapy

Table 2. Characteristics of the studies included in the systematic review

Study	Country	Study design	Total participants and entry criteria	Risk zone of nomogram	Diagnostic criteria (significant hyperbilirubinemia)	Diagnostic accuracy (AUC)
TcB nomogram						
Maisels, 2009[23]	USA	One center, validation of a previously constructed TcB nomogram using JM-103 bilirubinometer[22]	11 456, healthy neonates (GA≥35 wk)	50th, 75th, and 95th percentiles	Above the 95th percentile on the Bhutani nomogram[23]	0.766
Dalal, 2009[25]	India	One center, development and validation of a TcB nomogram using BiliCheck bilirubinometer	322, healthy neonates (GA≥35 wk)	40th, 75th, and 95th percentiles	AAP guidelines (2004)[1]	0.870
Bental, 2009[26]	Israel	One center, development and validation of a TcB nomogram using JM-103 bilirubinometer	767, healthy neonates (GA≥35 wk)	40th, 75th, and 95th percentiles	TSB>13 mg/dL	0.971
Mishra, 2010[27]	India	One center, development and validation of a TcB nomogram using BiliCheck bilirubinometer	679, healthy neonates (GA≥35 wk)	25th, 50th, 75th, 90th and 97th percentiles	AAP guidelines (2004)	0.812
Yu, 2011[28]	China	One center, development and validation of a TcB nomogram using JM-103 bilirubinometer	6035, healthy neonates (GA≥35 wk)	40th, 75th, and 95th percentiles	AAP guidelines (2004)	0.920
Kaur, 2012[29]	India	One center, development and validation of a TcB nomogram using BiliCheck bilirubinometer	929, healthy neonates (GA≥35 wk)	40th, 75th, and 95th percentiles	AAP guidelines (2004)	0.720
Romagnoli, 2012[30]	Italy	Five centers, validation of a previously constructed TcB nomogram using BiliCheck bilirubinometer[30]	2087, healthy neonates (GA≥ 35 weeks)	50th, 75th, and 95th percentiles	AAP guidelines (2004)	0.883
TSB nomogram						
Bhutani, 1999[24]	USA	One center, development and validation of a TSB nomogram using TSB values	2840, healthy neonates (GA≥35 weeks)	40th, 75th, and 95th percentiles	Above the 95th percentile on the nomogram	0.931
Sarici, 2004[31]	Turkey	One center, development and validation of a TSB nomogram using TSB values	156, healthy neonates (GA≥35 weeks)	5th, 30th, 60th and 95th percentiles	AAP guidelines (1994)[36]	0.798
Newman, 2005[32]	USA	One center, validation of a previously constructed TSB nomogram by Bhutani[23]	5706, healthy neonates (GA≥36 weeks)	40th, 75th, and 95th percentiles	TSB>20 mg/dL	0.836
Keren, 2005[33]	USA	One center, validation of a previously constructed TSB nomogram by Bhutani[23]	899, healthy neonates (GA≥35 weeks)	40th, 75th, and 95th percentiles	Above the 95th percentile on the Bhutani nomogram[23]	0.830
Keren, 2008[34]	USA	One center, validation of a previously constructed TSB nomogram by Bhutani[23]	750, healthy neonates (GA≥35 weeks)	40th, 75th, and 95th percentiles	AAP guidelines (2004)	0.880
Romagnoli, 2012[35]	Italy	Five centers, development and validation of a TSB nomogram using TSB values	2167, healthy neonates (GA≥35 weeks)	50th, 75th, and 90th percentiles	AAP guidelines (2004)	0.923
Pathak, 2013[10]	India	One center, development and validation of a TSB nomogram using TSB values	928, healthy neonates (GA≥35 weeks)	40th, 75th, and 95th percentiles	AAP guidelines (2004)	0.731

AUC: area under the curve; TcB: transcutaneous bilirubin; TSB: total serum bilirubin; GA: gestational age; AAP: American Academy of Pediatrics.

Table 3. Summary of the predictive abilities of percentile values of predischarge TcB/TSB for subsequent significant hyperbilirubinemia

Test methods	Summary sensitivity (95% CI, %)	Summary specificity (95% CI, %)	Summary PLR (95% CI)	Summary AUC (SE)
95 th percentile				
TSB nomogram[24,31,33,34]	45.5 (39.8, 51.2)	95.9 (95.2, 96.5)	11.46 (8.68, 15.09)	0.931 (0.042)
TcB nomogram[23,25,28,29]	26.9 (24.0, 29.9)	95.8 (95.5, 96.1)	8.46 (7.25, 9.88)	0.925 (0.044)
75 th percentile				
TSB nomogram[10,24,32-35]	82.8 (80.0, 85.3)	65.3 (64.5, 66.1)	3.34 (2.00, 5.57)	0.875 (0.041)
TcB nomogram[23,25-30]	74.3 (71.5, 76.9)	77.5 (76.9, 78.0)	3.61 (3.07, 4.25)	0.864 (0.015)
40 th percentile				
TSB nomogram[10,24,32,33,35]	94.8 (92.9, 96.3)	38.8 (37.9, 39.6)	1.76 (1.21, 2.55)	0.591 (0.063)
TcB nomogram[25,28,29]	96.1 (94.4, 97.3)	45.7 (44.4, 46.9)	1.67 (1.40, 1.90)	0.512 (0.087)

CI: confidence interval; AUC: area under the curve; PLR: positive likelihood ratio; SE: standard error; TcB: transcutaneous bilirubin; TSB: total serum bilirubin.

also decreased to 1:11 995 in 2001 to 2003, compared with 1:1827 in 1990 to 2000.[37] Given the outstanding predictive ability of the TSB nomogram, its was widely accepted in clinical practice and is a crucial element of the clinical guidelines published by the AAP.[4]

The Bhutani-based nomogram was used and validated by some studies in their own hospitals.[32-34] These results showed that the AUC ranged from 0.830 to 0.880, which was lower than the value reported by Bhutani (0.931). This caused the use of the Bhutani

nomogram as a screening tool to be questioned; however, the data were generated in a retrospective study that included newborn infants from a single urban Pennsylvanian hospital, and the demographic, racial, genetic and environmental features of that population may not adequately represent other newborn populations.[11] Romagnoli et al[35] developed and validated a TSB nomogram based on newborn infants in their own region, which showed the same predictive ability as the Bhutani-based nomogram; the AUC was 0.923. We identified seven studies[10,24,31-35] that assessed diagnostic accuracy using the TSB nomogram; the diagnostic AUC values ranged from 0.731 to 0.931. The pooled AUC was 0.819. The summary result from the literature showed that a TSB nomogram was a simple and accurate method that identified subsequent significant hyperbilirubinemia.

However, measuring TSB is an invasive procedure that involves pain, neonatal stress and risk of infection. A noninvasive determination of TcB seems to be advantageous and suitable for universal neonatal screening.[38] The new-generation, noninvasive, TcB-measuring devices (BiliCheck™ and JM-103) showed a good correlation with TSB (BiliCheck™ was 0.8212, JM-103 was 0.8686).[39] In this study, we identified seven studies[23,25-30] that assessed diagnostic accuracy using the TcB nomogram. Three nomograms were constructed using the JM-103 bilirubinometer and four studies used the BiliCheck bilirubinometer; the diagnostic AUC ranged from 0.766 to 0.971. The pooled AUC was 0.819, which was not significantly different to the summary TSB nomogram (0.817). The result showed that TcB nomograms were just as efficient as TSB nomograms for identifying subsequent significant hyperbilirubinemia.

The study has some limitations. Firstly, there are many countries (such as the USA, Greece, Italy, and Japan) which have developed TcB nomograms using their own race/ethnicity data for TcB levels; however, these nomograms are still not validated and were excluded from the systematic review.[9,16-19,21] We were unable to assess their predictive ability. Secondly, twelve included studies[10,23-29,31-34] developed TSB/TcB nomograms based on the values of TSB or TcB in one center, which could not represent the entire national target population. The relative limitations of previously constructed TSB/TcB nomograms have prompted us to carry out a multicenter study (ClinicalTrials.gov Identifier: NCT01763632), in which 17 hospitals in China will participate, to develop an hour-specific TcB nomogram from January to December 2013. Thirdly, combining the TcB nomogram with other clinical risk factors, such as GA and exclusive breastfeeding, could improve the prediction of subsequent hyperbilirubinemia. One included study evaluated the predictive performance of the predischarge bilirubin risk zone (AUC=0.88); however, combined clinical risk factors (GA, and percentage of weight loss per day over the first 2 days) showed better accuracy (AUC=0.96).[34] Nine of the previously constructed TSB/TcB nomograms[10,24-29,31,32] did not assess the combination; therefore, we could not perform sub-analysis of the data. Fourthly, theoretically, a predictive nomogram should be developed in one sample and validated in another; the after-effect evaluation of the constructed nomogram is very important for future clinical application. However, only five studies[23,30,33-35] developed and validated a nomogram from a different study group using their own race/ethnicity data; the remaining nine studies[10,24-29,31,32] developed and validated a nomogram from the same study group. Fifthly, the study subjects were healthy term and late-preterm infants, which represent a large group of populations. Only in our hospital, where there are 15 000 healthy term and late-preterm infants born every year, the sample size was large. The sample sizes of eight included studies[10,25-27,29,31,33,34] were less than 1000 neonates; only three studies[23,28,32] had more than 5000 in the study population. Most of the constructed TSB/TcBs could not represent the entire national target population. Given these limitations, none of the included studies were considered as being of high methodological quality. Eleven studies (78.6%)[10,23-25,27-30,33-35] were considered to be of medium methodological quality. Sixthly, sources of bias in any meta-analysis are the selection and heterogeneity of the included studies. In this regard, a specific limitation of our systematic review and meta-analysis is related to the difficulty of combining studies that used different medical system (middle-income, developed), ethnicity and social background, and used different criteria of severe hyperbilirubinemia in the 2 groups; 5 of 7 AAP guideline (2004) in TcB group and 3 of 7 in TSB group. This is related directly to the lack of consensus about the criteria of severe hyperbilirubinemia in different countries.

Conclusions

This systematic review showed that a TcB nomogram has the same predictive value as a TSB nomogram, both of which could be used to identify subsequent significant hyperbilirubinemia. However, the included studies indicted some methodological limitations and should be interpreted cautiously, further studies are necessary to develop and validate an hour-specific nomogram in different study groups, using their own race/ethnicity data. The study group should represent the entire national target population. Combining TSB/

TcB nomograms with clinical risk factors (such as GA, exclusive breastfeeding, cephalhematoma, significant bruising or previous sibling with jaundice) should also be evaluated.

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Contributors: Yu ZB was responsible for research design, data analysis, manuscript writing and revision. Han SP and Chen C assisted in completing the analysis interpretation.

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