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A systematic review of global clinical practice guidelines for neonatal hyperbilirubinemia

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Abstract

Objective: Jaundice is one of the most common clinical symptoms in newborns. To improve patient outcomes, evidence-based and implementable guidelines were required. In this study, we systematically assessed the quality of guidelines by using the AGREE-II instrument and summarized the specific recommendations of neonatal hyperbilirubinemia, aiming to provided suggestions for guideline development in the future.

Methods: We searched for relevant studies of Pubmed, Embase, Medline and guideline databases on April 10th 2020. The studies were screened by two independent reviewers according to our inclusion criteria. Two reviewers independently extracted descriptive data. Four appraisers assessed the guidelines using the AGREE-II instrument.

Results: Our systematic review appraised 12 clinical practice guidelines for the diagnosis and management of neonatal hyperbilirubinemia. The 12 guidelines achieved an average score from 36% to 89%. The guidelines received the highest scores in clarity of presentation and lowest scores for rigour of development. Most recommendations of diagnosis were relatively consistent, while inconsistencies still existed in the risk factors, initiating threshold of treatment and pharmacotherapy.

Conclusions: Our study revealed that current guidelines varied in quality of developing process and inconsistent existed in recommendations despite some similarities. Future guidelines should pay more attention to the quality of methodologies in guideline development and more qualified evidence was needed to standardize the initiating threshold of treatment for neonatal hyperbilirubinemia.

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Conflict of Interest: All authors have no conflicts of interest to disclose.

Data availability: All data relevant to the study are included in the article.

Patient and Public Involvement Statement: It was not possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research

Article Summary

Strengths and limitations of this study:

- This study is the first English systematic appraisal of guidelines targeted to neonates with jaundice.
- The strengths also included the validated AGREE II instrument used and four independent reviewers to minimize subjective bias.
- A Chinese-language guideline by Chinese Pediatric society were appraised.
- The AGREE-II was used to evaluate guidelines with less attention to detailed recommendations.
- We only assessed guidelines through reported literature without other ways like contacting guidelines developers.

Introduction

Neonatal jaundice, with the elevation of total serum bilirubin (TSB), is one of the most common clinical symptoms in newborns, especially in preterm infants. Jaundice affected at least 60% of full-term and 80% of preterm neonates[1], suggesting that about one tenth newborn babies were likely to develop hyperbilirubinemia [2]. Additionally, neonatal hyperbilirubinemia accounted for 1309.3 deaths per 100,000 livebirths and was the seventh cause globally among neonatal deaths in the first week of life[3]. Effective and timely treatment with photography or exchange transfusion can decrease the occurrence of neurologic dysfunction.

Clinical practice guidelines aim at helping people to make clinical, policy-related and system-related decisions[4]. Evidence-based, timely and implementable guidelines are as bridges between research and clinical practice. They enhance high-quality care and consequently improve overall patient outcomes[5] [6]. Although several organizations from different regions have developed clinical practice guidelines, they may vary widely in quality. Moreover, the criteria for the diagnosis and treatment in published guidelines vary between regions and countries.

The Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument is a tool that assesses the methodological rigour and transparency in which a guideline is developed[7]. In this study, we systematically reviewed and assessed the quality of guidelines on neonatal hyperbilirubinemia by using the AGREE-II instrument, aiming to provided suggestions for guideline development in the future.

Method

Selection criteria

We included the clinical practice guidelines for the diagnosis and management of hyperbilirubinemia in the newborn infants. The guidelines were included if they followed the criteria: (1) published in English or Chinese; (2) based on systematic evidence synthesis and containing specific statements to guide decisions about hyperbilirubinemia; (3) including recommendations of diagnosis and treatment of neonatal hyperbilirubinemia; (4) published between 2000 and 2020, and only the most recent editions of updated guidelines was considered.

Search strategy

A systematic literature search was performed in April 10th 2020. We searched for relevant studies of the following databases: Pubmed, Embase, Medline. In addition, we searched following guideline database and website of organization: the Guidelines International Network (GIN), the National Health Service (NHS) Evidence website, the National Institute for Health and Care Excellence (NICE) website, the Scottish Intercollegiate Guidelines Network (SIGN) website, the Turning Research Into Practice Database (TRIP) and the Wan fang Database. The titles and abstracts of searched citations were screened by two independent reviewers（MZ, YH）. Any

discrepancies between the reviewers were resolved by discussion. The detail searching strategy of Pubmed was shown in the supplementary material.

Guideline characteristic

Two independent reviewers (MZ, YH) extracted general characteristics of included guidelines: country, founding organization, year of publication or updating status, method of evidence identification and funding.

Appraisal of guideline quality

Four appraisers (MZ, YH, WXL, ZC) independently assessed the selected guidelines using the AGREE-II instrument. AGREE II is an international, validated and rigorously developed tool to evaluate the quality of clinical practice guidelines and consensus statements[8]. The AGREE II consists of 23 key items organized within 6 domains (Scope and Purpose, Stakeholder Involvement, Rigour of Development, Clarity of Presentation Applicability, Editorial Independence) followed by 2 global rating items (Overall Assessment). Each domain points to an unique dimension of guideline quality[9]. Each of the AGREE II items are rated on a 7-point scale (1–strongly disagree to 7–strongly agree). Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain[9]. The score for each domain of each document is calculated as follows: (obtained score−minimal possible score)/ (maximal possible score - minimal possible score)[7]. All reviewers had been trained online though the AGREE training tools. Every discrepancy over 3 points differences of score would be discussed in consensus meeting.

Analysis

We extracted descriptive data from guideline recommendations to identify consistencies and discrepancies. Then, the recommendations were summarized according to different items which related to diagnosis and treatment strategies of neonatal hyperbilirubinemia, such as the test for early prediction and diagnosis of neonatal jaundice, the timing to start phototherapy and exchange transfusion for neonatal hyperbilirubinemia, the recommendation of drug using, the criterion for discharge and timing or frequency of follow-up.

Result

Search result

Figure 1 showed the process by which we searched and selected the guidelines. The systematic search retrieved 725 records, of which we excluded 701 after deleting duplicates and reviewing titles and abstracts because of not meeting eligibility criteria. Consequently, after the full-text evaluation of remaining records, 12 CPGs were excluded for the following reasons: not in English or Chinese, not original guidelines, not clinical practice guidelines or consensus. Ultimately, we included twelve clinical practice guidelines from twelve different national or regional organizations.

General characteristics of guidelines

Table 1 and 2 shows the summary of general characteristics of the included clinical practice guidelines. Twelve clinical practice guidelines documents were published by national or regional organizations including American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (AAP)[10], Canadian Pediatric Society (CPS) Fetus and Newborn Committee[11], Chinese Pediatric society (ChPS) Chinese medical Association[12], Israel Neonatal Society (INS)[13], Italian Society of Neonatology (ISN)[14], Malaysia Health Technology Assessment Section (MaHTAS)[15], National Institute for Health and Care Excellence (NICE) in the United Kingdom[16], Norwegian Pediatric Association (NPA)[17], Queensland Clinical Guidelines (QCG) in Australia[18], Spanish Association of Pediatrics (SAP)[19], Swiss Society of Neonatology (SSN)[20] and Turkish Pediatric Association (TPA)[21]. Five of these guidelines are new and the rest of them have been updated or reaffirmed. Four guidelines of the United States[10], Canada[11], Italy[14] and Swiss[20] included their target population as neonates with more than 35 weeks of gestation while the others covered all preterm and term babies. Eight organizations reported undertaking a systematic review and appraisal of the evidence and were explicit about the level of evidence that underpinned their recommendations. Three groups were funded by governmental institutions (QCG[18], NICE[16] and MaHTAS[15]), one declared no financial support (TPA[21]); the remainder did not disclose a funding source.

Appraisal of guidelines

Table 3 shows the scores for each guideline for the six domains with the AGREE II instrument. The overall quality of the guideline development process varied widely both between guidance documents and within guidance documents between domains. The 12 guidelines achieved an average score from 36.3% to 89.3%. Most had average scores below 50% in four of the six domains, only two received an average over 50%. The included guidelines received the highest scores in domains of clarity of presentation and lowest scores for rigour of development.

Domain 1: scope and purpose had a mean score of 88.8%±6.5% and the MaHTAS[15] scored the highest at 98.6%. Domain 2: stakeholder involvement received a mean score of 47.6%±22.4% with the ChPS[12] having the lowest score at 9.7%. Domain 3: rigor of development had the poorest mean score of 31.9%±22.6%. NICE[16] scoring the highest for this domain at 85.9% with the most extensive development process while TPA[21] received the lowest at only 9.9%. Domain 4: clarity of presentation obtained the highest mean of 91.7%±5.7%. For this domain, most of the guidelines obtained a score over 90%. Domain 5: applicability had a poor mean score of 43.0%±18.9% with five guidelines scoring under 30%. Domain 6: editorial independence also had a poor mean score at 36.8%±36.1% and for this domain four CPGs obtained 0%. In terms of overall quality, half of the guidelines received an average score of over 50%. The guideline of NICE recived the highest score of 89.3%±5.7%.

For the inter-rater reliability analysis, the intraclass correlation coefficients for the six domains were calculated to assess the reliability of the scores between investigators. Table 4 shows the intraclass correlation coefficients, 95% confidence intervals and P values for each domain between four evaluators. The intraclass correlation coefficients ranged from 0.818 to 0.995. The analysis of the reliability study was performed with Statistical Package for Social Sciences (SPSS).

Clinical guideline recommendations

Approaches to risk factors and diagnostic strategies for neonatal hyperbilirubinemia

Nine guidelines covered risk factors of severe neonatal hyperbilirubinemia including maternal and neonatal risk factors. All guidance documents gave recommendations of diagnosis. Table 5 and 6 shows the main risk factors and some diagnostic strategies of neonatal jaundice. Guidelines differed somewhat in their report of risk factors of severe neonatal jaundice. Regarding the neonatal risk factors, nearly all guidelines reported prematurity, exclusive breastfeeding, G6PD deficiency. Cephalohematoma or bruises, male were defined as risk factors in some guidelines, while NICE[16] stated that the evidence was inconclusive and results from most studies show no statistically significant association between these factors and hyperbilirubinemia.

Visual assessment was recommended as a first step of diagnostic strategy by most organization and the guideline of Malaysia[15] specifically mentioned that Kramer's rule could be widely practiced. All guidelines advocated TSB measurement was the gold standard for detecting and determining the level of hyperbilirubinemia. Non-invasive method like transcutaneous bilirubinometer was introduced and gained acceptance by all guidelines. Other method for detecting like icterometer were not recommended by NICE[16] and MaHTAS[15] because there was no good quality evidence to indicate its reliability. In addition, nearly all guidelines recommended additional laboratory tests for babies with prolonged jaundice that could be of value to evaluate and identify the underlying disease. These tests included complete blood count, blood group compatibility, direct antiglobulin test (DAT), septic workup, urinalysis, urine culture, thyroid functions, G6PD, reticulocyte count and conjugated component of bilirubin.

Approaches to treatment for neonatal hyperbilirubinemia

Table 7 showed the recommendations of the management for neonatal jaundice. The key areas included the initiating threshold and details of different kinds of therapies and care of babies during therapy. Guidelines distinguished treatment scenarios based on the level of hyperbilirubinemia including phototherapy, exchange transfusion and pharmacotherapy.

All guidelines discussed the threshold of phototherapy and exchange transfusion, and most of the organizations divided patients into groups according to gestational age and risk factors. As an example, we reported the detailed initiating TSB level for

full-term neonates with and without risk factors in the table, finding that there were little differences between guidelines. The majority of the guidelines proposed a number of general cares during phototherapy such as temperature measurement, eye protection and continued breastfeeding. For other forms of phototherapy, home phototherapy was recommended by AAP[10] and MaHTAS[15] while sunlight exposure was not supported by four organizations (AAP, NICE, QCG, SAP). Moreover, seven guidelines mentioned the complications of phototherapy.

For initiating exchange transfusion, the threshold was higher than phototherapy in all risk groups. Potential signs of acute bilirubin encephalopathy were important conditions in all guidelines. Most guidelines reported the details in performing exchange transfusion like blood product and blood volume. Double-volume exchange transfusion was advocated by majority. Furthermore, observations during exchange transfusion including heart rate, blood pressure, respiratory rate, oxygen saturation, skin temperature were only proposed by three organizations (MaHTAS[15], ChPS[12] and ISN[14]). After exchange transfusion, seven guidelines recommended maintaining intensive phototherapy and six suggested monitoring TSB at varied time points. Besides, pharmacotherapy was also mentioned by ten guidelines. However, the recommendation of medication varied greatly.

Discussion

Our systematic review appraised 12 clinical practice guidelines for diagnosis and management of neonatal hyperbilirubinemia. The quality of the guidelines was highly variable, particularly in certain domains. The included guidelines received the highest scores in clarity of presentation and lowest scores for rigor of development. Evaluated by the AGREE II instrument, most guidelines indicated good clarity regarding their objective, clinical questions and scope. As the AGREE II mentioned in stakeholder involvement domain, many guideline development groups represented a variety of relevant professional areas[9]. Also, it was valuable to explore the views of the target population, or their parents for neonates with jaundice. However, even some guidelines targeted their users as healthcare providers and parents, almost all development groups ignored the preferences of parents of the jaundice neonates.

In terms of the "Rigor of Development" domain, which was considered as the indicator of quality of all the domains[22], varied a lot among different guidelines. Guidelines with low scores in this domain were usually because of poor report in systematic methods for searching evidence and formulating recommendations, lack of external review and updating mechanisms. Some guidelines like NICE[16], for example, provided detailed search strategy, evidence table and reasons for excluded studies to prove their systematic methods, while some guidelines did not give complete information about methods of searching and selecting evidence. The clarity of presentation of the recommendations was specific and unambiguous in most guidelines apprised.

The scores of applicability domain played a significant role reflecting the implementation of guidelines. Additional materials including summary documents and educational tools could be beneficial. However, more than half of included guidelines did not discuss facilitators and barriers to their application or tools for practicing, so they might have a limitation of effect[23]. Therefore, future guideline developers should consider more about the potential resource implications and facilitators to application especially for guidelines published for developing regions. Regarding the editorial independence domain, the views of the funding body and interests of the developers should be reported as part of standard practice of guidelines development.

In this study, we also summarized and compared the specific recommendations of diagnosis and treatment of neonatal hyperbilirubinemia. All guidelines covered the threshold of phototherapy and exchange transfusion, while most of the guidelines stated that the threshold graph was reproduced and adapted with permission from guideline of AAP[10]. However, AAP noted that the suggested levels represented a consensus of most of the committee but were based on limited evidence, and the levels shown were approximations[10]. Therefore, more qualified studies of different populations were needed to standardize treatment methods. In terms of pharmacotherapy, the variations of different guidelines also existed. The discrepancy was mainly because of varying qualities of evidence, limitation of studies generalization and unapproved by national administration.

To our knowledge, our study proposed the first systematic critical appraisal of guidelines with diagnostic and treatment recommendations targeted to neonates with jaundice. The strengths of our review included the integration of comprehensive search strategies, the validated AGREE II instrument used and four independent reviewers to minimize subjective bias. Additionally, not only guidelines written in English were included, but also a Chinese-language guideline by Chinese Pediatric society were appraised in our study. As a representative of developing country, the inclusion of Chinese-language guideline may minimize the overestimation of the quality of guidelines to some degree.

However, there were several possible limitations in our study. First, guidelines written entirely in other languages except for English and Chinese might have been overlooked. The data showed that the disease burden was greatest in sub-Saharan Africa and south Asia[2], while the guidelines from these areas were not found. Second, the AGREE-II was an instrument used to evaluate guidelines with less attention to detailed recommendations. Although it had said that a global appraisal on a guideline's developing process may reflect the strength of recommendations[24], the quality of specific recommendations had direct influence on practice. Finally, we only assessed guidelines through reported literature without other ways like contacting guidelines developers to get additional clarification. This may underestimate the systematic methods of the guideline development by organizations.

Conclusion

In general, our study evaluated the quality of methodologies and rigorous strategies in the guideline development process and summarized the recommendations on diagnosis and treatment of neonatal hyperbilirubinemia. The results revealed that current guidelines varied in quality of developing process and inconsistent existed in recommendations despite some similarities. Therefore, future guidelines should pay more attention to the quality of methodologies in the guideline development process and more qualified evidence were needed to standardize the initiating threshold of treatment for neonatal hyperbilirubinemia.

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Author Statement

Dr Zhang conceptualized and designed the study, screened the titles and abstracts of searched citations, extracted general characteristics and descriptive data from guideline recommendations, assessed the selected guidelines using the AGREE-II instrument and drafted the initial manuscript.

Dr He screened the titles and abstracts of searched citations, extracted general characteristics and descriptive data from guideline recommendations, assessed the selected guidelines using the AGREE-II instrument and revised the manuscript.

Dr Wenxing Li and Dr Chen assessed the selected guidelines using the AGREE-II instrument, reviewed and revised the manuscript.

Prof Tang conceptualized and designed the study, coordinated and supervised guideline assessment, and critically reviewed the manuscript for important intellectual content.

Dr Xiong and Prof Youping Li coordinated and supervised guideline assessment, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Legends:

Figure 1. Study selection diagram

Table 1. General characteristics of included guidelines
Table 2. General characteristics of included guidelines
Table 3. Domain scores (%) of the nine guidelines assessed by using the AGREE-II instrument
Table 4. Inter rater reliability study results
Table 5. Summary of risk factors of severe neonatal jaundice
Table 6. Summary of recommendations for approaches to diagnosis of neonatal hyperbilirubinemia
Table 7. Summary of recommendations for approaches to treatment of neonatal hyperbilirubinemia

Table 1 General characteristics

Guidelines	Organization (country)	Last update year (update times)	Target population		Target users
			Inclusion criteria	Exclusion criteria	
QCG	Queensland Clinical Guidelines (Australia)	2019 (7)	All preterm and term babies	Conjugated hyperbilirubinaemia, surgical management	Parents and carers
CPS	Canadian Pediatric Society, Fetus and Newborn Committee (Canada)	2018 (1)	Newborn Infants >=35 Weeks of Gestation	Not reported	Not reported
TPA	Turkish Pediatric Association (Turkey)	2018 (0)	All preterm and term babies	Not reported	Pediatricians and family physicians
SAP	Spanish Association of Pediatrics (Spain)	2017 (0)	All preterm and term babies	Not reported	Not reported
NICE	National Institute for Health and Care Excellence (the United Kingdom)	2016 (1)	All preterm and term babies	Conjugated hyperbilirubinaemia, surgical management	Healthcare professionals, families and carers
ChPS	Chinese Pediatric Society, Chinese Medical Association (China)	2014 (1)	All preterm and term babies	Not reported	Not reported
ISN	Italian Society of Neonatology (Italy)	2014 (0)	Newborn Infants >=35 Weeks of Gestation	Not reported	Neonatologists and family pediatricians
MaHTAS	Malaysia Health Technology Assessment Section (Malaysia)	2014 (1)	All preterm and term babies	Conjugated hyperbilirubinaemia, prolonged jaundice	Pediatricians and pharmacists, parents and carers
NPA	Norwegian Pediatric Association (Norway)	2010 (0)	All preterm and term babies	Not reported	Healthcare personnel
AAP	American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (America)	2009 (1)	Newborn Infants >=35 Weeks of Gestation	Not reported	Healthcare personnel
INS	Israel Neonatal Society (Israel)	2008 (0)	All preterm and term babies	Not reported	Neonatologists, pediatricians and family doctors
SSN	Swiss Society of Neonatology (Swiss)	2007 (2)	Newborn Infants >=35 Weeks of Gestation	Not reported	Not reported

QCG: Queensland Clinical Guidelines (Australia); CPS: Canadian Pediatric Society, Fetus and Newborn Committee (Canada); TPA: Turkish Pediatric Association (Turkey); SAP: Spanish Association of Pediatrics (Spain); NICE: National Institute for Health and Care Excellence (the United Kingdom); ChPS: Chinese Pediatric Society, Chinese Medical Association (China); ISN: Italian Society of Neonatology (Italy); MaHTAS: Malaysia Health Technology

Assessment Section (Malaysia); NPA: Norwegian Pediatric Association (Norway); AAP: American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (America); INS: Israel Neonatal Society (Israel); SSN: Swiss Society of Neonatology (Swiss).

Table 2 General characteristics

Guidelines	identification of evidence					guideline review process	Fundings
	database	search terms	dates	detailed search strategy	inclusion/exclusion criteria		
QCG	PubMed, CINAHL, Medline, Cochrane Central Register of Controlled Trials, EBSCO, Embase	Reported	After 2004	Not reported	Not reported	Not reported	Healthcare Improvement Unit, Queensland Health
CPS	MEDLINE, the Cochrane library	Reported	Before 2007	Not reported	Not reported	Reported	Not reported
TPA	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	No financial support
SAP	PubMed	Reported	Not reported	Not reported	Not reported	Not reported	Not reported
NICE	Medline, EBM Reviews, CDSR, DARE, Embase, CINAHL	Reported	Before 2008	Reported	Not reported	Not reported	National Institute for Health and Care Excellence
ChPS	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
ISN	Guidelines from other countries, Studies in Italy	Not reported	Before 2013	Not reported	Not reported	Not reported	Not reported
MaHTAS	GIN, Medline, Pubmed, CDSR	Reported	After 2001	Reported	Reported	External review	Ministry of Health Malaysia
NPA	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
AAP	Not reported	Not reported	Not reported	Not reported	Not reported	Peer review	Not reported
INS	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
SSN	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

QCG: Queensland Clinical Guidelines (Australia); CPS: Canadian Pediatric Society, Fetus and Newborn Committee (Canada); TPA: Turkish Pediatric Association (Turkey); SAP: Spanish Association of Pediatrics (Spain); NICE: National Institute for Health and Care Excellence (the United Kingdom); ChPS: Chinese Pediatric Society, Chinese Medical Association (China); ISN: Italian Society of Neonatology (Italy); MaHTAS: Malaysia Health Technology Assessment Section (Malaysia); NPA: Norwegian Pediatric Association (Norway); AAP: American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (America); INS: Israel Neonatal Society (Israel); SSN: Swiss Society of Neonatology (Swiss).

Table 3 Domain scores (%) of the nine guidelines assessed by using the AGREE-II instrument (%)

	NICE	MaHTAS	QCG	ISN	AAP	TPA	NPA	INS	SAP	SSN	CPS	ChPS	mean±SD
Domain 1	91.7	98.6	91.7	90.3	97.2	84.7	86.1	87.5	73.6	90.3	91.7	81.9	88.8±6.5
Domain 2	93.1	61.1	66.7	61.1	51.4	44.4	50.0	56.9	18.1	36.1	22.2	9.7	47.6±22.4
Domain 3	85.9	62.5	51.0	17.2	40.6	9.9	19.8	18.2	28.1	17.2	22.4	10.4	31.9±22.6
Domain 4	98.6	98.6	98.6	94.4	94.4	87.5	80.6	83.3	91.7	88.9	94.4	88.9	91.7±5.7
Domain 5	85.4	64.6	61.5	26.0	38.5	25.0	57.3	37.5	24.0	39.6	29.2	27.1	43.0±18.9
Domain 6	81.3	89.6	31.3	64.6	25.0	93.8	0.0	4.2	52.1	0.0	0.0	0.0	36.8±36.1
mean±SD	89.3±5.7	79%±17%	66.8±23.0	58.9±29.2	57.9±27.9	57.6±32.8	49.0±30.8	47.9±31.1	47.9±27.2	45.3±33.9	43.3±36.3	36.3±35.7	

Domain 1: scope and purpose; Domain 2: stakeholder involvement; Domain 3: rigor of development; Domain 4: clarity of presentation; Domain 5: applicability; Domain 6: editorial independence.

NICE: National Institute for Health and Care Excellence (the United Kingdom); MaHTAS: Malaysia Health Technology Assessment Section (Malaysia); QCG: Queensland Clinical Guidelines (Australia); INS: Israel Neonatal Society (Israel); AAP: American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (America); TPA: Turkish Pediatric Association (Turkey); NPA: Norwegian Pediatric Association (Norway); ISN: Italian Society of Neonatology (Italy); SAP: Spanish Association of Pediatrics (Spain); SSN: Swiss Society of Neonatology (Swiss); CPS: Canadian Pediatric Society, Fetus and Newborn Committee (Canada); ChPS: Chinese Pediatric Society, Chinese Medical Association (China).

Table 4 Inter rater reliability study results

	ICC	n	k	Lower 95% CI	Upper 95% CI	P value
Domain 1	0.863	12	4	0.670	0.956	0.000
Domain 2	0.989	12	4	0.974	0.997	0.000
Domain 3	0.994	12	4	0.986	0.998	0.000
Domain 4	0.818	12	4	0.561	0.941	0.000
Domain 5	0.995	12	4	0.988	0.998	0.000
Domain 6	0.993	12	4	0.984	0.998	0.000

Domain 1: scope and purpose; Domain 2: stakeholder involvement; Domain 3: rigor of development; Domain 4: clarity of presentation; Domain 5: applicability; Domain 6: editorial independence.

Table 5 Summary of risk factors of severe neonatal jaundice

	NICE	MaHTAS	QCG	INS	AAP	TPA	NPA	ISN	SAP	SSN	CPS	ChPS
Maternal												
Blood group O	NA	+	+	+	+	NA	NA	NA	NA	NA	+	NA
Rhesus negative	NA	+	+	+	+	NA	NA	NA	NA	NA	+	NA
Diabetes	NA	+	+	NA	+	NA	NA	NA	NA	NA	NA	NA
Neonatal												
G6PD deficiency	NA	+	+	+	+	+	NA	NA	+	NA	+	+
Prematurity	+	+	+	NA	+	+	NA	NA	+	NA	+	+
Exclusive breastfeeding	+	+	+	NA	+	NA	NA	NA	+	NA	+	+
Cephalhaematoma or bruises	-	+	+	NA	+	NA	NA	NA	+	NA	+	+
Sepsis	NA	+	+	NA	+	+	NA	NA	+	NA	-	+
Sibling with severe hyperbilirubinemia	+	+	+	NA	+	NA	NA	NA	NA	NA	+	NA
Visible jaundice at younger than 24 h	+	+	NA	+	+	NA	NA	NA	NA	NA	+	NA
Male	-	NA	+	NA	+	NA	NA	NA	NA	NA	+	NA

NA: not available

NICE: National Institute for Health and Care Excellence (the United Kingdom); MaHTAS: Malaysia Health Technology Assessment Section (Malaysia); QCG: Queensland Clinical Guidelines (Australia); INS: Israel Neonatal Society (Israel); AAP: American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (America); TPA: Turkish Pediatric Association (Turkey); NPA: Norwegian Pediatric Association (Norway); ISN: Italian Society of Neonatology (Italy); SAP: Spanish Association of Pediatrics (Spain); SSN: Swiss Society of Neonatology (Swiss); CPS: Canadian Pediatric Society, Fetus and Newborn Committee (Canada); ChPS: Chinese Pediatric Society, Chinese Medical Association (China).

Table 6 Summary of recommendations for approaches to diagnosis of neonatal hyperbilirubinemia

	NICE	MaHTAS	QCG	ISN	AAP	TPA	NPA	INS	SAP	SSN	CPS	ChPS
Clinical assessment												
Visual assessment (do not rely on it alone)	+	+	+	NA	+	+	NA	NA	+	+	NA	NA
Measurement of bilirubin												
TCB transcutaneous bilirubinometer	+	+	+	+	+	+	+	+	+	+	+	+
TSB	+	+	+	+	+	+	+	+	+	+	+	+
B/A	-	-	NA	NA	+	NA	NA	NA	NA	NA	NA	+
Icterometer	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	+
Test for prolonged jaundice												
Blood group compatibility	+	+	+	+	+	+	NA	+	+	+	+	NA
Direct antiglobulin test (DAT)	+	+	+	+	+	+	NA	+	+	+	+	NA
G6PD	+	+	+	+	+	+	NA	+	+	NA	+	NA
Conjugated component of bilirubin	+	NA	+	NA	+	+	NA	+	+	+	+	NA
Complete blood count	+	+	+	+	+	+	NA	NA	NA	NA	+	NA
Septic workup (if suspected)	+	+	+	NA	+	+	NA	NA	+	NA	+	NA
Thyroid functions	NA	NA	+	NA	+	+	NA	+	+	NA	NA	NA
Urinalysis, urine culture	NA	NA	+	NA	+	+	NA	+	+	NA	NA	NA
Reticulocyte count	NA	+	+	NA	+	+	NA	NA	NA	NA	NA	NA

NA: not available

NICE: National Institute for Health and Care Excellence (the United Kingdom); MaHTAS: Malaysia Health Technology Assessment Section (Malaysia); QCG: Queensland Clinical Guidelines (Australia); INS: Israel Neonatal Society (Israel); AAP: American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (America); TPA: Turkish Pediatric Association (Turkey); NPA: Norwegian Pediatric Association (Norway); ISN: Italian Society of Neonatology (Italy); SAP: Spanish Association of Pediatrics (Spain); SSN: Swiss Society of Neonatology (Swiss); CPS: Canadian Pediatric Society, Fetus and Newborn Committee (Canada); ChPS: Chinese Pediatric Society, Chinese Medical Association (China).

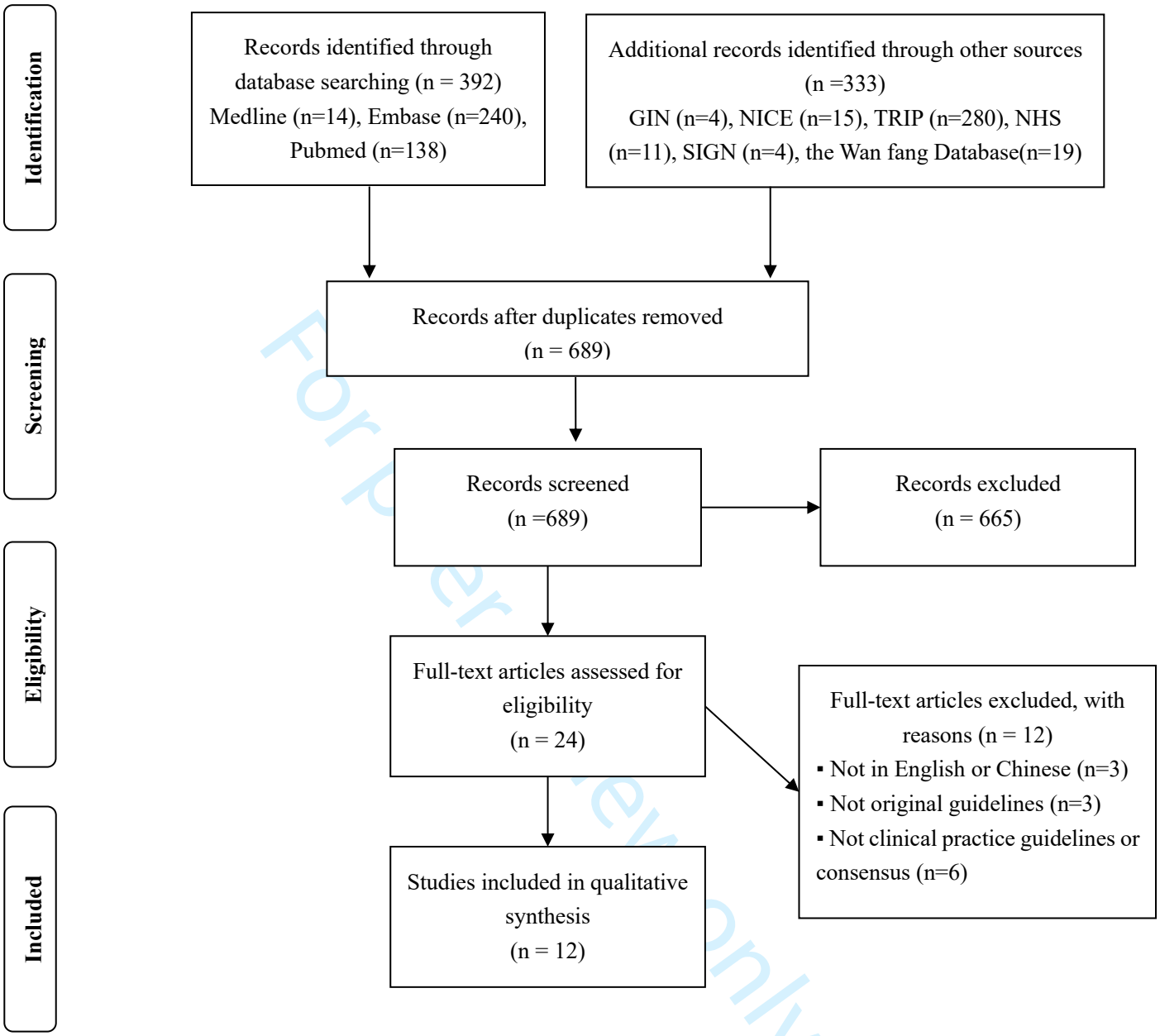
Table 7 Summary of recommendations for approaches to treatment of neonatal hyperbilirubinemia

		NICE	MaHTAS	QCG	ISN	AAP	TPA	NPA	INS	SAP	SSN	CPS	ChPS
Phototherapy													
Conventional irradiance (μW/cm²/nm)		NA	>15	25-30	NA	NA	8-10	NA	NA	8-12	NA	NA	8-10
Intensive irradiance (μW/cm²/nm)		NA	>30	>30	> 35	>30	30-65	>20	>30	>30	NA	>30	>30
Distance between light and baby (cm)		NA	< 30 - 50	10–15	NA	About 10	35-40	20	about 10	10	NA	10	NA
Intensive phototherapy threshold for fullterm babies>96h (μmol/L)	**Well**	350	359	359	343	359	359	359	359	359	350	359	359
	With risk factors	NA	308	308	NA	308	291	308	308	308	300	257	308
Home phototherapy		NA	NA	+	NA	+	NA	NA	+	NA	NA	NA	NA
Sunlight Exposure		-	NA	-	NA	-	NA	NA	-	-	NA	NA	NA
Complications		+	NA	+	NA	+	+	NA	+	NA	NA	+	+
Exchange transfusion													
Exchange transfusion threshold for fullterm babies>96h (μmol/L)	**Well**	450	428	428	428	428	428	450	428	428	430	428	428
	With risk factors	NA	393	393	NA	376	393	NA	376	376	370	325	376
Detail observation during ET		NA	+	NA	+	NA	NA	NA	NA	NA	NA	NA	+
Maintain intensive PT after ET		+	+	+	+	NA	+	NA	NA	NA	NA	+	+
Measure TSB after ET		within 2h	4 – 6h	within 2h	within 2h	NA	within 2h	NA	NA	NA	NA	NA	within 4h
Complications		+	+	+	+	+	+	NA	+	NA	NA	+	NA
Pharmacotherapy													
Intravenous immunoglobulin		+	-	-	+	+	+	NA	+	+	NA	+	+
Human albumin		-	-	-	NA	NA	NA	NA	NA	NA	NA	NA	+
Clofibrate		-	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tin-mesoporphyrin		NA	-	NA	NA	-	NA	NA	NA	NA	NA	+	NA

NA: not available

NICE: National Institute for Health and Care Excellence (the United Kingdom); MaHTAS: Malaysia Health Technology Assessment Section (Malaysia); QCG: Queensland Clinical Guidelines (Australia); INS: Israel Neonatal Society (Israel); AAP: American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (America); TPA: Turkish Pediatric Association (Turkey); NPA: Norwegian Pediatric Association (Norway); ISN: Italian Society of Neonatology (Italy); SAP: Spanish Association of Pediatrics (Spain); SSN: Swiss Society of Neonatology (Swiss); CPS: Canadian Pediatric Society, Fetus and Newborn Committee (Canada); ChPS: Chinese Pediatric Society, Chinese Medical Association (China).

Figure 1 Study selection diagram



GIN: the Guidelines International Network, NICE: the National Institute for Health and Care Excellence, TRIP: the Turning Research Into Practice Database, NHS: the National Health Service Evidence, SIGN: the Scottish Intercollegiate Guidelines Network

Searching strategy of PubMed

#1 Neonatal hyperbilirubinemia [Mesh] OR Neonatal Hyperbilirubinemia OR Hyperbilirubinemia During Infancy OR During Infancies, Hyperbilirubinemia OR Infancy, Hyperbilirubinemia During OR Indirect Hyperbilirubinemia, Neonatal OR Hyperbilirubinemia, Neonatal Indirect OR Neonatal Indirect Hyperbilirubinemia OR Direct Hyperbilirubinemia, Neonatal OR Hyperbilirubinemia, Neonatal Direct OR Neonatal Direct Hyperbilirubinemia

#2 Jaundice, Neonatal [Mesh] OR Neonatal Jaundice OR Physiological Neonatal Jaundice OR Jaundice, Physiological Neonatal OR Neonatal Jaundice, Physiological OR Severe Jaundice in Newborn OR Severe Jaundice in Neonate OR Icterus Gravis Neonatorum

#3 Clinical practice guidelines [Mesh]

#4 #1 OR #2

#5 #3 AND #4

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMAreporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
Title			
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured	#2	Provide a structured summary including, as applicable:	2

summary		background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	
Introduction			
Rationale	#3	Describe the rationale for the review in the context of what is already known.	3
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
Methods			
Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	NA
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	3
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	3-4

Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	The supplementary material
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	3-4
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	4
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	4
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	NA
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	4

Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
Results			
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	Table 1 and 2
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	NA
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	5-7
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	5-7
Risk of bias	#22	Present results of any assessment of risk of bias across	NA

across studies		studies (see Item 15).	
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 3 and 4
Discussion			
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	7-8
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
Funding			
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	1

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A systematic review of global clinical practice guidelines for neonatal hyperbilirubinemia

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A systematic review of global clinical practice guidelines for neonatal hyperbilirubinemia

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Keyword: neonatal hyperbilirubinemia, clinical practice guidelines, systematic review

Word count: 2999

ABSTRACT

Objective: Hyperbilirubinemia is one of the most common clinical symptoms in newborns. To improve patient outcomes, evidence-based and implementable guidelines are required. However, clinical guidelines may vary in quality, criteria, and recommendations among regions and countries. In this study, we aimed to systematically assess the quality of guidelines using the AGREE-II instrument and summarize the specific recommendations for neonatal hyperbilirubinemia in order to provide suggestions for future guideline development.

Design: Systematic review.

Interventions: We searched the PubMed, Embase, Medline, and guideline databases for relevant articles on April 10th 2020. The studies were screened by two independent reviewers according to our inclusion criteria. Two reviewers independently extracted the descriptive data. Four appraisers assessed the guidelines using the AGREE-II instrument.

Results: Our systematic review appraised 12 clinical practice guidelines for the diagnosis and management of neonatal hyperbilirubinemia. The 12 guidelines achieved an average score of 36-89%. The guidelines received the highest scores for clarity of presentation and lowest scores for rigor of development. Most recommendations for diagnosis were relatively consistent, but recommendations regarding risk factors, the initiating threshold of treatment, and pharmacotherapy varied.

Conclusions: Our study revealed that current guidelines vary in the quality of the developing process and are inconsistent with regard to recommendations. Future guidelines should afford more attention to the quality of methodologies in guideline development, and more qualified evidence is needed to standardize the initiating threshold of treatment for neonatal hyperbilirubinemia.

Strengths and limitations of this study

- This study is the first English systematic appraisal of guidelines targeted to neonates with hyperbilirubinemia.
- The strengths also included the use of the validated AGREE II instrument and four independent reviewers to minimize subjective bias.
- A Chinese-language guideline by the Chinese Pediatric Society was appraised.
- The AGREE-II was used to evaluate guidelines with less attention on detailed recommendations.
- We only assessed guidelines through the reported literature without the use of additional methods such as contacting guideline developers.

INTRODUCTION

Neonatal hyperbilirubinemia, characterized by the elevation of total serum bilirubin (TSB), is one of the most common clinical conditions affecting newborns, particularly preterm infants. Hyperbilirubinemia affects approximately 60% of full-term and 80% of preterm neonates.[1] Approximately 10% of newborns are likely to develop clinically significant hyperbilirubinemia requiring close monitoring and treatment.[2] In the early period (0-6 days), neonatal hyperbilirubinemia accounted for 1309.3 deaths per 100,000 livebirths and was the seventh most common cause of neonatal deaths.[3] Effective and timely treatment with phototherapy or exchange transfusion can reduce the occurrence of neurological dysfunction in neonates with hyperbilirubinemia.

Clinical practice guidelines are in place to aid clinical, policy-related, and system-related decisions.[4] Guidelines have also been developed to bridge the gap between research and clinical practice.[5] Therefore, guidelines have become increasingly popular in recent years.[6]Although several organizations from different regions have developed clinical practice guidelines, these guidelines may vary widely in quality.[7 8] Moreover, the criteria for diagnosis and treatment in published guidelines vary among regions and countries.[9]

The Appraisal of Guidelines for Research & Evaluation (AGREE) instrument is used to assess methodological rigor and transparency of a guideline.[10] In this study, we aimed to systematically review and assess the quality of guidelines on neonatal hyperbilirubinemia using the AGREE-II instrument in order to provide suggestions for future guideline development.

METHODS

Selection criteria

We included clinical practice guidelines produced by local, regional, national or international groups or affiliated governmental organizations for the diagnosis and management of hyperbilirubinemia in newborn infants. The guidelines were included if they met the following criteria: (1) published in English or Chinese language; (2) based on systematic evidence synthesis and containing specific statements to guide decisions regarding hyperbilirubinemia; (3) include recommendations for the diagnosis and/or treatment of neonatal hyperbilirubinemia; and (5) published between 2000 and 2020, and only the most recent editions of updated guidelines were considered.

Search strategy

A systematic literature search was performed on April 10th 2020. We searched for relevant studies in the PubMed, Embase, and Medline databases. In addition, we searched the Guidelines International Network (GIN), National Health Service (NHS) Evidence website, National Institute for Health and Care Excellence (NICE) website, Scottish Intercollegiate Guidelines Network (SIGN) website, Turning Research Into Practice Database (TRIP), and Wan fang Database. The titles and abstracts of the searched citations were screened by two independent reviewers (MZ and YH). Any

discrepancies between the reviewers were resolved by discussion. The detailed search strategy for PubMed is shown in the supplementary material.

Guideline characteristics

Two independent reviewers (MZ and YH) extracted the general characteristics of the included guidelines: country, founding organization, year of publication or updating status, method of evidence identification, and funding.

Appraisal of guideline quality

Four appraisers (MZ, YH, WXL, and ZC) independently assessed the selected guidelines using the AGREE-II instrument. The AGREE II is an international, validated, and rigorously developed tool to evaluate the quality of clinical practice guidelines and consensus statements.[11] The AGREE II consists of 23 key items organized within six domains (scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence) followed by two global rating items (overall assessment). Each domain points to a unique dimension of guideline quality.[12] Each of the AGREE II items is rated on a seven-point scale (1 = strongly disagree to 7 = strongly agree). Domain scores are calculated by summing the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain.[12] The score for each domain of each document is calculated as follows: (obtained score - minimal possible score)/(maximal possible score - minimal possible score).[10] All reviewers were trained online using the AGREE training tools. Discrepancies of >3 points were discussed in a consensus meeting.

Analysis

We extracted descriptive data from the guideline recommendations to identify the consistencies and discrepancies. The recommendations were then summarized according to different items related to the diagnosis and treatment strategies of neonatal hyperbilirubinemia, such as the test used for the early prediction and diagnosis, time to start phototherapy and exchange transfusion, recommendation for drug use, criterion for discharge, and timing or frequency of follow-up. The intraclass correlation coefficients for the six domains were calculated to assess the reliability of the scores between investigators. The analysis of the reliability study was performed using Statistical Package for Social Sciences (SPSS) V.24.0.

Patient and Public Involvement

No patient involved.

RESULTS

Search results

Figure 1 illustrates the search and guideline selection process. The systematic search retrieved 725 records, of which 701 were excluded after removing duplicates and articles that did not meet the eligibility criteria. Consequently, after the full-text

evaluation of the remaining records, 12 additional clinical practice guidelines were excluded for the following reasons: not written in English or Chinese, not original guidelines, and not clinical practice guidelines or consensuses. Ultimately, we included 12 clinical practice guidelines from 12 different national or regional organizations.

General characteristics of the guidelines

Tables 1 and 2 summarize the general characteristics of the included clinical practice guidelines. Twelve clinical practice guideline documents were published by national or regional organizations, including the American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (AAP),[13] Canadian Pediatric Society (CPS) Fetus and Newborn Committee,[14] Chinese Pediatric Society (ChPS) Chinese medical Association,[15] Israel Neonatal Society (INS),[16] Italian Society of Neonatology (ISN),[17] Malaysia Health Technology Assessment Section (MaHTAS),[18] National Institute for Health and Care Excellence (NICE) in the United Kingdom,[19] Norwegian Pediatric Association,[20] Queensland Clinical Guidelines (QCG) in Australia,[21] Spanish Association of Pediatrics (SAP),[22] Swiss Society of Neonatology (SSN)[23] and Turkish Pediatric Association (TPA).[24] Five of these guidelines are new and the others have been updated or reaffirmed. Four guidelines from the United States,[13] Canada,[14] Italy,[17] and Switzerland[23] were targeted toward neonates born at >35 weeks of gestation, while the other guidelines covered all preterm and term babies. Six organizations (QCG, [21]CPS, [14] SAP, [22]NICE, [19]INS, and MaHTAS[18]) reported performing a systematic review and appraisal of the evidence and were explicit about the level of evidence that underpinned their recommendations. Three groups were funded by governmental institutions (QCG,[21] NICE,[19] and MaHTAS[18]), one declared no financial support (TPA[24]), and the remainder did not disclose a funding source.

Appraisal of guidelines

Table 3 shows the scores for each guideline for the six domains of the AGREE II instrument. The overall quality of the guideline development process varied widely both among guidance documents and within guidance documents among different domains. The average score was 36.3-89.3%. Most guidelines achieved average scores of <50% in four of the six domains, and only two received an average score of >50%. The highest scores were achieved in the domains of clarity of presentation and the lowest scores were achieved for rigor of development.

Domain 1: the mean score for scope and purpose was 88.8±6.5% and the MaHTAS[18] guideline achieved the highest score at 98.6%. Domain 2: the mean stakeholder involvement score was 47.6±22.4% and ChPS[15] received the lowest score at 9.7%. Domain 3: The mean score for rigor of development was 31.9±22.6%. NICE[19] scored the highest for this domain at 85.9% with the most extensive development process, while TPA[24] received the lowest at only 9.9%. Domain 4: The mean score for clarity of presentation was 91.7±5.7%. For this domain, most of the guidelines obtained a score of >90%. Domain 5: The mean score for applicability was 43.0±18.9%, with five guidelines scoring <30%. Domain 6: the mean score for editorial independence was

36.8±36.1%, and four guidelines obtained scores of 0% for this domain. In terms of overall quality, 50% of the guidelines received an average score of >50%. The NICE guidelines received the highest score at 89.3±5.7%.

Table 4 shows the intraclass correlation coefficients, 95% confidence intervals, and P values for each domain between the four evaluators. The intraclass correlation coefficients ranged from 0.818 to 0.995.

Clinical guideline recommendations

Approaches to risk factors and diagnostic strategies for neonatal hyperbilirubinemia

Nine guidelines covered risk factors for severe neonatal hyperbilirubinemia, including maternal and neonatal risk factors. All guidance documents provided recommendations for diagnosis. Tables 5 and 6 show the main risk factors and some example diagnostic strategies for neonatal hyperbilirubinemia. The guidelines differed somewhat in their report of risk factors. Nearly all guidelines reported prematurity, exclusive breastfeeding, and G6PD deficiency as neonatal risk factors. Cephalohematoma or bruises and male sex were also defined as neonatal risk factors in some guidelines, while NICE[25] stated that the evidence was inconclusive and that the results of most studies revealed no significant association between these factors and hyperbilirubinemia.

Visual assessment was recommended as a first step in diagnosis by most organizations, and the guideline of Malaysia[18] specifically mentioned that Kramer's rule could be widely practiced. All guidelines advocated TSB measurement as the gold standard for detecting and determining the level of hyperbilirubinemia. Non-invasive methods such as a transcutaneous bilirubinometer are accepted by all guidelines. Other methods of detection such icterometers were not recommended by NICE[19] and MaHTAS[18] because there was no good quality evidence to indicate their reliability. In addition, nearly all guidelines recommended additional laboratory tests for babies with prolonged hyperbilirubinemia that could be of value to evaluate and identify the underlying disease. These tests included complete blood counts, blood group compatibility, a direct antiglobulin test, septic workup, urinalysis, urine culture, thyroid functions, G6PD, reticulocyte count, and conjugated component of bilirubin.

Approaches to treatment and follow-up for neonatal hyperbilirubinemia

Table 7 shows the recommendations for the management of neonatal hyperbilirubinemia. The key areas included the initiating threshold and details of different types of therapies and care for babies during therapy. The guidelines distinguished treatment scenarios based on the level of hyperbilirubinemia, including phototherapy, exchange transfusion, and pharmacotherapy.

All guidelines discussed the threshold of phototherapy and exchange transfusion, and most of the organizations divided patients into groups according to gestational age and risk factors. As an example, we reported the detailed initiation TSB levels for full-term

neonates according to the presence and absence of risk factors in table 7, finding that there were few differences among the guidelines regarding to the initiation TSB levels. The majority of the guidelines proposed a number of general care strategies during phototherapy, such as temperature measurement, eye protection, and continued breastfeeding. Among other forms of phototherapy, home phototherapy was recommended by AAP[13] and MaHTAS,[18] while sunlight exposure was not supported by four organizations (AAP, NICE, QCG, SAP). Moreover, seven guidelines mentioned the complications of phototherapy.

The threshold for initiating exchange transfusion was higher than that for phototherapy in all risk groups. Potential signs of acute bilirubin encephalopathy were highlighted as important in all guidelines. Most guidelines reported the details of performing exchange transfusion such as the blood product and blood volume. Double-volume exchange transfusion was advocated by the majority of guidelines. Furthermore, observations during exchange transfusion including heart rate, blood pressure, respiratory rate, oxygen saturation, and skin temperature were only proposed by three organizations (MaHTAS,[18] ChPS,[15] and ISN[17]). After the exchange transfusion, seven guidelines recommended maintaining intensive phototherapy and six suggested monitoring the TSB at varied time points. Pharmacotherapy was also mentioned by ten guidelines. However, the recommendation of medication varied greatly.

Most of the guidelines discussed follow-up after discharge, and some provided different follow-up time recommendations according to the time of discharge and risk factors. In addition, some guidelines focused on the follow-up of children with severe hyperbilirubinemia. The CPS guidelines recommend that the hearing screen of patients with severe hyperbilirubinemia should include brainstem auditory evoked potentials. The MaHTAS guideline reported that term and late preterm babies with TSB of >20 mg/dL or exchange transfusions should have auditory brainstem response (ABR) testing performed within the first 3 months of life. If the ABR is abnormal, neurodevelopmental follow-up should be continued. The ABR test was also recommended by the Turkish guidelines for babies with hyperbilirubinemia requiring treatment. Moreover, two of the guidelines (SSN and ISN) mentioned the national institute for monitoring the incidence of kernicterus and severe hyperbilirubinemia.

DISCUSSION

This systematic review appraised 12 clinical practice guidelines for the diagnosis and management of neonatal hyperbilirubinemia. The quality of the guidelines was highly variable. The included guidelines received acceptable AGREE II scores in the domains of clarity of presentation and scope and purpose, but the mean scores were moderate or low in the stakeholder involvement, rigor of development, applicability, and editorial independence domains. This finding was similar to that of the 2010 review by Alonso-Coello et al.[26] In recent years, although the number of guidelines has increased, the quality of guidelines still needs to be improved.

As evaluated by the AGREE II instrument, most guidelines had good clarity regarding their objective, clinical questions, and scope. Further, as the AGREE II revealed in the stakeholder involvement domain, many guideline development groups represented a variety of relevant professional areas.[12] It is valuable to explore the views of the target population, i.e., healthcare providers or the parents of neonates with hyperbilirubinemia. However, although some guidelines targeted healthcare providers and parents, almost all development groups ignored the preferences of parents of the hyperbilirubinemia neonates.

The mean score of the rigor of development domain, which was considered the indicator of quality in all domains,[27] varied significantly among different guidelines. Guidelines typically received low scores in this domain because of poor reporting of systematic methods for searching for evidence and formulating recommendations, lack of external review, and updating mechanisms. Some guidelines, such as NICE,[19] provided detailed search strategies, evidence tables, and reasons for excluded studies to confirm their systematic methods, while some guidelines did not provide complete information regarding methods of searching and selecting evidence. Muka et al. provided a 24-step guide on how to perform a systematic review and meta-analysis in 2020.[28] The guide described the most important 24 steps, such as defining the search strategy, designing the data collection form, checking reporting bias, etc. We suggest that these methodologically sound tools should be used to help future guideline designers conduct or appraise systematic reviews. Guidelines need to reflect current research, but most of the guidelines did not provide a statement about the procedure for updating. Alonso-Coello et al. conducted an international survey of the updating practices of guidelines in 2011 and concluded that there was an urgent need to develop rigorous international standards for the updating process.[29]

The clarity of presentation of the recommendations was specific and unambiguous in most guidelines. The scores of the applicability domain were highly reflective of the implementation of guidelines. Additional materials, including summary documents and educational tools, could be beneficial in this respect. However, >50% of the included guidelines did not discuss facilitators and barriers to their application or tools for practicing; thus, the guidelines might have a limited effect.[30] Therefore, future guideline developers should afford greater consideration to the potential resource implications and facilitators of application, particularly for guidelines published in developing regions. Regarding the editorial independence domain, the views of the funding body and interests of the developers should be reported as part of the standard practice of guideline development.

In this study, we also summarized and compared the specific recommendations for the diagnosis and treatment of neonatal hyperbilirubinemia. All guidelines covered the threshold of phototherapy and exchange transfusion, while most of the guidelines stated that the threshold graph was reproduced and adapted with permission from the AAP[13]. However, the AAP noted that the suggested levels represented a consensus of

committee but were based on limited evidence, and the levels shown were approximations.[13] Therefore, more qualified studies of different populations are needed to standardize treatment methods. In terms of pharmacotherapy, variations also existed among different guidelines. The discrepancies were mainly due to varying evidence quality, limitations in generalizability, and lack of approval by a national administration.

The burden of hyperbilirubinemia is highest in South Asia and sub-Saharan Africa.[2] Hyperbilirubinemia is the seventh leading cause of neonatal mortality in South Asia, eighth in sub-Saharan Africa, ninth in western Europe, and 13th in North America.[2] In our review, we appraised five guidelines from Europe with a mean score of 55.9%, four guidelines from Asian countries with mean scores of 55.2%, and two guidelines from North America with mean scores of 50.6%. In 2015, Olusanya et al. provided a practical framework for the management of late-preterm and term infants (≥35 weeks of gestation) with clinically significant hyperbilirubinemia in low- and middle-income countries lacking local practice guidelines.[31] They provided recommendations for comprehensive management, including primary prevention, early detection, diagnosis, monitoring, treatment, and follow-up.[31]

To our knowledge, our study is the first systematic critical appraisal of guidelines with diagnostic and treatment recommendations targeted to neonates with hyperbilirubinemia. The strengths of our review include the integration of comprehensive search strategies, use of the validated AGREE II instrument, and use of four independent reviewers to minimize subjective bias. Further, in addition to guidelines written in English, a Chinese-language guideline by the Chinese Pediatric Society was appraised in our study. As a representative of developing countries, the inclusion of Chinese-language guidelines may minimize the overestimation of the quality of guidelines to some degree.

However, there were several possible limitations to our study. First, guidelines written entirely in languages other than English and Chinese might have been overlooked. Second, the AGREE-II was used to evaluate guidelines with less attention on detailed recommendations. Although it is thought that a global appraisal of a guideline's developing process may reflect the strength of recommendations,[9] the quality of specific recommendations has a direct influence on practice. Finally, we only assessed guidelines through reported literature without the use of additional methods such as contacting guideline developers to obtain further clarification. This may have underestimated the systematic methods of guideline development by organizations.

Conclusion

Our study evaluated the quality of methodologies and rigorous strategies in the guideline development process and summarized the recommendations on the diagnosis and treatment of neonatal hyperbilirubinemia. The results revealed that current guidelines varied in the quality of the development process and were inconsistent in their recommendations, despite some similarities. Therefore, future guidelines should

afford greater attention to the quality of methodologies in the guideline development process, and more qualified evidence is needed to standardize the initiating threshold of treatment for neonatal hyperbilirubinemia.

Contributorship statement:
Dr Zhang conceptualized and designed the study, screened the titles and abstracts of searched citations, extracted general characteristics and descriptive data from guideline recommendations, assessed the selected guidelines using the AGREE-II instrument and drafted the initial manuscript.
Prof Tang conceptualized and designed the study, coordinated and supervised guideline assessment, and critically reviewed the manuscript for important intellectual content.
Dr He screened the titles and abstracts of searched citations, extracted general characteristics and descriptive data from guideline recommendations, assessed the selected guidelines using the AGREE-II instrument and revised the manuscript.
Dr Wenxing Li and Dr Chen assessed the selected guidelines using the AGREE-II instrument, reviewed and revised the manuscript.
Dr Xiong, Prof Qu, Prof Youping Li and Prof Mu coordinated and supervised guideline assessment, and critically reviewed the manuscript for important intellectual content.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
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Legends:

Figure 1. Study selection diagram

Table 1. General characteristics of included guidelines
Table 2. General characteristics of included guidelines
Table 3. Domain scores (%) of the nine guidelines assessed by using the AGREE-II instrument
Table 4. Inter rater reliability study results
Table 5. Summary of risk factors of severe neonatal jaundice
Table 6. Summary of recommendations for approaches to diagnosis of neonatal hyperbilirubinemia
Table 7. Summary of recommendations for approaches to treatment of neonatal hyperbilirubinemia

Table 1 General characteristics

Guidelines	Organization (country)	Last update year (update times)	Target population		Target users
			Inclusion criteria	Exclusion criteria	
QCG	Queensland Clinical Guidelines (Australia)	2019 (7)	All preterm and term babies	Conjugated hyperbilirubinaemia, surgical management	Parents and carers
CPS	Canadian Pediatric Society, Fetus and Newborn Committee (Canada)	2018 (1)	Newborn Infants >=35 Weeks of Gestation	Not reported	Not reported
TPA	Turkish Pediatric Association (Turkey)	2018 (0)	All preterm and term babies	Not reported	Pediatricians and family physicians
SAP	Spanish Association of Pediatrics (Spain)	2017 (0)	All preterm and term babies	Not reported	Not reported
NICE	National Institute for Health and Care Excellence (the United Kingdom)	2016 (1)	All preterm and term babies	Conjugated hyperbilirubinaemia, surgical management	Healthcare professionals, families and carers
ChPS	Chinese Pediatric Society, Chinese Medical Association (China)	2014 (1)	All preterm and term babies	Not reported	Not reported
ISN	Italian Society of Neonatology (Italy)	2014 (0)	Newborn Infants >=35 Weeks of Gestation	Not reported	Neonatologists and family pediatricians
MaHTAS	Malaysia Health Technology Assessment Section (Malaysia)	2014 (1)	All preterm and term babies	Conjugated hyperbilirubinaemia, prolonged jaundice	Pediatricians and pharmacists, parents and carers
NPA	Norwegian Pediatric Association (Norway)	2010 (0)	All preterm and term babies	Not reported	Healthcare personnel
AAP	American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (America)	2009 (1)	Newborn Infants >=35 Weeks of Gestation	Not reported	Healthcare personnel
INS	Israel Neonatal Society (Israel)	2008 (0)	All preterm and term babies	Not reported	Neonatologists, pediatricians and family doctors
SSN	Swiss Society of Neonatology (Swiss)	2007 (2)	Newborn Infants >=35 Weeks of Gestation	Not reported	Not reported

QCG: Queensland Clinical Guidelines (Australia); CPS: Canadian Pediatric Society, Fetus and Newborn Committee (Canada); TPA: Turkish Pediatric Association (Turkey); SAP: Spanish Association of Pediatrics (Spain); NICE: National Institute for Health and Care Excellence (the United Kingdom); ChPS: Chinese Pediatric Society, Chinese Medical Association (China); ISN: Italian Society of Neonatology (Italy); MaHTAS: Malaysia Health Technology

Assessment Section (Malaysia); NPA: Norwegian Pediatric Association (Norway); AAP: American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (America); INS: Israel Neonatal Society (Israel); SSN: Swiss Society of Neonatology (Swiss).

Table 2 General characteristics

Guidelines	identification of evidence					guideline review process	Fundings
	database	search terms	dates	detailed search strategy	inclusion/exclusion criteria		
QCG	PubMed, CINAHL, Medline, Cochrane Central Register of Controlled Trials, EBSCO, Embase	Reported	After 2004	Not reported	Not reported	Not reported	Healthcare Improvement Unit, Queensland Health
CPS	MEDLINE, the Cochrane library	Reported	Before 2007	Not reported	Not reported	Reported	Not reported
TPA	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	No financial support
SAP	PubMed	Reported	Not reported	Not reported	Not reported	Not reported	Not reported
NICE	Medline, EBM Reviews, CDSR, DARE, Embase, CINAHL	Reported	Before 2008	Reported	Not reported	Not reported	National Institute for Health and Care Excellence
ChPS	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
ISN	Guidelines from other countries, Studies in Italy	Not reported	Before 2013	Not reported	Not reported	Not reported	Not reported
MaHTAS	GIN, Medline, Pubmed, CDSR	Reported	After 2001	Reported	Reported	External review	Ministry of Health Malaysia
NPA	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
AAP	Not reported	Not reported	Not reported	Not reported	Not reported	Peer review	Not reported
INS	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
SSN	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

QCG: Queensland Clinical Guidelines (Australia); CPS: Canadian Pediatric Society, Fetus and Newborn Committee (Canada); TPA: Turkish Pediatric Association (Turkey); SAP: Spanish Association of Pediatrics (Spain); NICE: National Institute for Health and Care Excellence (the United Kingdom); ChPS: Chinese Pediatric Society, Chinese Medical Association (China); ISN: Italian Society of Neonatology (Italy); MaHTAS: Malaysia Health Technology Assessment Section (Malaysia); NPA: Norwegian Pediatric Association (Norway); AAP: American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (America); INS: Israel Neonatal Society (Israel); SSN: Swiss Society of Neonatology (Swiss).

Table 3 Domain scores (%) of the nine guidelines assessed by using the AGREE-II instrument (%)

	NICE	MaHTAS	QCG	ISN	AAP	TPA	NPA	INS	SAP	SSN	CPS	ChPS	mean±SD
Domain 1	91.7	98.6	91.7	90.3	97.2	84.7	86.1	87.5	73.6	90.3	91.7	81.9	88.8±6.5
Domain 2	93.1	61.1	66.7	61.1	51.4	44.4	50.0	56.9	18.1	36.1	22.2	9.7	47.6±22.4
Domain 3	85.9	62.5	51.0	17.2	40.6	9.9	19.8	18.2	28.1	17.2	22.4	10.4	31.9±22.6
Domain 4	98.6	98.6	98.6	94.4	94.4	87.5	80.6	83.3	91.7	88.9	94.4	88.9	91.7±5.7
Domain 5	85.4	64.6	61.5	26.0	38.5	25.0	57.3	37.5	24.0	39.6	29.2	27.1	43.0±18.9
Domain 6	81.3	89.6	31.3	64.6	25.0	93.8	0.0	4.2	52.1	0.0	0.0	0.0	36.8±36.1
mean±SD	89.3±5.7	79%±17%	66.8±23.0	58.9±29.2	57.9±27.9	57.6±32.8	49.0±30.8	47.9±31.1	47.9±27.2	45.3±33.9	43.3±36.3	36.3±35.7	

Domain 1: scope and purpose; Domain 2: stakeholder involvement; Domain 3: rigor of development; Domain 4: clarity of presentation; Domain 5: applicability; Domain 6: editorial independence.

NICE: National Institute for Health and Care Excellence (the United Kingdom); MaHTAS: Malaysia Health Technology Assessment Section (Malaysia); QCG: Queensland Clinical Guidelines (Australia); INS: Israel Neonatal Society (Israel); AAP: American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (America); TPA: Turkish Pediatric Association (Turkey); NPA: Norwegian Pediatric Association (Norway); ISN: Italian Society of Neonatology (Italy); SAP: Spanish Association of Pediatrics (Spain); SSN: Swiss Society of Neonatology (Swiss); CPS: Canadian Pediatric Society, Fetus and Newborn Committee (Canada); ChPS: Chinese Pediatric Society, Chinese Medical Association (China).

Table 4 Inter rater reliability study results

	ICC	n	k	Lower 95% CI	Upper 95% CI	P value
Domain 1	0.863	12	4	0.670	0.956	0.000
Domain 2	0.989	12	4	0.974	0.997	0.000
Domain 3	0.994	12	4	0.986	0.998	0.000
Domain 4	0.818	12	4	0.561	0.941	0.000
Domain 5	0.995	12	4	0.988	0.998	0.000
Domain 6	0.993	12	4	0.984	0.998	0.000

Domain 1: scope and purpose; Domain 2: stakeholder involvement; Domain 3: rigor of development; Domain 4: clarity of presentation; Domain 5: applicability; Domain 6: editorial independence.

Table 5 Summary of risk factors of severe neonatal jaundice

	NICE	MaHTAS	QCG	INS	AAP	TPA	NPA	ISN	SAP	SSN	CPS	ChPS
Maternal												
Blood group O	NA	+	+	+	+	NA	NA	NA	NA	NA	+	NA
Rhesus negative	+	+	+	+	+	NA	NA	NA	NA	NA	+	NA
Diabetes	NA	+	+	NA	+	NA	NA	NA	NA	NA	NA	NA
Neonatal												
G6PD deficiency	+	+	+	+	+	+	NA	NA	+	NA	+	+
Under 38 weeks	+	+	+	NA	+	+	NA	NA	+	NA	+	+
Exclusive breastfeeding	+	+	+	NA	+	NA	NA	NA	+	NA	+	+
Cephalhaematoma or bruises	-	+	+	NA	+	NA	NA	NA	+	NA	+	+
Sepsis	+	+	+	NA	+	+	NA	NA	+	NA	-	+
Sibling with severe hyperbilirubinemia	NA	+	NA	+	NA	NA	NA	NA	NA	NA	+	NA
Sibling with clinically significant jaundice requiring phototherapy	+	NA	+	NA	+	NA	NA	NA	NA	NA	NA	NA
Visible jaundice at younger than 24 h	+	+	NA	+	+	NA	NA	NA	NA	NA	+	NA
Male	-	NA	+	NA	+	NA	NA	NA	NA	NA	+	NA

NA: not available

NICE: National Institute for Health and Care Excellence (the United Kingdom); MaHTAS: Malaysia Health Technology Assessment Section (Malaysia); QCG: Queensland Clinical Guidelines (Australia); INS: Israel Neonatal Society (Israel); AAP: American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (America); TPA: Turkish Pediatric Association (Turkey); NPA: Norwegian Pediatric Association (Norway); ISN: Italian Society of Neonatology (Italy); SAP: Spanish Association of Pediatrics (Spain); SSN: Swiss Society of Neonatology (Swiss); CPS: Canadian Pediatric Society, Fetus and Newborn Committee (Canada); ChPS: Chinese Pediatric Society, Chinese Medical Association (China).

Table 6 Summary of recommendations for approaches to diagnosis of neonatal hyperbilirubinemia

	NICE	MaHTAS	QCG	ISN	AAP	TPA	NPA	INS	SAP	SSN	CPS	ChPS
Clinical assessment												
Visual assessment (do not rely on it alone)	+	+	+	NA	+	+	NA	NA	+	+	NA	NA
Measurement of bilirubin												
TCB transcutaneous bilirubinometer	+	+	+	+	+	+	+	+	+	+	+	+
TSB	+	+	+	+	+	+	+	+	+	+	+	+
B/A	-	-	NA	NA	+	NA	NA	NA	NA	NA	NA	+
Icterometer	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA	+
Test for prolonged jaundice												
Blood group compatibility	+	+	+	+	+	+	NA	+	+	+	+	NA
Direct antiglobulin test (DAT)	+	+	+	+	+	+	NA	+	+	+	+	NA
G6PD	+	+	+	+	+	+	NA	+	+	NA	+	NA
Conjugated component of bilirubin	+	NA	+	NA	+	+	NA	+	+	+	+	NA
Complete blood count	+	+	+	+	+	+	NA	NA	NA	NA	+	NA
Septic workup (if suspected)	+	+	+	NA	+	+	NA	NA	+	NA	+	NA
Thyroid functions	NA	NA	+	NA	+	+	NA	+	+	NA	NA	NA
Urinalysis, urine culture	NA	NA	+	NA	+	+	NA	+	+	NA	NA	NA
Reticulocyte count	NA	+	+	NA	+	+	NA	NA	NA	NA	NA	NA

NA: not available

NICE: National Institute for Health and Care Excellence (the United Kingdom); MaHTAS: Malaysia Health Technology Assessment Section (Malaysia); QCG: Queensland Clinical Guidelines (Australia); INS: Israel Neonatal Society (Israel); AAP: American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (America); TPA: Turkish Pediatric Association (Turkey); NPA: Norwegian Pediatric Association (Norway); ISN: Italian Society of Neonatology (Italy); SAP: Spanish Association of Pediatrics (Spain); SSN: Swiss Society of Neonatology (Swiss); CPS: Canadian Pediatric Society, Fetus and Newborn Committee (Canada); ChPS: Chinese Pediatric Society, Chinese Medical Association (China).

Table 7 Summary of recommendations for approaches to treatment of neonatal hyperbilirubinemia

		NICE	MaHTAS	QCG	ISN	AAP	TPA	NPA	INS	SAP	SSN	CPS	ChPS
Phototherapy													
Conventional irradiance (μW/cm²/nm)		NA	>15	25-30	NA	NA	8-10	NA	NA	8-12	NA	NA	8-10
Intensive irradiance (μW/cm²/nm)		NA	>30	>30	> 35	>30	30-65	>20	>30	>30	NA	>30	>30
Distance between light and baby (cm)		NA	< 30 - 50	10–15	NA	About 10	35-40	20	about 10	10	NA	10	NA
Intensive phototherapy threshold for fullterm babies>96h (μmol/L)	**Well**	350	359	359	343	359	359	359	359	359	350	359	359
	With risk factors	NA	308	308	NA	308	291	308	308	308	300	257	308
Home phototherapy		NA	NA	+	NA	+	NA	NA	+	NA	NA	NA	NA
Sunlight Exposure		-	NA	-	NA	-	NA	NA	-	-	NA	NA	NA
Complications		+	NA	+	NA	+	+	NA	+	NA	NA	+	+
Exchange transfusion													
Exchange transfusion threshold for fullterm babies>96h (μmol/L)	**Well**	450	428	428	428	428	428	450	428	428	430	428	428
	With risk factors	NA	393	393	NA	376	393	NA	376	376	370	325	376
Detail observation during ET		NA	+	NA	+	NA	NA	NA	NA	NA	NA	NA	+
Maintain intensive PT after ET		+	+	+	+	NA	+	NA	NA	NA	NA	+	+
Measure TSB after ET		within 2h	4 – 6h	within 2h	within 2h	NA	within 2h	NA	NA	NA	NA	NA	within 4h
Complications		+	+	+	+	+	+	NA	+	NA	NA	+	NA
Pharmacotherapy													
Intravenous immunoglobulin		+	-	-	+	+	+	NA	+	+	NA	+	+
Human albumin		-	-	-	NA	NA	NA	NA	NA	NA	NA	NA	+
Clofibrate		-	-	-	NA	NA	NA	NA	NA	NA	NA	NA	NA
Tin-mesoporphyrin		NA	-	NA	NA	-	NA	NA	NA	NA	NA	+	NA

NA: not available

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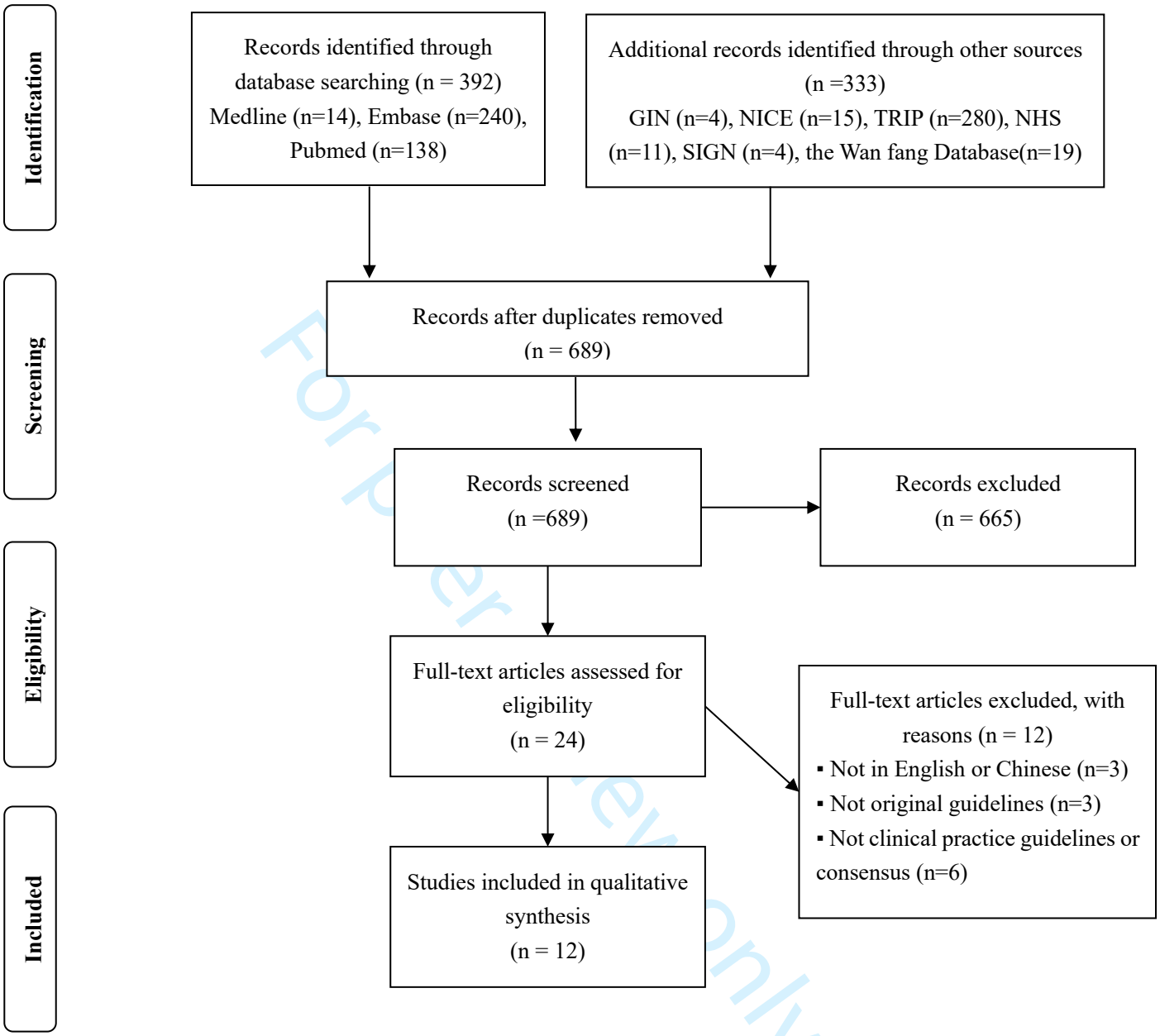
Figure 1 Study selection diagram



GIN: the Guidelines International Network, NICE: the National Institute for Health and Care Excellence, TRIP: the Turning Research Into Practice Database, NHS: the National Health Service Evidence, SIGN: the Scottish Intercollegiate Guidelines Network

Searching strategy of PubMed

#1 Neonatal hyperbilirubinemia [Mesh] OR Neonatal Hyperbilirubinemia OR Hyperbilirubinemia During Infancy OR During Infancies, Hyperbilirubinemia OR Infancy, Hyperbilirubinemia During OR Indirect Hyperbilirubinemia, Neonatal OR Hyperbilirubinemia, Neonatal Indirect OR Neonatal Indirect Hyperbilirubinemia OR Direct Hyperbilirubinemia, Neonatal OR Hyperbilirubinemia, Neonatal Direct OR Neonatal Direct Hyperbilirubinemia

#2 Jaundice, Neonatal [Mesh] OR Neonatal Jaundice OR Physiological Neonatal Jaundice OR Jaundice, Physiological Neonatal OR Neonatal Jaundice, Physiological OR Severe Jaundice in Newborn OR Severe Jaundice in Neonate OR Icterus Gravis Neonatorum

#3 Clinical practice guidelines [Mesh]

#4 #1 OR #2

#5 #3 AND #4

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMAreporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

		Reporting Item	Page Number
Title			
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured	#2	Provide a structured summary including, as applicable:	2

summary		background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	
Introduction			
Rationale	#3	Describe the rationale for the review in the context of what is already known.	3
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
Methods			
Protocol and registration	#5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number.	NA
Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	3
Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	3-4

Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	The supplementary material
Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	3-4
Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	4
Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	4
Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	NA
Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	4

Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
Results			
Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	Table 1 and 2
Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	NA
Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	5-7
Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	5-7
Risk of bias	#22	Present results of any assessment of risk of bias across	NA

across studies		studies (see Item 15).	
Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 3 and 4
Discussion			
Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	7-8
Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
Funding			
Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	1