# The association between serum bilirubin and kernicterus spectrum disorder: A systematic review and meta-analysis

# Online supplementary data

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## Appendix 1: search strategies

## 1 Medline (PubMed) search strategy

#1 infant\* [TIAB]

#2 "Infant, newborn"[Mesh]

#3 newborn\* [TIAB]

#4 neonat\* [TIAB]

#5 (#1 OR #2 OR #3 OR #4)

#6 bilirubin [Mesh]

#7 bilirubin [TIAB]

#8 (#6 OR #7)

#9 bilirubin encephalopathies[MeSH Terms]

#10 bilirubin encephalopath\*[Title/Abstract]

#11 kernicterus[MeSH Terms]

#12 kernicterus[Title/Abstract]

#13 "bilirubin induced neurologic dysfunction"[Title/Abstract]

#14 brain injuries[MeSH Terms]

#15 brain injur\*[Title/Abstract]

#16 (#9 or #10 OR #11 OR #12 OR #13 OR #14 OR #15)

#17 (#5 AND #8 AND #16)

## 2 EMBASE search strategy

1. (Infant\*) in TI, AB

2. Explode “infant, newborn”/all subheadings

3. (newborn\*) in TI, AB

4. (neonat\*) in TI, AB

5. #1 OR #2 OR #3 OR #4

6. Explode “bilirubin”/all subheadings

7. (bilirubin) in TI, AB

8. #6 OR #7

9. Explode “bilirubin encephalopathies”/all subheadings

10. (bilirubin encephalopath\*) in TI, AB

11. Explode “kernicterus”/all subheadings

12. (kernicterus) in TI, AB

13. (“bilirubin induced neurologic dysfunction”) in TI, AB

14. Explode “brain injuries”/all subheadings

15. (brain injur\*) in TI, AB

16. #9 or #10 OR #11 OR #12 OR #13 OR #14 OR #15

17. #5 AND #8 AND #16

## 3 CENTRAL search strategy

1. MeSH descriptor: [Infant, Newborn]explode all trees

2. (newborn\*):ti,ab,kw

3. (neonat\*):ti,ab,kw

4. (infant\*):ti,ab,kw

5. #1 OR #2 OR #3 OR #4

6. MeSH descriptor: 43explode all trees

7. (Bilirubin):ti,ab,kw

8. #6 OR #7

9. MeSH descriptor: [Kernicterus] explode all trees

10. (kernicterus):ti,ab,kw

11. (bilirubin encephalopath\*):ti,ab,kw

12. (“bilirubin induced neurologic dysfunction”):ti,ab,kw

13. MeSH descriptor: [Brain Injuries] explode all trees

14. (brain injur\*):ti,ab,kw

15. #9 OR #10 OR #11 OR #12 OR #13 OR #14

16. #5 AND #8 AND #15

## Appendix 2: Detailed description of the methods

## Data collection and analysis

***Data extraction and management***

Two review authors (JPG and NML) independently screened the articles based on the titles and abstracts and generated a shortlist of potentially eligible studies. We then assessed the shortlisted studies in more detail to determine final eligibility. We coded all data from each eligible study using a pro forma designed specifically for this review, developed according to the CHARMS checklist1. We focused on TSB value, or any classification of infants based on a certain TSB threshold, and extracted the information as our main predictive or prognostic factor, as this is the main parameter on which management on neonatal jaundice is currently based. We also extracted, as our secondary prognostic factors, clinical and other laboratory risk factors, and the outcome of KSD and its related complications. Each review author cross-checked entry made initially by another author to detect error or duplication, and resolved disagreement by discussion leading to a consensus, with referral to a third review author (CFG) if necessary.

***Assessment of risk of bias in included studies***

Two authors (JPG and NML) assessed the risk-of-bias (RoB) of the included studies in duplicates using the QUIPS tool2, which comprises 28 items under six domains (study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting), with possible ratings of low, moderate or high risk. We judged the overall RoB of the study based on a global assessment on the RoB across the six domains, using the following criteria as a guide3 after a round of deliberation among the review authors: if all domains are classified as having low RoB or not more than one medium RoB, the study is considered to have an overall low RoB. If one or more domains are classified as having high RoB or ≥3 with medium RoB, the study is then considered to have high RoB. All studies in between are considered to have medium RoB. We discussed any disagreement with the third author (AAK) serving as arbitor if necessary. We planned to use the overall risk of bias status of the study in two areas: first, our sensitivity analysis, in which we determined the impact of excluding studies with overall high risk of bias on the pooled estimate (as detailed under the heading of Sensitivity analysis), and next, the certainty of evidence rating using the GRADE approach, where we downgrade the certainty of evidence by one or two levels if we considered the study to be of serious or very serious concern with regards to its risk-of-bias status (as detailed in the subsequent segment on certainty of evidence rating).

***Measures of association between the predictive or prognostic factor and the outcome***

We extracted the adjusted effect measures, mainly in the form of adjusted odds ratio or risk ratio. Our chief independent variable was TSB measured either in mg/dl or micromol/L. Additionally, we extracted other possible prognostic factors such as haemolysis, sepsis, acidosis, prematurity and demographic factors. Our chief dependent variable was KSD, defined broadly as in our definition of outcome.

The effect measures were extracted with their uncertainties, expressed as standard errors, variances or 95% confidence intervals to be pooled in our meta-analysis. We converted the adjusted risk ratio to adjusted odds ratio in our analysis using the RevMan calculator, and expressed our results using adjusted odds ratio.

We summarised the results of the trials narratively if pooled analyses were not possible.

***Dealing with missing data***

If effect measures (such as adjusted odds ratio or risk ratio) and their measures of precision (such as 95% confidence interval, SE or SD) were not reported in the included studies, we would attempt to derive the corresponding measures where possible by using information provided in the paper by referring to the approach suggested in Altman et al 20034. If this was impossible, we would summarise the findings of the studies narratively.

We determined the dropout rates from each trial, and considered a dropout rate of higher than 20% as significant. If we found a significant dropout rate with no reasonable explanation, we assigned the trial as having high risk-of-bias in the criterion related to missing data. If we considered the extent of missing data to be critical to the final estimates in our meta-analysis, we planned to contact the authors of the individual trials to request further information.

In this review, most studies were judged to have low risk of bias in the area of missing data as most studies had complete follow-up especially when the outcomes were assessed during the NICU stay. Should there have been studies that were at high risk of attrition bias, we would have performed sensitivity analyses to assess how the overall results were affected with and without the inclusion of such studies.

***Dealing with heterogeneity***

We used I² statistics to quantify the degree of inconsistency in the results, in accordance with the recommendations of the Cochrane Handbook. We used the cut-off of 75% to indicate substantial heterogeneity. As heterogeneity is inherent in a body of prognostic studies, our adopted threshold is higher than that usually adopted for a review of randomised controlled trials5.

If the I statistics was above 75%, we would explore the following criteria to determine plausible factor/s that could explain the degree of heterogeneity:

* Baseline characteristics of the participants (gestational age, birth weight, presence of concurrent risk factors such as haemolysis), and definition of hyperbilirubinaemia (namely, by the use of different cut-offs of TSB).
* Clinical settings of the studies (e.g. tertiary or secondary neonatal unit).
* Interventions used to manage neonatal hyperbilirubinaemia
* Risk of bias.

If we identified plausible factor/s from the criteria above that could explain a major part of heterogeneity, by virtue of a substantial reduction of I2 estimate following the removal of the studies concerned, we would determine whether the difference between study characteristics was too great for a meta-analysis to be appropriate, and if a meta-analysis is still appropriate, whether to separate the studies into different subgroups based on the plausible sources of heterogeneity.

***Assessment of reporting deficiencies***

We used the funnel plot to screen for reporting deficiencies or publication bias if there were sufficient included studies (greater than 10) using the same measures to report the association. If reporting deficiencies or publication bias was suggested by a clear asymmetry of the funnel plot, we planned to include a statement in our results with a corresponding note of caution in our discussion, bearing in mind the limitations of funnel plot in detecting publication bias especially in studies on prognosis6. We planned to use statistical test recommended for prognosis studies, such as the Begg's test to quantify possible degree of publication bias, as the test is robust across situations of high and low heterogeneity with normally and non-normally distributed data7. In this review, there were insufficient studies for each reported association, so no formal assessments of reporting deficiencies were performed. However, a suspicion on publication bias has been incorporated in our assessment on the certainty of evidence for the analysis that compared TSB values between infants with and without KSD with an explanation on the footnote, because we considered it reasonable to expect more publication than that were currently available (please refer to the GRADE rating document in *Appendix 6*)

***Data synthesis and meta-analysis approaches***

While we extracted all outcome data that were suitable for meta-analysis, meta-analysis was possible if there were at least two studies with sufficiently robust and comparable estimates of the association between the predictive factor and the outcomes. Specifically, we pooled study data on the association of TSB with KSD assessed in the same period in a similar manner using the same estimates such as adjusted Odds Ratio (OR), or risk ratio (RR). We converted all estimates to Odds Ratio (OR) using the RevMan calculator to standardise the estimates. We extracted all data from adjusted estimates from multivariate analysis, apart from the data in analysis 3 that compared the TSB values of infants with and without KSD. We performed meta-analysis via generic inverse variant approach8 using a random effect model to allow for unexplained heterogeneity across studies that is inherent in all prognosis studies9.

For studies in which meta-analysis was impossible, for example, studies with descriptive reports of serum bilirubin and KSD without an appropriate evaluation of their association via methods such as logistic regression, we summarised the results narratively.

For the outcome of developmental screening test scores between infants with and without hyperbilirubinaemia, we pooled effect estimates from studies that used different scales of assessment using standardised mean difference. We converted all mean differences into standardised mean differences by dividing the mean differences and their corresponding SEM with the SD of the whole participant group (which we either derived from combining the SDs of the exposed and non-exposed groups or where these were not provided, adopted a typical SD of the scale as given by the author10).

***Subgroup analysis and investigation of heterogeneity***

If sufficient data were available, we planned to perform the following subgroup analyses:

1. Study design (cohort or registry-based, RCT-based or case control)
2. Population (setting of the study (developed vs developing countries), term vs preterm infants, general newborn population vs selected "high-risk" infants based on serum bilirubin value and/or clinical assessment)
3. Predictive factors (methods of serum bilirubin measurement (e.g. serum or transcutaneous), e.g. maximum value vs mean value, timing of measurement)
4. Outcome measurement, e.g. different conditions in the spectrum of KSD, different definition of each condition.

We planned to use random effect meta-regression (Berkey et al, 1995) to test subgroup differences if one or more study-level covariate that we consider as possible effect modifier for the outcomes concerned (risk of KSD and related conditions) are clearly stated in the studies, such as the gestation period, birth weight, presence or absence of symptoms suggestive of KSD, presence or absence of symptoms suggestive of pathological hyperbilirubinaemia, such as that due to haemolytic process from any cause, and/or infection, and if there were more than 10 included studies.

In this review, data were insufficient for us to perform the subgroup analysis based on the aforementioned factors.

***Sensitivity analysis***

We planned to perform sensitivity analyses provided a sufficient number of trials were included to assess the impact of excluding trials with high risk of attrition bias, although such analysis was not required, as most studies had complete data for the major outcomes assessed.

***Rating of certainty of evidence and summary of findings table***

We rated the certainty of evidence using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach adapted for studies on prognosis11,12. Two review authors (NML, KHCJ) independently assessed the certainty of the evidence. We considered evidence from a body of well-conducted observational studies or a single arm of randomised controlled trials (RCT) as high-certainty by default, but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: phase of investigation, study limitations (risk-of-bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We accepted greater degree of heterogeneity compared to interventional studies, as detailed under the previous heading of dealing with heterogeneity, because differences in measurement methods, adjustment factors and statistical analyses, amongst others give rise to inevitable heterogeneity among studies on prognosis. We also put due consideration in the domain of publication bias, as selective reporting or publication bias is considered as more likely in prognosis than intervention studies due probably to the greater proportion of negative results in studies considered as exploratory or preliminary, suboptimal reporting and inappropriate analysis methods13. We upgraded the certainty of evidence based on the following criteria: large effect and a dose-response gradient. We manually constructed a 'Summary of findings' tables to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades:

* High: we are very confident that the true effect lies close to that of the estimate of the effect.
* Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
* Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
* Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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# Appendix 3

# eTable 1: Characteristics of included studies

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Last name of first author** | **Year** | **Study design** | **Population description**  | **Participant Exclusion criteria** | **Country (s)**  | **Total no of participants**  | **Names of outcome (e.g. kernicterus, BIND, hearing impairment etc)** | **Time of outcome measurement**  | **Rate of KSD (%)** | **Name of predictor**  | **Other covariates (to be adjusted, like gestational age, birth weight, co-morbidities etc)**  |
|
| Amin  | 2001 | Prospective cohort study | All premature newborn, 28 to 32 weeks’ gestational age, admitted to the NICU from July 1996 to July 1998 | Hypothermia, chromosomal abnormalities, TORCH infections, instability for baseline testing | US | 143 | Auditory brainstem responses (ABR) | During the first postnatal week | 38.40 | Serum total bilirubin (peak), serum, albumin (B/A ratio) | Gestational age, birth weight, gender, Apgar score, hemolysis, sepsis, pC02, pH, p02, intraventricular hemorrhage, albumin |
| Ardakani  | 2011 | Prospective cohort study | Admission in neonatal ward and severe hyperbilirubinemia (SB > 18 mg/dl) | Hydrops fetalis, congenital nephritic syndrome, diseases that mimic BIND, death due to other reasons | Iran | 52 | Acute BIND (based on clinical findings) | At discharge | 9.60 | Total serum bilirubin (mean), B/A ratio | Blood group incompatibility (ABO, rh), mode of delivery (univariate) |
| Arnolda  | 2015 | Retrospective cohort study | Diagnose of ABE at hospital presentation | None | Myanmar | 590 | Acute bilirubin encephalopathy |   | 17.60 | Risk factors for ABE, Total serum bilirubin (TSB) (on admission) | Preterm, previous sibling, significant "bruising", suspected infection, G6PD, ABO, Rh (univariate) |
| Bao  | 2013 | Retrospective observational study | Infants with GA > 35 weeks and with ABE | Chromosomal disorders, cranio-facial malformations, family history of hearing loss since childhood | China | 116 | Acute bilirubin encephalopathy or kernicterus |   |   | Peak total serum bilirubin (peak)  | Perinatal asphyxia, ABO and Rh, sepsis and infection, birth trauma (univariate) |
| Behjati-Ardakani  | 2006 | Prospective study | Neonates with icterus admitted for treatment of hyperbilirubinemia from 2003-2004 |  | Iran | 305 | ABE or kernicterus, hearing loss | “As soon as signs and symptoms appear” | 8.20 | Total serum bilirubin (peak) |  |
| Besli | 2020 | Prospective cohort study  | Gestational age, ≥ 37 weeks, birth weight, ≥2500 g; sTB levels above physiological limits that required treatment | Asphyxia, birth trauma, metabolic disorders (hypoglycemia, hypocalcemia, acidosis, electrolyte disorder and hypoalbuminemia); neonatal infections; intrauterine infection, congenital metabolic disease, congenital anomaly, pathologies that may lead to neonatal cerebral damage such as intracranial hemorrhage; and family history of hearing loss, and suitability for long term follow-up | Turkey  | 207 | Hearing acuity (ABR, OAE and tympanometry), Auditory Brainstem responses Otoacoustic emissions, Denver II Developmental Screening Test. | Postnatal 18-24th months | 12.2 | TSB (peak) and duration of exposure to sTB levels >20 mg/dl  | Neurological dysfunction (clinical assessment) (univariate) |
| Bozkurt  | 2020 | Prospective cohort study  | Infants with ≥35 weeks of gestation admitted with diagnosis of severe hyperbilirubinemia in a period of 18 months.  | Infants born at <35 weeks of gestation and with congenital /chromosomal anomalies were excluded.  | Turkey  | 115 | “Severe hyperbilirubinemia”, acute bilirubin encephalopathy (ABE) | First 6 h of admission | 39.10 | Total serum bilirubin (mean), B/A ratio | G6PD, ABO and Rh, being refugee, early discharge (univariate), G6PD, early discharge, being refugee, rh isoimmunisation (multivariate) |
| **Colak**  | 2016 | Retrospective study | Hospitalized infants with serum total bilirubin levels ≥25 mg/dl  |   | Turkey | 36 | Neurodevelopmental outcomes  | Postnatal 12 and 24 months |   | Total serum bilirubin > 25 mg/dl (peak) | No other factors mentioned (abstract only)  |
| Diala  | 2018 | Prospective longitudinal hospital-based observational study | Newborns treated for jaundice between February 2014 and June 2015 (9 major hospitals) | Undocumented outcomes, deaths from unrelated causes, weighing < 1000g | Nigeria | 1040 | Presence of ABE subdivided into mild ABE, moderate/ severe ABE, death from ABE, or ABE/ suspect sepsis | Not stated | 15.30 | Risk factors for ABE, TSB (on admission) | TSB, age at admission, weight, mother’s age, no of antenatal care, site of birth (hospital or outside) (univariate), non-alloimmune hemolysis, 1 or no antenatal visit, delayed in receiving care, out-of-hospital birth and type of birth attendance (multivariate) |
| Donneborg  | 2020 | Retrospective registry-based study  | TsB ≥ 450 µmol/L, ratio of conjugated to total bilirubin < 0.30, gestational age ≥35 weeks and age ≤4 weeks. (nationwide study) | Conjugated hyperbilirubinemia, gestational age <35 weeks, and postnatal age >4 weeks | Denmark | 408 | KSD, ABE | Not stated | 2.94 | total serum bilirubin (TSB, peak) ≥ 450 µmol/L, ratio of conjugated to total bilirubin < 0.30 | ABO isohemolytic disease, cephalohematoma, galactosemia, rhesus hemolytic disease, spherocytosis, G6PD def, congenital hypothyroidism (descriptive)  |
| Duman  | 2004 | Prospective study | Otherwise healthy singleton term newborn infants with marked indirect hyperbilirubinemiaduring first 2 weeks of life. | Blood group incompatibilities, positive Coombs' test, G6PD deficiency, any laboratory evidence of hemolytic disease, perinatal factors such as maternal diabetes mellitus, polycythemia,cephalhematoma, asphyxia, intracranial hemorrhage, perinatal infection, dehydration, infants with metabolic or major congenital abnormalities  | Turkey | 60 | Clinical and laboratory features of ABE | 2-6 years of age |   | Marked hyperbilirubinemia > 20 mg/dl, peak TSB (during first two weeks of life) | Sociodemographic characteristics, mode of delivery (univariate) |
| Ebbesen  | 2012 | Retrospective study | All infants born at gestational age > 35 weeks in Denmark between 2000-2007 with a TSB > 450µmol/L | Not stated | Denmark | 502766 | Bilirubin encephalopathy |   | 0.01 | Total serum bilirubin levels (peak)  | Clinical signs and symptoms of infants with ABE, possible aetiology including ABO incompatibility, G6PD deficiency (descriptive)  |
| ElTatawy  | 2019 | Prospective cohort study  | 177 term/near-term infants admitted for neonatal hyperbilirubinemia.  | admission age > 14 days, perinatal hypoxia, < 35 weeks gestation, clinical disease other than jaundice and unable to attend follow up | Egypt  | 177 | Psychomotor (PDI) and mental developmental indices (MDI) using BSIDII. Auditory impairment using Auditory Brainstem Response (ABR) | In the first year of life  | 13.60 | Total serum bilirubin (TSB) (on admission) | BIND score, duration of exposure to hyperbilirubinaemia, hemolysis (correlation with impaired MDI and PDI at different periods of assessment) |
| Hameed  | 2011 | Retrospective observational study | Term and late preterm infants admitted to Children Welfare Teaching Hospital for management of severe neonatal jaundice during a 4-month period in 2007 and 2008 | Direct hyperbilirubinemia, cholestasis, low risk hyperbilirubinemia | Iraq, US | 162 |  Acute , advanced and chronic bilirubin encephalopathy |   | 22.20 | Total serum bilirubin (peak)  | Home delivery, sepsis, ABO/Rh disease, presence of ABE (for long-term adverse outcomes - chronic kernicterus or death) (univariate) |
| **Harris**  | **2001** | Retrospective study | Infants (from 1993-1996) >/=36 weeks' gestational age who were readmitted to the hospital during the first week of life with bilirubin levels >25 mg/dL |  | US | **6** | Bilirubin encephalopathy |  |  | Total serum biliruin > 25 mg/dl (peak)  | Clinical signs, sepsis (descriptive).  |
| Iskander  | 2014 | Prospective longitudinal observational study | Term/ near term infants admitted for severe jaundice  | Not stated | Egypt  | 193 | Neurologic status, auditory impairment, BIND score | At admission and post-treatment | 30 | TSB (peak), B/A ratio | Clinical risk factors (like low birth weight, hemolysis) not included in univariate or multivariate analyses.  |
| Jangaard  | 2008 | Retrospective population-based cohort study | Healthy term/ near term infants > 35 weeks gestational age with serum bilirubin levels > 325µmol/L born between 1994 and 2000 | Rh factor isoimmunization, significant congenital or chromosomal abnormalities, orsevere peripartum asphyxia Apgarscores of 3 at 5 minutes of age, or documented hypoxic-ischemic encephalopathy | Canada | 56019 | Deafness, cerebral palsy, developmental delay, gazepalsy, attention-deficit disorder, autism spectrum disorders and a composite of all outcomes | Follow-up periods ranged from 2 to 9 years |   | Total serum bilirubin (peak) defined as TSB levels of 230 mol/L ( 13.5 mg/dL) | Year of birth, region of residence, marital status, maternal age, parity (number of previous viable pregnancies), gravidity (number of previouspregnancies), multiple birth, any breastfeeding at discharge, maternal smoking at the time of birth admission, type of delivery (vaginal versus cesarean), pretermdelivery, infant gender, small-for-gestational age status, infection, fetal malnutrition, evidence of mild birth depression, respiratory distress syndrome, infant anemia, intrauterine hypoxia (defined as polycythemia or reticulocytosis), ABO isoimmunization, gestational diabetes mellitus, and pre-existing maternal diabetes mellitus (effect sizes not reported in multivariate analysis)  |
| Kang  | 2020 | Prospective nested case control study | Newborns of gestational age ≥ 35 weeks and diagnosed with ABE were includedin the study |  (1) Hypoxic-ischemic encephalopathy, hypoglycemic encephalopathy, and neonatal encephalopathy with infection; (2) Congenital brain injury such as genetic, metabolic, and malformationdiseases; (3) Congenital auditory deformity.  | China | 87 | ABE (BIND score), hearing (AABR), brain MRI.  | Surviving infants were followed up at 3, 6, 12, and 18 months  |   | TSB peak value and B/A ratio  | Hemolysis (ABO and Rh), sepsis, haemorrhage, MRI abnormal, abnormal ABR, BIND score (bivariate logistic regression) (we only included sepsis in the meta-analysis as we considered abnormal BIND score and abnormal AABR findings as part of the criteria for diagnosing ABE) |
| Kumar  | 2016 | Prospective study | Neonates > 35 weeks gestation admitted to NICU with a serum bilirubin >20 mg% in first 72 h of life or >25 mg% | Neonates with Apgar score <3 at 5 min, hypoxic ischemic encephalopathy at stage 3, major congenital malformations, conjugated bilirubin >2 mg%, metabolic disorders, and meningitis were excluded.  | North India | 64 | Bilirubin encephalopathy, mortality, risk factors for development of ABE. | Discharged neonates were followed at 1, 3, and 6 months for chronic bilirubin encephalopathy (CBE). | 44 | TSB not assessed as a predictor (infants enrolled were those with high TSB).  | Admission weight, home delivery, top feeding, Rh or ABO incompatibility, positive Coombs, sibling's with jaundice, G6PD def., culture proven sepsis, hypalbuminaemia, normal vaginal delivery, early discharge (all univariate OR not reported)  |
| Morioka  | 2015 | Retrospective cohort study | Extremely low birth weight (ELBW) infants with clinical kernicterus | Not stated | Japan | 18 | Clinical kernicterus | Retrospective |   | Total bilirubin (peak), serum unbound bilirubin |  |
| Murki  | 2001 | Prospective cohort study  | Term neonates with severe non-hemolytic jaundice  | Hemolysis, major congenital malformations | India  | 64 | Kernicterus |   | 21.80 | Peak. total serum bilirubin, free bilirubin, serum albumin, B/A ratio, free fatty acid level | Gestation, birth weight, asphyxia |
| Nabavi  | 2011 | Prospective descriptive analytic study - only English abstract provided | Healthy term infants > 37 weeks who required treatment or was treated with phototherapy or exchange transfusion for elevated bilirubin levels or jaundice | Not stated | Germany | 64 | Hearing impairment | 2 year period (2007-2009) | 4.70 | Serum bilirubin  | Not stated |
| Nakamura  | 1992 | Prospective cohort study | Low birthweight infants treated with phototherapy for non-hemolytic hyperbilirubinemia | Hemolytic diseases, grade 3 IVH, CNS abnormalities | Japan | 138 | Kernicterus | 3 years follow up period |   | Serum unbound bilirubin, total serum bilirubin | Birth weight and gestational age (all descriptive)  |
| Nasiri  | 2018 | Retrospective cohort study | Infants with hyperbilirubinemia referred to the clinic of pediatric neurology during the years 2011 to 2016 |   | Iran | 19 | Kernicterus | Clinic follow-up |   | TSB, other risk factors of kernicterus | ABO, Rh incompatilibity, G6PD (only narrative description)  |
| Newman  | 1993 | Prospective cohort study | Infants with TSB recorded and survived beyond 1 year  | “Nonsingleton births, and 5827 with birth weight <2500 g (n = 5601) or unknown (n = 226). Second, we excluded 3595 infants with race other than black or white, because the number of such infants was too small for separate consideration and the differences observed between blacks and whites made us reluctant to include infants of other races with either group. Finally, we excluded 2510 infants for whom no bilirubin measurements were recorded, and 391 who died before their first birthday.”  | US | 41324 | IQ, neurologic examination, sensorineural hearing loss | IQ at age 7 years, neurologic examination at age 1 and 7 years, sensorineural hearing loss at age 3 and 8 years. | 0.16 | Peak TSB, total serum bilirubin > 25 mg/dl  | birth weight, birth weight squared, maternal education, feeding method, gender oxytocin use, direct Coombs’ test, prematurity and race (results of analysis in these factors not reported)  |
| Newman  | 2006 | Prospective cohort study | Infants with total serum bilirubin levelsof 25 mg per deciliter or more within 30 daysafter birth (the case subjects) or were randomlyselected (the controls) from the birth cohorts of1995 through 1996 and 1997 through 1998 in a1:1 ratio of projected subjects  |  | US | 559 | Adverse neurodevelopmental outcomes of hyperbilirubinemia (kernicterus) | Data on outcomes were obtained fromelectronic records, interviews responses to questionnaires, and neurodevelopmentalevaluations |   | Total serum bilirubin > 25 mg/dl (peak)  | Assessments of parental depression , G6PD status, haemolysis (results of direct antiglobulin test). family income, parents’ races and educational levels, maternal age, maternal smoking status, sex, gestational age, small size for gestational age (below the 10th percentile), five-minute Apgar score, initial exclusive breast-feeding, parental depression,and examining clinician (these factors were either not included in multivariate analysis or their effects not reported) |
| Ochigbo  | 2016 | Retrospective descriptive review | Newborns diagnosed with bilirubin encephalopathy from January 2010 to December 2014 | Not stated | Nigeria | 21 | Bilirubin encephalopathy |  |   | Total serum bilirubin (peak) | Septicaemia, ABO incompatibility, G6PD deficiency (descriptive only)  |
| Ogunlesi  | 2011 | Prospective cohort study | Term infants presenting with moderate to severe jaundice defined as total serum bilirubin (TSB) of at least 15 mg/dl at the point of admission | Preterm babies, babies with TSB<15 mg/dl and babies who developed jaundice afterhospitalization | Nigeria | 152 | Acute bilirubin encephalopathy |   | 49.30 | Total serum bilirubin (admission)  | Severe anaemia, acidosis, hypoglycaemia, low social economic classes, delayed presentation  |
| Oh  | 2003 | Retrospective cohort study | ELBW infants (401–1000 g) who survived to 14 days of age in the 12 participating centers of the National Institute of Child Health and Human Development Neonatal Research Network between January 1, 1994, and December 31, 1997 | PSBs that were recorded beyond the first 14 days oflife | US | 3246 | Neurodevelopmental outcomes (cerebral palsy, hearing impairment, blindness) | At 18-22 months' corrected age |   | Peak total serum bilirubin | Demographic risk factors of birth weight; male sex; mother younger than 20 years; mother not a high school graduate; Medicaid insurance recipient; and clinical risk factors of antenatal steroids, surfactant therapy, intraventricular haemorrhage (IVH) grade 3 or 4, chronic lung disease (CLD), periventricular leukomalacia (PVL),late-onset sepsis, proven necrotizing enterocolitis (NEC), postnatal steroids. |
| Ou | 2020 | Retrospective observational study | Extreme hyperbilirubinemia newborns hospitalized from January 1, 2012 to December 31, 2019. The inclusion criteria were as follows: TSB ≥ 25mg/dl (428 μmol/L), gestational age (GA) ≤ 35 weeks, and age at admission ≤14 days. | Conjugated bilirubin >20% TSB, intracranial infection, hypoxic–ischemic encephalopathy, chromosome abnormality, and congenital craniocerebral malformation | China  | 517 | ABE | Within 24 hours of admission  | 19.7 | Total serum bilirubin  | GA, premature rupture of membranes, type of delivery, birth weight (BW), type of feeding, mother's age, hypertensive disorders in pregnancy, gestational diabetes mellitus, intrauterine distress, and meconium-stained amniotic fluid. The pathological information included cranial hematoma, intracranial hemorrhage, isoimmune hemolysis, sepsis, polycythemia, and asphyxia. The admission examination results included WBC, red blood cell (RBC), hemoglobin (Hb), platelet, C-reactive protein, albumin, blood glucose |
| **Pledger**  | 1982 | Retrospective study | Jaundiced, low birthweight neonates |   | UK | 39052 | Kernicterus | 10-year review period | 0.04 | Serum bilirubin (peak), albumin-binding capacity |   |
| Ritter  | 1982 | Prospective study | Infants with birth weigh < 1500g with postnatal age < 24 hours, appropriate weight, respiratory distress requiring oxygen or mechanical ventilation, negative direct Coombs test and informed consent from parents | Not stated | US | 91 | Kernicterus | Not stated | 7.70 | Total bilirubin (peak), free bilirubin and serum albumin | HMD, IVH, sepsis, hyopglycaemia (descriptive analysis)  |
|  Unal  | 2010 | Prospective study | Term and near term infants treated in the NICU with total bilirubin level over 25mg/dl  | Not stated | Turkey | 30 | Bilirubin encephalopathy (value of BAER as reliable test for neurologic outcome) | 3 years follow up period | 16.70 | Total bilirubin > 25 mg/dl (not stated peak or admission) | ABO incompatability, low birth weight, G6PD deficiency, breast milk jaundice, cephalohaematoma (descriptive only)  |
| Vandborg  | 2012 | Controlled descriptive follow-up cohort study | All live-born infantsin Denmark from 2004 to 2007 with a gestational age >35 weeks andsevere hyperbilirubinemia in the neonatal period, defined as at least 1measure of total serum bilirubin level >25 mg/dL during the first 3weeks of life. | Infantswith intermediate or advanced acutebilirubin encephalopathy, rhesus isoimmunization,and conjugated hyperbilirubinemia | Denmark | 414 | Developmental delay | Age 1-5 years | 55 | Total serum bilirubin (peak)  | Gender, age, GA |
| Vandborg  | 2015 | Nested double-cohort study | 167 exposed children born in Denmark 2000 to 2005 at gestational age ≥35 weeks with a total serumbilirubin ≥450 micromol/L (26.3mg/dL) and 163 age-, sex-, and gestational age-matchedunexposed children | Not stated | Denmark | 330 (167 exposed, 163 unexposed) | Long-term sequelae, withimpairment of motor development, executive function, or hearing | At age 5-10 years old, mean age of 7.7 |   | Total serum bilirubin > 450 µmol/L (peak)  | Sex, age, GA |
| Weng  | 2011 | Retrospective cohort study | Neonates admitted to the NICU from 1995 to 2007 with peak total serum bilirubin value > 20 mg/dl | Cholestasis (biliary atresia, hepatitis), gestational age < 34 weeks | Taiwan | 288 | Adverse outcomes of hyperbilirubinemia (mortality, kernicterus) | NICU stay  | 6.25 | Clinical, etiologic and laboratory factors which potentiate adverse outcomes of hyperbilirubinemia, including TSB | Positive Coombs, anaemia, sepsis, GI obstructon, hemolysis (Rh, ABO, G6PD, spherocytosis)  |
| **Zhang**  | 2005 | Prospective cohort study | Full term neonates with total serum bilirubin > 205 mmol/L between January 2003 and December 2004  |   | China | 106 (56 cases, 50 controls) | Bilirubin encephalopathy |   |   | Total serum bilirubin (not stated peak or admission) bilirubin/ albumin ratio  |  |

# Appendix 4: Included and excluded studies

# Included studies

# 1. Amin SB, Ahlfors C, Orlando MS, Dalzell LE, Merle KS, Guillet R. Bilirubin and serial auditory brainstem responses in premature infants. Pediatrics. 2001;107(4):664-70.

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**Appendix 5: full report of effect estimates**

### Analysis 1. Association between total serum bilirubin value with KSD and sensorineural hearing loss (adjusted Odds Ratio per unit rise in TSB)

**1.1 Association between TSB and KSD**

Seven studies contributed data to this analysis, of which five studies enrolled high-risk infants, one enrolled infants already diagnosed with ABE (with further adverse effects relating to KSD as the outcome evaluated) and one general newborn population. Because of the very high degree of heterogeneity when data from all studies were pooled (I square of 92%), contributed mainly by the difference in the direction of results between studies that enrolled high-risk infants and the other studies, we decided to report pooled analysis only at the subgroup level.

Among high-risk infants, meta-analysis shows a positive association between TSB and KSD or related complications (pooled aOR 1.10, 95% CI 1.07 to 1.13; participants = 4484; studies = 5) (moderate-certainty evidence), but there is no clear association between TSB and KSD in general neonatal population (pooled aOR 1.10, 95% CI 0.98 to 1.23; participants = 34533; studies = 1) (moderate-certainty evidence, downgraded one level for study limitation). There is no clear association between the diagnosis of ABE and further adverse outcomes such as cerebral palsy and developmental problems (pooled aOR 0.99, 95% CI 0.97 to 1.01; participants = 76; studies = 1) (low-certainty evidence, downgraded one level each for study limitation and imprecision) (*Figure 4*).

Among studies with high-risk infants, different studies evaluated different risk factors, including infants in high-prevalent setting1, ELBW infants2 or preterm and late-preterm infants3, and infants admitted with high TSB, defined by a TSB cut-off value of 25 mg/dl3,4 and a TSB value that included all cases of kernicterus in the study, namely 18 mg/dl5. In [Murki 2001](#STD-Murki-2001)5, 21.4% of infants with kernicterus had asphyxia. Within this subgroup of studies, there was overall high heterogeneity, as evident by an I2 of 87%. The heterogeneity was contributed solely by [Qu 2020](#STD-Qu-2020)3, as removal of this study reduces to I square to 0%. We explored plausible explanation that might have contributed to the heterogeneity, and identified a plausible explanation, as follows: [Qu 2020](#STD-Qu-2020)3 has the same direction of effects but greater effect sizes (stronger positive association) compared to the other studies, possibly because the entire population enrolled in this study had two major risk factors (namely, high TSB on admission (with a higher cut-off than other studies with similar criteria) and prematurity), as opposed to the population in the other studies, all of whom had only one major risk factor in the entire population enrolled, as detailed above. The authors team decided to pool this study with others having found a plausible explanation with the same category of risk factors as that identified in other studies in this subgroup. However, the high degree of heterogeneity has resulted in one level of downgrade in certainty of evidence rating (*Appendix 6*).

\*[Weng 2011](#STD-Weng-2011)4 performed multivariate analysis in the form of logistic regression using strata of total serum bilirubin values above that of the normal range (< 25 mg/dL). We obtained raw data of the study from the authors and re-analysed the data using the value of total serum bilirubin values as a continuous covariate, and included our re-analysed adjusted Odds Ratio in the current meta-analysis.

**1.2 Association between TSB and sensorineural hearing loss**

There is a possible association between serum bilirubin and sensorineural hearing loss among high-risk infants (pooled aOR 1.14, 95% CI 1.00 to 1.30; participants = 2595; studies = 1) (moderate-certainty evidence, downgraded one level for imprecision) and among general neonatal population (pooled aOR 0.95, 95% CI 0.75 to 1.20; participants = 17260; studies = 1) (low-certainty evidence, downgraded one level each for study limitation and imprecision).

[Ogunlesi 2011](#STD-Ogunlesi-2011)6 reported "TSB at high-risk zone" as having significant association with ABE in bivariate analysis, but the significance was lost in multivariate analysis. However, the authors did not report the adjust Odds Ratio of TSB in high-risk zone in multivariate analysis to enable extraction and pooling of data. The authors reported that outborn (pooled aOR 9,7, 95% CI 1.125, 11.614), low social classes (pooled aOR 2.2 (95% CI 1.721, 10.345), severe anaemia (pooled aOR 11.6 (95% CI 5.942, 13.064) and acidosis (pooled aOR 8.2 (95% CI 4.395, 15.390) as independent predictors.

**Narrative synthesis**

There are 13 other studies that evaluated the association between TSB and KSD, but they did not contain data that were suitable to be extracted for meta-analysis. We summarised the results of these studies narratively, as follows: In a study involving two hospital sites in Myanmar, median TSB on admission was significantly higher in those with ABE versus those without in both sites (694 vs 291 µmol/L (40.6 vs 17.1 mg/dl) at Hospital A, and 496 vs 287 µmol/L (29.0 vs 16.8 mg/dl) at hospital B)7. However, two other studies reported a wide range of TSB in infants with kernicterus8,9.Another study in Japan reported that 44% of the enrolled infants < 30 weeks gestational with kernicterus had peak TSB below 15mg/dL (256 µmol/L)10. Although one study reported a positive correlation between TSB and lower PDI and MDI scores using Spearman's correlation11, six other studies found that TSB levels on its own does not correlate well with the risk of developing KSD and related adverse outcomes12-17.Various threshold levels of TSB for urgent treatment were proposed, including 600 µmol/L (35.1 mg/dl) in studies from Denmark where incidence of KSD is low18,19, and lower levels in studies with higher incidence of KSD, such as 494 µmol/L (28.9 mg/dl) and 530 µmol/L (31 mg/dl) for high and low-risk infants respectively in a study from Egypt14, and 382 µmol/L (22.4 mg/dl) and 477 µmol/L (27.9 mg/dl) in high and low-risk infants respectively in a study in Iran8. Overall, apart from the findings that neonates with very high bilirubin levels were at higher risk of adverse outcomes than those with low levels, these studies showed no clear and consistent associations between the range of TSB levels and the risk of KSD.

### Analysis 2 Association between hyperbilirubinaemia status and KSD or developmental problems (adjusted Odds Ratio for infants with hyperbilirubinaemia versus those without)

**2.1 Association between hyperbilirubinaemia and cerebral palsy or other neurological diagnosis**

Meta-analysis of two studies shows no clear association between hyperbilirubinaemia and cerebral palsy or other neurological diagnosis (pooled aOR 1.00, 95% CI 0.51 to 1.95; participants = 56578; studies = 2) (moderate-certainty evidence, downgraded one level for imprecision) (*Figure 5*).

**2.2 Association between hyperbilirubinaemia and developmental delay or abnormal neurological examination in the long term**

Meta-analysis of two studies shows no clear association between hyperbilirubinaemia and developmental delay or abnormal neurological examination in the long term (pooled aOR 0.90, 95% CI 0.46 to 1.76; participants = 52837; studies = 2) (moderate-certainty evidence, downgraded one level for imprecision).

**2.3 Comparison between infants with and without hyperbilirubinaemia on the scores of developmental screening test (including IQ test and Ankara Inventory, combined using standardised mean difference)**

Meta-analysis of four studies shows no clear difference between infants with and without hyperbilirubinaemia on the scores of developmental screening test (SMD 0.02, 95% CI -0.12 to 0.17; participants = 632; studies = 4) (moderate-certainty evidence, downgraded one level for imprecision).

**2.4 Association between hyperbilirubinaemia and deafness**

From a single study that enrolled term and late-preterm infants, there is no clear association between hyperbilirubinaemia and deafness (pooled aOR 1.30, 95% CI 0.55 to 3.09; participants = 52588; studies = 1) (moderate-certainty evidence, downgraded one level for imprecision).

**2.5 Association between hyperbilirubinaemia and attention deficit disorder**

From a single study that enrolled term and late-preterm infants, there is a positive association between hyperbilirubinaemia and attention deficit disorder (pooled aOR 1.90, 95% CI 1.10 to 3.28; participants = 52588; studies = 1) (moderate-certainty evidence, downgraded one level for imprecision).

**2.6 Association between hyperbilirubinaemia and autistic spectrum disorder**

From a single study that enrolled term and late-preterm infants, there is a positive association between hyperbilirubinaemia and autistic spectrum disorder (pooled aOR 1.60, 95% CI 1.03 to 2.49; participants = 56019; studies = 1) (moderate-certainty evidence, downgraded one level for imprecision).

### Analysis 3 Comparison between infants with KSD and infants without: total serum bilirubin value (mg/dL)

In studies that enrolled preterm or LBW infants, there appeared to be no clear differences in total serum bilirubin between those diagnosed with KSD and those without (MD 1.40 mg/dl, 95% CI -0.42 to 3.23; participants = 294; studies = 3; I2 = 55%) (low-certainty evidence, downgraded one level each for study limitation and publication bias). However, among term and late-preterm infants, total serum bilirubin appeared higher in infants with KSD (MD 10.28, 95% CI 7.73 to 12.84; participants = 305; studies = 5; I2 = 44%) (moderate-certainty evidence, downgraded one level for publication bias). The single small study that enrolled a mixture of term and preterm infants showed no clear difference in serum bilirubin between the two groups (MD 2.10, 95% CI -0.09 to 4.29; participants = 28; studies = 1), although the certainty of evidence for this result was very low due to serious concerns on study limitations, imprecision and reporting or publication bias.

### Analysis 4 Association between demographic, clinical and laboratory factors with KSD (adjusted Odds Ratio of KSD for infants with the possible risk factor versus those without)

Among the included studies that evaluated the association of total serum bilirubin with KSD, we extracted data on other factors that were evaluated concurrently, including demographic, clinical and laboratory factors. We only extracted data from adjusted analysis. Following are the analysis results according to categories.

**Maternal/demographic factors**

4.1. Advanced maternal age

Based on a single study, a higher proportion of infants with advanced maternal age developed KSD (aOR 2.62, 95% CI 1.10 to 6.25, participants = 517; studies = 1) (moderate-certainty evidence, downgraded one level for imprecision).

4.2. Low maternal education

Based on two studies, there was no clear association between low maternal education and risk of KSD (aOR 0.89, 95% CI 0.59 to 1.35; participants = 3398; studies = 2) (moderate-certainty evidence, downgraded one level for imprecision).

4.3 Refugee status

Based on a single study, a higher proportion of infants with family status as a refugee developed KSD (aOR 6.84, 95% CI 1.81 to 25.83, participants = 115, study = 1) (moderate-certainty evidence, downgraded one level for imprecision).

4.4 Incomplete antenatal visits

Based on a single study, a higher proportion of infants whose mothers had incomplete antenatal visits developed KSD (aOR 2.3, 95% CI 1.2 to 4.4; participants = 1040; studies = 1) (low-certainty evidence, downgraded one level each for study limitation and imprecision).

4.5 Delay in receiving antenatal care

Based on a single study, a higher proportion of infants whose mothers had delayed antenatal care developed KSD (aOR 4.5, 95% CI 2.3 to 8.5; participants = 1040; studies = 1) (low-certainty evidence, downgraded one level each for study limitation and imprecision).

4.6 self-referral

Based on a single study, a higher proportion of infants whose mothers referred themselves for antenatal care developed KSD (aOR 2.63, 95% CI 1.16 to 5.99; participants = 582; studies = 1) (Moderate-certainty evidence, downgraded one level for imprecision).

4.7 Out-of-hospital birth

Based on three studies, a higher proportion of infants born out of hospital developed KSD (aOR 2.63, 95% CI 1.82 to 3.81; participants = 1774; studies = 3, I2=0%) (moderate-certainty evidence, downgraded one level for study limitation).

4.8 Early discharge

Based on a single study, there was no clear association between early discharge and risk of developing KSD (aOR 2.50, 95% CI 0.84 to 7.41; participants = 115; studies = 1) (moderate-certainty evidence, downgraded one level for imprecision).

**Clinical factors**

4.9 Prematurity or low birth weight (< 2.5 kg)

Based on two studies, there was a negative association between prematurity/low birth weight and risk of developing KSD (aOR 0.40, 95% CI 0.18 to 0.87; participants = 738; studies = 2) (low-certainty evidence, downgraded one level each for study limitation and imprecision).

4.10 Asphyxia

Based on a single study, a higher proportion of infants with asphyxia developed KSD (aOR 8.29, 95% CI 1.17 to 59.01; participants = 64; studies = 1) (low-certainty evidence, downgraded two levels for imprecision). We were unable to reproduce the effect estimate figures quoted by the study authors (aOR 8.29, 95% CI 1.17 to 111.8) in our analysis.

4.11 Gastrointestinal obstruction

Based on a single study, infants with gastrointestinal obstruction appeared more likely to develop KSD (aOR 39.23, 95% CI 2.71 to 567.32; participants = 288; studies = 1) (low-certainty evidence, downgraded two levels for marked imprecision).

4.12 Sepsis

As the three included studies that evaluated sepsis enrolled three distinctly different population groups with different risk factors, we decided to separate them into three subgroups, as follows:

i). Term and late-preterm infants with high TSB on admission: a single study in this subgroup analysis showed that markedly more infants in this cohort with concurrent sepsis developed KSD as compared to infants without sepsis (aOR 161.66, 95% CI 11.65 to 2243.01; participants = 288; studies = 1) (low-certainty evidence, downgraded two levels for marked imprecision).

ii). Term and late-preterm infants diagnosed with ABE: a single study in this subgroup analysis showed no clear difference between infants with and without concurrent sepsis in the likelihood of developing KSD (aOR 1.43, 95% CI 0.19 to 11.03; participants = 87; studies = 1) (very-low-certainty evidence, downgraded one level for study limitations and two levels for marked imprecision).

iii). ELBW infants: a single study in this subgroup analysis showed no clear difference between infants with and without sepsis in the likelihood of developing KSD (aOR 1.36, 95% CI 0.96 to 1.92; participants = 3246; studies = 1) (moderate-certainty evidence, downgraded one level for imprecision).

**Laboratory factors**

4.13 Acidosis

Based on a single study, there was a higher proportion of infants with acidosis who developed KSD (aOR 8.20, 95% CI 4.39 to 15.30; participants = 156; studies = 1) (very-low-certainty evidence, downgraded one level for study limitations and two levels for marked imprecision).

4.14 Rh incompatibility

Based on a single study, there was a higher proportion of infants with rhesus incompatibility who developed KSD (aOR 30.97, 95% CI 5.08 to 188.93; participants = 288; studies = 1) (low-certainty evidence, downgraded two levels for marked imprecision).

4.15 ABO incompatibility

Based on a single study, there was a higher proportion of infants with ABO incompatibility who developed KSD (aOR 5.12, 95% CI 1.33 to 19.67; participants = 288; studies = 1) (low-certainty evidence, downgraded two levels for marked imprecision).

4.16 G6PD Deficiency

Based on two studies, there was a higher proportion of infants with G6PD deficiency who developed KSD (aOR 5.84, 95% CI 2.01 to 16.96; participants = 403; studies = 2) (low-certainty evidence, downgraded two levels for marked imprecision).

4.17 Hereditary spherocytosis

Based on a single study, there was a higher proportion of infants with hereditary spherocytosis who developed KSD (aOR 19.62, 95% CI 1.63 to 235.53; participants = 288; studies = 1) (low-certainty evidence, downgraded two levels for marked imprecision).

4.18 Hemolytic conditions not otherwise specified (Coomb's test positive)

Based on three studies, there was a higher proportion of infants who had positive Coomb's test (without specifying the diagnosis of haemolysis) who developed KSD (aOR 2.74, 95% CI 1.68 to 4.48; participants = 1443; studies = 3) (moderate-certainty evidence, downgraded one level for imprecision).

4.19 Anaemia

Based on two studies, there was a higher proportion of infants with anaemia who developed KSD (aOR 11.65, 95% CI 6.44 to 21.09; participants = 444; studies = 2) (low-certainty evidence, downgraded two levels for marked imprecision).

4.20 Abnormal white cell count

Based on a single study, there was a higher proportion of infants with abnormal white cell count who developed KSD (aOR 6.50, 95% CI 2.23 to 19.00; participants = 517; studies = 1) (very-low-certainty evidence, downgraded one level for indirectness and two levels for marked imprecision).

4.21 Hypoglycemia

Based on a single study, there was no clear association between hypoglycaemia and the likelihood of developing KSD (aOR 2.25, 95% CI 0.36 to 14.15; participants = 156; studies = 1) (very-low-certainty evidence, downgraded one level for indirectness and two levels for marked imprecision).

4.22 Serum albumin value

Based on a single study, there appeared to be an inverse association between serum albumin value and the likelihood of developing KSD (aOR 0.81, 95% CI 0.73 to 0.91; participants = 517; studies = 1) (moderate-certainty evidence, downgraded one level for imprecision).

**Narrative synthesis**

There are 11 other studies that reported the association between the other concurrent risk factors and KSD, evaluated in addition to the association between TSB and KSD, but they did not contain data that were suitable to be extracted for meta-analysis. We summarise the results of these studies narratively, as follows:

Among other factors associated with KSD, the most commonly reported were ABO incompatibility8,9,13,16,18,20,21, G6PD deficiency7,9,21, Rhesus incompatibility21 and a positive Coombs's test20, although evidence of haemolysis was not consistently documented in these studies. Septicaemia, defined variably, was a risk factor for KSD in five studies8-10,14,20. Other risk factors included lower admission/birth weight16,20, vaginal delivery20, respiratory distress and acidosis8 and inadequate establishment of breastfeeding16,22. Homebirth was not identified as a risk factor in two studies13,20. Amongst sick premature babies < 1500gm, prolonged hypothermia, acidosis or hypoxaemia, rather than peak TSB levels, were identified as risk factors of kernicterus23.

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**Appendix 6: eTable 2 - GRADE rating of certainty of evidence**

**Analysis 1. Association between total serum bilirubin value with KSD (Adjusted Odds ratio of KSD per unit rise in TSB)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Prognostic factors: Association with Kernicterus spectrum disorder (KSD)**  | No of studies (participants) | Phase of investigation  | Study limitations (risk of bias) | Inconsistency | Indirectness | Imprecision  | Publication bias | Moderate/large effect size | Dose effect  | Overall certainty of evidence  |
| Total serum bilirubin valueSubgroup:High-risk infants | 5 (4484) | √ | √ | X | √ | √ | √ | No | No | Moderate |
| Subgroup:General group of infants  | 1 (4320)  | √ | X | √ | √ | √ | √ | No | No | Moderate |
| Subgroup:Infant diagnosed with ABE | 1 (76) | √ | X | √ | √ | X | √ | No | No | Low |
| **Association with Sensorineural hearing loss** |  |  |  |  |  |  |  |  |  |  |
| Total serum bilirubin valueSubgroup: High-risk infants | 1 (2595) | √ | √ | V | V | X | √ | No | No | Moderate |
| Subgroup:General group of infants | 1 (17260) | √ | X | √ | √ | X | √ | No | No | Low |

**Footnotes**

√ No serious concern, X Serious concern, XX Very serious concern, N/A: not applicable/unknown

**Analysis 2 Association between hyperbilirubinaemia status and KSD or developmental problems (Adjusted Odds ratio of KSD for infants with hyperbilirubinaemia versus those without)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcome** **(comparison between infants with hyperbilirubinaemia and those without)**  | No of studies (participants) | Phase of investigation  | Study limitations (risk of bias) | Inconsistency | Indirectness | Imprecision  | Publication bias | Moderate/large effect size | Dose effect  | Overall certainty of evidence  |
| Cerebral palsy or other neurological diagnosis  | 2 (56578) | √ | √ | √ | √ | X | √ | No | No | Moderate  |
| Developmental delay or abnormal neurological examination  | 2 (52837) | √ | √ | √ | √ | X | √ | No | No | Moderate |
| Developmental tests (SMD)  | 4 (632) | √ | √ | √ | √ | X | √ | No | No | Moderate |
| Deafness  | 1 (56019) | X | √ | √ | √ | X | √ | No | No | Low |
| Attention deficit disorder  | 1 (56019) | X | √ | √ | √ | X | √ | No | No | Low |
| Autism spectrum disorder  | 1 (56019)  | X | √ | √ | √ | X | √ | No | No | Low |

**Footnotes**

√ No serious concern, X Serious concern, XX Very serious concern, N/A: not applicable/unknown

**Analysis 3 Comparison between infants with KSD and infants without: total serum bilirubin value (mg/dL)**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Prognostic factor (TSB) (univariate analysis)**  | No of studies (participants) | Phase of investigation  | Study limitations (risk of bias) | Inconsistency | Indirectness | Imprecision  | Publication bias\* | Moderate/large effect size | Dose effect  | Overall certainty of evidence  |
| Subgroup: Preterm/LBW infants  | 3 (294)  | √ | X | √ | √ | √ | X | No | No | Low  |
| Subgroup: Term or late-preterm infants  | 5 (305)  | √ | √ | √ | √ | √ | X | No | No | Moderate |
| Subgroup: Term and preterm infants  | 1 (28)  | √ | X | √ | √ | X | X | No | No | Very low  |

**Footnotes**

√ No serious concern, X Serious concern, XX Very serious concern, N/A: not applicable/unknown

\*We considered reporting or publication bias to be highly likely, as there are a number of studies that appeared relevant without suitable extractable data for meta-analysis. These included some of the included studies that we had to synthesise narratively. We downgrade here and not in other analyses as we considered total serum bilirubin data is routinely obtained in the daily care of the infants and standard univariate analyses as performed in the analysis here could be performed readily.

**Analysis 4 Association between demographic, clinical and laboratory factors with KSD**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Prognostic factors (association with Kernicterus spectrum disorder (KSD))**  | No of studies (participants) | Phase of investigation  | Study limitations (risk of bias) | Inconsistency | Indirectness\* | Imprecision  | Publication bias\*\* | Moderate/large effect size | Dose effect  | Overall certainty of evidence  |
| **Maternal/demographic factors** |  |  |  |  |  |  |  |  |  |  |
| Advanced maternal age | 1 (517) | √ | √ | √ | √ | X | √ | No | No | Moderate |
| Low maternal education | 2 (3398) | √ | √ | √ | √ | X | √ | No | No | Moderate |
| Refugee status  | 1 (115) | √ | √ | √ | √ | X | √ | No | No | Moderate |
| Incomplete antenatal visits  | 1 (1040) | √ | X | √ | √ | X | √ | No | No | Low |
| Delay in receiving antenatal care | 1 (1040)  | √ | X | √ | √ | X | √ | No | No | Low |
| Self-referral  | 1 (582) | √ | √ | √ | √ | X | √ | No | No | Moderate |
| Out of hospital birth | 3 (1774)  | √ | X | √ | √ | √ | √ | No | No | Moderate |
| Early discharge  | 1 (115) | √ | √ | √ | √ | X | √ | No | No | Moderate |
| **Clinical factors** |  |  |  |  |  |  |  |  |  |  |
| Prematurity or low Birth weight  | 2 (738) | √ | X | √ | √ | X | √ | No | No | Low |
| Asphyxia | 1 (64) | √ | √ | √ | √ | XX | √ | No | No | Low |
| Gastrointestinal obstruction  | 1 (288)  | √ | √ | √ | √ | XX | √ | No | No | Low |
| Sepsis Subgroup: Term and late-preterm infants with high TSB on admission | 1 (288)  | √ | √ | √ | √ | XX | √ | No | No | Low |
| Sepsis Subgroup: Term and late-preterm infants diagnosed with ABE | 1 (87) | √ | X | √ | √ | XX | √ | No | No | Very low  |
| Sepsis Subgroup: ELBW infants  | 1 (3246) | √ | √ | √ | √ | X | √ | No | No | Moderate  |
| **Laboratory factors** |  |  |  |  |  |  |  |  |  |  |
| Acidosis | 1 (156)  | √ | X | √ | √ | XX | √ | No | No | Very low |
| Hemolytic condition:Rh incompatibility | 1 (288)  | √ | √ | √ | √ | XX | √ | No | No | Low  |
| Hemolytic condition: ABO incompatibility | 1 (288)  | √ | √ | √ | √ | XX | √ | No | No | Low  |
| Hemolytic condition: G6PD deficiency | 2 (403) | √ | √ | √ | √ | XX | √ | No | No | Low  |
| Hemolytic condition: Hereditary spherocytosis  | 1 (288)  | √ | √ | √ | √ | XX | √ | No | No | Low  |
| Hemolytic condition not otherwise specified (Coomb’s positive) | 3 (1443)  | √ | √ | √ | √ | X | √ | No | No | Moderate  |
| Anaemia | 2 (444)  | √ | √ | √ | √ | XX | √ | No | No | Low  |
| Abnormal white cell count | 1 (517)  | √ | √ | √ | X | XX | √ | No | No | Very low  |
| Hypoglycaemia | 1 (156)  | √ | X | √ | X | XX | √ | No | No | Very low  |
| Serum albumin value  | 1 (517)  | √ | √ | √ | X | √ | √ | No | No | Moderate |

**Footnotes**

√ No serious concern, X Serious concern, XX Very serious concern, N/A: not applicable/unknown

\*We considered a parameter to have serious concern on indirectness if the parameters were not routinely considered as directly relevant in decision-making in the day-to-day management of newborn with hyperbilirubinaemia.

\*\*Although we considered more similar studies should have been published as the parameters gathered were common parameters in daily practice, we agreed that that might be issues with reliability of data and access to expertise in data collection and analyses, especially when analysed as part of multivariate analyses with total serum bilirubin as a parameter. Because of this, there is no reliable way of determining the basis on which to judge the likelihood of publication bias. Consequently, we have chosen not to downgrade any parameter in this domain.