Supplementary resource 1: Search strategy

Databases searched: PubMed, Cochrane CENTRAL, and Google Scholar

Date of last search: April 12, 2025

Search language restrictions: None

Search period: Inception to April 2025

PubMed

("bilirubin"[MeSH] OR "total serum bilirubin" OR "TSB" OR "serum bilirubin") AND ("bilirubin-albumin ratio" OR "bilirubin/albumin ratio" OR "B/A ratio") AND ("bilirubin encephalopathy" OR "kernicterus"[MeSH] OR "bilirubin-induced neurologic dysfunction" OR "BIND" OR "acute bilirubin encephalopathy") AND (predict* OR diagnosis OR "diagnostic accuracy" OR sensitivity OR specificity OR "ROC curve" OR "area under curve" OR "AUC")

Filters: None

Results: 11

Google Scholar

"bilirubin" AND ("bilirubin-albumin ratio" OR "bilirubin/albumin ratio" OR "B/A ratio") AND ("neurologic dysfunction" OR "BIND" OR kernicterus OR "acute bilirubin encephalopathy") AND (predict OR diagnosis OR "ROC curve")

Filters: None

Results: 426

Cochrane CENTRAL (via Cochrane Library)

#1 "bilirubin-albumin ratio" OR "bilirubin/albumin ratio" OR "B/A ratio"

#2 neonate* OR newborn* OR infant*

#3 "neurologic dysfunction" OR "bilirubin-induced neurologic dysfunction" OR "acute bilirubin encephalopathy" OR "bilirubin encephalopathy" OR kernicterus

#4 #1 AND #2 AND #3

Filters: None (no limits on date, language, or publication status)

Results: 7

Supplementary resource 2: Data extraction

Number	Ref.	Journal link	Study design	Country	Quality assessment based on (NOAS)	Risk of Bias	Time Period	Sample Size	M	F	BIND cases	Non-BIND cases	Diagnostic Tool for BIND	B/A cutoff used (mg/g)	Sensitivity (%)	Specificity (%)	TSB cutoff used (mg/dL)	Sensitivity (%)	Specificity (%)	B/A in BIND (mg/g)		B/A in non-BIND (mg/g)		TSB in BIND (mg/dL)		TSB in non-BIND (mg/dL)		SA in BIND (g/dL)		SA in non-BIND (g/dL)	
																				Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	Ardakani *et al*[8], 2011	Bilirubin/Albumin Ratio for Predicting Acute Bilirubin-induced Neurologic Dysfunction - PMC	Prospective Cohort Study	Iran	Poor	Moderate	2007 2008	- 52			47	5	Clinical Diagnosis	8	100	94				10	1.6	6.1	2.4	31.2	6.6	21.4	4.1	3.1	0.2	3.7	0.6
2	Mosallam *et al*[10], 2019	Use of serum bilirubin/albumin ratio for early prediction	Prospective Cohort Study	Egypt	Poor	Moderate	2016	100	56	44	50	50	Clinical Diagnosis	6.68	82	64	28.55	66	84	8.38	2.34	6.46	1.84	29.24	7.78	23.04	5.41	3.54	0.7	3.63	0.55

		of bilirubin induced neurologic al dysfunctio n | Egyptian Pediatric Associatio n Gazette | Full Text																																		
3	Wan g *et al*[11] , 2020	Increased serum total bilirubin-al bumin ratio was associated with bilirubin encephalo pathy in neonates - ScienceDir ect	Retros pective Cohort Study	China	Fair	Low	2015 2018	- 669	414	255	153	516	Clinica l Diagno sis	8.1 1	1.6 1	6.45	1.13	28.44	5.18	22.47	3.08	3.51	0.28	3.48	0.38
4	Solim an *et al*[12] , 2021	Can bilirubin/a lbumin ratio	Prospe ctive Cohort Study	Egypt	Poor	Moder ate	2012	117	70	47	16	101	Clinica l Diagno sis	9.6	100	91.4	25	100	57	11. 7	1.4 9	7.42	1.48	38.8	4.5	25	4.4									

		predict neurodevelopmental outcome in severe neonatal hyperbilirubinemia? A 3-month follow up study																													
5	Alaba *et al*[13], 2024	Utilizing the Bilirubin-Albumin Ratio as a Predictive Marker for Bilirubin-Induced Neurologic Dysfunction: A Comparative Analysis in Two Referral	Prospective Cohort Study	Nigeria	Poor	Moderate	2019 2020	- 84	30	54	57	27	Clinical Diagnosis	6.46	84.2	81.5	25.1	82.5	81.5	7.77	1.76	5.43	1.27	30.29	7.07	21.63	4.31	3.91	0.41	4.01	0.26

Hospitals in Abeokuta

Supplementary resource 3: QUADAS-2 quality assessment

Assessment tool

The methodological quality of included studies was evaluated using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool. The tool assesses risk of bias and applicability concerns across four key domains: (1) Patient selection; (2) Index test; (3) Reference standard; and (4) Flow and timing. Each domain is rated as "low risk", "high risk", or "unclear risk" based on predefined signaling questions adapted for this review. Customization of the QUADAS-2 tool for this study is shown below.

Number	Domain	Signaling questions (customized for this review)
1	Patient selection	Was a consecutive or random sample of neonates enrolled? Were inclusion/exclusion criteria clearly defined? Were case-control designs avoided? Was inappropriate exclusion avoided?
2	Index test (B/A ratio and TSB)	Were B/A ratio and TSB measured without knowledge of the reference standard result? Were predefined thresholds for B/A and TSB applied consistently? Were commercially validated or standardized laboratory methods used?
3	Reference standard (diagnosis of BIND)	Was BIND diagnosed using accepted clinical or neuroimaging criteria? Was the reference standard likely to correctly classify BIND? Was the interpretation of the reference standard blinded to index test results?
4	Flow and timing	Was there an appropriate interval between index test and reference standard? Did all patients receive the same reference standard? Were all enrolled patients included in the analysis?

Risk of bias and applicability judgments

Ref.	Patient selection	Index test	Reference standard	Flow and timing	Overall risk	Applicability concerns
Iskander *et al*[7], 2014	Low	Low	Low	Low	Low	Low
Ardakani *et al*[8], 2011	Low	Unclear	Low	Unclear	Moderate	Low
Wang *et al*[11], 2020	Low	Low	Low	Low	Low	Low

Soliman *et al*[12], 2021	Unclear	Low	Low	Unclear	Moderate	Low
Alaba *et al*[13], 2024	Low	Low	Low	Low	Low	Low

Most studies demonstrated low or moderate risk of bias overall.

The greatest methodological concerns were related to unclear blinding of index test interpretation and variable diagnostic criteria for BIND.

Applicability concerns were generally low, as all studies assessed neonatal populations using clinically relevant bilirubin and albumin assays.

NIHR | National Institute for Health and Care Research

PROSPERO
International prospective register of systematic reviews

Comparison of the Bilirubin-Albumin Ratio and Total Serum Bilirubin for Predicting Bilirubin-Induced Neurological Dysfunction (BIND) in Neonates: A Systematic Review and Meta-Analysis of Diagnostic Accuracy

Nabeel Ahmad, Uzair Ahmed

Citation

Nabeel Ahmad, Uzair Ahmed. Comparison of the Bilirubin-Albumin Ratio and Total Serum Bilirubin for Predicting Bilirubin-Induced Neurological Dysfunction (BIND) in Neonates: A Systematic Review and Meta-Analysis of Diagnostic Accuracy. PROSPERO 2025 CRD420251089237. Available from https://www.crd.york.ac.uk/PROSPERO/view/CRD420251089237.

REVIEW TITLE AND BASIC DETAILS

Review title

Comparison of the Bilirubin-Albumin Ratio and Total Serum Bilirubin for Predicting Bilirubin-Induced Neurological Dysfunction (BIND) in Neonates: A Systematic Review and Meta-Analysis of Diagnostic Accuracy

Condition or domain being studied

We include studies of neonates (≤28 days) with hyperbilirubinemia who underwent assessment with bilirubin–albumin ratio (BAR) and/or total serum bilirubin (TSB) to predict bilirubin-induced neurological dysfunction (BIND), including clinical kernicterus. Studies must allow calculation of diagnostic accuracy metrics (e.g., sensitivity, specificity).

Rationale for the review

Neonatal hyperbilirubinemia is common, and while total serum bilirubin (TSB) is widely used to assess risk, it does not always accurately predict bilirubin-induced neurological dysfunction (BIND). Emerging evidence suggests that the bilirubin-albumin ratio (BAR) may offer improved diagnostic accuracy by reflecting the unbound bilirubin fraction responsible for neurotoxicity. However, the relative diagnostic performance of BAR compared to TSB remains unclear. This systematic review and meta-analysis aims to synthesize existing evidence to determine whether BAR provides superior diagnostic accuracy for predicting BIND in neonates. The findings may inform clinical guidelines and improve early identification of infants at risk of neurological injury.

Review objectives

To compare the diagnostic accuracy of the bilirubin-albumin ratio (BAR) versus total serum bilirubin (TSB) for predicting bilirubin-induced neurological dysfunction (BIND) in neonates.

Keywords
Kernicterus; Albumin bilirubin grade; Diagnostic accuracy; Neonatal jaundice

Country
Pakistan; Sudan

ELIGIBILITY CRITERIA

Population

Included
We will include studies involving neonates (≤28 days of age), including both term and preterm infants, who are evaluated for hyperbilirubinemia and assessed for risk of bilirubin-induced neurological dysfunction (BIND), including acute bilirubin encephalopathy and kernicterus. Studies must report sufficient data to assess diagnostic accuracy (e.g. sensitivity, specificity) of bilirubin-albumin ratio or total serum bilirubin in predicting BIND as defined by clinical or neuroimaging criteria.

Excluded
We will exclude:

Case reports, case series, reviews, editorials, letters, and conference abstracts without primary data, Animal studies or in vitro studies, Studies not involving neonates (older infants or children), Studies without sufficient data, Studies using reference standards for BIND not based on clinical diagnosis, neuroimaging, or recognized neurologic assessment, Studies not reporting on either bilirubin-albumin ratio or total serum bilirubin in relation to BIND

Intervention(s) or exposure(s)

Included
We will include studies that evaluate the diagnostic accuracy of the bilirubin-albumin ratio (B/A ratio) for predicting bilirubin-induced neurological dysfunction (BIND) in neonates. Eligible studies must report B/A ratio values obtained through laboratory measurement of serum bilirubin and serum albumin levels. We will include studies that assess any B/A ratio threshold and compare it against a clinical or neuroimaging diagnosis of BIND.

Comparator(s) or control(s)

Included
We will include studies that report the diagnostic accuracy of total serum bilirubin (TSB) as a comparator for predicting bilirubin-induced neurological dysfunction (BIND) in neonates. The TSB must be measured using standard laboratory methods, and results should be compared against a reference standard diagnosis of BIND based on clinical assessment and/or neuroimaging. Studies that report both B/A ratio and TSB for the same population will be eligible for inclusion.

Study design
Only nonrandomized study types will be included.

Context

Neonatal hyperbilirubinemia is a common condition globally, but progression to bilirubin-induced neurological dysfunction (BIND), including kernicterus, carries significant risks of mortality and long-term disability, especially in low- and middle-income countries. Accurate early prediction of BIND is critical for timely intervention. While total serum bilirubin (TSB) is widely used for risk assessment, it does not always reflect the unbound bilirubin responsible for neurotoxicity. The bilirubin-albumin (B/A) ratio has been proposed as a potentially more accurate predictor by accounting for binding capacity. This review synthesizes evidence on the diagnostic accuracy of B/A ratio compared with TSB in predicting BIND, to inform clinical decision-making and potential guideline updates across different healthcare settings.

TIMELINE OF THE REVIEW

Date of first submission to PROSPERO
07 July 2025

Review timeline
Start date: 1 January 2025. End date: 15 August 2025.

Date of registration in PROSPERO
07 July 2025

AVAILABILITY OF FULL PROTOCOL

Availability of full protocol
A full protocol has been written but is not available because:

The full protocol has been written to guide the review team internally, but it has not been published or shared publicly at this stage. The review team intends to complete the project and submit the findings for peer-reviewed publication, at which point the protocol details will be made available.

SEARCHING AND SCREENING

Search for unpublished studies
Only published studies will be sought.

Main bibliographic databases that will be searched
The main databases to be searched are *CENTRAL - Cochrane Central Register of Controlled Trials*, *PubMed* and *Scopus*.

Search language restrictions
The review will only include studies published in English.

Search date restrictions
There are no search date restrictions.

Other methods of identifying studies
No other methods will be used.

Link to search strategy

A full search strategy is available in the full protocol as described in the *Availability of full protocol* section

Selection process
Studies will be screened independently by at least two people (or person/machine combination) with a process to resolve differences.

Other relevant information about searching and screening
None

DATA COLLECTION PROCESS

Data extraction from published articles and reports
Data will be extracted independently by at least two people (or person/machine combination) with a process to resolve differences.

Authors will be asked to provide any required data not available in published reports.

Study risk of bias or quality assessment
Risk of bias will be assessed using: *Newcastle-Ottawa*

Data will be assessed independently by at least two people (or person/machine combination) with a process to resolve differences.

Additional information will be sought from study investigators if required information is unclear or unavailable in the study publications/reports.

Reporting bias assessment
Risk of bias due to missing results will be assessed

Certainty assessment
Certainty of findings will not be assessed

OUTCOMES TO BE ANALYSED

Main outcomes
Predicting Bilirubin-Induced Neurological Dysfunction (BIND) in Neonates

Additional outcomes
There are no additional outcomes.

PLANNED DATA SYNTHESIS

Strategy for data synthesis
We will perform a formal meta-analysis using a bivariate random-effects model to obtain pooled estimates of sensitivity, specificity, diagnostic odds ratios, and area under the summary receiver operating characteristic (SROC) curve. Heterogeneity will be assessed through forest plots, I^2 statistics, and SROC inspection. Where appropriate, meta-regression and subgroup analyses (e.g., by gestational age, B/A ratio thresholds, study quality) will be conducted to explore sources of heterogeneity.

CURRENT REVIEW STAGE

Stage of the review at this submission

Review stage	Started	Completed
Pilot work	✓	✓
Formal searching/study identification	✓	✓
Screening search results against inclusion criteria	✓	✓
Data extraction or receipt of IPD		
Risk of bias/quality assessment		
Data synthesis		

Review status
The review is currently planned or ongoing.

Publication of review results
Results of the review will be published.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members
Dr Nabeel Ahmad (review guarantor and contact) Lahore General Hospital. Pakistan.

No conflict of interest declared.

Dr Uzair Ahmed. Ameer-ud-Din Medical College. Pakistan.

No conflict of interest declared.

Named contact
Dr Nabeel Ahmad (nabeelahmad921@gmail.com). Lahore General Hospital. Pakistan.

Review affiliation
Lahore General Hospital, Lahore, Pakistan

Funding source
Review has no funding and no agreed support from an academic institution and is done in authors' own time.

Peer review
There has been no peer review of this planned review.

ADDITIONAL INFORMATION

Review conflict of interest
Declared individual interests are recorded under team member details.. No additional interests are recorded for this review.

Medical Subject Headings

Bilirubin; Hematologic Diseases; Hematologic Tests; Humans; Infant, Newborn; Kernicterus; Neuroimaging; Serum Albumin

SIMILAR REVIEWS

Check for similar records already in PROSPERO

I am confident this review addresses a specific question — the comparative diagnostic accuracy of bilirubin-albumin ratio versus total serum bilirubin for predicting BIND — which has not been covered in existing PROSPERO-registered protocols to my knowledge.

PROSPERO version history

- Version 1.0, published 07 Jul 2025

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