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Clinical Profile and Factors Associated with Severe Neonatal Hyperbilirubinemia in a Tertiary Care Special Newborn Care Unit: A Prospective Observational Analytical Study

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Abstract

Background: Neonatal hyperbilirubinemia is a leading contributor to neonatal admissions and carries a risk of bilirubin-induced neurological dysfunction.

Objective: To evaluate demographic parameters, clinical presentation, and factors associated with severe hyperbilirubinemia among jaundiced neonates admitted to a tertiary Special Newborn Care Unit (SNCU).

Methods: A prospective observational analytical study was conducted over one year (August 2025-July 2026) at the SNCU of a tertiary care hospital in Raipur, Chhattisgarh, India. One hundred neonates aged 1-28 days with clinical jaundice were enrolled. Severe hyperbilirubinemia was defined a priori as peak total serum bilirubin (TSB) ≥20 mg/dL. Univariable logistic regression was used for factors without zero cells; Fisher's exact test was used when complete separation prevented finite odds-ratio estimation.

Results: Among 100 neonates, mean gestational age was 37.2 ± 2.1 weeks and mean birth weight was 2.85 ± 0.52 kg; 58% were male. Median age at presentation was 72 hours (IQR: 48-96), and median peak TSB was 18.4 mg/dL (IQR: 15.2-21.7). Severe hyperbilirubinemia occurred in 40% (n = 40). Sepsis was associated with severe hyperbilirubinemia (OR 9.00; 95% CI 2.97-27.24; P < 0.001), as was hypoalbuminemia (OR 3.24; 95% CI 1.15-9.17; P = 0.026). Hypocalcemia showed a borderline association (OR 3.00; 95% CI 0.99-9.07; P = 0.052). Hemolytic/immunologic factors and acidosis occurred only in the severe group and were associated with severity by Fisher's exact test (both P < 0.001).

Conclusion: Several clinical factors, including sepsis, hypoalbuminemia, hemolytic/immunologic factors, and acidosis, were associated with severe hyperbilirubinemia in this single-centre cohort. Because the analyses were unadjusted and exploratory, larger multi-centre studies with adjustment for confounding are required.

Keywords: Neonatal hyperbilirubinemia; Neonatal sepsis; Risk factors; Special newborn care unit; Kernicterus; Observational study

1. Introduction

Neonatal hyperbilirubinemia is among the most common clinical problems in the early neonatal period. Although transient physiological jaundice is frequent, severe unconjugated hyperbilirubinemia can lead to acute bilirubin encephalopathy and permanent neurological injury (kernicterus) [1-3].

Severe hyperbilirubinemia is multifactorial and may reflect increased bilirubin production, impaired conjugation or clearance, hemolysis, prematurity, infection, and other neonatal morbidities [4-6]. Systemic infection may aggravate hyperbilirubinemia through effects on erythrocyte survival, hepatic handling of bilirubin, and neurotoxicity risk.

Low- and middle-income settings carry a substantial burden of clinically significant neonatal jaundice, and the distribution of associated factors may vary by referral patterns and local neonatal care practices [6,7]. Regional data

from SNCUs can therefore help describe the clinical profile of affected neonates and generate hypotheses for better risk stratification.

This study was undertaken at the SNCU of a tertiary care hospital in Raipur, Chhattisgarh, India, to describe clinical characteristics and evaluate factors associated with severe hyperbilirubinemia among jaundiced neonates.

2. Materials and Methods

2.1 Study Design and Setting

This prospective observational analytical study was conducted at the Special Newborn Care Unit (SNCU) of a tertiary care hospital in Raipur, Chhattisgarh, India, over one year from August 2025 to July 2026.

2.2 Ethics Approval and Consent

The study was approved by the Institutional Human Ethics Committee (IHEC). Written informed consent was obtained from the parents or legally authorised representatives of enrolled neonates before participation, in accordance with the Declaration of Helsinki.

2.3 Sample Size Justification

A sample size of approximately 96 was obtained using a single-proportion formula with an assumed proportion of 50%, 95% confidence level, and 10% absolute precision; this was rounded to 100 neonates. The association analyses were exploratory and were not powered a priori for a multivariable model.

2.4 Selection Criteria

Inclusion criteria

- Neonates aged 1-28 days.
- Clinical jaundice confirmed by a TSB level exceeding the age- and gestation-appropriate phototherapy threshold used by the unit.

Exclusion criteria

- Parental refusal or failure to obtain informed consent.
- Direct (conjugated) bilirubin >1.0 mg/dL or >20% of TSB.
- Neonatal mortality before completion of the clinical evaluation.

2.5 Data Collection and Outcome Definition

Demographic information, gestational age, birth weight, sex, age at presentation, peak TSB, and prespecified clinical variables were recorded. Severe hyperbilirubinemia was defined a priori as peak TSB ≥20 mg/dL. This fixed research cutoff was used to identify the upper end of the bilirubin distribution in this cohort and should not be interpreted as a universal treatment or neurotoxicity threshold; current management thresholds depend on postnatal age, gestational age, and neurotoxicity risk factors [3].

2.6 Operational Definitions

Sepsis: Culture-proven sepsis was defined by isolation of a recognized pathogen from blood or cerebrospinal fluid in a neonate with clinical signs of infection. Clinical sepsis was defined by compatible clinical signs plus at least one laboratory criterion (WBC $<4.0 \times 10^9$/L or $>20 \times 10^9$/L, absolute neutrophil count outside the reference range, or C-reactive protein >10 mg/L) in the absence of an alternative diagnosis.

Hypoalbuminemia: Serum albumin <3.0 g/dL, measured at admission before phototherapy or exchange transfusion; albumin <3.0 g/dL is recognized as a neurotoxicity risk factor in the AAP guideline for infants ≥35 weeks [3].

Hypocalcemia: Total serum calcium <8 mg/dL (2.0 mmol/L) in term infants and <7 mg/dL (1.75 mmol/L) in preterm infants, measured at admission before phototherapy.

Hemolytic/immunologic factors: A positive direct antiglobulin test with documented ABO or Rh incompatibility and/or laboratory evidence of hemolysis.

Acidosis: Arterial blood pH <7.20 with base deficit ≥12 mmol/L on admission blood-gas analysis.

2.7 Statistical Analysis

Data were analyzed using R statistical software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as mean ± standard deviation or median with interquartile range (IQR), as appropriate; categorical variables are presented as n (%). For binary factors with nonzero cells, univariable logistic regression was used to estimate unadjusted odds ratios (ORs) with 95% confidence intervals (CIs), and Wald P-values are reported. For factors with a zero cell (complete separation), a finite unadjusted OR could not be estimated by standard logistic regression; raw 2 × 2 counts are therefore shown and a two-sided Fisher's exact test was used for group comparison. A two-sided P < 0.05 was considered statistically significant. Missing data were reported to be <2% for all variables and complete-case analysis was used. No multivariable adjustment for confounding was performed.

3. Results

3.1 Baseline Characteristics and Clinical Profile

A total of 100 jaundiced neonates meeting the eligibility criteria were enrolled. Mean gestational age was 37.2 ± 2.1 weeks (range: 32-42) and mean birth weight was 2.85 ± 0.52 kg (range: 1.8-4.0). Male neonates comprised 58% (n = 58). Median age at presentation was 72 hours (IQR: 48-96). Median peak TSB was 18.4 mg/dL (IQR: 15.2-21.7), and 40 neonates (40.0%) met the study definition of severe hyperbilirubinemia.

Table 1. Baseline Demographics and Clinical Characteristics (N = 100)

Variable	Summary statistic
Gestational age (weeks), mean ± SD (range)	37.2 ± 2.1 (32-42)
Birth weight (kg), mean ± SD (range)	2.85 ± 0.52 (1.8-4.0)
Sex, male, n (%)	58 (58.0)
Age at presentation (hours), median (IQR)	72 (48-96)
Peak TSB (mg/dL), median (IQR)	18.4 (15.2-21.7)
Severe hyperbilirubinemia (peak TSB ≥20 mg/dL), n (%)	40 (40.0)

TSB = total serum bilirubin; IQR = interquartile range; SD = standard deviation.

3.2 Factors Associated with Severe Hyperbilirubinemia

Univariable analysis showed higher odds of severe hyperbilirubinemia among neonates with sepsis (OR 9.00; 95% CI 2.97-27.24; P < 0.001) and hypoalbuminemia (OR 3.24; 95% CI 1.15-9.17; P = 0.026). Hypocalcemia showed a borderline association (OR 3.00; 95% CI 0.99-9.07; P = 0.052). Hemolytic/immunologic factors were present in 14/40 severe cases and 0/60 non-severe cases; acidosis was present in 8/40 severe cases and 0/60 non-severe cases. Because these zero cells produced complete separation, finite standard-logistic ORs were not estimated; Fisher's exact testing showed P < 0.001 for both comparisons.

Table 2. Univariable Analysis of Factors Associated with Severe Hyperbilirubinemia (Peak TSB ≥20 mg/dL)

Factor	Severe (n = 40), n (%)	Non-severe (n = 60), n (%)	Unadjusted OR (95% CI)	P-value	Method
Sepsis	18 (45.0)	5 (8.3)	9.00 (2.97-27.24)	<0.001	Univariable logistic regression
Hypoalbuminemia	12 (30.0)	7 (11.7)	3.24 (1.15-9.17)	0.026	Univariable logistic regression
Hypocalcemia	10 (25.0)	6 (10.0)	3.00 (0.99-9.07)	0.052	Univariable logistic regression
Hemolytic/immunologic factors	14 (35.0)	0 (0.0)	Not estimable*	<0.001	Fisher's exact test
Acidosis	8 (20.0)	0 (0.0)	Not estimable*	<0.001	Fisher's exact test

**OR = odds ratio; CI = confidence interval. A finite standard-logistic OR was not estimated for factors with complete separation (zero events in the non-severe group). Two-sided Fisher's exact P-values are reported for those comparisons.*

4. Discussion

In this prospective observational cohort of 100 jaundiced neonates, 40% met the study definition of severe hyperbilirubinemia (peak TSB ≥20 mg/dL). The analysis identified associations with sepsis, hypoalbuminemia, hemolytic/immunologic factors, and acidosis, while the association with hypocalcemia was borderline. These findings should be interpreted as unadjusted associations rather than independent causal effects.

4.1 Sepsis and Severe Hyperbilirubinemia

Sepsis was strongly associated with severe hyperbilirubinemia (OR 9.00; 95% CI 2.97-27.24). Infection may increase bilirubin burden through hemolysis and impaired hepatic handling and may also increase susceptibility to bilirubin neurotoxicity [2,4,6,8,9]. The wide confidence interval indicates imprecision and is consistent with the modest sample size.

4.2 Hypoalbuminemia and Hypocalcemia

Hypoalbuminemia was associated with severe hyperbilirubinemia (OR 3.24; 95% CI 1.15-9.17). Albumin is the principal plasma binding protein for unconjugated bilirubin, and reduced binding capacity may increase the unbound bilirubin fraction [9,10]. Hypocalcemia showed a borderline association (P = 0.052). Because calcium was measured at admission before phototherapy, the baseline comparison in this study was not confounded by treatment-related hypocalcemia occurring after enrollment.

4.3 Hemolytic/Immunologic Factors and Acidosis

Hemolytic/immunologic factors and acidosis occurred only in the severe group, producing complete separation. The raw counts and Fisher's exact tests indicate a strong group difference, but an ordinary logistic OR is not finite when one comparison cell is zero. Hemolytic disease and metabolic derangements are biologically plausible contributors to severe bilirubin accumulation and neurotoxicity [4,5,8].

4.4 Limitations

1. **Sample size:** The study was sized for proportion estimation rather than for a multivariable association model; effect estimates are therefore imprecise.
2. **Single-centre design:** Referral patterns and local practice may limit generalizability.
3. **Unadjusted analysis:** The study did not control for confounding; associations should not be interpreted as independent effects.
4. **Complete separation:** Zero events in the non-severe group for hemolytic/immunologic factors and acidosis prevented finite standard-logistic OR estimation.
5. **Missing data:** Although reported to be <2%, complete-case analysis can introduce bias if missingness is not completely random.
6. **Fixed TSB cutoff:** The research definition of peak TSB ≥20 mg/dL does not incorporate postnatal age, gestational age, or neurotoxicity risk factors and is not a universal treatment threshold. The AAP 2022 guideline applies to infants ≥35 weeks; management of infants <35 weeks requires separate gestation-specific guidance [3].

5. Conclusion

In this single-centre cohort of jaundiced neonates, sepsis, hypoalbuminemia, hemolytic/immunologic factors, and acidosis were associated with severe hyperbilirubinemia in unadjusted analyses, while hypocalcemia showed a borderline association. The findings are exploratory and do not establish independent causality. Larger, adequately powered multi-centre studies with multivariable adjustment are needed before practice recommendations are based on these estimates.

Declarations

Ethics approval and consent: The study was approved by the Institutional Human Ethics Committee (IHEC). Written informed consent was obtained from the parents or legally authorised representatives of all enrolled neonates before participation.

Funding: None.

Conflicts of interest: The authors declare no conflicts of interest.

Data availability: The de-identified dataset and statistical analysis code supporting the findings are available from the corresponding author upon reasonable request.

AI-assisted technology declaration: The authors state that no generative AI or automated tools were used in the preparation of the manuscript.

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