Analysis of Factors Associated with Adverse Digestive System Outcomes in Neonates with Jaundice

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1.Abstract

Objective To explore the factors associated with adverse digestive system outcomes in neonates with jaundice.

Methods A retrospective analysis was conducted on clinical data of hospitalized neonates admitted to the Department of Neonatology, the First Hospital of Jilin University, within 7 days after birth from December 2019 to December 2024. Included neonates underwent serum total bilirubin testing, with post birth serum total bilirubin levels exceeding the High risk neonatal phototherapy threshold. Propensity score matching and inverse probability weighting were used to group the jaundiced neonates according to the presence or absence of adverse digestive system outcomes. Factors including basic demographic information of the neonates and their mothers, relevant laboratory examinations, and therapeutic interventions were collected. Traditional logistic regression and Cox proportional hazards models were applied to analyze and predict risk factors for adverse digestive system outcomes in jaundiced neonates.

Results A total of 3,218 jaundiced neonates were included, comprising 3,064 without digestive system outcomes and 154 with digestive system outcomes. After propensity score matching, multivariate logistic regression showed that a history of intravenous intravenous immunoglobulin (IVIG) administration (OR = 4.11, 95% CI: 1.87–9.83, P = 0.0007), history of blood transfusion (OR = 3.51, 95% CI: 1.60–7.82, P = 0.0018), and elevated direct bilirubin (OR = 1.04, 95% CI: 1.02–1.07, P = 0.0003) were independent risk factors for adverse digestive outcomes, while elevated total bilirubin (OR = 0.995, 95% CI: 0.992 –0.998, P = 0.0012) was an independent protective factor. Multivariate Cox regression indicated that history of blood transfusion (HR = 3.42, 95% CI: 1.90–6.16, P = 4.23e-05), history of IVIG use (HR = 3.57, 95% CI: 1.87–6.81, P = 0.0001), history of phototherapy (HR = 2.21, 95% CI: 1.11–4.40, P = 0.023), and elevated direct bilirubin (HR = 1.03, 95% CI: 1.01–1.04, P = 3.70e-06) were independent risk factors, whereas total bilirubin level (HR = 0.99, 95% CI: 0.992–0.998, P = 0.0001), history of exchange transfusion (HR = 0.36 , 95% CI: 0.16–0.79, P = 0.023), albumin level (HR = 0.97, 95% CI: 0.93–1.03, P = 0.011), and comorbid hemolytic disease of the newborn (HR = 0.50, 95% CI: 0.25–0.99, P = 0.

046) were independent protective factors. After inverse probability weighting, multivariate logistic regression revealed that history of IVIG administration (OR = 3.06, 95 % CI: 1.61–5.95, P = 0.0008) and history of blood transfusion (OR = 3.38, 95% CI: 1.81–6.13, P = 8.87e-05) were independent risk factors, while premature rupture of membranes (OR = 0.64, 95% CI: 0.45–0.91, P = 0.014) and elevated total bilirubin (OR = 0.995, 95% CI: 0.992–0.998, P = 0.0012) were independent protective factors. Multivariate Cox regression showed that history of blood transfusion (HR = 2.84, 95% CI: 1.62–4.96, P < 0.001), history of IVIG use (HR = 2.78, 95% CI: 1.59–4.86, P < 0.001), and elevated direct bilirubin (HR = 1.01, 95% CI: 1.002–1.018, P = 0.016) were independent risk factors, while total bilirubin level was an independent protective factor (HR = 0.996, 95% CI: 0.993–0.999, P = 0.003).

Conclusion History of blood transfusion, history of intravenous immunoglobulin administration, and elevated direct bilirubin levels are independent risk factors for adverse digestive system outcomes in neonates with jaundice.

2.Background

Neonatal jaundice is one of the most common medical conditions globally during the neonatal period and a leading cause of hospitalization for term and near-term infants in neonatal units. The majority of newborns experience jaundice, with some progressing to pathological hyperbilirubinemia requiring medical intervention. The most severe complications of neonatal jaundice are acute bilirubin encephalopathy and kernicterus, which can lead to irreversible neurological sequelae. Current treatments for neonatal jaundice—including phototherapy and exchange transfusion—effectively reduce serum bilirubin levels, prevent neurotoxicity, and improve neurological outcomes in this population.

However, in clinical practice, we often observe that some jaundiced neonates, especially those receiving treatment, present with a range of digestive symptoms such as feeding

intolerance, vomiting, abdominal distension, diarrhea, and even bloody stools or intestinal necrosis. This suggests a potential link between hyperbilirubinemia, its treatment, and gastrointestinal morbidity.

While extensive research has focused on the neurotoxicity of jaundice and the efficacy of its treatments, systematic reviews and mechanistic analyses of how hyperbilirubinemia and its therapies affect the immature neonatal digestive system remain insufficient. Relevant discussions are scattered and often overlooked. Therefore, we conducted this study to explore factors associated with adverse digestive outcomes in jaundiced neonates, including hyperbilirubinemia-related factors, treatment modalities, hemolytic factors, neonatal characteristics, and maternal history. The study aims to clarify whether adverse digestive outcomes such as necrotizing enterocolitis (NEC) in jaundiced neonates are merely coincidental events with no pathophysiological link, whether jaundice itself increases the risk of digestive morbidity, or whether the treatments for jaundice contribute to a higher incidence of digestive complications. If digestive outcomes are purely coincidental, current diagnostic and treatment approaches may be maintained. However, if they are caused by the disease itself or its treatment, further optimization of the management of jaundiced neonates will be necessary.

To date, there is a lack of research both domestically and internationally addressing the "jaundice–treatment–digestive outcome" pathway. To address this gap, we conducted this retrospective cohort study to investigate the causal relationships and risk factors linking neonatal jaundice, its treatments, and adverse digestive outcomes—particularly NEC.

3.Study Objectives & Hypotheses

Primary Objective:

To identify independent risk factors for adverse digestive system outcomes in neonates with hyperbilirubinemia.

Secondary Objectives:

To evaluate the association between specific treatments (phototherapy, exchange transfusion, immunoglobulin（IVIG）, blood transfusion) and digestive outcomes;

To assess the role of direct bilirubin, hemolytic disease, and maternal factors;

To compare results between propensity score matching and inverse probability weighting methods.

Hypothesis:

History of blood transfusion, IVIG administration, and elevated direct bilirubin are independent risk factors for adverse digestive outcomes in jaundiced neonates.

4. Study Design

Type: Observational, retrospective cohort study

Center: Single center (Department of Neonatology, The First Hospital of Jilin University)

Time Period: December 2019 – December 2024

Data Source: Electronic medical records (HIS)

Study Groups:

Group 1: Jaundiced neonates with adverse digestive outcomes

Group 2: Jaundiced neonates without adverse digestive outcomes

5. Study Population

5.1 Inclusion Criteria

1.Admitted to the Department of Neonatology within 7 days after birth;

2.Clinical diagnosis of neonatal jaundice;

3.Serum total bilirubin level **exceeding the phototherapy threshold** for high-risk neonates (according to AAP or local guidelines);

4.Complete medical records available.

5.2 Exclusion Criteria

1.Major congenital gastrointestinal malformations;

2.Complex congenital heart disease;

3.Missing data on primary outcome or key exposure variables.

6. Outcome Measures

The primary outcome of this study is the occurrence of adverse digestive system outcomes in neonates. An adverse digestive system outcome is defined as any condition affecting digestive system functions such as feeding and defecation during hospitalization, including but not limited to any of the following events:

(1) **Necrotizing enterocolitis (NEC)**, diagnosed as Bell's stage ≥ IIA, characterized by the presence of systemic signs (e.g., lethargy, temperature instability, apnea) and radiological evidence (e.g., pneumatosis intestinalis, portal venous gas) ;

(2) **Clinically significant gastrointestinal bleeding**, defined as hematemesis or hematochezia requiring medical intervention (including but not limited to cessation of enteral feeding, blood transfusion, administration of hemostatic agents, or endoscopic examination)];

(3) **Food protein-induced allergic proctocolitis (FPIAP)**, defined as hematochezia occurring after ingestion of dairy products, with symptom resolution following dietary elimination (e.g., switching to extensively hydrolyzed or amino acid-based formula, or

maternal avoidance of dairy products), after exclusion of other etiologies such as infectious enteritis or NEC ;

(4) **Appendicitis**, confirmed by surgical findings, pathological examination, or imaging studies (e.g., ultrasound, computed tomography) ;

(5) **Intestinal obstruction**, confirmed by imaging studies (e.g., abdominal plain radiography, contrast study, ultrasound) and requiring surgical intervention or conservative management (e.g., fasting, gastrointestinal decompression) ;

(6) **Spontaneous intestinal perforation (SIP)**, confirmed by surgical or autopsy findings, without typical radiological features of NEC such as pneumatosis intestinalis .

7. Data Collection & Variables

(1) Neonatal baseline characteristics: gestational age, birth weight, sex, mode of delivery, presence of premature rupture of membranes, postnatal asphyxia, etc.;

(2) Maternal obstetric complications: presence of gestational hypertension, gestational diabetes mellitus, antenatal administration of corticosteroids, magnesium sulfate, etc.;

(3) Laboratory examinations: hemoglobin, albumin, serum total bilirubin, serum direct bilirubin, etc.;

(4) Therapeutic interventions for jaundice: phototherapy, intravenous immunoglobulin (IVIG), exchange transfusion, blood transfusion, etc.;

(5) Discharge diagnoses: hemolytic disease of the newborn, neonatal necrotizing enterocolitis, allergic enterocolitis, etc.

8. Statistical Analysis Plan

8.1 Descriptive Analysis

Continuous variables: mean ± SD or median (IQR), compared using t-test or Mann–Whitney U test;

Categorical variables: n (%), compared using chi-square or Fisher's exact test.

8.2 Confounding Adjustment

Propensity Score Matching (PSM): 1:1 ratio, caliper 0.2, nearest neighbor method;

Inverse Probability of Treatment Weighting (IPTW): stabilized weights;

Covariates included: gestational age, birth weight, peak total bilirubin, albumin, mode of delivery, PROM, hemolytic disease.

8.3 Regression Models

Logistic regression: to estimate odds ratios (OR) with 95% CI;

Cox proportional hazards regression: to estimate hazard ratios (HR) with 95% CI;

Variables with $P < 0.10$ in univariable analysis will be entered into multivariable models.

Software: R version 4.2.0 or later

Significance level: Two-sided $P < 0.05$

9. Ethical Considerations

Ethics Approval: This study has been approved by the Ethics Committee of the First Hospital of Jilin University (Approval No.: 2025-MS-074).

Informed Consent: Waived due to the retrospective, non-interventional nature of the study and the use of fully de-identified data.

Confidentiality: All patient identifiers will be removed prior to analysis. Data will be stored on password-protected institutional servers accessible only to the research team.

10. Data Sharing & Publication Plan

IPD Sharing: Individual participant data will not be shared due to hospital data governance policies and patient privacy regulations.

Supporting Information: De-identified summary data tables and analytic code (R scripts) will be made available upon reasonable request to the corresponding author after publication.

Publication: Results will be submitted to a peer-reviewed journal regardless of the direction of findings.

11. Study Status & Timeline

Data collection start date: December 2019 (retrospective)

Data collection end date: December 2024

Data analysis: January 2025 – June 2025

Manuscript submission: Q4 2025Current status: Data analysis completed; manuscript in preparation.

12. References

[1] Li J, Ye S, Huang X, Yang G, Wang Y, Zeng J, Lai C. Analysis of the intestinal microbiota and profiles of blood amino acids and acylcarnitines in neonates with hyperbilirubinemia. BMC Microbiol. 2024 May 18;24(1):171. doi: 10.1186/s12866-024-03328-y. PMID: 38760685; PMCID: PMC11102171.

[2] Chen W, Zhang P, Zhang X, Xiao T, Zeng J, Guo K, Qiu H, Cheng G, Wang Z, Zhou W, Zeng S, Wang M. Machine learning-causal inference based on multi-omics data reveals the association of altered gut bacteria and bile acid metabolism with neonatal jaundice. Gut Microbes. 2024 Jan-Dec;16(1):2388805. doi: 10.1080/19490976.2024.2388805. Epub 2024 Aug 21. PMID: 39166704; PMCID: PMC11340767.

[3] Zhou, S.; Wang, Z.; He, F.; Qiu, H.; Wang, Y.; Wang, H.; Zhou, J.; Zhou, J.; Cheng, G.; Zhou, W.; et al. Association of serum bilirubin in newborns affected by jaundice with gut microbiota dysbiosis. J. Nutr. Biochem. 2019, 63, 54–61.

[4] Gottstein R, Cooke RW. Systematic review of intravenous immunoglobulin in haemolytic disease of the newborn. Arch Dis Child Fetal Neonatal Ed 2003; 88: 6–10.

13. Version History

Version	Date	Description of Changes
1.0	20251201	Initial version