



Physiological and Pharmacological Determinants of Neonatal Hyperbilirubinemia: A Hospital Based Cross Sectional Study in Nasiriyah, Iraq

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Article Information

Received: 11-7-2026

Accepted: 14-8-2026

Published: 1-10-2026

Abstract

Background; In low- and middle-income countries, newborn hyperbilirubinemia is a major cause of preventable neurological illness. Risk assessment and early intervention require clinical and physiologic predictors of severe hyperbilirubinemia.

To investigate the physiological characteristics and pharmacological interventions related with severe neonatal hyperbilirubinemia and its independent predictors in hospitalised neonates in Nasiriyah, Iraq.

Methods: From October 2024 to May 2025, 200 babies with hyperbilirubinemia were studied in two prominent Nasiriyah hospitals, Bint Al-Huda Hospital and Mohammed Al-Moussawi Children Hospital. Age, sex, birth weight, gestational age, and ABO/Rh blood group incompatibility were gathered. Hyperbilirubinemia was characterised by TSB level as mild, moderate, or severe. To find severe hyperbilirubinemia predictions, multivariate logistic regression was used.

Results: The average age of infants was 6.9 ± 4.2 days, with a 71.4% male predominance. The severity of hyperbilirubinemia was 25.7%. Twenty-two percent of babies were Rh-incompatible and 42.9% ABO-incompatible. Low birth weight was the only independent risk factor for severe hyperbilirubinemia in multivariate. Serious cases were more likely to have ABO incompatibility, however this was not significant after confounders adjustment. Further, the therapy significantly reduced TSB levels (13.4 ± 4.5 mg/dL versus 7.2 ± 2.5 mg/dL, $p < 0.05$).

Conclusions: In conclusion, babies with severe hyperbilirubinemia are still frequent. Low birth weight is the highest independent predictor of hepatic immaturity and poor bilirubin metabolism, requiring rigorous supervision of this high-risk group. Despite its prevalence, ABO incompatibility has little effect once bilirubin is normalised. Prevention of serious neurological sequelae requires early clinical detection and management of high-risk neonates.

Keywords: Neonatal hyperbilirubinemia; Jaundice; ABO incompatibility; physiological factors

Introduction

Clinical practice shows that hyperbilirubinemia is common in the neonatal period. It has been shown that this phenomenon occurs in sixty percent of term infants and eighty percent of preterm neonates in the first week of life (Maisels & McDonagh, 2008). Unconjugated hyperbilirubinemia is usually self-limiting; but if not detected and treated promptly, it may lead to acute bilirubin encephalopathy and kernicterus (Bhutani et al., 2013; Kemper et al., 2022).

Neonatal hyperbilirubinemia is a multifactorial disease with complex pathophysiology that includes increased bilirubin production, immature hepatic conjugation mechanisms and increased enterohepatic circulation. Clinical and demographic variables that increase the severity of illness include prematurity, low birth weight, haemolytic disorders, and newborn infections (Diala et al., 2023). Rh immunoprophylaxis has dramatically reduced the incidence of Rh haemolytic illness in some areas. ABO incompatibility remains an important cause of haemolytic jaundice (Jackson & Baker, 2021; Parastatidou et al., 2025).

Despite advancements in neonatal care, hyperbilirubinemia remains a major health concern worldwide, especially in low- and middle-income countries. Restricted access to early screening, late medical attention, and inadequate follow-up contribute to increased prevalence of severe disease and its complications in such settings (Hamdi et al., 2025; Huang et al., 2025). Identification of neonates at increased risk for developing severe hyperbilirubinemia remains a major challenge in these settings.

Phototherapy is the treatment of choice for efficient reduction of blood bilirubin levels by photoisomerization of bilirubin into water soluble isomers that are excreted without hepatic conjugation (Lindqvist et al., 2025). The identification of independent predictors of severe disease is needed, as early risk assessment and initiation of therapy are of great importance for clinical outcomes.

Neonatal hyperbilirubinemia was studied in detail but there is lack of information about clinical features and physiological factors that lead to severe hyperbilirubinemia in southern Iraq. Most of the existing studies are descriptive and fail to adequately evaluate independent risk factors. The aim of the present study was to assess the physiological factors and pharmacological therapies of severe neonatal hyperbilirubinemia and to identify its independent predictors in hospitalised neonates in Nasiriyah, Iraq. Understanding these variables can enhance early risk assessment, improve physiologic monitoring and drug therapy, and decrease the burden of preventable sequelae in similar resource-limited settings

Methods

Study Design and Setting

Design and Setting of Study

This cross-sectional study was carried out in the neonatal care units of two major hospitals in Nasiriyah city, southern Iraq, namely Bint Al-Huda Hospital and Mohammed Al-Moussawi Children's Hospital. The study was conducted over a given period of time during October 2024 to May 2025. Methods: To assess clinical risk factors for severe neonatal hyperbilirubinemia.

Participants

A total of 200 newborns with hyperbilirubinemia were included in the study. Inclusion criteria were all infants with clinically and laboratory confirmed high total serum bilirubin (TSB) levels. The data were checked for accuracy and consistency and infants with significant congenital anomalies, haemoglobinopathies or insufficient clinical data were excluded.

Data Collection

Data were collected retrospectively from organised clinical records using a standardised data collection tool. The variables collected were demographic (sex, neonatal age in days) and perinatal data (birth weight, gestational age). Moreover, laboratory data including total serum bilirubin before and after treatment were collected. Relevant clinical risk factors including ABO and Rh blood group incompatibility were noted.

In all cases data on clinical management including the type of treatment provided were recorded. All data were checked and confirmed carefully in an effort to avoid possible information bias and to ensure the accuracy.

Severity Grading of Hyperbilirubinemia

Neonatal hyperbilirubinemia was categorised as mild, moderate and severe in accordance with standard clinical recommendations based on total blood bilirubin concentrations. For analytical purposes, these categories were grouped into a binary outcome by collapsing mild and moderate cases as non-severe and comparing them against severe hyperbilirubinemia. This dichotomisation was used to improve statistical analysis and to identify independent factors associated with severe disease.

TREATMENT PLAN

All the neonates were managed as per the standard hospital protocol. In all cases, phototherapy has always been the first-line treatment. Supportive care consisted of adequate nutrition and IV fluids as needed. Other treatments like antibiotics were given according to the clinician's judgement.

A statistics analysis

Statistical software was used for analytical procedures. Continuous variables were expressed as mean $\pm$ standard deviation (SD), and categorical variables were expressed as frequencies and percentages. The categorical factors and the severity of hyperbilirubinemia were assessed by Chi-square test and the continuous variables were assessed by independent t-test. In multivariate logistic regression analysis, birth weight, gestational age, sex and ABO incompatibility were independent predictors of severe hyperbilirubinemia. Odds ratios (OR) with 95% confidence intervals (CI) were considered significant at $p < 0.05$.

Results

Mean age was 6.9 ± 4.2 days and most newborns (65.7%) were seen during the first week of life (Table 1). The average birth weight was 2.9 ± 0.6 kg, and 80% of the newborns had a birth weight of ≥ 2.5 kg. Males were clearly predominant (71.4%) which is consistent with previous reported epidemiological trends in newborn hyperbilirubinemia.

Table 1. Demographic and Perinatal Characteristics of Neonates with Hyperbilirubinemia

Variable	Category/Value	%
Age (days)	Mean $\pm$ SD (6.9 ± 4.2)	
	≤ 7 days	65.7
	> 7 days	34.3
Birth Weight (kg)	Mean $\pm$ SD (2.9 ± 0.6)	
	< 2.5 kg	20
	≥ 2.5 kg	80
Sex	Male	71.4
	Female	28.6

Table 2 illustrates the distribution of blood group incompatibilities. ABO incompatibility was identified in 42.9% of the newborns, representing a significant fraction of the cohort. Rh incompatibility occurred with a frequency of 22.9%. The significant incidence of ABO incompatibility indicates its potential function as a primary contributing factor in this population.

Table 2. Distribution of Blood Group Incompatibility (ABO and Rh) Among Neonates with Hyperbilirubinemia

Variable	Category	%
ABO incompatibility	Yes	42.9
	No	57.1
Rh incompatibility	Yes	22.9
	No	77.1

Table 3 summarises the total serum bilirubin (TSB) levels prior to and following treatment. The average pre-treatment total serum bilirubin was 13.4 ± 4.5 mg/dL, which diminished to 7.2 ± 2.5 mg/dL following the intervention. This reduction constitutes a clinically significant therapeutic response, specifically in relation to phototherapy, which was consistently administered in this group.

Table 3. Mean Total Serum Bilirubin (TSB) Levels Pre- and Post-Treatment Among Study Participants

Variable	Mean $\pm$ SD
TSB before treatment	13.4 ± 4.5
TSB after treatment	7.2 ± 2.5

The distribution of severity is presented in Table 4. The predominant proportion was intermediate hyperbilirubinemia (48.6%), succeeded by similar proportions of mild and severe cases (25.7% each). Significantly, over two-thirds of newborns were classified as moderate-to-severe, highlighting the substantial clinical burden and the necessity for timely identification and intervention.

Table 4. Severity Classification of Neonatal Hyperbilirubinemia According to Total Serum Bilirubin (TSB) Levels

Severity	TSB (mg/dL)	Percentage (%)
Mild	<10	25.7
Moderate	10–15	48.6
Severe	>15	25.7

Table 5 presents the treatment strategies. All infants (100%) had phototherapy and received breastfeeding support, adhering to established care procedures. Adjunctive therapy comprised intravenous fluids (57.1%) and antibiotics (51.4%), potentially indicating the existence of related risk factors such as dehydration or suspected infection in a subset of patients.

Table 5. Distribution of Therapeutic Interventions Among Neonates with Hyperbilirubinemia

Treatment	Percentage (%)
Phototherapy	100
Breastfeeding	100
Antibiotics	51.4
IV Fluids	57.1

Multivariate logistic regression analysis indicated that low birth weight is an independent predictor of severe newborn hyperbilirubinemia (OR = 3.12, 95% CI: 1.01–9.65, $p = 0.047$). Preterm birth demonstrated a slight correlation, and neither ABO incompatibility nor male sex were significant predictors.

Table 6. Multivariate logistic regression analysis of factors associated with severe neonatal hyperbilirubinemia

Variable	OR	95% CI	p-value
ABO incompatibility	1.48	0.38–5.72	0.56
Low birth weight	3.12	1.01–9.65	0.047*
Preterm	2.85	0.91–8.90	0.071
Male (vs female) sex	1.36	0.42–4.40	0.60

Discussion

This study provides an insight into the prevalence and clinical characteristics of neonatal hyperbilirubinemia in the hospital setting in Nasiriyah. The results show that this disorder has a multifactorial aetiology including haematological, physiological and clinical variables, with a high percentage of newborns presenting a clinically severe disease. This supports the notion that both clinical characteristics and underlying physiological mechanisms impact disease severity in this cohort.

Most of the neonates in this study presented in the first week of life with mean age of 6.9 ± 4.2 days. This is in keeping with the usual course of neonatal hyperbilirubinaemia which peaks in the third to fifth days of life due to increased bilirubin production secondary to increased turnover of red blood cells and immature hepatic conjugation systems, especially reduced activity of uridine diphosphate glucuronosyltransferase (Ayalew et al., 2024; Jirsa & Sticová, 2013; Nawaz et al., 2021; Par et al., 2023; Reiser, 2004). The early presentation in our population may be explained possibly by increased parental awareness or hospital referral patterns. This timing also indicates substantial physiological changes in neonatal bilirubin metabolism in the early postnatal period.

The male predominance of 71.4% is in agreement with the literature that male infants are at an increased risk for hyperbilirubinemia. The exact mechanism is unclear but it has been suggested that hormonal influences and genetic predispositions affecting bilirubin metabolism may play a role (Fatima & Anil, 2023; Tioseco et al., 2005). In many groups this gender difference has been consistently reported but its therapeutic significance is usually small. However, sex-related differences seem to have little physiological impact on the severity of hyperbilirubinemia.

Mean birth weight was 2.9 ± 0.6 kg and most of the neonates were of normal birth weight. In the present study, low birth weight was the only independent predictor for severe hyperbilirubinemia. This finding is biologically plausible, since the hepatic immaturity, the reduced albumin binding capacity and the increased enterohepatic circulation are often present in low birth weight neonates, all contributing to bilirubin accumulation (Hansen et al., 2020; Tioseco et al., 2005). Feeding problems are common in this group and can worsen jaundice. This suggests that a low birth weight is an important physiologic factor and independent clinical predictor of severe disease.

In this study, a higher prevalence of ABO incompatibility (42.9%) was observed as compared to Rh incompatibility (22.9%). The present finding is in agreement with previous studies which have shown that ABO incompatibility has become an important aetiological factor of haemolytic neonatal jaundice especially in areas where Rh immunoprophylaxis is widely used (Gishu et al., 2026; Khorsheed et al., 2022; Mahapatra et al., 2024). In the early phases, the frequency of ABO haemolysis may be higher, and

the rapid rise in bilirubin levels may be due to increased red blood cell destruction. These data suggest that mechanisms of haemolysis are significant physiological contributors to bilirubin overproduction.

Post-intervention, analysis of treatment outcome showed a significant decrease in total serum bilirubin (TSB) levels from 13.4 ± 4.5 mg/dL to 7.2 ± 2.5 mg/dL. This means phototherapy is effective and continues to be the mainstay of treatment. Phototherapy converts bilirubin into water-soluble isomers that can be excreted without hepatic conjugation (Lindqvist et al., 2025; Parastatidou et al., 2025). These positive findings may be due in part to the fact that all patients in this cohort had received phototherapy. This indicates the efficacy of targeting the physiological basis of accumulation of bilirubin in therapeutic therapy.

More than half of the newborns had mild hyperbilirubinemia and about one quarter had severe disease in terms of severity of the disease. At least two-thirds were moderate to severe and posed a considerable clinical burden. This pattern may be due to late presentation, lack of adequate screening in the early period or poor postnatal follow-up, particularly in low resource settings (Hamdi et al., 2025; World Health Organization, 2026). Similar trends have been observed in low and middle income countries where severe neonatal jaundice remains a major contributor to neonatal morbidity and preventable neurologic sequelae (Tobcu et al., 2026). This distribution emphasises the importance of early recognition of high risk newborns for therapeutic purpose.

All infants in this study were given phototherapy and support for breastfeeding, many of whom require further interventions including IV fluids and antibiotics. The use of these adjunctive medications indicates the presence of contributory conditions such as dehydration or suspected newborn infection, known to increase hyperbilirubinemia by increasing bilirubin production or decreasing clearance (Parastatidou et al., 2025; Wang et al., 2024). This suggests the need for a complete management plan addressing the underlying causes and reducing bilirubin levels. These considerations further highlight the interplay of clinical circumstances and physiological pathways in disease progression.

Although the association was not statistically significant in adjusted multivariate analysis, ABO incompatibility was associated with an increased risk for severe hyperbilirubinemia. This implies that its effect might be complicated by factors such as birth weight and gestational age. Recent studies suggest that ABO incompatibility might play a role in illness aetiology, but might not be an independent predictor of severity when other risk variables are taken into account (Aljanabi, 2023; Huang et al., 2004; Lin et al., 2022). This points to the physiological immaturity of bilirubin elimination processes in premature infants.

Gestational age was slightly associated with severe hyperbilirubinaemia. This is in line with the current evidence that preterm newborns are at increased risk because of hepatic immaturity, reduced enzyme activity and impaired ability to clear bilirubin (Al-Jiboury et al., 2023; Biniwale, 2025; Oryza, n.d.; Saleh et al., 2023; Windiana et al., 2024). The non-significance of the study may be due to the relatively small sample size .

The results are consistent with the concept of neonatal hyperbilirubinemia as a complex disease that is affected by biological immaturity and clinical risk factors. Of these, low birth weight appears to be the most important driver of disease severity in this setting. The findings emphasise the significance of targeted screening, early diagnosis, and intensive follow-up in high-risk newborns, especially in resource-poor environments. When taken together, these results support the use of clinical and physiological factors in combination to predict disease severity.

Limitations of this study include a small sample size and single-center study design, which may limit the generalisability of the results. It however provides important baseline information for future large scale studies and may improve local neonatal care. Further research should investigate clinical predictors and the physiological explanation of the phenomenon in larger populations.

Conclusion

Low birth weight was an independent predictor of severe newborn hyperbilirubinemia, reflecting physiologic immaturity in bilirubin metabolism. Increased risk was associated with ABO incompatibility and preterm, although their independent effects were limited by confounding variables. The current study was cross-sectional and single-centered limiting generalisability and causality. The findings should be interpreted with caution due to the small sample size. This study provides localised insights into the patterns and causes of newborn hyperbilirubinemia. Larger, longitudinal, multi-center trials that include standardised screening and early detection are needed to reduce problems and improve newborn outcomes.

Ethical approval: The study was carried out according to the ethical standards of the College of Pharmacy, University of Thi-Qar and approved by the committee of scientific research. To preserve patient confidentiality and ethical principles of research, all data were anonymised prior to analysis.

Conflict of interest. None declared.

Funding: No funding was obtained.

Author Contribution : ,Amena L Muttlaq design the study , writing part of manuscript data collection, responsible for data analysis and writing part of manuscript and write part of manuscript. review the manuscript before submission .

Acknowledgment: Authors of be thankful for Bint Al-Huda ,Mohammed Al-Moussawi Children's Hospitals and college of pharmacy , university of Thi-Qar for their facilities to complete this work.

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