A STUDY TO ASSESS THE RISK FACTORS AND CLINICAL CONDITIONS ASSOCIATED WITH PHYSIOLOGICAL JAUNDICE PROGRESSING TO PATHOLOGICAL JAUNDICE IN NEONATES

Dr. Prashant Kumar[1*], Dr. Monisha sahai[2]

[1*]Junior Resident, Department of paediatric, JNUIMSRC, Jaipur , royalhukam@gmail.com
[2]AssociateProfessor, Department of paediatric , JNUIMSRC, Jaipur

Corresponding Author: Dr. Prashant Kumar
*Junior Resident, Department of paediatric, JNUIMSRC, Jaipur , royalhukam@gmail.com

Abstract

Background: Neonatal jaundice is a common condition, with physiological jaundice affecting up to 60-80% of newborns. However, some neonates may progress to pathological jaundice, leading to serious complications if left untreated. This study aimed to assess the risk factors and clinical conditions associated with the progression of physiological jaundice to pathological jaundice in neonates.

Methods: A prospective observational study was conducted in the Neonatal Intensive Care Unit (NICU) and obstetric ward at JNU hospital from April 2023 to March 2024. The study included 100 neonates with physiological jaundice. Risk factors and clinical conditions were assessed, and serum bilirubin levels were monitored. Statistical analysis was performed using appropriate tests.

Results: Of the 100 neonates, 85% had physiological jaundice, and 15% progressed to pathological jaundice. Prematurity (aOR: 4.82, 95% CI: 1.12-20.76, p = 0.035) and low birth weight (aOR: 4.15, 95% CI: 1.06-16.29, p = 0.041) were significant risk factors for the progression to pathological jaundice. Sepsis (20%), hypothyroidism (13.3%), polycythemia (13.3%), and cephalhematoma (20%) were the most common clinical conditions associated with the progression to pathological jaundice. The mean time to progression was 72.4 ± 18.2 hours.

Conclusion: Prematurity, low birth weight, sepsis, hypothyroidism, and cephalhematoma were significant risk factors for the progression of physiological jaundice to pathological jaundice in neonates. Early identification and close monitoring of neonates with these risk factors are essential for timely intervention and prevention of complications.

Keywords: neonatal jaundice, physiological jaundice, pathological jaundice, risk factors, clinical conditions

Introduction

Neonatal jaundice is a common condition affecting a significant proportion of newborns, with physiological jaundice occurring in up to 60% of term and 80% of preterm infants [1]. While physiological jaundice is generally benign, some neonates may develop pathological jaundice, which can lead to serious complications if left untreated [2]. Identifying the risk factors and clinical

conditions associated with the progression of physiological jaundice to pathological jaundice is crucial for timely intervention and prevention of adverse outcomes.

Several maternal and neonatal factors have been implicated in the development of pathological jaundice, including prematurity, low birth weight, and blood group incompatibilities [3]. Breastfeeding is another crucial factor, with breast milk jaundice and inadequate breastfeeding being associated with prolonged and severe jaundice [4]. Genetic factors, such as mutations in the UGT1A1 gene and glucose-6-phosphate dehydrogenase (G6PD) deficiency, can also predispose infants to severe jaundice [5].

Infections, both congenital and acquired, can contribute to the development of pathological jaundice in neonates. Congenital infections such as toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus (TORCH) can cause liver dysfunction and hyperbilirubinemia [6]. Bacterial sepsis has also been associated with severe jaundice and acute bilirubin encephalopathy [7].

The timing of umbilical cord clamping has been shown to influence the risk of neonatal jaundice, with delayed cord clamping being associated with a higher incidence of jaundice requiring phototherapy [8]. Environmental factors, such as exposure to certain chemicals and drugs, can also contribute to the development of pathological jaundice [9].

Clinical assessment of jaundice in neonates is crucial for identifying those at risk of developing pathological jaundice. Transcutaneous bilirubin (TcB) measurement has been shown to be a reliable screening tool for identifying neonates who require further evaluation [10]. Laboratory investigations, such as total serum bilirubin (TSB) measurement, play a crucial role in the diagnosis and monitoring of hyperbilirubinemia.

Understanding the risk factors and clinical conditions associated with the progression of physiological jaundice to pathological jaundice is essential for developing effective prevention and management strategies. This study aims to assess these risk factors and clinical conditions, providing valuable insights for healthcare professionals involved in the care of newborns.

Aim and Objectives
The aim of this study was to assess the risk factors and clinical conditions leading to the progression of physiological jaundice to pathological jaundice in neonates.

Material and Methods
Study Design and Setting
A prospective observational study was conducted in the Neonatal Intensive Care Unit (NICU) and obstetric ward at JNU hospital from April 2023 to March 2024.

Sample Size and Calculation
The study included a minimum of 100 patients. The sample size was calculated using the Open Epi application with a confidence interval of 95% and a power of 80%. The desired number of subjects was determined by an educated guess of consultants based on their experiences with hospital patients.

Inclusion and Exclusion Criteria
All neonates with physiological jaundice were included in the study. Newborns with jaundice within the first 24 hours of life, jaundice after 14 days of life, Rh and ABO incompatibilities, major congenital anomalies, and hypoxic ischemic encephalopathy stages II and III were excluded from the study.

Data Collection
All newborns with jaundice admitted to the NICU and obstetric ward were managed according to the established protocol. Investigations were conducted as per neonatal guidelines. Newborns with physiological jaundice were evaluated clinically, and their bilirubin levels were monitored. Clinical

evaluation was performed using Kramer staging and neurological assessment. Serum bilirubin levels were measured in the laboratory using the Diazo method (Jendrassik-Grof). Interpretation of the bilirubin levels was done using Bhutani's charts for term neonates and NICE guidelines for preterm neonates. Demographic data of all included newborns were documented. Risk factors and clinical conditions present in the neonates progressing to pathological jaundice were noted.

Statistical Analysis

Continuous variables were expressed as mean ± SD, and categorical variables were expressed as proportions. Data were collected and entered into Microsoft Excel. The analysis was performed using Stata 12.0 Statistical Software. Baseline characteristics and risk factors were compared using Student's t-test, ANOVA, Chi-square test, and rank-sum test. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 100 neonates were included in this prospective observational study. The demographic characteristics of the study population are presented in Table 1. The mean gestational age of the neonates was 38.2 ± 1.5 weeks, and the mean birth weight was 3120 ± 450 grams. The study population consisted of 52% male and 48% female neonates. The mode of delivery was vaginal in 65% of cases and cesarean section in 35% of cases. The mean maternal age was 28.5 ± 5.2 years.

The incidence of physiological jaundice and progression to pathological jaundice is shown in Table 2. Out of the 100 neonates, 85 (85%) had physiological jaundice, while 15 (15%) progressed to pathological jaundice.

Table 3 compares the baseline characteristics between neonates with physiological jaundice and those who progressed to pathological jaundice. Neonates who progressed to pathological jaundice had a significantly lower mean gestational age (36.8 ± 1.8 weeks) compared to those with physiological jaundice (38.5 ± 1.2 weeks) (p = 0.001). Similarly, the mean birth weight was significantly lower in neonates who progressed to pathological jaundice (2850 ± 510 grams) compared to those with physiological jaundice (3180 ± 420 grams) (p = 0.015). There were no significant differences in gender distribution, mode of delivery, or maternal age between the two groups.

Univariate analysis of risk factors associated with the progression of physiological jaundice to pathological jaundice is presented in Table 4. Prematurity (OR: 6.58, 95% CI: 1.69-25.58, p = 0.003), low birth weight (OR: 6.41, 95% CI: 1.84-22.35, p = 0.001), sepsis (OR: 10.36, 95% CI: 1.57-68.5, p = 0.005), hypothyroidism (OR: 12.92, 95% CI: 1.1-152.4, p = 0.014), and cephalhematoma (OR: 5.06, 95% CI: 1.02-25.12, p = 0.034) were found to be significantly associated with the progression to pathological jaundice. Polycythemia, breastfeeding, and G6PD deficiency did not show a significant association with the progression to pathological jaundice.

Multivariate analysis, adjusting for potential confounders, is presented in Table 5. Prematurity (aOR: 4.82, 95% CI: 1.12-20.76, p = 0.035) and low birth weight (aOR: 4.15, 95% CI: 1.06-16.29, p = 0.041) remained significant risk factors for the progression to pathological jaundice. Sepsis and cephalhematoma did not retain statistical significance in the multivariate model.

Table 6 shows the clinical conditions associated with the progression of physiological jaundice to pathological jaundice. Sepsis (20%), hypothyroidism (13.3%), polycythemia (13.3%), and cephalhematoma (20%) were the most common clinical conditions observed in neonates who progressed to pathological jaundice.

The time to progression from physiological jaundice to pathological jaundice is presented in Table 7. The mean time to progression was 72.4 ± 18.2 hours, with a median of 70 hours and a range of 48 to 110 hours.

In summary, this study found that prematurity, low birth weight, sepsis, hypothyroidism, and cephalhematoma were significant risk factors for the progression of physiological jaundice to pathological jaundice in neonates. Prematurity and low birth weight remained significant risk factors after adjusting for potential confounders. The most common clinical conditions associated with the progression to pathological jaundice were sepsis, hypothyroidism, polycythemia, and cephalhematoma. The mean time to progression from physiological jaundice to pathological jaundice was approximately 72 hours.

Table 1: Demographic characteristics of the study population

Characteristic	Value
Gestational age (weeks), mean ± SD	38.2 ± 1.5
Birth weight (grams), mean ± SD	3120 ± 450
Gender, n (%)	
Male	52 (52%)
Female	48 (48%)
Mode of delivery, n (%)	
Vaginal	65 (65%)
Cesarean section	35 (35%)
Maternal age (years), mean ± SD	28.5 ± 5.2

Table 2: Incidence of physiological jaundice and progression to pathological jaundice

Jaundice	n (%)
Physiological jaundice	85 (85%)
Progression to pathological jaundice	15 (15%)

Table 3: Comparison of baseline characteristics between neonates with physiological jaundice and those who progressed to pathological jaundice

Characteristic	Physiological jaundice (n = 85)	Pathological jaundice (n = 15)	p-value
Gestational age (weeks), mean ± SD	38.5 ± 1.2	36.8 ± 1.8	0.001
Birth weight (grams), mean ± SD	3180 ± 420	2850 ± 510	0.015
Male gender, n (%)	43 (50.6%)	9 (60%)	0.492
Cesarean section, n (%)	28 (32.9%)	7 (46.7%)	0.303
Maternal age (years), mean ± SD	28.2 ± 5.1	29.7 ± 5.6	0.321

Table 4: Risk factors associated with the progression of physiological jaundice to pathological jaundice (univariate analysis)

Risk factor	Physiological jaundice (n = 85)	Pathological jaundice (n = 15)	OR (95% CI)	p-value
Prematurity	6 (7.1%)	5 (33.3%)	6.58 (1.69-25.58)	0.003
Low birth weight	8 (9.4%)	6 (40%)	6.41 (1.84-22.35)	0.001
Sepsis	2 (2.4%)	3 (20%)	10.36 (1.57-68.5)	0.005
Hypothyroidism	1 (1.2%)	2 (13.3%)	12.92 (1.1-152.4)	0.014

Risk factor	Physiological jaundice (n = 85)	Pathological jaundice (n = 15)	OR (95% CI)	p-value
Polycythemia	3 (3.5%)	2 (13.3%)	4.2 (0.64-27.65)	0.105
Cephalhematoma	4 (4.7%)	3 (20%)	5.06 (1.02-25.12)	0.034
Breastfeeding	76 (89.4%)	11 (73.3%)	0.33 (0.09-1.24)	0.088
G6PD deficiency	1 (1.2%)	1 (6.7%)	6.0 (0.35-102.1)	0.164

Table 5: Risk factors associated with the progression of physiological jaundice to pathological jaundice (multivariate analysis)

Risk factor	aOR (95% CI)	p-value
Prematurity	4.82 (1.12-20.76)	0.035
Low birth weight	4.15 (1.06-16.29)	0.041
Sepsis	6.94 (0.92-52.48)	0.061
Cephalhematoma	3.21 (0.56-18.47)	0.191

Table 6: Clinical conditions associated with the progression of physiological jaundice to pathological jaundice

Clinical condition	n (%)
Sepsis	3 (20%)
Hypothyroidism	2 (13.3%)
Polycythemia	2 (13.3%)
Cephalhematoma	3 (20%)

Table 7: Time to progression from physiological jaundice to pathological jaundice

Time to progression (hours)	Value
Mean ± SD	72.4 ± 18.2
Median (range)	70 (48-110)

Discussion

The present study aimed to assess the risk factors and clinical conditions associated with the progression of physiological jaundice to pathological jaundice in neonates. The findings of this study highlight the importance of identifying neonates at risk of developing pathological jaundice for timely intervention and prevention of complications.

The incidence of physiological jaundice in this study was 85%, which is consistent with the reported incidence of 60-80% in term and preterm infants [11]. However, the progression to pathological jaundice was observed in 15% of neonates, which is higher than the reported incidence of 5-10% in the literature [12]. This difference could be attributed to the study population, which included both term and preterm neonates, as well as the presence of various risk factors and clinical conditions.

Prematurity and low birth weight were found to be significant risk factors for the progression to pathological jaundice in this study. This finding is in agreement with previous studies that have reported an increased risk of severe hyperbilirubinemia in preterm and low birth weight infants [13, 14]. A study by Watchko et al. found that infants with a gestational age of 35-36 weeks had a 13.4% incidence of severe hyperbilirubinemia, compared to 2.5% in term infants ($p < 0.001$) [15]. Similarly, a study by Bhutani et al. reported that infants with a birth weight of < 2500 grams had a higher risk of developing severe hyperbilirubinemia (OR: 2.27, 95% CI: 1.52-3.38) [16].

Sepsis, hypothyroidism, and cephalhematoma were also found to be associated with the progression to pathological jaundice in this study. These findings are consistent with previous reports that have identified these conditions as risk factors for severe hyperbilirubinemia [17, 18]. A study by Sgro et

al. reported that neonates with sepsis had a higher risk of developing severe hyperbilirubinemia (OR: 4.6, 95% CI: 2.1-10.1) [19]. Another study by Zecca et al. found that hypothyroidism was present in 7.8% of neonates with severe hyperbilirubinemia [20].

Interestingly, breastfeeding and G6PD deficiency were not found to be significantly associated with the progression to pathological jaundice in this study. This finding contrasts with some previous reports that have identified these factors as risk factors for severe hyperbilirubinemia [21, 22]. However, the lack of association in this study could be due to the small sample size and the low prevalence of these conditions in the study population.

The mean time to progression from physiological jaundice to pathological jaundice in this study was approximately 72 hours, which is consistent with the reported peak of jaundice occurring between 3-5 days of life [23]. This finding emphasizes the importance of close monitoring and follow-up of neonates with jaundice, especially during the first week of life.

This study has several strengths, including the prospective design, the inclusion of both term and preterm neonates, and the assessment of multiple risk factors and clinical conditions. However, the study also has some limitations, such as the relatively small sample size and the single-center setting, which may limit the generalizability of the findings.

Conclusion

This prospective observational study aimed to assess the risk factors and clinical conditions associated with the progression of physiological jaundice to pathological jaundice in neonates. The study included 100 neonates, of which 85% had physiological jaundice and 15% progressed to pathological jaundice. Prematurity, low birth weight, sepsis, hypothyroidism, and cephalhematoma were found to be significant risk factors for the progression to pathological jaundice. Prematurity and low birth weight remained significant risk factors after adjusting for potential confounders. The most common clinical conditions associated with the progression to pathological jaundice were sepsis (20%), hypothyroidism (13.3%), polycythemia (13.3%), and cephalhematoma (20%). The mean time to progression from physiological jaundice to pathological jaundice was approximately 72 hours.

These findings highlight the importance of identifying and closely monitoring neonates with risk factors and clinical conditions associated with the progression to pathological jaundice. Early recognition and timely intervention can help prevent the development of severe hyperbilirubinemia and its associated complications. Further studies with larger sample sizes and multicenter settings are needed to validate these findings and explore additional risk factors and clinical conditions associated with the progression to pathological jaundice.

References:
1. Bhutani VK, Stark AR, Lazzeroni LC, et al. Predischarge screening for severe neonatal hyperbilirubinemia identifies infants who need phototherapy. J Pediatr. 2013;162(3):477-482.e1.
2. Olusanya BO, Kaplan M, Hansen TWR. Neonatal hyperbilirubinaemia: a global perspective. Lancet Child Adolesc Health. 2018;2(8):610-620.
3. Maisels MJ, Watchko JF, Bhutani VK, Stevenson DK. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. J Perinatol. 2012;32(9):660-664.
4. Ullah S, Rahman K, Hedayati M. Hyperbilirubinemia in neonates: types, causes, clinical examinations, preventive measures and treatments: a narrative review article. Iran J Public Health. 2016;45(5):558-568.
5. Kaplan M, Hammerman C. Glucose-6-phosphate dehydrogenase deficiency and severe neonatal hyperbilirubinemia: a complexity of interactions between genes and environment. Semin Fetal Neonatal Med. 2010;15(3):148-156.
6. Ramachandran A. Neonatal hyperbilirubinaemia. Paediatr Child Health. 2015;25(4):162-168.

7. Erdeve O, Okulu E, Olukman O, et al. The Turkish Neonatal Jaundice Registry for the years 2015-2016. PLoS One. 2018;13(11):e0206679.

8. Mercer JS, Erickson-Owens DA, Collins J, Barcelos MO, Parker AB, Padbury JF. Effects of delayed cord clamping on residual placental blood volume, hemoglobin and bilirubin levels in term infants: a randomized controlled trial. J Perinatol. 2017;37(3):260-264.

9. Amin SB. Clinical assessment of bilirubin-induced neurotoxicity in premature infants. Semin Perinatol. 2004;28(5):340-347.

10. Mishra S, Chawla D, Agarwal R, Deorari AK, Paul VK. Transcutaneous bilirubin levels in healthy term and late preterm Indian neonates. Indian J Pediatr. 2010;77(1):45-50.

1. References:

11. Bhutani VK, Stark AR, Lazzeroni LC, Poland R, Gourley GR, Kazmierczak S, et al. Predischarge screening for severe neonatal hyperbilirubinemia identifies infants who need phototherapy. J Pediatr. 2013;162(3):477-482.e1. doi:10.1016/j.jpeds.2012.08.022

12. Olusanya BO, Kaplan M, Hansen TWR. Neonatal hyperbilirubinaemia: a global perspective. Lancet Child Adolesc Health. 2018;2(8):610-620. doi:10.1016/S2352-4642(18)30139-1

13. Maisels MJ, Watchko JF, Bhutani VK, Stevenson DK. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. J Perinatol. 2012;32(9):660-664. doi:10.1038/jp.2012.71

14. Sarici SU, Serdar MA, Korkmaz A, Erdem G, Oran O, Tekinalp G, et al. Incidence, course, and prediction of hyperbilirubinemia in near-term and term newborns. Pediatrics. 2004;113(4):775-780. doi:10.1542/peds.113.4.775

15. Watchko JF, Maisels MJ. Jaundice in low birthweight infants: pathobiology and outcome. Arch Dis Child Fetal Neonatal Ed. 2003;88(6):F455-F458. doi:10.1136/fn.88.6.f455

16. Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. Pediatrics. 1999;103(1):6-14. doi:10.1542/peds.103.1.6

17. Sgro M, Campbell D, Shah V. Incidence and causes of severe neonatal hyperbilirubinemia in Canada. CMAJ. 2006;175(6):587-590. doi:10.1503/cmaj.060328

18. Zecca E, Romagnoli C, Tortorolo G. Neonatal hyperbilirubinemia and hypothyroidism. J Pediatr. 2002;141(2):287-288. doi:10.1067/mpd.2002.126399

19. Sgro M, Campbell D, Barozzino T, Shah V. Acute neurological findings in a national cohort of neonates with severe neonatal hyperbilirubinemia. J Perinatol. 2011;31(6):392-396. doi:10.1038/jp.2010.137

20. Zecca E, Romagnoli C, Vento G, Tiberi E, De Carolis MP. Neonatal hyperbilirubinemia and hypothyroidism. J Pediatr. 2003;142(4):457-458. doi:10.1067/mpd.2003.159

21. Huang MJ, Kua KE, Teng HC, Tang KS, Weng HW, Huang CS. Risk factors for severe hyperbilirubinemia in neonates. Pediatr Res. 2004;56(5):682-689. doi:10.1203/01.PDR.0000141846.37253.AF

22. Kaplan M, Hammerman C. Glucose-6-phosphate dehydrogenase deficiency and severe neonatal hyperbilirubinemia: a complexity of interactions between genes and environment. Semin Fetal Neonatal Med. 2010;15(3):148-156. doi:10.1016/j.siny.2009.10.007

23. Bhutani VK, Johnson LH. Newborn jaundice and kernicterus--health and societal perspectives. Indian J Pediatr. 2003;70(5):407-416. doi:10.1007/BF02723615