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PREVALENCE AND RISK FACTORS OF NEONATAL JAUNDICE AND ITS ETIOLOGIES IN A TERTIARY HOSPITAL IN MANIPUR: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Neonatal jaundice is among the most common clinical findings among neonates and is also the most common reason of delayed discharge from the hospital or readmission within first week of life. An evidence-based strategy is needed for prevention, early detection and treatment of neonatal jaundice to decrease the economic and social burden on the patients' families but there is a paucity of quality population data on the prevalence of hyperbilirubinemia and related outcomes to formulate such a strategy in the study area. With the above background, this study was conducted to determine the prevalence of Neonatal Jaundice in neonates born in our hospital and to study the various risk factors associated with neonatal jaundice. **Objectives:** The objectives to determine the prevalence of Neonatal Jaundice in neonates born in JNIMS Hospital, Manipur, India, to identify the various risk factors and etiologies associated with neonatal jaundice and to compare these various risk factors and etiologies between neonates with and without jaundice. **Materials and Methods:** A hospital-based prospective observational study was done in JNIMS, Manipur during the period July 2023-June 2024. A total of 304 newborns selected by consecutive sampling during this period was selected. Anthropometric measurements, routing investigations and if necessary, direct Coomb's test were performed. Necessary treatment with phototherapy, exchange transfusion etc. were provided as per guidelines. The neonates were followed up until discharged. **Results:** The prevalence of jaundice in our study was 68.4%. More than three fourth neonates had physiological jaundice (76.4%) whereas remaining 23.6% neonates had pathological jaundice. Jaundice was observed in significantly higher proportions of males as compared to females (p=0.027). Again, pre-term neonates (46; 93.9%) had higher proportion of jaundice compared to term neonates. Similarly, jaundice was seen more among low neonatal weight (p=0.001), neonates with mixed feeding or exclusive breastfeeding (p=0.001), ABO mismatch (p=0.001) and neonates with comorbidities (p=0.001). Rh mismatch and maternal comorbidities were not found to be significant factors associated with neonatal jaundice. Gender of neonate, maturity and neonatal weight were comparable between the two types of jaundice. But sepsis was found in 17 (34.7%) neonates as compared to neonates with physiological jaundice (30; 18.9%) and the observed association between sepsis and type of jaundice was statistically significant (p<0.05). Lastly, there was no statistically significant association between mismatches in ABO or Rh with the type of jaundice. Most common etiology of jaundice in our study were exclusive breast feeding (52.4%) and ABO mismatch (47.1%). **Conclusion:** The prevalence of neonatal jaundice in our study was 68.4%. Neonatal jaundice is significantly associated with male gender, small for gestational age, exclusive breast feeding, sepsis, ABO incompatibility, maternal hypothyroidism and other neonatal comorbidities. Formula feeding, absence of maternal comorbidities and appropriate weight for gestational age are protective against neonatal jaundice. Overall, ABO incompatibility and exclusive breast feeding are common etiologies of neonatal jaundice.

INTRODUCTION

Neonatal jaundice, also called as hyperbilirubinemia has been defined as total bilirubin levels above normal limits for neonates (>5 mg/dl).[1,2] It is among the most common clinical findings among neonates and is also the most common reason of delayed discharge from the hospital or readmission within first week of life. The incidence of neonatal jaundice in India have been reported to range from 54.6% to 77.2%. However, pathological jaundice have been reported in 4 to 8% of the neonates and is often associated with prematurity, G6PD deficiency, sepsis or blood group incompatibility.[3] The common causes of neonatal jaundice are physiological jaundice, breastmilk jaundice, prematurity and various pathological causes like ABO incompatibility, RH incompatibility, biliary atresia, neonatal hepatitis, neonatal sepsis, deficiency of G6PD enzyme, hypothyroidism and rare conditions such as Gilbert's syndrome.[4]

Though neonatal jaundice is usually not harmful and is self-limiting condition, severe neonatal jaundice is associated with increased morbidity and mortality. In addition to the considerable risk of premature death, severe neonatal jaundice causes acute bilirubin encephalopathy or kernicterus, which can result in long-term neurologic impairment such as cerebral palsy, sensory nerve hearing loss, intellectual issues, or gross developmental delays. The incidence of severe newborn jaundice and its role in neonatal morbidity and death are yet unknown and may be greatly underreported.[5]

An evidence-based strategy is needed for prevention, early detection and treatment of neonatal jaundice to decrease the economic and social burden on the patients' families but there is a paucity of quality population data on the prevalence of hyperbilirubinemia and related outcomes to formulate such a strategy in the study area. With the above background, this study was conducted to determine the prevalence of Neonatal Jaundice in neonates born in our hospital and to study the various risk factors associated with neonatal jaundice. This study would help in understanding the risk factors of neonatal jaundice, formulation of measures to improve prevention, early detection, treatment of neonatal jaundice and mitigation of neonatal jaundice related morbidity and mortality.

Aims & objectives

The main aim of this study is to reduce the burden of neonatal jaundice by identifying and understanding the underlying risk factors and etiologies. Consequently, the objectives were made as (i) To determine the prevalence of Neonatal Jaundice in neonates born in JNIMS Hospital, Manipur, India (ii) To identify the various risk factors and etiologies associated with neonatal jaundice and (iii) To compare these various risk factors and etiologies between neonates with and without jaundice.

MATERIALS AND METHODS

The present study was conducted as a facility-based prospective observational study on all neonates delivered in Jawaharlal Nehru Institute of Medical Sciences (JNIMS), Imphal, a tertiary health care centre in Manipur, during the study period of 12 months from July, 2023 till June, 2024.

All newborns delivered during the period and their mother duo were the study participants. Neonates with mothers/caretakers who refused to give consent and neonates who were discharged against medical advice were excluded from the study. A sample size of 304 was calculated taking into account of an incidence of neonatal jaundice as 61.8% from an earlier study conducted by Khound MM et al in India,[6] 95% precision and a probable non-participation rate of 20%. The eligible neonates were consecutively included till the required sample size was reached.

Detailed history was taken in a pre-tested proforma and all the neonates were subjected, detailed general physical and systemic examination were recorded in the proforma. The naked weight of neonate with minimal clothing was taken with the help of weighing Machine: Beurer GmbH, soflinger str.218,89077 Ulm, Germany.BY 80 (digital). Max= 20kg, d = 5g and infantometer (Indosurgical product, code =20014, Made in India) was used to determine length of neonates. All the routine investigations were performed. Blood was drawn in plain vial using aseptic precautions for assessment of total serum bilirubin, direct and indirect bilirubin estimation. ABO Rh typing was also done. Samples were sent immediately to the Department of Biochemistry, JNIMS for serum bilirubin estimation. These are investigations sent routinely and have established patient safety. If indicated, thyroid profile, G6PD level, direct antiglobulin test or direct coomb's test and sepsis screening were performed.

After initial assessment, all neonates included in the study were given enteral feeding or intravenous fluids, phototherapy or exchange transfusion as per standard recommended protocol.

Neonatal jaundice was defined as total serum bilirubin level above 5 mg/dl. Physiological jaundice was defined having visible jaundice appears between 24 to 72 hours of age and TSB level peaks up to 12 to 15 mg/dl by 3rd day of age in mature infants and in pre-term infants, the peak level occurring on the 3-7 days of age and TSB can rise over 15mg/dl. Pathological jaundice was defined as the presence of one of the following conditions: visible jaundice in first 24 hours of life, presence of jaundice on arms and legs on the second day of life, yellowish discoloration up to palms and soles anytime, serum bilirubin concentration increasing more than 0.2 mg/dL/hour or more than 5mg/dL in 24 hours, if TSB concentration more than 95" centile as per age specific bilirubinnomogram, signs of acute bilirubin encephalopathy or kernicterus or clinical jaundice

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persisting beyond 2 weeks in term and 3 weeks in preterm neonates. Risk designation of term and near-term well newborns was based on their-specific serum bilirubin values by BHUTANI chart (predictive ability of a pre-discharge hour specific serum bilirubin for subsequent hyperbilirubinemia).[7]

Phototherapy was given based on the Guidelines from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia.[106] and NICE guidelines for newborns less than 35 weeks of gestation.[10] Exchange transfusion was given based on the Guidelines from American Academy of Pediatrics Subcommittee on Hyperbilirubinemia.[8]

All the cases were closely monitored and their clinical progress was recorded daily. Neonates included in this study were followed up during their stay in the hospital and immediate outcome was evaluated.

The data was entered in Microsoft Excel and then analysed using SPSS (IBM) version 22.0 software for Windows. For descriptive statistics, mean and standard deviation or median with interquartile range was assessed whereas for categorical variables percentage and proportion were used. Chi square test or its modification was used to find the association between relevant categorical variables. A p-value of <0.05 was considered as statistically significant.

Ethical approval from the Institutional Ethical Committee, JNIMS was taken before enrolment of the participants. Informed consent was obtained from the parents of the study participants before recruitment. Confidentiality of the study participants was maintained by limiting the identifying variables to the minimum.

RESULTS

A total of 4193 babies were delivered in Jawaharlal Nehru Institute of Medical Sciences (JNIMS), Imphal, Manipur from July 2023 to June 2024. The current study was conducted on a total of 304 selected neonates. The number of babies having neonatal jaundice was found to be 208 giving a prevalence of 68.4%. Of these 208 newborns with jaundice, 159 (76.4%) were physiological jaundice while the rest (49; 23.6%) had pathological jaundice.

More than half (124; 59.6%) neonates with jaundice were males. Jaundice was observed in significantly higher proportions of males as compared to females (p=0.027). Again, pre-term neonates (46; 93.9%) had higher proportion of jaundice compared to term neonates. This difference was statistically significant (p=0.001). Similarly, jaundice was seen more among low neonatal weight (p=0.001), neonates with mixed feeding or exclusive breastfeeding (p=0.001), ABO mismatch (p=0.001) and neonates with comorbidities (p=0.001). Rh mismatch and maternal comorbidities were not found to significant factors associated with neonatal jaundice. [Table 1]

Table 1: Association of neonatal jaundice with background characteristics of neonates

Variable	Jaundice				χ^2 value	P value
	Present (n=208)		Absent (n=96)			
	N	%	N	%		
Sex						
• Male	124	73.8	44	26.2	5.35	0.027
• Female	84	61.8	52	38.2		
Maturity						
• Term	162	63.5	93	36.5	17.52	0.001
• Preterm	46	93.9	3	6.1		
Neonatal weight						
• AGA	150	61.5	94	38.5	26.64	0.001
• SGA	51	89.5	2	10.5		
• LGA	7	100	0	-		
Feeding practice						
• Mixed feeding	92	73.6	33	26.4	31.32	0.001
• Excl. breastfeeding	109	74.1	40	26.9		
• Formula feeding	7	23.3	23	76.7		
ABO mismatch						
• Present	98	79.7	25	20.3	12.11	0.001
• Absent	110	60.8	71	39.2		
Rh mismatch						
• Present	4	100	0	-	1.87	0.171
• Absent	204	68	96	32		
Maternal comorbidities						
• Hypothyroidism	14	100	0	-		
• Hypertension	2	100	0	-		
• Diabetes	4	80	1	20		
• Rh negative	5	100	0	-	15.32	0.032
• Others	6	100	0	-		
• Hypothyroidism + DM	1	100	0	-		
• Hypothyroidism+ others	1	100	0	-		
• Nil	175	71.7	95	28.3		
Other neonatal comorbidities					19.85	0.001

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• Present • Absent	39 169	97.5 64	1 95	2.5 36		

The risk factors identified were further analysed for any association with the type of jaundice i.e., physiological jaundice and pathological jaundice. Gender of neonate, maturity and neonatal weight were comparable between the two types of jaundice. But sepsis was found in 17 (34.7%) neonates as compared to neonates with physiological jaundice (30; 18.9%) and the observed association between sepsis and type of jaundice was statistically significant ($p<0.05$). Lastly, there was no statistically significant association between mismatches in ABO or Rh with the type of jaundice. [Table 2]

Table 2: Association of risk factors with type of jaundice (n=208)

Variable	Physiological jaundice (%)	Pathological jaundice (%)	X^2 value	P value
Gender • Male • Female	 96 (60.4) 63 (39.6)	 28 (57.1) 21 (42.9)	0.163	0.69
Maturity • Term • Preterm	 122 (75.3) 37 (80.4)	 40 (24.7) 9 (19.6)	0.523	0.470
Neonatal weight • AGA • SGA • LGA	 115 (76.7) 38 (74.5) 6 (3.8)	 35 (71.4) 13 (26.5) 1 (2.0)	0.444	0.801
Sepsis • Present • Absent	 30 (18.9) 129 (81.1)	 17 (34.7) 32 (65.3)	0.02	<0.05
ABO mismatch • Present • Absent	 71 (44.7) 88 (55.3)	 27 (55.1) 22 (44.9)	1.64	0.20
Rh mismatch • Present • Absent	 3 (1.9) 156 (98.1)	 1 (2.0) 48 (98)	0.005	0.945

Only 10 of the 208 neonates with jaundice were subjected to Direct Coomb's test according to need. And only one gave positive result.

The mean day (SD) of appearance of jaundice was 4.26 (1.812) days and total mean (SD) serum bilirubin levels was 14.79 (4.34) mg/dl. [Table 3]

Table 3: Distribution of neonates with jaundice according to treatment received (n=208)

Treatment	Number of neonates (%)
Phototherapy only	127 (61.1)
Phototherapy with Exchange transfusion	3 (1.4)
Phototherapy with IVIG	1 (0.5)
No phototherapy	77 (37)

About 61.1% neonates with jaundice received only phototherapy. All the neonates with sepsis were given antibiotics (22.6%) and one case required IVIG in addition to antibiotics. Phototherapy was not required in 37% of the neonates with jaundice.

Table 4: Distribution of neonatal jaundice by etiology

Aetiologies	Number (n=208)	Percentage
Sepsis	47	22.6
ABO mismatch	98	47.1
Rh mismatch	4	1.9
Preterm	46	22.1
Exclusive breastfeeding	109	52.4
Formula feeding	3	3.4
Other neonatal comorbidities	39	18.8

Most common etiology of jaundice in our study was ABO mismatch (47.1%). Exclusive breast feeding was observed in 44.2% neonates, sepsis in 22.6% neonates, preterm birth in 22.1%, other neonatal comorbidities in 18.8% and formula feeding was noted in 3.4% neonates. Rh mismatch was an underlying etiology in 1.9%.

DISCUSSION

In the present study, the prevalence of neonatal jaundice was 68.4% and out of 208 cases with jaundice, 76.4% neonates had physiological jaundice whereas 23.6% neonates had pathological jaundice. The mean day at the onset of jaundice was 4.26±1.812 days and total serum bilirubin levels were

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14.79±4.34 mg/dl. Similar findings were reported by Khound MM et al (2021), the incidence of neonatal jaundice being 61.8% and 66% neonates had physiological jaundice and 34% neonates had pathological jaundice.[6] Van der Geest BA et al (2022) documented neonatal jaundice in 71.9% neonates .[9]

The prevalence of neonatal jaundice in a study of Brits H et al (2018) was 55.2%.[10] The findings of present study were concordant with the findings of Sahoo M et al (2016), in which 48.8% neonates developed clinical jaundice and 61% neonates had physiological jaundice whereas 19% neonates had pathological jaundice.[11] Dorji N et al (2022) reported the prevalence of newborn jaundice as 33% and 47% in 2019 and 2020 respectively.[12] Kumar S et al (2019) reported the prevalence of neonatal jaundice in 44.4% neonates and 58% neonates had physiological jaundice whereas 42% neonates had pathological jaundice.[13]

In a study of Scafford CG et al (2013), the incidence of neonatal jaundice was 29.3 per 1000 live births and the median age at appearance of jaundice was 6 days, with jaundice appearing within first week of life in majority of neonates (55.8%).[14] In a study of Mishra S et al (2024), 30.5% developed jaundice during the first 24 hours, whereas 53.5% developed jaundice after 72 hours.[15] Thus, the prevalence of neonatal jaundice varies widely and the difference in the prevalence rate between the present study and reference studies could be attributed to difference in population being studied. The present study was conducted on newborns delivered in JNIMS and admitted in postnatal ward and kept with the mothers.

Phototherapy is the first line of treatment of neonatal jaundice as it is helpful in lowering the risk of bilirubin toxicity as well as the need for exchange transfusion. Exchange transfusion is the second-line treatment for severe unconjugated hyperbilirubinemia. Intravenous immunoglobulin is indicated when TSB remains within 2 to 3 mg/dL of the exchange threshold even after phototherapy in immune-mediated hemolysis.[16] More than half of the neonates were given phototherapy and 1.4% neonates were given phototherapy and exchange transfusion. IVIG was given in 1 neonate in our study. On the other hand, in a study of Sahoo M et al (2006), 39% neonates required treatment in the form of phototherapy and/ or exchange transfusion.[11] In a study of Van der Geest BA et al (2022), 3.6% neonates underwent phototherapy and none of the neonates required exchange transfusion.[9] The prevalence of neonatal jaundice in a study of Brits H et al (2018) was 55.2% and 19% neonates received phototherapy whereas 10.4% neonates were possibly qualified for phototherapy.[10] The need of phototherapy and exchange transfusion was higher in present study as compared to other studies and this could be attributed to higher prevalence of moderate to severe jaundice in our study as compared to other studies.

In our study, jaundice was observed in significantly higher proportions of males as compared to females (59.6% cs. 40.4%; $p<0.05$), however, we observed no significant association of physiological and pathological jaundice with sex of neonates ($p>0.05$). The findings of present study were concordant with the findings of Scafford CG et al (2013), where the authors found significantly higher incidence of neonatal jaundice among males.[14] The findings of present study were concordant with the findings of Ayalew T et al (2024), in which male newborns were 4.3 times more likely than female neonates to experience neonatal jaundice.[17]

The findings of present study were also supported by the findings of Saadat SH et al (2018) in which 54.2% of the neonates with jaundice were males neonates had the higher risk of jaundice on the first day.[18] Similarly, Acharya N et al (2020) reported male predominance for jaundice in their study with male to female ratio of 1.79:1.[19] About 55.2% neonates with jaundice were males in a study of Saboth PK et al (2019), but the authors found no significant association of gender with jaundice in their study.[20]

The higher risk of jaundice in male could be attributed to genetic and X linked aetiologies of neonatal jaundice, making male neonates more susceptible to neonatal jaundice.[17] Furthermore, males may be more likely than females to have a glucose-6-phosphate dehydrogenase (G6PD) deficiency, which can cause jaundice. However, as there are few population-based studies on G6PD deficiency and routine G6PD screening is not widely used in medical institutions, more studies are required. Additionally, bilirubin levels are often higher in males, which might cause pathologic jaundice.[21]

About 22.1% neonates with jaundice were preterm in the present study and 19.6% preterm neonates had pathological jaundice and 24.7% term neonates had pathological jaundice. We found no significant association of pathological and physiological jaundice with maturity of neonate ($p>0.05$). However, in a study of Saadat SH et al (2018), 73.8% neonates with jaundice were term and 26.2% neonates were preterm and the authors found a significantly higher levels of bilirubin in term neonates on the first day, which was contrasting to the findings of present study.[18] On the other hand, Saboth PK et al (2019) observed neonatal jaundice in 27% preterm neonates and the authors observed a significant association of neonatal jaundice with preterm births ($p=0.003$).[20] Hansen TW et al (2021) also observed neonatal jaundice to be more common in preterm newborns, who also have weak bilirubin metabolism.[22]

The findings of present study were also supported by findings of Fanello C et al (2023), in which newborns with preterm births were at significantly higher risk of neonatal jaundice.[23] About 65% preterm neonates had pathological jaundice in a study of Sharma M et al (2022).[24] Tessema M et al (2024) also observed preterm (< 37 weeks) birth as the main contributing

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variables to newborn jaundice.[25] The higher risk of jaundice in preterm neonates could be attributed to reduced efficiency of the immature liver and gastrointestinal system in metabolizing bilirubin in preterm neonates.[26,27]

In the present study, significantly higher proportions of neonates with neonatal jaundice were small for gestational age (24.5% vs. 2.1%; $p<0.05$) whereas significantly higher proportions of neonates with no jaundice were AGA neonates (97.9% vs. 72.1%; $p<0.05$). When we stratified neonates with jaundice based upon type of jaundice, we observed no significant association of physiological and pathological jaundice with weight of neonate ($p>0.05$).

Our study findings were supported by the findings of Hegedus C et al (2022), in which 14.4% neonates were SGA and 85.6% were non SGA and median direct bilirubin levels were observed to be significantly higher in SGA neonates as compared to non SGA neonates ($p<0.05$).[28] Liu Q et al (2019) also observed a significant association of hyperbilirubinemia with small for gestational age.[29] Asefa CG et al (2019) also observed a significant association of neonatal jaundice with low birth weight.[30] In a study of Saboth PK et al (2019), 39% neonates with jaundice had low birth weight and over half had normal birth weight.[20] Hyperbilirubinemia in the SGA neonates could be attributed to relatively hypoxic environment among such neonates, which might cause compensatory increases in red blood cell count and/or acidosis.[31,32]

Literature suggests that about 15% of neonates who are breastfed will experience physiologic Unconjugated Hyperbilirubinemia that lasts longer than three weeks.[33] During the first week of life, breastfed newborns are more likely to experience physiological jaundice than bottle-fed babies. Breastfed newborns are also more likely to experience prolonged jaundice, or jaundice that lasts longer than the first 14 days.[34] We found formula feeding to be protective against neonatal jaundice and higher number of neonates with jaundice was seen with exclusive breastfeeding. In a study of Scafford CG et al (2013), feeding habits were found to be significantly associated with neonatal jaundice. The authors found that exclusive breastfeeding was protective for infants who did not have feeding difficulties, but it was a risk factor for newborn jaundice in infants who had feeding difficulties.[14] Sahoo M et al (2016) observed breastfeeding jaundice in 48% of neonates with non-physiological jaundice in their study.[11] Similarly, Agrawal V et al (2016) observed breast milk jaundice in 66% neonates.[35] Hansen TW et al (2021) reported jaundice to be more common in breastfed babies and neonatal jaundice in breastfed neonates may persist for a longer period of time according to the authors.[22] Breast milk jaundice could be attributed to the constituents of breastmilk such as pregnanediol, epidermal growth factor, IL B, alpha-fetoprotein and B-glucuronidases which may attribute to decrease conjugation or increased enterohepatic circulation of bilirubin following deconjugation in intestine. Breastfeeding jaundice is attributable to improper breastfeeding leading to reduced calorie intake, complications such as lethargy, dehydration, severe weight loss and delayed meconium emptying.[36]

In the present study, about 22.6% neonates with jaundice had sepsis and it was found to be associated with pathological jaundice i.e. significantly higher proportions of neonates with pathological jaundice had sepsis as compared to neonates with physiological jaundice (34.7% vs. 18.9%; $p<0.05$). Agrawal V et al (2016) reported sepsis in 4% neonates and the authors found no significant association of sepsis with period of gestation.[35] Valiyat S et al (2017) on the other hand found sepsis in 10% neonates with jaundice suggesting sepsis as an underlying etiology in one tenth of neonates with jaundice.[37] In a study of Acharya N et al (2020), neonatal sepsis (44.52%) was the most frequent cause of pathological jaundice.[19] Tessema M et al (2024) in their cross sectional study found Sepsis as one of the main contributing variables to newborn jaundice.[38] Bante A et al (2024) found a significant association of neonatal jaundice with sepsis.[103] Mishra S et al (2024) also observed a significant association of neonatal jaundice with sepsis (4%) in their study.[15] Association of sepsis with pathological jaundice could be attributed to increase in the bilirubin burden and oxidative damage to RBCs as a result of sepsis, making neonates susceptible to UHB.[39]

Blood group incompatibility (such as ABO and Rh incompatibility) can cause immune-mediated hemolysis. The most common cause of pathologic hyperbilirubinemia is excessive hemolysis due to immunological or nonimmune factors. Hemolytic disease of the newborn (HDN) is caused by immune-mediated hemolysis, which happens in cases with ABO/Rh mismatch. ABO mismatch may be observed in 15% pregnancies and about 4% of neonates with ABO mismatch are prone to develop hemolytic disease of newborn.[40] In the present study, we found a significant association of neonatal jaundice with ABO mismatch i.e. significantly higher proportions of neonates with jaundice had ABO mismatch. On the other hand, the association of ABO mismatch with pathological and physiological jaundice was statistically insignificant ($p>0.05$). Rh mismatch is also a cause of severe neonatal jaundice as Rh antigen is highly immunogenic. In some cases, it can result in severe hemolytic disease and even hydrops fetalis in neonates.[41] However, we found no such association of jaundice and type of jaundice with RH mismatched ($p>0.05$). This could be attributed to use of anti D prior to delivery.

In a study of Sahoo M et al (2016), ABO incompatibility was observed in 16% neonates with jaundice.[11] On the other hand, Agrawal V et al (2016) reported ABO incompatibility in 3% neonates with jaundice.[35] Valiyat S et al (2017) observed

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ABO incompatibility in 21.8% neonates with jaundice and among them, 50% resulted from incompatibility with OA, and 50% from incompatibility with OB.[37]

Saadat SH et al (2018) observed ABO incompatibility in 36.6% neonates with jaundice, Rh incompatibility in 6.2% neonates and 1.6% neonates had both ABO and Rh incompatibilities.[18] Acharya N et al (2020) reported ABO incompatibility as second common cause of neonatal jaundice (12.18%) and Rh incompatibility was observed in 7.03% neonates.[19] Saeedi Z et al (2020) found that ABO incompatibility was the most frequent cause of first-day jaundice (41%), followed by RH incompatibility in 14.3% of cases. 3.4% of infants had simultaneous ABO and Rh incompatibility.[42] In a study of Dorji N et al (2022), neonatal jaundice was significantly correlated with maternal B blood group and maternal O blood group.[12] Fanello C et al (2023) observed significantly higher serum bilirubin levels in neonates with feto-maternal ABO incompatibility and G6PD deficiency.[23] Tessema M et al (2024) observed a significant association of ABO incompatibility and Rh incompatibility with neonatal jaundice.[38] Mishra S et al (2024) found Rh incompatibility (11%), as well as ABO incompatibility (5.5%) to be significantly associated with neonatal jaundice.[15]

One Recent research has revealed that the Coombs' or direct antibody test (DAT) is incredibly ineffective for forecasting the onset of severe hyperbilirubinemia, although being a crucial test for determining the etiology of newborn hyperbilirubinemia.[43] Coomb's test was done in only 10 neonates, and among them, it was found to be positive in 1 neonate. Bertini G et al (2001) observed a significant association of severe hyperbilirubinemia with positive Coombs' test.[44]

Our study found a significant association of neonatal jaundice with maternal comorbidities. We found that significantly higher proportions of mothers of neonatal jaundice had associated hypothyroidism (6.7% vs. 0%; $p<0.05$). The findings of present study were concordant with the findings of Kiran Z et al (2021), in which neonatal jaundice was observed in 37.6% neonates in mothers with hypothyroidism.[45] In a study of Turunen S et al (2023), jaundice was observed in 6.9% term and 7.7% preterm neonates of mothers with hypothyroidism. Preterm as well as term neonates with jaundice had significantly higher odds of NICU admissions in case when mother had hypothyroidism.[46] Mannisto T et al (2013) and Ali SM et al (2020) reported higher risk of neonatal jaundice in neonates of mothers with hypothyroidism.[47,48] Dorji N et al (2022) observed a significant association of neonatal jaundice with maternal medical complications during pregnancy.[12]

Small proportions of neonates enrolled in our study had associated comorbidities such as Down's syndrome, congenital anomalies, G6PD deficiency, cephalhematoma, hypothyroidism and birth asphyxia. Neonatal jaundice was significantly associated with these comorbidities as significantly higher proportions of neonates with jaundice had associated neonatal comorbidities (18.8% vs. 1%; $p<0.05$). The findings of the present study were supported by the findings of Saadat SH et al (2018) in which Down's syndrome was associated with conjugated hyperbilirubinemia, 8.4% neonates had both a G6PD deficit and ABO incompatibility whereas 1.6% had G6PD deficits and RH incompatibility.[18] Amongst neonatal complications, Saeedi Z et al (2020) reported caput succedaneum and cephalhematoma in 4.9% neonates with jaundice and G6PD deficiency in 2.6% neonates with jaundice.[42] Fanello C et al (2023) in their study documented that neonates with G6PD deficiency were at significantly higher risk of neonatal jaundice and compared to other newborns, those with G6PD deficiency showed significantly higher bilirubin levels at delivery.[23] Bante A et al (2024) found a significant association of neonatal jaundice with birth injuries and hyaline membrane disease.[103] Dorji N et al (2022) documented higher odds of neonatal jaundice in neonates with associated complications.[49]

Overall, the most common etiology of neonatal jaundice was exclusive breast feeding (52.4%), followed by ABO incompatibility (47.1%), mixed feeding due to inadequate breastmilk (44.2%), sepsis (22.6%) and preterm birth (22.1%). Other aetiologies included neonatal comorbidities (18.8%), formula feeding (3.4%), Rh mismatch (1.9%). Amongst these, ABO mismatch, neonatal comorbidities and breastfeeding were significantly associated with neonatal jaundice ($p<0.05$). However, in a study of Sahoo M et al (2016), Sahoo M et al (2016), the most common cause of neonatal jaundice was breastfeeding jaundice (48%), followed by ABO incompatibility (16%) and preterm (7.54%).[83] Agrawal V et al (2016) reported breast milk jaundice as the most common etiology of chronic jaundice in both term and preterm infants (66%), with isoimmunization (10%), cephalhematomas (7%), hypothyroidism (7%), sepsis (4%) and ABO incompatibility (3%).[35] In a study of Valiyat S et al (2017), 21.8% neonates had ABO incompatibility, followed by sepsis (10%), idiopathic (8%) and preterm birth (7.3%). Breastfeeding and cephalhematoma both accounted for 7 instances (6.4%). Hereditary spherocytosis was identified as the cause of one case of hemolytic anemia.[37]

Saadat SH et al (2018) reported G6PD deficiency in 30.8% neonates, ABO incompatibity in 36.6% neonates, Rh incompatibility in 6.2% neonates, G6PD deficiency in 8.4% neonates.[18] Bedi N et al (2018) found ABO incompatibility and Rh incompatibility as the most common cause of neonatal jaundice and 46% neonates had idiopathic jaundice.[49] In a study of Acharya N et al (2020), neonatal sepsis (44.52%) was the most frequent cause of pathological jaundice among the different etiologies, followed by ABO incompatibility (12.18%) and Rh incompatibility (7.03%).[19]

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Saeedi Z et al (2020) showed that ABO incompatibility was the most frequent cause of first-day jaundice (41%), followed by RH incompatibility in 14.3% of cases. 3.4% of infants had simultaneous ABO and Rh incompatibility, followed by caput succedaneum and cephalhematoma (4.9%), G6PD deficiency (2.6%), sepsis (2.1%), and infections (2%).[42] Mishra P et al (2023) found fetal preterm (30 instances), birth asphyxia (7 cases), physiological (129 cases), and extended labor (18 cases) as the common causes of neonatal jaundice. There were 28 cases with idiopathic reasons, 7 cases with ABO incompatibility, and 7 cases with Rh incompatibility.[3] Zelelew AM et al (2024) found neonatal jaundice to be predicted by a number of factors, including male gender, preterm, maternal Rh negative, neonatal Rh positive, maternal blood type AB, and ABO incompatibility.[50] Our study had certain limitations. First, the study was conducted on neonates admitted in the postnatal ward, delivered either via LSCS or normal vaginal delivery and neonates who were discharged early or mothers who left against medical advice were not enrolled in the study. Lastly, this study was conducted as a unicentric study and the etiologies might vary depending on the geographical location. Thus, the findings of present study were not representative of the general population and findings could not be generalized.

CONCLUSION

Neonatal jaundice is among the common clinical finding observed in neonates and more than half of the neonates experience jaundice within first week of life. Though, jaundice is physiological in majority of neonates, pathological jaundice is not uncommon.
The prevalence of neonatal jaundice in our study was 68.4%. Neonatal jaundice is significantly associated with male gender, small for gestational age, exclusive breast feeding, sepsis, ABO incompatibility, maternal hypothyroidism and other neonatal comorbidities. Formula feeding, absence of maternal comorbidities and appropriate weight for gestational age are protective against neonatal jaundice. Overall, ABO incompatibility and exclusive breast feeding are common etiologies of neonatal jaundice. Though neonatal jaundice is self-limiting and may require no treatment, few cases are managed with phototherapy and when high bilirubin levels persist despite phototherapy, exchange transfusion is second line treatment.

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