Section: Pediatrics

Original Research Article

CLINICOETIOLOGICAL STUDY AND OUTCOME OF NEONATAL UNCONJUGATED HYPERBILIRUBINEMIA

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Received *: 18/06/2026*
Received in revised form *: 29/07/2026*
Accepted *: 13/08/2026*

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DOI: 10.70034/ijmedph.2026.3.592

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (3); 3801-3812

ABSTRACT

Background: Neonatal unconjugated hyperbilirubinemia is a common condition that may be physiological or secondary to pathological causes. Early identification of risk factors and timely treatment are essential to prevent bilirubin-induced neurological complications. **Aim:** To study the etiology, clinical features and complications of neonatal hyperbilirubinemia & also to determine the response and outcome to various modalities of the treatment.

Objectives

- To study clinical features & complications of different neonatal unconjugated hyperbilirubinemia.
- To study risk factors & mode of treatment of neonatal unconjugated hyperbilirubinemia.
- To identify the response and it's outcome to various modalities of the treatment of neonatal unconjugated hyperbilirubinemia.

Materials and Methods: A prospective hospital-based descriptive analytical study was conducted in the Departments of Pediatrics and Obstetrics, Government General Hospital, Vijayawada, from December 2022 to December 2023. A total of 100 neonates with unconjugated hyperbilirubinemia were included from 625 neonatal admissions. After obtaining informed consent and institutional ethical clearance, detailed maternal and neonatal histories and clinical examinations were performed. Investigations included total and direct serum bilirubin, maternal and neonatal blood grouping, Direct Coombs test, sepsis screening, thyroid profile, peripheral smear, reticulocyte count, and other investigations as clinically indicated. Treatment included phototherapy and exchange transfusion according to clinical and biochemical indications.

Results: The incidence of unconjugated hyperbilirubinemia was 16% (100/625). Males predominated over females (63% vs. 37%). Vaginal and cesarean deliveries accounted for 52% and 48%, respectively. The mean Apgar score at 5 minutes was 8.5. A significant negative association was observed between birth weight and hyperbilirubinemia. The mean serum unconjugated bilirubin levels at admission and discharge were 19.74 ± 3.97 mg/dL and 18.53 ± 2.18 mg/dL, respectively. Hyperbilirubinemia was more common among babies born to multigravida mothers than primigravida mothers (69% vs. 31%, $p<0.05$). Reticulocytosis was significantly associated with risk factors for hyperbilirubinemia ($p=0.001$). Among the identified etiologies, ABO incompatibility, Rh incompatibility, and urosepsis/UTI were important pathological causes. Higher bilirubin levels (≥20 mg/dL) were associated with poorer response to treatment and increased need for intensive management, including exchange transfusion.

Conclusion: The results of this study concluded that although breastfeeding is considered as a major cause of prolonged neonatal jaundice, identification of

other pathological factors is also of paramount importance. Early diagnosis and treatment of these disorders could effectively prevent further complications in neonates. Early detection of factors can aid in immediate management to prevent serious complications of this common condition in infants.
Keywords: Neonatal hyperbilirubinemia, unconjugated hyperbilirubinemia, neonatal jaundice, ABO incompatibility, Rh incompatibility, phototherapy, exchange transfusion.

INTRODUCTION

Neonatal hyperbilirubinemia is a major concern for both pediatricians& parents. Severe unconjugated hyperbilirubinemia is potentially neurotoxic & conjugated hyperbilirubinemia is a harbinger of underlying serious illness.[1] Neonatal Jaundice is evidenced in 2/3rd of healthy term newborns and in a greater proportion of preterm [80%] in the first week of life.[1] This is a reflection of liver's immature excretory pathway for bilirubin at the time of heightened production. The resultant jaundice is referred to as physiological jaundice. However non-physiological (or) pathological hyperbilirubinemia is known to occur in 5 –10% of healthy term newborns & it is the common reason for readmission of newborn.[2,3]

In the current era of early postnatal discharge of mothers & babies from the hospital, (as it is not possible to keep the mothers & babies for a long time in the maternity ward) it is vital to identify the newborns at risk of significant hyperbilirubinemia before they're discharged from hospital.

The American Academy of Pediatrics (AAP) recommends to stay a minimum of 48 hours.4 But it is not possible in our country due to limited facilities. Hence the concept of early prediction has become crucial to spot the newborns at risk of significant jaundice.

Bilirubin is a byproduct of red blood cell (RBC) destruction. Initially Hemoglobin is released; then, it gets broken down in spleen, liver, and bone marrow and forms the unconjugated bilirubin. Unconjugated bilirubin binds albumin to be transported in the circulation to the liver, where it combines with glucuronic acid to produce the more water-soluble form, the conjugatedbilirubin. Disruptions in any step in this pathway can lead to unconjugated, conjugated, or mixed hyperbilirubinemia. The management of hyperbilirubinemia is essential to prevent complications such as recurrence, kernicterus, and even death.[5]

Neonatal hyperbilirubinemia risk factors such as low birth weight, O blood group in mothers, Rh-negative mothers, sepsis, infants of diabetic mothers, prematurity, failed lactation in exclusively breast-fed infants, and a family history of neonatal jaundice.

Several management options were implicated for unconjugated hyperbilirubinemia. The first step is phototherapy. If hyperbilirubinemia is very severe, exchange transfusion (ET) may be considered. ET eliminates bilirubin and possibly antibodies from the blood in suspected cases of Rh isoimmunization (or) ABO incompatibility. Other treatment options include phenobarbitone, intravenous immunoglobulin (IVIG), & metalloporphyrin.

Since studies about risk factors of neonatal indirect hyperbilirubinemia in our region are scarce, this study is aimed to identify the most common etiological factors of unconjugated hyperbilirubinemia & at comparing neonates with feto maternal complications in order to provide an updated data about this condition.

Therefore, prediction of significant hyperbilirubinemia using admitted day serum bilirubin has been attempted in order to implement early treatment to minimize the risk of bilirubin dependent brain damage. Current study aimed to study the etiology, clinical features, and complications of neonatal unconjugated hyperbilirubinemia and to determine the response and outcome to various modalities of the treatment.

Aims & objectives

Aim

- To study the etiology, clinical features and complications of neonatal hyperbilirubinemia & also to determine the response and outcome to various modalities of the treatment.

Objectives

- To study clinical features & complications of different neonatal unconjugated hyperbilirubinemia.
- To study risk factors & mode of treatment of neonatal unconjugated hyperbilirubinemia.
- To identify the response and it's outcome to various modalities of the treatment of neonatal unconjugated hyperbilirubinemia.

MATERIALS AND METHODS

Study Design: Prospective Hospital based Descriptive Analytical study.

Study period: December 2022 to December 2023.

Study area: Department of Pediatrics& Department of Obstetrics, Government General Hospital, Vijayawada.

Ethics: The study was conducted after institutional ethical clearance and obtaining informed consent signature from infant parent.

Sample size calculation: sample calculation done according to previous study of Kulkarni SK, et al.41 The sample size calculated was: 100.

N = 100

Sampling technique: Purposive sampling technique on consecutive cases.

Source of the data: NICU of Department of Pediatrics, Old Government Hospital, Vijayawada

Inclusion Criteria

1. Neonates both male and female babies and both term & preterm babies are clinically assessed regarding the extent of jaundice & careful physical examination is to be carried out, total serum bilirubin and fractionation, blood groups of mothers and babies done.
2. Sepsis screen, direct comb's test, thyroid profiles, ultrasound abdomen,chest x-ray, peripheral smear, reticulocyte count are done wherever necessary.

Exclusion Criteria

- Newborns with conjugated hyperbilirubinemia,
- Prolonged hyperbilirubinemia,
- Term babies-more than 14 days,
- Preterm babies-more than 21 days.

Method of collection of data

- 100 new-borns suffering with unconjugated hyperbilirubinemia are selected for study. Depending upon clinical & biochemical severity of neonatal unconjugated hyperbilirubinemia, babies were treated with phototherapy alone or with phototherapy & exchange transfusion.
- Outcome is assessed both clinically and biochemically.

Type of Treatment

- Phototherapy
- Phototherapy + exchange transfusion
- Phototherapy + Exchange Transfusion + phenobarbital

Data collection

The collected data includes

A) Maternal characteristics: (i) age, (ii) parity, (iii) mode of delivery, (iv) Diabetes, (v) Mode of management.

B) Neonatal characteristics: (i) sex, (ii) gestational age, (iii) birth weight. (iv) Family history of neonatal jaundice. (v) Age at which jaundice firstly appear

C) Physical examination that was performed.

D) Laboratory investigations;

1) Total serum bilirubin

- Direct
- Indirect

2 ml blood collected in plain vacutainer left to clot and centrifuged to separate serum which is used for liver function tests: Serum bilirubin (total and indirect).

2).baby's blood group and Rh type

3).mothers blood group and Rh type

4).Direct coomb's test

5).Hb percentage

6).total count

7).differential count

8).Peripheral smear-RBC morphology

9).Total RBC.

Procedure

- Under strict aseptic precautions blood samples were collected from all newborns for the analysis of serum bilirubin levels, hemoglobin, and blood grouping & typing.
- This method is based on the fact that diazonium salt 3,5-dichlorophenyl diazonium tetrafluoroborate (DPD) couples directly with direct (conjugated) bilirubin to produce direct azobilirubin. The absorbance of this dye is directly proportional to the direct bilirubin in the sample.
- Complete blood picture, peripheral blood smear, septic screen, reticulocyte count, direct coombs test (DCT), blood grouping & Rh typing of mother & baby hematocrit, thyroid function test, G6PD levels, serum bilirubin total & direct were done whenever necessary.
- All the babies were followed for 5 days and serum bilirubin was estimated on day 5. The values of day-5 bilirubin were compared with cord blood bilirubin levels. The main outcome of the study was inferred in terms of hyperbilirubinemia. Serum bilirubin level ≥15 mg/dl in first 5 days of life was taken as significant hyperbilirubinemia. Babies with icterus upto the palms and soles and with significant hyperbilirubunemia (total serum bilirubin levels >15mg/dl) were kept under phototherapy as per the unit guidelines. Babies with significant jaundice on day 5 were investigated further.

Birth Weight

- The birth weight was calculated using an electronic weighing scale to the nearest 10 grams. Lubchenco's intrauterine growth charts were used toclassify the neonates as SGA, AGA, or LGA.
- **Length:** With the baby supine and knees fully extended, the crown heel length is measured to the nearest 0.1 cm with an infantometer.
- **Head circumference:** Measured to the nearest 0.1cm above the supra orbital ridges and ears at the occipital protuberance level.
- **Chest circumference:** Measured at the level of the nipple in a plane perpendicular to the spine and recorded while breathing normally.
- **Hyperbilirubinemia:** BILIRUBIN estimation is performed on the fourth and fifth days, or earlier, if necessary, to detect hyperbilirubinemia, which is diagnosed and treated according to the AAP (American Academy of Paediatrics) charts.
- Management of neonates regarding phototherapy and exchange transfusion was according to American academy of paediatrics guidelines (American academy of paediatrics & IAP)

Statistical Analysis: The statistical methods used were ANOVA, Chi-Square test, Odds ratio, multiple logistic forward stepwise, multiple logistic

regression likelihood ratio, student's test and ROC curves (receiver operating characteristic curves). The serum bilirubin level having the highest sensitivity and specificity was determined with the ROC curve analysis. ROC curves were plotted using 1-specificity on the x axis and the sensitivity on the y-axis. Serum bilirubin levels were used for developing 'prediction test'. SPSS ver 22.0 (SPSS Inc., Chicago, IL, USA) Windows software was used to compare clinical and laboratory findings.

RESULTS

Table 1: Maternal and Neonatal Characteristics

Variables	Characteristics	Frequency	Percent
Maternalagein	<35years	84	82
years	≥35 years	16	16%
Antenatal follow-up	No	15	15
	Irregular	16	16
	Regular	69	69
Mode of Delivery	Spontaneous vaginal delivery	41	41%
	Instrumental delivery	11	11%
	Assisted delivery	46	46%
Place of delivery	Home	7	7%
	Hospital	93	93%
Premature rupture of membrane	Yes	7	7%
	No	93	93%
Duration of labor	Normal	86	86%
	Prolonged	14	14%
Maternal intrapartum fever	Yes	10	10%
	No	90	90%
Gestational age	28-32 wks	19	19%
	33-36 wks	10	10%
	>37 wks	71	71%
Birth weight	<1 kg (extreme lower weight)	0	0
	Very low birth weight (1000-1500 g)	3	3%
	Low birth weight (1500 – 2500 g	49	49%
	Normal(>2500 g)	48	48%
1st minute Apgar score	<7	33	33%
	≥7	67	67%
5th minute Apgar score	<7	14	14%
	≥7	86	86%

Table 2: Age of onset & Method of Neonatal jaundice detection data of neonates

	No. (100)	%
Ageof onset:		
Day1	1	1%
Day2	4	4%
Day3-7	81	81%
Day>7	14	14%
MethodofNeonataljaundicedetection:		
Hospital	10	10%
Family	18	18%
OutpatientClinic	6	6%
NICU	65	65%

Table 3: Treatment used in the unconjugated hyperbilirubinemic neonates

	No. (100)	%
Treatmentgiven:		
No(Follow-up)	52	52%
Phototherapy	30	30%
Phototherapy+Extensivephototherapy	12	12%
Phototherapy+Extensivephototherapy+Phenobarbital	6	6%

Table 4: Outcome of study neonates

Outcome:	N	Frequency,%
Death	8	8%
Discharge	92	92%
Causeofdeath:(n=8)		
Respiratorydistress	2	25%
Sepsis	2	25%
CHD	1	12.5%
Kernicterus	2	25%
Birthasphyxia	1	12.5%

Table 5: Mean Demographic & laboratory variables of study neonates

Variables	(Mean±SD)
Gestationalage(weeks)	38.4±1.2
Birthweight(kg)	2.47±0.53
Maternalage(years)	29.6±8.5
Postnatal ageofadmission (days)	4.15±2.8
Indirectbilirubinlevel onadmission (mg/dl)	19.74±3.97
Indirectbilirubinlevelatdischarge(mg/dl)	18.53±2.18
Positivedirectcoombs	8
Durationofphototheraphy(hours)	39.9±35.9
HemoglobinLevel(g/dL)-neonates	14.75±2.26
ReticCount(%)	3.64±1.6
TotalBilirubinLevel (mg/dL)	20.13±3.96
ConjugatedBilirubinLevel(mg/dL)	0.71±0.32
TSH(mU/L)	6.01±1.6
T4(mU/L)	15.04±1.38

Table 6: Demographic and laboratory characteristics who were treated with phototherapy ≤24 hours &>24 hours.

Variables	Phototherapyduration		P value
	≤24 hours(n=11)	>24hours(n=37)	
Gestationalage(weeks)	37.2±2.22	38.2±2.11	0.1791
Birthweight(gr)	2.41±0.49	2.46±0.56	0.7565
Maternalage(years)	28.9±6.5	29.8±9.4	0.7685
Postnatalageof admission (days)	4.07±1.98	4.32±0.2	0.4426
Indirectbilirubinlevelon	18.2±2.9	19.85±4.1	0.2208
admission (mg/dl)			
Indirect bilirubin level at discharge (mg/dl)	17.8± 2.6	18.95± 3.5	0.3192

Table 7: Factors Associated with the Treatment Outcome of Jaundice among Neonates Treated in Neonatal Intensive Care Unit

Variables	Treatment Outcome		COR(95% CI)	AOR(95% CI)	p-value
	Improved	Dead			
Residence					
Urban	52	6	1.00	1.00	1.00
Rural	40	2	0.31(0.2,0.8)*	0.35(0.2,0.9)	0.03
Originofadmission					
Inborn	17	2	1.00	1.00	1.00
Outborn	77	4	0.39(0.2,0.6)*	0.31(0.2,0.7)	0.00
Lengthofstay					
≤7days	54	3	1.00	1.00	1.00
>7days	38	5	1.6(0.9,2.9)	0.52(0.4,1.1)	0.29
Rhincompatibility					
No	85	5	1.00	1.00	1.00
Yes	7	3	0.29(0.19,0.6)*	0.48(0.2,1.19)	0.35
Gestationalage					
≥37weeks	68	3	1.00	1.00	1.00
<37weeks	24	5	0.21(0.1,0.5)*	0.25(0.1,0.7)	0.04
Birthweight					
>2.5Kgs	42	0	1.00	1.00	1.00
≤2.5Kgs	50	8	0.32(0.2,0.7)*	0.69(0.3,1.8)	0.62
1stApgarscore					
≥7	30	3	1.00	1.00	1.00
<7	62	5	0.29(0.2,0.7)*	0.89(0.5,2.2)	0.85
5thApgarscore					
≥7	86	6	1.00	1.00	1.00
<7	14	2	0.25(0.1,0.6)*	0.49(0.2,1.3)	0.3
Totalserumbilirubin					
<20	48	0	1.00	1.00	1.00
≥20	52	8	0.21(0.1,0.4)*	0.39(0.2,0.7)	0.04
Treatmentstype					
Followup	52	0	1.00	1.00	1.00
PT	30	1	0.32(0.2,0.6)*	0.59(0.2,1.5)	0.42
EBT+PT	12	4	0.28(0.1,0.8)*	0.72(0.2,1.9)	0.35
EBT+PT+ Phenobarbital.	6	3	0.21(0.1,0.5)*	0.25(0.1,0.7)	0.04

Table 8: Etiology of jaundice in term and preterm neonate with unconjugated hyperbilirubinemia

		Termbaby (n= 71)		Pre-termbaby (n= 29)		Total	P value
		No	Frequency, %	No	Frequency, %		
1	Physiological	31	43.67	3	10.34	34	0.229*
2	Prematurity	3	4.23	19	65.62	22	
3	Breastfeeding	9	12.67	1	3.44	10	
4	ABOincompatibility	5	7.04	1	3.44	6	
5	Hematoma/Haemolyticanemia	2	2.82	0	0	2	
6	Hypothyroidism	2	2.82	0	0	2	
7	Urosepsis/UTI	2	2.82	2	6.9	4	
8	Rhincompatibility	9	12.67	1	3.44	10	
9	Cephalhematoma	5	7.04	2	6.9	7	
10	G-6-P-Ddeficiency	1	1.41	0	0	1	
11	Idiopathic	2	2.82	0	0	2	
	Total	71	100%	29	100%	100	

***ANOVA**

Table 9: Association between Aetiology and Type of treatment

		Typeof treatment				
		No treatment (Follow-up)	**Photo**	**Photo+ EBT**	**Photo+EBT+ Phenobarbital**	**P value**
	code	0	1	2	3	
1	Physiological	34	0	0	0	
2	Prematurity	13	7	1	1	
3	Breastfeeding	4	4	2	0	0.28*
4	ABO incompatibility	0	3	2	1	
5	Haemolytic anemia	0	0	0	2	
6	Hypothyroidism	1	1	0	0	
7	Urosepsis/UTI	0	1	2	1	
8	Rhincompatibility	0	5	4	1	
9	Cephalhematoma	0	6	1	0	
10	G-6-P-D deficiency	0	1	0	0	
11	Idiopathic	0	2	0	0	
	TOTAL	52	30	12	6	

***ANOVA**

Table 10: Association between mode of DELIVERY & Risk factors of unconjugated Hyperbilirubinemia

NO	ETIOLOGY	MODEOFDELIVERY				P VALUE
		Total No. of case s	**Vaginal delivery**	**Instrument a l delivery**	**C-section delivery**	
1	Physiological	34	13	6	15	
2	Prematurity	22	11	4	7	
3	Breastfeeding	10	7	1	2	
4	ABO	6	1	0	5	
	incompatibility					0.0277*
5	Haemolytic anemia	2	0	0	2	
6	Hypothyroidism	2	1	0	1	
7	Urosepsis/UTI	4	0	0	4	
8	Rh incompatibility	10	3	0	7	
9	Cephalhematoma	7	4	0	3	
10	G-6-P-D deficiency	1	1	0	0	
11	Idiopathic	2	0	0	2	
	Total	100	41	11	49	

***ANOVA**

Table 11: Association between type of feeding & Risk factors of unconjugated Hyperbilirubinemia

NO	ETIOLOGY	TYPEOF FEEDING				P VALUE
		Total No. of case s	**Breast feed**	**Formulafeed**	**Mixed feed**	
1	Physiological	34	34	0	0	0. 0635*
2	Prematurity	22	7	14	1	
3	Breastfeeding	10	1	8	1	

4	ABO incompatibility	6	0	2	4	
5	Haemolytic anemia	2	0	0	2	
6	Hypothyroidism	2	2	0	0	
7	Urosepsis/UTI	4	3	0	1	
8	Rhincompatibility	10	9	0	1	
9	Cephalhematoma	7	6	1	0	
10	G-6-P-D deficiency	1	0	0	1	
11	Idiopathic	2	2	0	0	
	TOTAL	100	64	25	11	

***ANOVA**

Table 12: Association between MORTALITY & Risk factors for unconjugated Hyperbilirubinemia

NO	ETIOLOGY	MORTALITY		P VALUE
		Discharged	Death	
1	Physiological	34	0	0.021*
2	Prematurity	20	2	
3	Breastfeeding	10	0	
4	ABOincompatibility	5	1	
5	Haemolyticanemia	2	0	
6	Hypothyroidism	2	0	
7	Urosepsis/UTI	3	1	
8	Rhincompatibility	7	3	
9	Cephalhematoma	6	1	
10	G-6-P-Ddeficiency	1	0	
11	Idiopathic	2	0	
	TOTAL	92	8	

Table 13: Association between the etiology of unconjugated hyperbilirubinemia and Birth weight of newborn

NO	ETIOLOGY	Birthweightofnewborn			Total	P value
		Normal(>2500 g)	Low birth weight (1500–2500g	Verylow birth weight (1000-1500g)		
1	Physiological	25	9	0	34	
2	Prematurity	5	16	1	22	
3	Breastfeeding	6	4	0	10	
4	ABO	2			6	
	incompatibility		4	0		
						0.089*
5	Haemolytic	1			2	
	anemia		1	0		
6	Hypothyroidism	0	2	0	2	
7	Urosepsis/UTI	2	2	0	4	
8	Rhincompatibility	2	6	2	10	
9	Cephalhematoma	4	3	0	7	
10	G-6-P-D	0			1	
	deficiency		1	0		
11	Idiopathic	1	1	0	2	
		48	49	3	100	

Table 14: Association between mode of treatment & outcome

	Total	Discharge (n=92)	Death(n=8)	P-value
Notreatment (Follow-up)	52	52	0	0. 000011
Phototherapy alone	30	29	1	
Photo+ EBT	12	8	4	
Photo+EBT+ Phenobarbital	6	3	3	

Table 15: Association between Age group and AIOS score at Day1

			AIOS_D1			Total
			< 10	**11-15**	**>= 16**	
Age_Gro up	2-12 Months	Count	19	6	19	44
		% within Age_Group	43.2%	13.6%	43.2%	100.0%
		% within AIOS_D1	47.5%	40.0%	42.2%	44.0%

	13-36 Months	Count	14	7	18	39
		% within Age Group	35.9%	17.9%	46.2%	100.0%
		% within AIOS D1	35.0%	46.7%	40.0%	39.0%
	37-60 Months	Count	7	2	8	17
		% within Age Group	41.2%	11.8%	47.1%	100.0%
		% within AIOS D1	17.5%	13.3%	17.8%	17.0%
Total		Count	40	15	45	100
		% within Age Group	40.0%	15.0%	45.0%	100.0%
		% within AIOS D1	100.0%	100.0%	100.0%	100.0%

Table16: Association between mode of delivery & outcome

	Total	Discharge (n=92)	Death(n=8)	P-value
Vaginaldelivery	41	40	1	0.1337
Instrumental delivery	11	11	0	
C-sectiondelivery	48	41	7	

Table 17: Relation between serum bilirubin & outcome.

		Discharge (n=92)	Death(n=8)	P-value
Mean±SD	Total bilirubin	18.39±3.2	24.5±2.97	<0.0001
Mean±SD	Indirect bilirubin	19.129± 3.33	26.87±3.84	<0.0001

Table 18: Distribution of risk factors in neonatal unconjugated hyperbilirubinemia

		Factorsaggravatingjaundice					
		Maternal				Fetal	
Etiology	**tot al**	**Prematurerupture of membra ne >18hrs**	**Toxemia**	**Prolong ed Labour**	**Oxytocin induction**	**Prematurity**	**Birth asphyxia**
Rh incompatibility	10	1	1	-	-	2	-
ABO incompatibility	6	1	-	1	-	1	1
Cephalhemato ma	7	2	-	1	1	2	1
Idiopathic	2	-	-	-	-	-	-
Physiological	34	2	1	-	-	10	2
Septicemia	4	1	1	1	-	1	1
G-6-PD	1	-	-		-	-	-
deficiency							
Total		7	3	3	1	16	5

Table 19: Multivariate logistic regression analysis of risk factors associated with phototherapy duration of >24 hours

Variables	Odds ratio	95%CI	Pvalue
Malegender	0.90	0.078–1.5	0.04
Formulaasthefirstprelactealfeed	6.9	5.9–12.1	0.02
ABOincompatibility	2.4	1.1-9.2	0.03
Rhisoimmunization	6.2	4.5–10.5	0.005
Cephalohematoma	4.1	3.5–5.5	0.05
Sepsis	1.2	0.85–1.9	0.05

DISCUSSION

This study is designed to determine the predictive value and their correlation with clinico-etiological factors to identify the newborns at risk of significant hyperbilirubinemia and to study their outcome.

Incidence of jaundice:

In the present study duration, there were total of 625 neonates were treated in our NICU setup. Among these total NICU admissions, it is found that the incidence of significant hyperbilirubinemia to be around 16% (100 out off 625). The incidence of neonatal hyperbilirubinemia varies from 5.9% to 12.8% in several previous Indian studies. This was a descriptive study of all neonates admitted into NICU at Govt. Old maternity Hospital pediatrics department that were diagnosed unconjugated hyperbilirubinemia between the study period. In this study duration, 625 neonates admitted to our NICU unit.

Sex of the newborn:

In the present study, study group is uniformly distributed with 63 male and 37 female babies. There is no significant correlation between the neonatal hyperbilirubinemia and the sex of the newborn. Hence the present study infers that the

neonatal hyperbilirubinemia is independent of the sex of the newborn. The present study is in correlation with the study done by Amar Taksande et al (2005).[6] Rudy Satrya et al (2009),[7] showed significant correlation between the sex of the newborn and neonatal hyperbilirubinemia with p< 0.05.

Mode of delivery:

Regarding the type of delivery, (52%) of neonates through vaginal delivery than C-Section. An association between the neonatal hyperbilirubinemia & the mode of delivery was studied. 52% of vaginal delivery cases had serum bilirubin ≥15 mg/dl developed significant hyperbilirubinemia. In the present study, no significant association seen between neonatal hyperbilirubinemia & mode of delivery. Esma Keleş Alp et al8 study shows that 59.5% neonates and 40.5% neonates were delivered by vaginal and caesarean section. This study is in correlation with previous studies Rostami et al,[9] and Rudy Satrya et al.[7]

APGAR score

Esma Keleş Alp et al,[8] study shows that the mean Apgar score of babies was 8.2 at 5 minutes. 62.9% infants were breastfed as the first prelacteal feeds. Our study shows that the mean Apgar score of babies was 8.5 at 5 minutes.

Association between the neonatal hyperbilirubinemia (≥15mg/dl) and Oxytocin induction of labour

In the present study, there is no significant association between the neonatal hyperbilirubinemia and the oxytocin induction of labour. 60 cases were delivered by oxytocin induction developed hyperbilirubinemia and 40 cases who did not received oxytocin developed hyperbilirubinemia. This was in accordance with the previous studies.

Narang et al,[10] study found oxytocin induction as a cause of hyperbilirubinemia in 2.4% cases. Singhal et al,[11] study found prematurity as a cause of jaundice in 16.7% of neonates. They have also found birth asphyxia as aggravating factor for hyperbilirubinemia in 12.1% cases out of which maximum were in idiopathic group. Our study findings correlate with findings observed by Singhal et al 49. study. Knudsen 56 (1989) found no correlation among the jaundiced and non jaundiced infants with oxytocin induction of labour. Amar Taksande et al (2005),[6] in his study showed no significant association (p=0.245) between the Oxytocin induction of labour and neonatal hyperbilirubinemia. The present study is in correlation with studies Knudsen et al,[12] and Amar Taksande et al.[6]

Hospital stay

Regarding the duration of hospital stay, (57%) of cases stayed for < 7days, and no cases were stayed for >28 days. The mean Length of Hospital stay was 9.2± 9.9 days. Sabzehei MK et al,[13] study shows that the mean length of Hospital Stay was 4.07±2.09 days.

Gestational age

As regards gestational age, (19%) of neonates were 28-32 wks, (10%) of neonates were 33-36 wks,and (71%) of neonates were >37 wks of gestational age. Mean gestational age was 38.4±1.2 weeks. Ekin et al,[14] showed that gestational week of the cases was 38.42±1.3 weeks.

Type of feeding:

Regarding type of feeding, 64% was breast fed, 25% of neonates were formula fed, and 11% were mixed pattern of feeding to neonates. Sabzehei MK et al 13 study shows that Breast feeding, Bottle-feeding, and Mixed feeding were followed in 71%, 1% and 28% neonates respectively.

Body weight:

- Regarding birth weight, (3%) of cases were 1-1.5 kg, (49%) of cases were 1.5-2.5 kg and (48%) of cases were 2.5-4kg. hence 49% of neonates were low birth weight. The mean birth weight was 2.47±0.53 kg. Ekin et al,[14] study showed that birth weight of 3051.2±457.1 gr.Esma Keleş Alp et al,[8] study showed that birth weight was 3171.12±436.2 grams. Sabzehei MK et al,[13] study showed that birth weight was 2.99±0.77 kg.

Type of birth

As regards the type of birth, most of the neonates were single (94%) and only (6%) of neonates were twins.

Postnatal age

In our study, the mean postnatal age of the neonates at admission was 4.15±2.8 days. Ekin et al,[14] study shows that the mean postnatal age of the neonates at the time of admission was 5.46±3.9 days.

In our Current study of 100 neonatal indirect hyperbilirubinemia, etiology was detected as physiological hyperbilirubinemia in 34%, Rh incompatibility in 10%, ABO incompatibility in 6% neonates, septicaemia in 4% neonates, cephalhematoma in 7% neonates, and Idiopathic in 2% neonates respectively.

Sabzehei MK et al,[13] study shows that urinary tract infection, ABO incompatibility, hypothyroidism and glucose-6-phosphate dehydrogenase deficiency in 14%, 5%, 6% and 5% of neonates.

- Kulkarni S.K et al,[15] in their study, among 120 neonates, the etiology was detected as idiopathic hyperbilirubinemia in 35% neonates, physiological hyperbilirubinemia seen in 30% neonates, ABO incompatibility in 14.16% neonates, septicaemia in 8.33% neonates ,Rh incompatibility in 6.66% neonates, cephalhematoma in 2.5% neonates, G-6-PD deficiency in 0.83% neonate and miscellaneous in 0.83% neonates respectively.

Our findings are close to Singhal et al,[11] study. G-6-PD deficiency was found in 2.6% neonates by Merchant et al study, in 5.1% neonates by Singhal et al study, and in 3.4% neonates by Narang et al,[10] study. Our findings are closer to Merchant et al study. Cephalhematoma as a cause of jaundice was

found in 2.6% neonates by Merchant et al study, in 2.9% neonates by Singhal et al,[11] in 6.3% neonates by Narang et al,[10] study.

Ekin et al 42 study reported etiological reasons such as ABO incompatibility in 42.4% of neonates, and the cases with ABO incompatibility alone were 15.2%, those with ABO incompatibility with subgroup incompatibility were 10% of neonates, those with nutritional deficiencies with ABO incompatibility were 2.4% of neonates, and those with ABO incompatibility with Rh incompatibility, and subgroup incompatibility were 2% of neonates. G6PD deficiency was found in 16% of the neonates. Congenital Hypothyroidism identified in 4.4% of the neonates. No etiology other than congenital hypothyroidism was found in 27.2% of these cases. UTI detected in 28.4% of the neonates. The rate of suspected breast-milk jaundice seen in 0.4% of neonate and the rate of those with unknown cause is 3.6% of neonates.

Association between the neonatal hyperbilirubinemia and antenatal complications

In the present study, PIH is a risk factor for 22 cases with hyperbilirubinemia. No significant association seen between the neonatal hyperbilirubinemia andthe pregnancy induced hypertension with p >0.05. Various maternal risk factors such as PROM, prolonged labour, toxemia of pregnancy and oxytocin induction of labour were identified. Various fetal complications of which the most important prematurity and other birth asphyxia were identified.

Other studies are Awasthi et al,[16] showed no association between the neonatal hyperbilirubinemia & pregnancy induced hypertension. In the present study, PROM is observed in 7 neonates without association between the neonatal hyperbilirubinemia & PROM. Among these one neonate had ABO incompatibility, one neonate had cephalhematoma, one neonate had physiological hyperbilirubinemia and one neonate had septicaemia.

In 2009, Rudy Satrya et al,[7] showed that cord bilirubin level of ≥2.54mg/dl was determined to have high sensitivity(90.5%), specificity of 85% in predicting the significant neonatal hyperbilirubinemia, is in correlation with present study.

Zakia Nahar et al. in 2009 showed that cord bilirubin >2.5mg/dl has sensitivity 77%, specificity 98.6%, with PPV of 91%and NPV of 96% in predicting the neonatal hyperbilirubinemia.This study is in correlation with the present study.[17]

In 2013, Farahat A et al,[18] concluded that the cut-off point of 2mg/dl for umbilical cord bilirubin, sensitivity was obtained to be 68.86% & the specificity was obtained to be 61.18% in predicting the risk for significant hyperbilirubinemia.[19]

The present study infers that the indirect or unconjugated serum bilirubin level ≥ 15mg/dl can be used as early predictor of neonatal hyperbilirubinemia.

Serum Bilirubin levels and hyperbilirubinemia:

In our study, the mean total serum bilirubin is 20.13±3.96 gm/dL in neonates admitted at NICU with jaundice. Whereas mean indirect serum bilirubin is 19.74±3.97 gm/dL and mean direct serum bilirubin is 0.71±0.32 gm/dL. In term babies, physiological jaundice was observed between 30-72hrs of age, maximum intensity of jaundice i.e. 81% was noted on the fourth day &jaundice disappears by 10th day of the life. Total serum bilirubin does not exceed upto 32mg% & unconjugated bilirubin does not exceed upto 31.7mg%.

Among preterm babies age of onset of physiological jaundice was similar to the term babies, the maximum intensity of jaundice is reached on the 5th-6th day and it may persistsupto 14 days.

Assessment of jaundice will be done in the natural light. The pulp of finger or thumb is pressed on baby's skin, preferably, over a bony part till it blanches and underlying skin is noted for yellowish colour. Clinical jaundice manifests on face at 8mg%, upper trunk at 12mg%, lower trunk and thigh at 16mg%, arms and lower legs at 18mg%. In addition staining of soles and palms happen at total serum bilirubin level > 15mg% (Ramesh Agarwal et al).

Association between aetiology risk factors & bilirubin levels:

- The association between aetiology, risk factors and serum bilirubin levels were depicted in the table. As table shows there was significant association observed between aetiology, risk factors and total bilirubin levels. Similarly significant association noted between aetiology risk factors and direct bilirubin levels. Similarly significant association noted between aetiology risk factors and unconjugated bilirubin levels.

Outcome of neonates with unconjugated hyperbilirubinemia:

• There were totally 8% of mortality noted in the present study. Majority cases of mortality noted in C-section than vaginal delivery (87.5% vs 12.5%, p<0.05). Majority death occurred in Breast fed neonates i.e. 50% than compared with Formula fed and mixed feeding patterns, i.e. 37.5% and 12.5% respectively. Mortality observed in five male cases than female (62.5% vs 37.5%, p<0.05).Mortality observed in five neonates delivered from multigravida women than primigravida (62.5% vs 37.5%, p<0.05%). Higher mortality observed in neonates deliverer from anemic women than normal hemoglobin levels (75% vs 25%, p<0.05).

In terms of residence, neonates came from rural were less likely to improve than their urban counterparts. Infants admitted from outside were almost less likely to improve than compared with those infants who were born inside. Compared to treatment outcome in terms of gestational age, babies who born ≥37 weeks of gestation, keeping other variables constant. When compared to infants

with total serum bilirubin of ≥20 mg/dl were 60% less likely to improve.

Relation between serum bilirubin & outcome

The mean total serum bilirubin level was significantly high among those babies who were discharged in comparison to those who died [18.39±3.2 vs 24.5±2.97 respectively, p<0.05]. The mean indirect serum bilirubin level was significantly high in babies who were discharged than who died [26.875±3.847 vs 19.129±3.3305 respectively, p<0.05].Sabzehei Mk et al study showed that mean of serum bilirubin level was estimated at 17.54±4.07.

Maternal risk Factors:

Premature rupture of membrane (PROM) was seen in 7 neonates of which one neonate had Rh incompatibility, one neonate had ABO incompatibility, 2 neonates had cephalhematoma, one neonate had physiological hyperbilirubinemia and one neonate had septicaemia. Toxaemia of pregnancy was noted in 3 cases of which one case had Rh incompatibility, one case had Physiological jaundice, and another case had septicaemia. Prolonged labour was seen in 3 cases of which, one case had ABO incompatibility, one neonate had cephalhematoma, and another case had septicaemia. Oxytocin induced hyperbilirubinemea seen in one case of cephalhematoma.

Study by Kulkarni S.K et al,[15] showed that Toxaemia of pregnancy was seen in 7 cases of which 1 had Rh incompatibility, two cases had idiopathic jaundice, three neonates had physiological hyperbilirubinemia and one neonate had septicaemia. Prolonged labour was seen in 11 cases of which, one neonate had ABO incompatibility, 2 neonates had cephalhematoma, 3 neonates had septicaemia and 5 neonates had idiopathic hyperbilirubinemia. Oxytocin induction was done in 4 cases, out of which 3 neonates had idiopathic hyperbilirubinemia and one neonate had cephalhematoma.

Fetal risk Factors

Prematurity was aggravating factor in 16 neonates of which two neonates had Rh incompatibility, one neonate had ABO incompatibility, 10 neonates had physiological hyperbilirubinemia and one neonate had Septicemia. One full term baby had both cephalhematoma and septicaemia.

Study by Kulkarni S.K et al,[15] showed that Prematurity was aggravating factor in 26 neonates of which 3 neonates had ABO incompatibility, 3 neonates had septicaemia,1 neonate had Rh incompatibility, 18 neonates had physiological hyperbilirubinemia and one neonate had various congenital anomalies. One premature baby had both ABO incompatibility and septicaemia. One full term baby had both cephalhematoma and septicaemia.[13] neonates had birth asphyxia of which one neonate had ABO incompatibility, one neonate had septicaemia and 6 neonates had idiopathic jaundice and 5 neonates had physiological hyperbilirubinemia.

In our study, among total 100 neonates with indirect hyperbilirubinemia, 30% neonates were treated with phototherapy only, 12% neonates undergo exchange transfusion along with phototherapy, 6% neonates were treated with phototherapy as well as exchange transfusion along with Phenobarbital. Kulkarni S.K et al,[15] in their study, among total 120 neonates, 86.67% neonates were treated with phototherapy only and 13.33% neonates had to undergo exchange transfusion along with phototherapy.Sabzehei MK et al,[13] study shows that neonates with hyperbilirubinemea were treated by Single Phototherapy, Double Phototherapy, Intensive Phototherapy, Phototherapy + IVIG, Phototherapy + Exchange Transfusion in 29, 19, 48, and 1 and 3 neonates receptively.

Association between delivery and bilirubin levels

Study by Kulakarni et al,[15] shows that no association has been seen between the mode of delivery & total bilirubin levels. Various studies shows that the mean total bilirubin level has been found to be higher in infants born by NVD than those born by C-section. In our study, the mean total bilirubin value of neonates born through NVD was 18.519±2.67 mg/dL & the mean bilirubin of those delivered through C/S section was 21.875±4.38 mg/dL & it was found to be significantly higher in neonates delivered through C-section (p<0.05).A significant association between mode of delivery and bilirubin level is considered as a risk factor & closer monitoring of bilirubin levels in neonates born from NVD should be considered.

In our present study, G6PD deficiency was identified in one neonate only, which was varied with the rate reported by Abdel-Fattah et al.68 (14.4%) and 2.1% by Abolghasemi et al,[20] study reported the frequency of G6PD deficiency was 13.6% among neonates, and most of the cases were non hemolytic. G6PD deficiency is a one of the contributing factor associated with prolonged neonatal jaundice; hence, it is recommended that newborns to be screened for G6PD deficiency on a regular basis.

In our current study, ABO incompatibility was detected in 6% of neonates, which is similar with 5% a study by Sabzehei MK et al.[13] It was noted that prematurity directly contributes to the development of neonatal hyperbilirubinemia, and 22% of the neonates in our study were premature. Whereas other study was stated that premature neonates who were breastfed had higher peak bilirubin serum concentration, and consequently, were morecommonly presented with prolonged hyperbilirubinemia compared to infants using formula-feeding type.Phototherapy is very cost-effective and higher efficacy way to reduce bilirubin levels in neonatal jaundice. It is also effective in lowering the bilirubin levels in hemolytic hyperbilirubinemia and thus reducing the need for exchange transfusion. In case of total bilirubin level at admission, infants with TSB level ≥20mg/dl were

60% and less likely to improve as compared to neonates with total bilirubin level<20mg/dl.

CONCLUSION

With the above criteria, newborns who are at low risk to develop hyperbilirubinemia can be identified and discharged early. Neonates those with reticulocytosis (P = 0:001), and infants who received exchange transfusion (P = 0:001) were more prone to have associated risk factors.

ABO incompatibility, and older maternal age were the commonest neonatal and maternal risk factors for developing neonatal indirect hyperbilirubinemia. Determination of possible risk factors for neonatal jaundice can provide early hospital admissions by informing mothers before discharge after birth. According to the results of this study, although breastfeeding is considered as a major cause of prolonged neonatal jaundice, identification of other pathological factors is also of paramount importance.Early diagnosis and treatment of these disorders could effectively prevent further complications in neonates. Early detection of factors can aid in immediate management to prevent serious complications of this common condition in infants.

Conflict of Interest: None

Funding Support: Nil

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