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Original Article

Paediatrics Section

Cord Blood Predictive Markers of Haemolytic Jaundice in ABO Incompatible Neonates: A Cross-sectional Study

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ABSTRACT

Introduction: The ABO incompatibility occurs when the mother has blood group O and the baby has A/B/AB group. This occurs in 15-25% of pregnancies and is currently the most common cause of neonatal haemolytic jaundice and re-admission. If a test can predict those infants who are likely to develop haemolytic jaundice, such high-risk infants can be monitored more closely, while the others may be planned for early discharge.

Aim: To compare the Cord Blood (CB) markers of haemolysis in ABO incompatibility between neonates who develop haemolytic jaundice and those who do not, and derive predictors for haemolytic jaundice.

Materials and Methods: This cross-sectional study was conducted at the Department of Paediatrics, ESICMC and Hospital, Chennai, Tamil Nadu, India, from December 2020 to June 2022. Total 200 newborns who were ABO incompatible and Rh compatible with their mothers were enrolled in the study and CB samples were collected for all. These neonates were followed-up and laboratory investigations were done at the onset of clinically significant jaundice. CB haemolytic markers such as Direct Coombs test (DCT), Haemoglobin (Hb), Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin Concentration (MCHC), Reticulocyte Count (RC), Total Serum Bilirubin (TSB) and peripheral smear study, were compared between the newborns who developed haemolytic jaundice and those who did not. Data were statistically analysed by using Student's t-test, Fisher's exact test and ROC curve analysis.

Results: A total of 200 term newborns were included in the study; among them 96 (48%) were male and 104 were female (52%). Among them, 86 had A+ (43%), 1 had B-(0.5%), and 113 had B+ (56.5%). Out of 200 newborn babies included in the study, 164 were found to develop clinically significant jaundice. Postnatal samples for TSB, Complete Blood Count (CBC), RC and smear for evidence of haemolysis were sent for each of these neonates. 28 neonates had haemolytic jaundice and were included in Group I, and the remaining 172 (no jaundice/ no evidence of haemolytic jaundice-non haemolytic group) were included in Group II. On retrospective analysis of their CB parameters, group I had higher cord TSB and lower Hb levels when compared to group II ($p<0.001$). The ROC cut-off value for CB TSB for predicting haemolytic jaundice was 2.9 mg/dL, and that of CB Hb was 15. 3g/dL.

Conclusion: In ABO incompatibility, mean CB bilirubin was significantly higher, and Hb concentrations were significantly lower in neonates who developed haemolytic jaundice compared to those who did not.

Keywords: Haemoglobin, Hyperbilirubinemia, Peripheral smear, Serum bilirubin, Umbilical cord blood

INTRODUCTION

Hyperbilirubinemia is the most common clinical condition requiring evaluation and management in the newborn period. It is the most common cause of readmission in the neonatal period [1]. Haemolysis is a serious cause of neonatal jaundice and can be secondary to Rh, ABO or minor blood group incompatibility between the mother and fetus. With Rh incompatibility being adequately addressed in the antenatal period with maternal screening and therapy with Anti-D, ABO incompatibility (mother having blood group O and baby A/B/AB group) occurring in 15-25% of pregnancies is currently the most common cause of neonatal haemolytic jaundice [2,3].

Mothers with blood group O have naturally occurring anti-A and anti-B antibodies, which are IgG; they can cross the placenta and destroy foetal RBCs [4]. In contrast to Rh incompatibility, prior sensitisation is not needed for this phenomenon, and even the first offspring can be affected. Prevalence of haemolytic jaundice in neonates of ABO incompatible mothers is between 5.5-17% [2,5]. Currently, there are no established cut-offs for CB markers of haemolysis for predicting haemolytic jaundice in these neonates.

Early discharge of mother and neonate after birth is recommended by the American Academy of Paediatrics, which defines very early and early discharge as 24 and 48 hours, respectively, following uncomplicated normal vaginal delivery [3]. This practice can lead to an increased rate of readmission due to neonatal jaundice [6]. Therefore, early prediction of newborns at risk of neonatal hyperbilirubinemia will aid us in identifying those infants who need a close follow-up after early discharge. CB screening for markers of haemolysis in ABO incompatibility, if identified, would act as a simple, non-invasive method for predicting haemolytic jaundice in at-risk neonates.

Globally, only limited studies have been done to find the cut-off value of CB bilirubin in ABO incompatible babies in predicting hyperbilirubinemia and fewer still in the Indian context [5,7,8]. Furthermore, studies which have derived cut-offs for other markers of haemolysis apart from CB bilirubin, like CB Hb, RC and others, are scarce. Hence, the present study was conducted to compare the CB markers of haemolysis between neonates who develop haemolytic jaundice and those who do not, and further to find predictive markers of haemolysis in the CB, in ABO incompatibility.

MATERIALS AND METHODS

This was a cross-sectional study conducted at the neonatal unit, Department of Paediatrics of ESIC Medical College and Hospital, Chennai, Tamil Nadu, India, from December 2020 to June 2022 (1 year, 6 months). Prior approval from the Institutional Ethics Committee was obtained to conduct the study (reference no. IEC/2020/2/41). Antenatal written informed consent was obtained from either parent for the collection of CB for the present study.

If the baby developed jaundice postnatally, routine consent as per hospital protocol was obtained for further investigations.

Inclusion criteria: Neonates aged ≥ 35 weeks of gestation, who were ABO incompatible but Rh compatible (that is, both mother and neonate are either Rh positive or negative), were included. A diagnosis of ABO incompatibility was considered in those neonates with blood groups A/B/AB born to mothers with O blood group.

Exclusion criteria: Neonates who were asphyxiated, diagnosed with sepsis, and those who had laboratory investigations suggestive of a cause other than ABO incompatibility were excluded.

Sample size calculation: From a recent study by Castillo A et al., the mean and standard deviation of CB bilirubin in newborns with and without haemolytic jaundice were 2.5±0.7 and 1.6±0.4 mg/dL, respectively [5]. Sample size was calculated using STATA software for detecting a significant difference in cord bilirubin level between neonates with and without haemolytic jaundice. The following were assumed: 1) Confidence level: 95%, power: 90%, mean and SD for total bilirubin in CB for haemolysis group: 2.4 (0.8), mean and SD for total bilirubin in CB non haemolysis group: 1.7 (0.4), prevalence of haemolysis among ABO incompatible neonates: 8%. With the above assumptions, the sample size was estimated to be 200. The sampling method followed was continuous sampling.

Study Procedure

At delivery, after clamping the umbilical cord, 2 mL of CB was collected from the umbilical vein for all O blood group mothers. The initial test sent was the blood group of the infants. If this was found to be ABO incompatible (A/ B/AB in the baby) and Rh compatible, further tests- DCT, Hb, MCV, MCHC, RC, TSB and peripheral smear study for evidence of haemolysis were performed on the collected sample. The results were collected, and data entry was done by a staff nurse. The investigator was blinded to the results of the CB tests.

These neonates were clinically followed-up by the principal investigator till 96 hours of life for the onset and progression of jaundice using Kramer's staging. The Kramers' staging is a non invasive method to approximately estimate the TSB. In a newborn, jaundice progresses in a cephalocaudal direction. Hence, when jaundice is seen in the face alone, levels are ~5 mg/dL, chest and abdomen ~6-8 mg/dL, thighs- 8-12 mg/dL, legs and forearms- 12-15 mg/dL, palms and soles >15 mg/dL [9].

Neonates who had jaundice would also be assessed for Bilirubin Induced Neurological Dysfunction (BIND) using the BIND score. This score uses three parameters- mental status, muscle tone and cry pattern to assess the degree of neurological impairment in neonates with jaundice [10].

The neonates who developed significant jaundice were subjected to blood investigations such as total and direct serum bilirubin, CBC, DCT, peripheral smear for evidence of haemolysis and RC.

The TSB was estimated using the diazo method, and direct bilirubin was measured using the Vitros 4600 automated analyser. DCT was performed using the gel card agglutination method. CBC was analysed using an automated Coulter haematology analyser. Peripheral blood smear examination was performed using Leishman staining, and RC was assessed by supravital staining. All laboratory investigations were performed at our ESIC medical college laboratory, which is a National Accreditation Board for Testing and Calibration Laboratories (NABL)-accredited laboratory, following standard operating procedures. Internal Quality Control (IQC) was run daily using manufacturer-provided control materials, and results were validated before sample analysis. The following parameters were used to define neonates with haemolysis- positive DCT, RC >5%, peripheral smear showing haemolysis or anaemia (Hb<15 g %) [2,11,12].

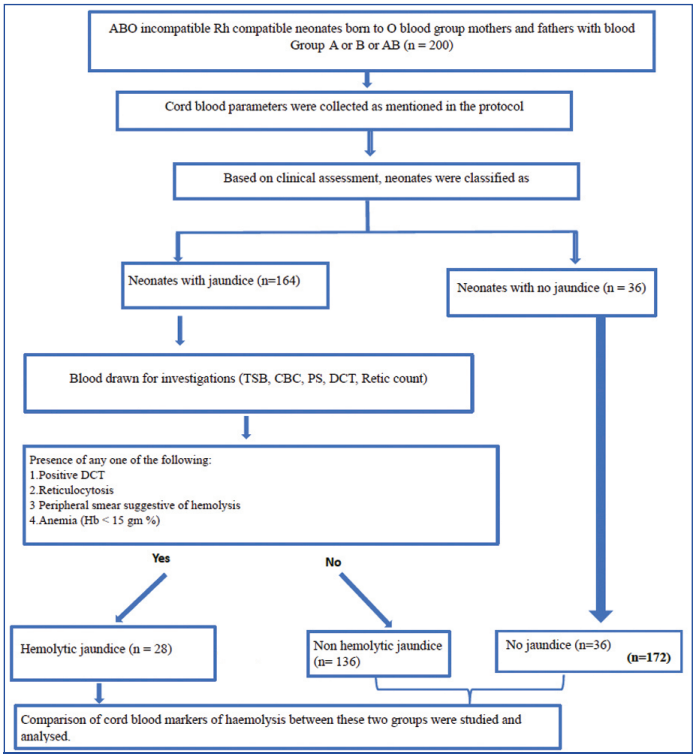
Decisions for phototherapy or exchange transfusions were made based on age and hour-specific American Academy of Paediatrics (AAP) chart, and further management was done as indicated [3]. Based on the above criteria, Group I- ABO incompatible neonates were classified as newborns with haemolytic jaundice and Group II- ABO incompatible neonates were classified as newborns without haemolytic jaundice. At the end of the study period, CB parameters of haemolysis were compared between these two groups.

STATISTICAL ANALYSIS

Analysis was done using statistical software Statistical Package for Social Sciences (SPSS) version 21.0. Continuous data such as TSB and red blood cell indices were expressed in terms of mean, standard deviation and percentage and Student's t-test was used to compare the mean values between the two groups. For categorical variables such as direct Coombs test and peripheral smear picture of haemolysis, the Fisher's exact test was used. With 95% confidence level, a p-value ≤0.05 was considered statistically significant. The Receiver Operator Characteristic (ROC) curve analysis was used to find the cut-off with optimal sensitivity and specificity.

RESULTS

A total of 200 babies beyond 35 weeks of gestation who were ABO incompatible and Rh compatible with their mothers were recruited in the study. Of these, 164 babies (82%) were found to have clinically significant jaundice in the postnatal period, and laboratory investigations (TSB, Hb, MCV, MCHC, peripheral smear, RC and DCT) were sent to determine the extent of jaundice and presence of haemolysis. A total of 28 newborns were found to have jaundice with evidence of haemolysis and hence classified as having haemolytic jaundice-Group I. The remaining neonates, those who did not have jaundice and those who had jaundice but no evidence of haemolysis, were classified under Group II [Table/Fig-1]. All babies recruited were followed-up and included in the study.



[Table/Fig-1]: Flow chart for enrollment and follow-up of study participants. N=200 and N=172

There were 96 (48%) male babies and 104 (52%) females. In the present study, 86 had A+ (43%), 1 had B-(0.5%) and 113 had B+ (56.5%) blood group. None of the babies had the AB blood group [Table/Fig-2].

None of the babies received an exchange transfusion. A total of 101 babies (51%) received phototherapy. The BIND score for all

Blood group n (%)		Group I n (%)	Group II n (%)
A+	86 (43)	12 (14)	74 (86)
B-	1 (0.5)	1 (100)	0
B+	113 (56.5)	15 (13.3)	98 (87)
Total	200	28	172

[Table/Fig-2]: Distribution of blood groups in the study and association with haemolytic jaundice.

the babies who required phototherapy was 0. The mean CB TSB in group I was 3.17 mg/dL, and in group II, it was 2.38 mg/dL. The difference between the two groups was statistically significant (p-value<0.001). The mean CB Hb in group I was 14.9 g/dL, and 16.3 g/dL in group II. The difference between the Hb levels in the two groups was also statistically significant (p<0.001). CB peripheral smear showed haemolysis in 28.6% of newborns in group I, whereas none of the newborns in group II demonstrated haemolysis.

The difference between the mean CB RC between the two groups was statistically significant (p-value <0.001). However, deriving a cut-off for RC was statistically not feasible. The difference between the mean CB MCHC and mean CB MCV among these two groups was not statistically significant [Table/Fig-3].

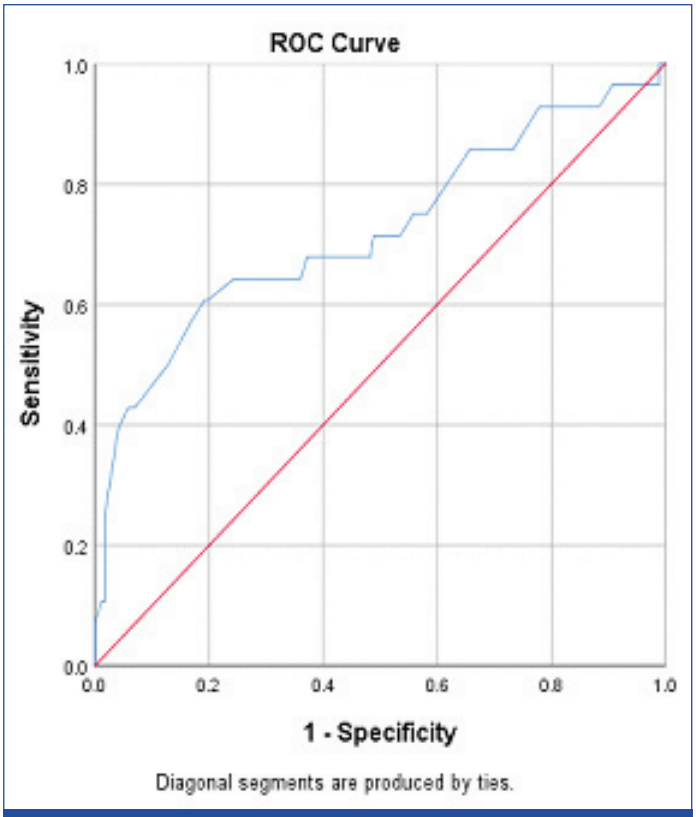
Test parameters	Group I (n=28)	Group II (n=172)	p-value*
Total Serum Bilirubin (TSB), mg/dL (Mean±SD)	3.17±1.12	2.38±0.65	<0.001
Haemoglobin (Hb), g/dL (Mean±SD)	14.9±1.55	16.3±1.72	<0.001
Direct Coombs Test (DCT), n (%)	3 (10.7%)	0	-
Reticulocyte Count (RC), % (Mean±SD)	5.00±2.70	3.13±1.36	<0.001
Mean Corpuscular Haemoglobin Concentration (MCHC), g/dL (Mean±SD)	32.94±1.90	33.30±1.77	0.328
Mean Corpuscular Volume (MCV), fL (Mean±SD)	109.84±5.86	109.76±4.68	0.988
Peripheral Smear (PS) Evidence of Haemolysis, n (%)	8 (28%)	0	-

[Table/Fig-3]: Comparison of Cord Blood (CB) values between Group I and Group II.
DCT: Direct coomb's test; Hb: Haemoglobin; TSB: Total serum bilirubin; MCHC: Mean corpuscular haemoglobin concentration; MCV; Mean corpuscular volume; PS: Peripheral smear; *Fisher's exact test was used to compare categorical variables, while Student's t-test was used for continuous variables.

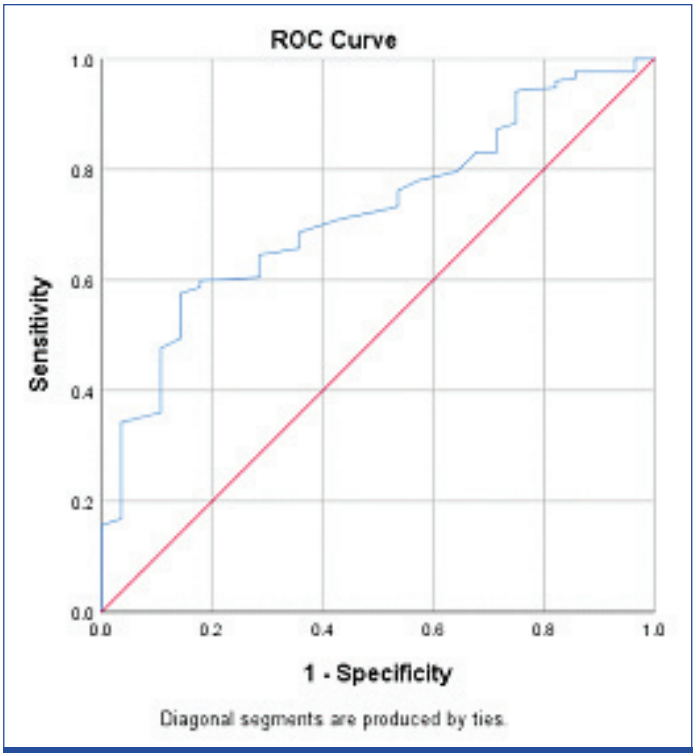
The ROC curve to assess the ability of umbilical cord serum total bilirubin to predict significant hyperbilirubinaemia in ABO incompatibility is shown in [Table/Fig-4]. Based on the ROC curve, the cut-off value for CB TSB was 2.89 mg/dL. Area Under the Curve (AUC)=0.722. (95%CI-0.604-0.840, p≤0.0001) with sensitivity 64.29%, specificity 75.58%, Positive Predictive Value (PPV)- 30.00% and Negative Predictive Value (NPV)- 82.86%.

The ROC curve to assess the ability of umbilical CB Hb to predict significant hyperbilirubinaemia in ABO incompatibility is shown in [Table/Fig-5]. Based on the ROC curve, the cut-off value derived for CB Hb was 15.35 g/dL (AUC=0.723) (95%CI, 0.605-0.841, p≤0.0001) with sensitivity-64.29%, specificity-68.60%, PPV-25.00% and NPV-92.19%.

The CB DCT was positive in (10.7%) of group I. The specificity of CB DCT for predicting haemolysis was 100%, the sensitivity was very less, only 10% [Table/Fig-6].



[Table/Fig-4]: Area Under the Curve (AUC) for Cord Blood (CB) TSB.



[Table/Fig-5]: Area Under the Curve (AUC) for Cord Blood (CB) Haemoglobin (Hb).

Parameters	Cut-off	AUC	Sensitivity %	Specificity %	PPV %	NPV %
CB Hb	15.35	0.723	64.29	68.6	25	92.19
CB TSB	2.9 mg/dL	0.722	64.29	75.58	30	82.86
Cord Blood (CB) DCT	Qualitative data	NA	10%	100%	100%	87.2%

[Table/Fig-6]: Predictive values of CB Hb and CB TSB and DCT at the proposed cut-offs.

DISCUSSION

The ABO haemolytic disease of newborn is a potential cause of neonatal morbidity. In the management of Rhesus iso-immunisation, CB screening for diagnostic and predictive purposes is a common practice. But the benefit of early detection of haemolytic jaundice in ABO incompatibility by this method has been outweighed by the increased workload required, the absence of severe disease

at birth, the benign course of the disorder in most newborns, and the lack of a valid diagnostic test. However, with the advent of the policy of early discharges from nurseries and prophylactic methods of treatment of jaundice, a simple means of detecting "at-risk" newborns is of great significance. This prospective observational study was done to compare the CB markers of haemolysis in ABO-incompatible neonates with and without haemolytic jaundice and identify the markers predictive of haemolysis.

Among the 200 neonates born to O-positive mothers, the majority of the babies had a blood group of B+ (56.5%), followed by A+ (43%). Similar distribution of A and B blood groups was seen in the studies of Bhat D and Purohit M and Alshammari S et al., [7,12].

Twenty-eight infants developed significant hyperbilirubinemia with evidence of haemolysis. This represents around 14% of all babies with ABO incompatibility. The prevalence of haemolysis in ABO incompatibility has ranged from 9% to 20 % in various studies [2,7,12].

Mean CB TSB in group I was 3.17 mg/dl, and it was 2.38 mg/dl in group II. The difference between the groups was found to be statistically significant (p-value=0.0001). In the presence of this significant difference, we attempted to find a cut-off of of CB bilirubin that could predict haemolytic jaundice in ABO incompatibility. Based on the ROC curve, the cut-off value for CB TSB was at 2.89 mg/dL (AUC=0.722) in predicting the severity of haemolytic jaundice in ABO incompatibility. AUC of 0.722 shows an acceptable discriminatory ability, and it is adequate for a screening test. There are several studies that have found varying cut-offs for CB bilirubin for the prediction of neonatal jaundice. Variability of cut-offs may arise due to differences in the populations studied or methodological differences in assays or statistical methods. Kardum D et al., in their study of 1360 newborns, found that an umbilical CB Bilirubin of 1.99 mg/dL was predictive of significant neonatal jaundice [13]. Calkins K et al., have proposed a cut-off of 2.5 mg/dL of CB Bilirubin for predicting significant neonatal jaundice in haemolytic conditions [14]. However, these studies are not specific for newborns with ABO incompatibility.

Janaki AN and Selvakumar P report the cut-off at 1.85 mg/dL in their study that included 92 ABO incompatible newborns [15]. In a study of 130 Indian newborns, 100 of which were ABO incompatible, Bhat D and Purohit M. have proposed a cord bilirubin cut-off of 2.5 mg/dL as predicting significant neonatal jaundice in ABO incompatibility [7]. This is very close to the cut-off that we derived. More studies from India will help to establish cut-off values with better sensitivity and specificity.

In the present study, the mean CB Hb of the haemolytic jaundice group was significantly lower than that of the non haemolytic group. This difference was statistically significant (16.3 g/dL vs 14.9 g/dL, p<0.001). Based on the ROC that we obtained, Hb cut-off for predicting haemolytic jaundice was 15.35 g/dL. Chen SH et al., in their sample of 3688, found a total of 555 infants of A/B blood group born to O group mothers [16]. The CB Hb in this group was significantly lower (p<0.001) compared to infants born to mothers with A/B blood groups. The Hb cut-off they proposed in their study was 11.2 g/dL. There are not many studies that have proposed a cut-off Hb level to define anaemia in ABO incompatibility. The present study derives importance in this context.

Among the current study participants, CB DCT was positive in 10.7% of the haemolytic jaundice group and negative in the remaining 89%, making it a marker with good specificity (100%) but very poor sensitivity (10%). The prevalence of DCT positivity in ABO incompatibility has been variable in other studies, from 1.9% to 46% [2,12,17]. No increased severity of haemolytic jaundice in the DCT positive infants of the present study group was observed, but many studies have shown that infants with DCT positivity had higher rates of jaundice requiring intervention [2,17,18].

In the current study, the peripheral smear picture of haemolysis in CB i.e., presence of microspherocytes and nucleated RBCs were seen in only 28.3% of infants with haemolytic jaundice. No previous studies have established the usefulness of cord peripheral smear so far to predict the severity of haemolytic jaundice in ABO incompatibility. This requires high expertise and is subject to significant inter- and intra-observer variation. Hence, this may not be a useful marker for predicting haemolytic jaundice.

In present study, mean CB RC in the haemolytic jaundice group was 5% and 3% in the other group. Though this was found to be significant, deriving a cut-off value for predicting haemolysis was not statistically feasible. Other researchers also have not mentioned CB RC as a useful predictor for haemolysis in neonates. Mean MCV and MCHC values were not statistically significant.

In summary, CB Hb and TSB were the most useful markers for predicting haemolytic jaundice in ABO incompatible neonates. Hence, CB TSB and Hb may be considered for risk stratification in newborns of mothers with O blood group; however, multicentric validation studies are warranted before routine implementation. Neonates identified as high risk based on cord blood bilirubin and haemoglobin levels may benefit from closer monitoring and timely initiation of phototherapy according to standard treatment guidelines. Though the screening tests will incur expenditure, the benefits of early identification of affected neonates, like timely management with simple bedside phototherapy, avoidance of the need for high-risk procedures like exchange transfusion and prevention of permanent neurological complications appear to be worthy outcomes that justify the cost.

Limitation(s)

Limitations of the study include its single-centre design, relatively small number of haemolytic cases, and absence of long-term neonatal follow-up.

CONCLUSION(S)

The ABO incompatibility is an important cause of neonatal jaundice. CB TSB and Hb demonstrated potential utility as screening markers for identifying neonates at increased risk of haemolytic jaundice. The cut-off derived in the present study for CB TSB and CB Hb were 2.89 mg/dL and 15.35 g/ dL, respectively. These neonates may be identified and treated for jaundice early with non invasive methods like phototherapy, potentially averting the dangers of late diagnosis of haemolytic jaundice like BIND and the need for invasive procedures like exchange transfusion. Other CB parameters, such as RC and peripheral smear, were not found to be useful predictors in the present study, while DCT demonstrated high specificity but low sensitivity.

Multicentric studies with large sample sizes are required to establish a more generalisable cut-off for CB TSB and CB Hb to predict haemolytic jaundice in ABO incompatibility.

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