Predictive value of umbilical cord blood bilirubin in neonatal hyperbilirubinemia

Alaa Eldin A. Zeitoun, Hala F. Elhagrasy, Doaa M. Abdelsatar

Pediatric Department, Faculty of Medicine, Suez Canal University, Egypt
Pediatric Department, Ismailia General Hospital, Egypt

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Abstract

Introduction: Jaundice is a clinical condition that is often present in pediatric practice and constitutes one of the major issues within the neonatal period. It occurs in both the physiological and pathological processes in newborns. Although most newborns with jaundice are otherwise healthy, they need to be monitored because bilirubin is potentially toxic to the central nervous system. The American Academy of Pediatrics (AAP) in 2004 recommended that newborns discharged within 48 h should have follow up visits after 2–3 days to detect significant jaundice. The aim of the work: This study was done to evaluate the predictive value of umbilical cord bilirubin in identifying infants for subsequent hyperbilirubinemia, in full-term (FT) and late pre-term (PT) newborns.

Subjects and methods: This study is a prospective clinical study which was carried out on 94 newborns taken from the delivery room (DR) and neonatal intensive care unit (NICU) of Ismailia General Hospital at Ismailia Governorate. The study population was followed up clinically and by laboratory investigations from birth and daily during the first week of life.

Results: The study population consisted of 50 males and 44 females with the mean gestational age of 38.70 ± 1.38 weeks in FT compared to 35.62 ± 0.64 in PT. It was shown that 40.4% of PT needed treatment in the form of phototherapy compared to 29.8% of FT, and no one of both groups needed exchange transfusion. The mean total cord bilirubin was higher among males, preterm, cesarean deliveries, and ABO and RH incompatibility positive newborns. It was found that when cord blood in late PT newborns was \( P \geq 1.75 \text{ mg/dl} \) and \( P \geq 1.85 \text{ mg/dl} \) in FT newborns, there was a probability that those newborns may need phototherapy and when the levels of total cord bilirubin...
Introduction

Jaundice is the most common condition that requires medical attention in newborns. Neonatal jaundice may have first been described in a Chinese textbook 1000 years ago. Medical theses, essays, and textbooks from the 18th and 19th centuries contain discussions about the causes and treatment of neonatal jaundice. Neonatal hyperbilirubinemia is extremely common because almost every newborn develops an unconjugated serum bilirubin level of more than 30 µmol/L (1.8 mg/dL) during the first week of life. Jaundice is observed during the first week of life in approximately 60% of term infants and 80% of pre-term infants.

Early discharge of healthy term newborns after delivery has become a common practice because of medical, social and economical reasons. The most common cause for readmission during the early neonatal period is hyperbilirubinemia. Such readmission, besides involving extra expenses for both family and the institution and also exposing a probably healthy newborn to the hospital environment, brings emotional problems and risks to breast-feeding, and is one of the causes of early weaning.

Concern regarding early discharge and hyperbilirubinemia in newborns has led to frequent discussions and many controversies. Early hospital discharge has had the implication of reexaming the approach toward neonatal jaundice, now taking into consideration the bilirubin levels presented in the first 24–48 h of life as a means of predicting severe hyperbilirubinemia. Thus, the investigation of parameters that might help the physician prevent the occurrence of severe hyperbilirubinemia is duly justifiable.

In recent years many efforts have been made to identify infants likely to develop neonatal jaundice. Reliable strategies can reduce hospital stay for normal babies and identify significant hyperbilirubinemia that may happen in the future. Universal follow-up within 1–2 days of early discharge, umbilical cord bilirubin concentration at birth, routine pre-discharge serum bilirubin and transcutaneous bilirubin measurement, as well as the universal clinical assessment of risk factors of developing jaundice are various strategies to predict significant hyperbilirubinemia.

So that, it would be desirable to be able to predict the risk of jaundice in order to implement early treatment and thereby minimize the risk of bilirubin dependent brain damage. The present study was conducted to evaluate the predictive value of cord bilirubin level for identifying infants for subsequent hyperbilirubinemia.

Study objective

The aim of this study is to evaluate the predictive value of umbilical cord bilirubin in identifying infants for subsequent hyperbilirubinemia, in full-term and late pre-term neonates.

Subjects and methods

Study design: It is a prospective clinical study carried out on all neonates who developed hyperbilirubinemia during their first week of life.

Study site: the study was carried out at the delivery room and neonatal intensive care unit (NICU) of Ismailia General Hospital in Ismailia Governorate.

Study population: This study was carried out on 94 newborns (47 each in FT and late PT groups) with the following criteria:

Inclusion criteria:

1. Sequentially born, any type of delivery, both genders.
2. Full term (gestational age is 37 weeks or more).
3. Late preterm (gestational age >34 weeks and <37 weeks).
4. APGAR score of over 7 at the first minute and 10 at fifth minute of life.
5. Absence of significant illness or of major congenital malformation.

Exclusion criteria

1. Significant illness (sepsis, RDS, asphyxia, IDM) that could aggravate hyperbilirubinemia
2. Gestational age <34 weeks

Both study groups were followed up clinically and by laboratory investigation from birth and daily during the first week of life.

All the study population was subjected to the following baseline assessment for each newborn by history, physical examination and investigations.

History included sex, type of delivery, detailed prenatal and natal history, gestational age, blood groups, and family history of neonatal jaundice.

Physical examination included APGAR score, anthropometric measurements, skin color, presence of bruises or
cephalohematoma, assessment of GA (according to New Ballard Score), and reflexes (Moro and suckling).

Laboratory investigations included: total serum bilirubin TSB in the umbilical cord blood at birth and in the serum of babies who develop significant hyperbilirubinemia that need treatment, complete blood count, serum albumin and investigations for hemolysis; (reticulocyte count, direct Combs test, and blood grouping for mothers and newborns).

Follow up of the degree of jaundice in those babies was carried out daily during the first week of life by transcutaneous bilirubinometry (Bilicheck), which works by directing white light into the skin and measures the intensity of the specific wavelengths returned.

Laboratory work

Three milliliters of cord venous blood was drained by a sterile syringe, put in clean capped tube, and then sent immediately to the Laboratory of the hospital. Serum was used, samples were protected from light during processing and storage and hemolyzed samples were excluded.

Methods of assay of serum bilirubin

Total serum bilirubin, conjugated bilirubin and unconjugated bilirubin were obtained via the colorimetric Diazo method.

Ethical considerations

The study was approved by the research ethics committee of faculty of Medicine, Suez Canal University. An informed consent was taken from parents of the studied newborns before taking any data or doing any investigations.

Data management and statistical analysis

The analysis was carried out using the statistical package for the social sciences (SPSS) program for windows (SPSS Inc., Chicago, version 15.0) and p values with significance of less than 0.05 were considered statistically significant.

Results

The study involved 94 newborns, 47 FT and 47 late PT, who presented to the delivery room, and NICU of Ismailia general Hospital.

Table 1 shows that the study population consisted of more boys than girls and more NSVD than CS.

Regarding the gestational age of the study population it was 38.70 ± 1.38 weeks in FT compared to 35.62 ± 0.64 in PT. On the other hand, the mean birth weight was 2.94 ± 0.32 kg in FT compared to 2.52 ± 0.51 kg in PT, with no significant difference in both gestational age and birth weight.

Table 2 shows that the mean hemoglobin level, the mean TLC and neutrophil count were significantly higher among PT compared to FT. However there was no statistically significant difference between PT and FT regarding the mean albumin level and retics count.

Table 3 shows the effect of gestational age and day of measurement of transcutaneous bilirubin. There was no statistically significant difference in the mean of transcutaneous bilirubin.

### Table 1 Distribution of newborns according to gender and mode of delivery.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>FT No. (%)</th>
<th>PT No. (%)</th>
<th>Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>26 (55.3)</td>
<td>24 (51.15)</td>
<td>50 (53.2)</td>
</tr>
<tr>
<td>Female</td>
<td>21 (44.7)</td>
<td>23 (48.9)</td>
<td>44 (46.8)</td>
</tr>
<tr>
<td>NSVD</td>
<td>23 (48.9)</td>
<td>28 (59.65)</td>
<td>51 (54.3)</td>
</tr>
<tr>
<td>CS</td>
<td>24 (51.1)</td>
<td>19 (40.45)</td>
<td>43 (45.7)</td>
</tr>
</tbody>
</table>

### Table 2 Comparison of laboratory parameters between FT and PT.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FT (n = 47) mean ± (SD)</th>
<th>PT (n = 47) mean ± (SD)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB (g/dl)</td>
<td>16.27 ± 0.87</td>
<td>16.89 ± 0.84</td>
<td>0.001*</td>
</tr>
<tr>
<td>TLC</td>
<td>13.77 ± 1.55</td>
<td>14.52 ± 1.35</td>
<td>0.013*</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>55.47 ± 0.96</td>
<td>56.23 ± 0.95</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Retics</td>
<td>3.83 ± 1.44</td>
<td>4.21 ± 1.48</td>
<td>0.204</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.50 ± 0.29</td>
<td>3.50 ± 0.25</td>
<td>0.97</td>
</tr>
</tbody>
</table>

TLC = Total Leukocytic count.
* Statistically significant at p < 0.05 and 95% confidence level.

### Table 3 The mean transcutaneous bilirubin of study groups.

<table>
<thead>
<tr>
<th>Day of measurement</th>
<th>FT mean ± SD</th>
<th>PT mean ± SD</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>3.6 ± 1.14</td>
<td>3.6 ± 1.25</td>
<td>0.952</td>
</tr>
<tr>
<td>Day 2</td>
<td>6.02 ± 2.04</td>
<td>6.35 ± 2.43</td>
<td>0.470</td>
</tr>
<tr>
<td>Day 3</td>
<td>8.99 ± 3.48</td>
<td>8.34 ± 3.64</td>
<td>0.375</td>
</tr>
<tr>
<td>Day 4</td>
<td>9.87 ± 5.35</td>
<td>8.79 ± 5.26</td>
<td>0.329</td>
</tr>
<tr>
<td>Day 5</td>
<td>7.41 ± 5.62</td>
<td>7.91 ± 6.03</td>
<td>0.674</td>
</tr>
<tr>
<td>Day 6</td>
<td>7.25 ± 5.41</td>
<td>6.45 ± 5.70</td>
<td>0.487</td>
</tr>
<tr>
<td>Day 7</td>
<td>6.92 ± 5.18</td>
<td>5.84 ± 5.34</td>
<td>0.322</td>
</tr>
</tbody>
</table>
bilirubin between FT and PT babies at any time of measurement.

Fig. 1 shows that the peak level of transcutaneous bilirubin in either FT or PT babies was on day 4 of life.

Figure 1  Comparison of time of the mean transcutaneous measurement during the first 7 days of life.

Fig. 2 shows that there was a significant association between total bilirubin in cord blood and the newborn’s total bilirubin level ($r = 0.778; p < 0.001$)
Regarding the needed treatment among study population, it was found that 40.4% of PT and 29.8% of FT needed phototherapy and no one of both groups needed exchange transfusion.

Table 4 shows that the ABO incompatibility was more common than RH incompatibility in all study population.

As shown in Table 5, it was found that total and direct cord bilirubin were slightly higher among FT compared to PT babies. However these differences were not significant.

Table 6 shows the three cut-off points for total cord bilirubin test at which we can predict the need for phototherapy in PT. The positive likelihood ratio is computed for each cut-off point as sensitivity/specificity. A high positive likelihood ratio is more important for a diagnostic test than for a screening test. Receiver operating characteristic (ROC) curves in Fig. 4 show that, the area under the curve was 0.98 of total area, \( p < 0.001 \), indicating the usefulness of the test in predicting the need for phototherapy.

ROC curves in Fig. 3 show that, the area under the curve was 0.98 of the total area; \( p < 0.001 \), indicating the usefulness of the test in predicting the need for phototherapy.

Table 7 shows the three cut-off points for total cord bilirubin test at which we can predict the need for phototherapy in PT. The positive likelihood ratio is computed for each cut-off point as sensitivity/specificity. A high positive likelihood ratio is more important for a diagnostic test than for a screening test. ROC curves in Fig. 4 show that, the area under the curve was 0.95 of total area, \( p < 0.001 \), indicating the usefulness of the test in predicting the need for phototherapy.

Table 8 shows the three cut-off points for total cord bilirubin test at which we can predict the need for phototherapy in PT. The positive likelihood ratio is computed for each cut-off point as sensitivity/specificity. A high positive likelihood ratio is more important for a diagnostic test than for a screening test. ROC curves in Fig. 4 show that, the area under the curve was 0.95 of total area, \( p < 0.001 \), indicating the usefulness of the test in predicting the need for phototherapy.

Table 9 shows the three cut-off points for total cord bilirubin test at which we can predict the need for phototherapy in PT. The positive likelihood ratio is computed for each cut-off point as sensitivity/specificity. A high positive likelihood ratio is more important for a diagnostic test than for a screening test. ROC curves in Fig. 4 show that, the area under the curve was 0.95 of total area, \( p < 0.001 \), indicating the usefulness of the test in predicting the need for phototherapy.

### Table 4

<table>
<thead>
<tr>
<th>Incompatibility</th>
<th>Positive No. (%)</th>
<th>Negative No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO</td>
<td>13 (13.8)</td>
<td>81 (86.2)</td>
</tr>
<tr>
<td>RH</td>
<td>3 (3.2)</td>
<td>91 (96.8)</td>
</tr>
</tbody>
</table>

### Table 5

<table>
<thead>
<tr>
<th>Cord bilirubin</th>
<th>FT mean ± SD</th>
<th>PT mean ± SD</th>
<th>( p )-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (mg/dl)</td>
<td>1.75 ± 0.41</td>
<td>1.72 ± 0.50</td>
<td>0.77</td>
</tr>
<tr>
<td>Direct (mg/dl)</td>
<td>0.35 ± 0.41</td>
<td>0.32 ± 0.50</td>
<td>0.81</td>
</tr>
</tbody>
</table>

### Table 6

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Cut-off value (mg/dl)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Pvp</th>
<th>Pvn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>1.75</td>
<td>100.0(80.0, 120.0)</td>
<td>85.7(76.1, 95.9)</td>
<td>100.0</td>
<td>85.7</td>
</tr>
<tr>
<td>Optimal</td>
<td>1.85</td>
<td>89.5(81.4, 98.6)</td>
<td>89.3(80.1, 97.9)</td>
<td>89.5</td>
<td>89.3</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>2.05</td>
<td>68.4(54.7, 81.3)</td>
<td>96.4(90.4, 101.6)</td>
<td>86.4</td>
<td>96.4</td>
</tr>
</tbody>
</table>

Pvp = predictive value positive.
Pvn = predictive value negative.
cord bilirubin and birth weight. The pre-term and low birth weight newborns are more likely to develop hyperbilirubinemia because of immaturity of the liver with low levels of ligand in hepatocytes, and low activity of bilirubin conjugating enzyme uridine diphoglucuronyltransferase (UDPGT), which cause a decreased excretory capacity of the liver cells.

Regarding the mode of delivery and its relation to cord bilirubin there was no significant difference between the normal delivery group and the cesarean section group, and this result matched with the results of Rostami and Mehrabi and Amar et al.7,10, who stated that type of delivery did not affect the umbilical cord bilirubin level.

Our study showed that 40.4% of preterm needed treatment in the form of phototherapy compared to 29.8% of full term. The mean total cord bilirubin for babies who received phototherapy was 2.19 ± 0.24 mg/dl which is significantly higher
than those who did not receive it which was 1.49 ± 0.34 mg/dl. These results agreed with the results of Adelia and Cancceicao, 2004 who found that phototherapy was significantly associated with higher levels of unconjugated bilirubin in cord blood as the mean unconjugated bilirubin in cord blood for children who received phototherapy was 2.12 ± 0.46 mg/dl and for those who did not receive phototherapy was 1.75 ± 0.46 mg/dl. Also Amar et al., showed that total cord blood was significantly higher in newborns who developed significant hyperbilirubinemia after 72 h of age, which means that cord bilirubin could be a useful indicator of risk of icterus in newborns.

Our study showed that ABO incompatibility was found in 13.8% of all study groups and 3.2% only with RH incompatibility. The mean total cord bilirubin was significantly higher among ABO positive babies compared to negative ones in both groups. These results did not agree with the results of Adalia and Cancceiao, which showed that there was no significant difference in cord bilirubin between babies with and without maternal fetal blood incompatibility.

In accordance with this, the study group was classified into two groups, who required phototherapy and who did not require it, which is related to the levels of cord blood bilirubin as follows: when cord bilirubin in preterm was ≥1.75 mg/dl and ≥1.85 mg/dl in full terms, there was a probability that those newborns may need phototherapy and when the levels were ≥2.05 mg/dl in preterm and ≥2.15 mg/dl in full terms means that those babies will actually need phototherapy.

Thus, by ROC analysis the cut-off points for total cord bilirubin in preterm and full term groups were 2.05 and 2.15 mg/dl respectively. Rudy et al., determined using ROC analysis that total bilirubin level in cord blood of >2.54 mg/dl had high sensitivity and specificity. Amar et al., found that cord bilirubin >2 mg/dl had the highest sensitivity and this critical bilirubin level had a very high negative predictive value and fairly low positive predictive value. According to these findings, a critical cut off level of cord bilirubin was 2 mg/dl predicted 90% of newborns who developed jaundice. However, cord bilirubin level < 2 mg/dl did not completely exclude the development of significant hyperbilirubinemia.

Rostami and Mehrabi, found that cord bilirubin above 3 mg/dl is not a useful predictor of jaundice and they concluded that cord bilirubin cannot identify newborns with subsequent significant hyperbilirubinemia. In comparison to these results Suresh and Clark, found that cord bilirubin could predict the development of hyperbilirubinemia in healthy term newborns. This study showed that bilirubin critical level of >2 mg/dl had positive predictive value for detection of developing significant hyperbilirubinemia. Another study done by Rataj et al., showed that critical level in cord blood >2.5 mg/dl had probability of 89% for the development of significant hyperbilirubinemia in newborns.

### Summary and conclusion

The present study was conducted to evaluate the predictive (cut-off) values of umbilical cord bilirubin in identifying infants for subsequent hyperbilirubinemia, in full term and preterm babies.

The study was carried out on 94 healthy newborns (47 FT and 47 PT) from the obstetrics department and NICU of Ismailia General Hospital. Babies were chosen according to specific inclusion and exclusion criteria.

The study group was followed up clinically and by laboratory investigations: total serum bilirubin in umbilical cord was measured at birth, and followed up using transcutaneous bilirubinometry during the first week of life to find out babies developing significant hyperbilirubinemia and in need for treatment.

The results of the study showed that boy’s number was insignificantly higher than the girl’s number. The mean gestational age was 38.70 ± 1.38 weeks in FT compared to 35.62 ± 0.64 in PT. The mean birth weight was 3.302 ± 0.207 Kg in FT compared to 2.936 ± 0.207 Kg in PT. The mean TLC and neutrophil count were significantly higher among PT compared to FT. However there was no statistically significant difference between PT and FT regarding the mean albumin level and retics count.
There was no statistically significant difference in the mean of transcutaneous bilirubin between FT and PT babies at any time of measurement. The peak level of transcutaneous bilirubin in either FT or PT babies was on day 4 of life.

Regarding the needed treatment among study population, it was found that 40.4% of PT and 29.8% of FT needed phototherapy and no one of both groups needed exchange transfusion.

ABO incompatibility was more common than RH incompatibility in all study population.

Total and direct cord bilirubin was slightly higher among FT compared to PT. However these differences were not significant.

The cut off points for total cord bilirubin in PT and FT was 2.05 and 2.15 mg/dl respectively.

The strongest predictor of receiving phototherapy was total cord bilirubin compared to gestational age, ABO incompatibility, RH incompatibility and sex.

The study concluded that the total serum bilirubin in cord blood was indicative of jaundice severity developed by healthy FT and late PT without complications, during the first week of life. Levels that were equal to or greater than 2.05 mg/dl and 2.15 in PT and FT respectively indicate the need for further treatment by phototherapy. In addition, it was also concluded that the presence of mother/baby blood group incompatibility was statistically significant for the occurrence of high total cord bilirubin that was indicative for phototherapy treatment.

**Recommendations**

1. Cord blood bilirubin could be used as an indicator of risk of icterus in newborns.
2. The use of the cut-off cord bilirubin levels of 2.05 mg/dl and 2.15 mg/dl in all healthy late pre-term and full-term newborns respectively could be a useful predictor of significant hyperbilirubinemia that will need phototherapy and avoid the risk of severe hyperbilirubinemia that may need exchange transfusion.
3. Transcutaneous bilirubinometry in the 4th day of life could be used as a screening test to all the same time with screening for hypothyroidism for early detection of severe hyperbilirubinemia.

**Conflict of interest**

There is no conflict of interest.

**References**