An Early (Sixth-Hour) Serum Bilirubin Measurement Is Useful in Predicting the Development of Significant Hyperbilirubinemia and Severe ABO Hemolytic Disease in a Selective High-Risk Population of Newborns With ABO Incompatibility

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ABSTRACT. *Objective.* **In the era of early discharge of newborns from the hospital, newborns with ABO incompatibility are at especially greater risk for developing a subsequent significant hyperbilirubinemia because some of these infants also may present with some degree of ABO isoimmune disease. In this study, we aimed to determine prospectively the critical serum total bilirubin level to predict significant hyperbilirubinemia and severe hemolytic disease in healthy term newborns with ABO incompatibility based on a serum bilirubin measurement made at a postnatal age at which all newborns are at the hospital before discharge and at which any therapeutic intervention, if necessary, could be started as early as possible.**

Methods. **A total of 136 healthy term newborns with ABO (O-A or O-B) blood group incompatibility were followed prospectively with daily serum total bilirubin measurements for the first 5 days of life. Newborns with serum total bilirubin levels of ≥5 mg/dL and an increase in serum total bilirubin concentration of >0.5 mg/dL/h in the first 24 hours, ≥12 mg/dL on day 2, ≥15 mg/dL on day 3, and ≥17 mg/dL on days 4 and 5 were defined to have significant hyperbilirubinemia and were started on phototherapy treatment. Additional treatment modalities, including intense phototherapy, intravenous immunoglobulin treatment, and exchange transfusion, were used when serum bilirubin concentrations exceeded 20 mg/dL or increased by >1 mg/dL/h despite a phototherapy treatment of at least 4 hours. The additional assessment of the predictive ability of the sixth-hour serum total bilirubin value in determining the development of significant hyperbilirubinemia was made on the basis of the placement of any of the first 5 days' serum bilirubin measurements in the ≥90th percentile of the study population. On the basis of the percentile tracks constructed from the 10th, 35th, 50th, 60th, and 90th percentiles of serum total bilirubin values, a nomogram demonstrating the 3 percentile tracks as risk zone demarcators with divided risk zones was produced.**

Results. **Twenty-nine newborns (21.3%) had significant hyperbilirubinemia. There were significant differences between the newborns who did and the newborns who did not develop significant hyperbilirubinemia with respect to the reticulocyte count (4.39 ± 3.46% vs 2.95 ± 1.63) and the presence of a direct antiglobulin test positivity (6 of 23 vs 0 of 107) and a sibling with neonatal jaundice (6 of 23 vs 5 of 102). A mean serum bilirubin level of ≥4 mg/dL at the sixth hour of life was determined to have the highest sensitivity (86.2%) and negative predictive value (94.5%) and a positive predictive value of 39.7% to predict the newborns who would develop significant hyperbilirubinemia. At the mean serum bilirubin level of 6 mg/dL, the sensitivity, specificity, and negative and positive predictive values were 100%, 91.5%, 100%, and 35.3%, respectively, in diagnosing 6 cases of severe ABO hemolytic disease. On the hour (age)-specific percentile-based nomogram, the zone above the 90th percentile was determined as high risk and that below the 35th percentile as low risk.**

Conclusions. **The reticulocyte count, a positive direct antiglobulin test, and the presence of a sibling with neonatal jaundice were determined to be the good predictors for the development of significant hyperbilirubinemia and severe hemolytic disease of the newborn. A serum bilirubin measurement and the use of the critical bilirubin levels of 4 mg/dL and 6 mg/dL at the sixth hour of life will predict nearly all newborns who will have significant hyperbilirubinemia and those who will develop severe hemolytic disease of the newborn, respectively. An hour (age)-specific percentile-based nomogram can be used to predict which newborn is at high risk (≥90th percentile), intermediate risk (35th–90th percentiles), and low risk (<35th percentile) for developing significant hyperbilirubinemia. The 35th and 90th percentile tracks, approximating the serum bilirubin levels of 3.3 mg/dL and 6.5 mg/dL at the sixth hour of life, respectively, can be used as safe risk demarcators in deciding about the time of discharge of ABO-incompatible newborns from the hospital.** *Pediatrics* **2002;109(4). URL: http://www.pediatrics.org/cgi/content/full/109/4/e53; *ABO incompatibility, early discharge, hyperbilirubinemia, newborn, prediction.***

ABBREVIATION. ROC, receiver operating characteristic.

Discharging healthy term newborns from the hospital after delivery at increasingly earlier postnatal ages has recently become a common practice for medical, social, and economic reasons. However, it has been shown that newborns whose postdelivery hospital stay is ≤72 hours are at a significantly greater risk for readmission than those whose stay is >72 hours.[1–5] Hyperbilirubinemia is

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the most commonly reported cause for readmission during the early neonatal period,[1–3,5–9] and 0.36% of healthy term newborns discharged after 72 hours of life with no more than mild hyperbilirubinemia may even develop a subsequent moderate to severe hyperbilirubinemia.[6] In the United States, there were 22 reported cases of kernicterus developing after discharge within 48 hours of birth between 1991 and 1995.[10] Furthermore, the safety of relying on follow-up visits after early discharge is questionable because 10% of the population fails to return for a follow-up visit.[11] Thus, a few recent studies, most of which did not include cases of ABO and/or Rh incompatibility, investigated the value of first-day bilirubin measurement in predicting the subsequent development of significant hyperbilirubinemia in healthy term newborns,[12–15] because early prediction and detection of threatening bilirubin levels permit initiation of phototherapy and prevent higher risks and cost of other therapies and kernicterus.

ABO incompatibility occurs in 15% to 20% of all pregnancies and produces a spectrum of hemolytic disease, the extreme end of which is recognized as ABO hemolytic disease.[16] Several cord blood parameters have been studied in an attempt to anticipate the clinical course of a newborn with ABO incompatibility; however, to our knowledge, no study has evaluated the usefulness of first-day bilirubin measurement in predicting the subsequent clinical course and development of significant hyperbilirubinemia in newborns who have ABO incompatibility and are at relatively greater risk for having a severe jaundice.

In this study, we therefore investigated the value of first-day (sixth-hour) bilirubin measurement in predicting the development of significant hyperbilirubinemia later during the first days of life in a selective high-risk population of newborns with ABO incompatibility by measuring serum bilirubin levels daily for the first 5 days of life.

METHODS

This study was performed at the Division of Neonatology of Hacettepe University Faculty of Medicine between June 2000 and March 2001. All healthy full-term (≥38 weeks' gestation) newborns with blood group system of groups A or B born to mothers with blood group O without a simultaneous Rhesus blood factor incompatibility at this hospital through this period were enrolled prospectively in the study.

Hematocrit and reticulocyte counts, blood group including Rhesus, a direct antiglobulin (Coombs) test, glucose-6-phosphate dehydrogenase activity, and serum direct and indirect bilirubin levels were performed routinely in all cases. Serum total bilirubin measurements were initially made at the sixth hour of life and were repeated daily for the next 4 days; each measurement was performed just 24 hours after the previous measurement. Newborns with serum total bilirubin levels of ≥5 mg/dL and an increase in serum total bilirubin concentration of >0.5 mg/dL/h in the first 24 hours, ≥12 mg/dL on day 2, ≥15 mg/dL on day 3, and ≥ 17 mg/dL on days 4 and 5 were defined to have significant hyperbilirubinemia[17] and were started on phototherapy treatment. Additional treatment modalities, including intense phototherapy,[18] intravenous immunoglobulin treatment,[19] and exchange transfusion, were used when serum bilirubin concentrations exceeded 20 mg/dL or increased by >1 mg/dL/h despite a phototherapy treatment of at least 4 hours. In all cases, gender; birth weight; gestational age; delivery route; feeding pattern; maternal age; Apgar scores; whether the mother smoked or had any chronic diseases (hypertension, diabetes mellitus, etc) before or during gestation; and whether there was enclosed hemorrhage, abnormal weight loss, or any siblings with neonatal jaundice were recorded. Informed consent was obtained from all parents of the newborns in the study.

Statistical data were analyzed with the independent sample t test and the descriptive analysis and χ^2 tests. The critical serum total bilirubin levels measured at the sixth hour of life with different sensitivity and specificity values were determined with the receiver operating characteristic (ROC) curve analysis. The additional assessment of the predictive ability of the sixth-hour serum total bilirubin value in determining the development of significant hyperbilirubinemia was made on the basis of the placement of any of the first 5 days' serum bilirubin measurements in the ≥90th percentile of the study population. A Gaussian distribution curve was obtained by determining the distribution of the population according to the mean serum total bilirubin values measured at the specific hours (daily serum bilirubin measurements). The 10th, 35th, 50th, 60th, and 90th percentiles of serum total bilirubin values were determined from the Gaussian distribution and connected as percentile tracks. On the basis of the percentile tracks, which give the highest sensitivity, specificity, and negative and positive predictive values, a nomogram demonstrating the 3 percentile tracks as risk zone demarcators with divided risk zones was produced. The zone above the 90th percentile was labeled as high risk, and that below the 35th percentile was labeled as low risk. Serum total bilirubin values between the 35th and 90th percentiles were designated as being in the intermediate-risk zone; this zone was subdivided further by the 60th percentile into high- and low-intermediate risk zones.

RESULTS

A total of 150 newborns were initially enrolled in the study, but 14 of these were excluded during the study because some of them were transferred to our neonatal intensive care unit as a result of various diagnoses or because some of the parents did not want to continue participating in the study. During the study period, 1014 full-term infants were born, and the incidence of ABO (O-A and O-B) incompatibility was 14.8%.

Twenty-nine newborns (21.3%) had significant hyperbilirubinemia with any of the 5 days' serum bilirubin levels exceeding the threshold levels defined for phototherapy. When the first 5 days' mean bilirubin levels of the newborns who did and the newborns who did not develop significant hyperbilirubinemia were compared, the newborns who later developed significant hyperbilirubinemia had significantly higher bilirubin levels on each day (Table 1).

Demographic characteristics of the newborns who did and the newborns who did not develop significant hyperbilirubinemia are shown in Table 2. Various factors that may be associated with the risk of developing hyperbilirubinemia, including hematocrit, type of ABO blood group incompatibility (O-A or O-B), gender, birth weight, gestational age, maternal smoking, delivery route, feeding pattern, enclosed hemorrhage, and abnormal weight loss at the end of 5 days, did not significantly differ, whereas the reticulocyte count and the presence of a direct antiglobulin test positivity and a sibling with neonatal jaundice were significantly different between the newborns who did and the newborns who did not develop significant hyperbilirubinemia (Table 2).

With a ROC analysis, a mean serum bilirubin level of ≥4 mg/dL at the sixth hour of life was determined to have the highest sensitivity (86.2%) to predict the newborns who would develop significant hyperbilirubinemia (Fig 1). At this critical mean serum bilirubin level, the negative predictive value was very

TABLE 1. First 5 Days' Bilirubin Levels of the Newborns Who Did and Who Did Not Develop Significant Hyperbilirubinemia*

	Day 1	Day 2	Day 3	Day 4	Day 5
Newborns with significant hyperbilirubinemia (n = 29)	6.0 ± 2.08 (5.21–6.79)	11.0 ± 2.71 (9.96–12.03)	14.64 ± 2.75 (13.6–15.69)	15.93 ± 2.14 (15.11–16.74)	15.98 ± 2.82 (14.91–17.06)
Newborns without significant hyperbilirubinemia (n = 107)	3.63 ± 1.0 (3.44–3.82)	7.09 ± 2.05 (6.69–7.48)	9.59 ± 2.65 (9.08–10.09)	10.85 ± 3.36 (10.21–11.5)	10.88 ± 3.81 (10.15–11.61)
P value	<.001	<.001	<.001	<.001	<.001

* Values (bilirubin, mg/dL) are given as mean ± standard deviation with 95% confidence interval.

TABLE 2. Demographic Characteristics of Newborns Who Did and Who Did Not Develop Significant Hyperbilirubinemia

Demographics	Newborns With Significant Hyperbilirubinemia (n = 29)	Newborns Without Significant Hyperbilirubinemia (n = 107)	P Value
Hematocrit (%)*	55.38 ± 6.47	57.05 ± 3.8	.193
Reticulocyte (%)*	4.39 ± 3.46	2.95 ± 1.63	.037
Direct antiglobulin test (positive/negative)	6/23	0/107	<.001
Type of ABO blood group incompatibility (O-A/O-B)	21/8	70/37	.478
Gender (male/female)	15/14	54/53	.904
Gestational age (wk)*	39.21 ± 1.18	39.45 ± 1.18	.759
Apgar score*	9.52 ± 0.69	9.62 ± 0.72	.507
Enclosed hemorrhage (present/absent)	1/28	2/105	.516
Birth weight (g)*	3214 ± 828	3212 ± 196	.975
Delivery mode (vaginal/cesarean)	15/14	59/48	.743
Abnormal (≥10%) weight loss at the end of first 5 d (present/absent)	4/25	13/94	.759
Any sibling with neonatal jaundice (present/absent)	6/23	5/102	.012
Maternal age (y)*	29.76 ± 5.9	28.96 ± 5.5	.498
Feeding pattern			
Breast milk	25	96	.690
Formula milk	—	1	
Partially breast milk	4	10	
Maternal chronic disease acquired before or during gestation (present/absent)	1/28	6/101	.538
Maternal gestational smoking (present/absent)	2/27	9/98	.572

* Values are given as mean ± standard deviation.

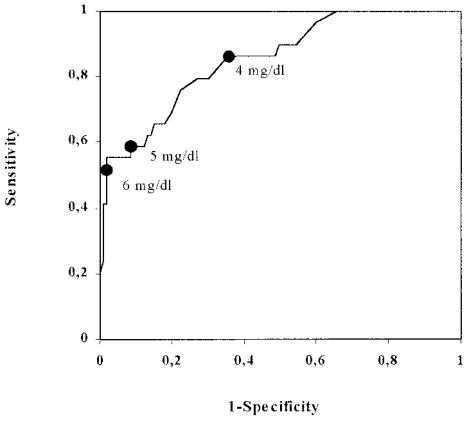

Fig 1. The ROC analysis of the various serum bilirubin levels at the sixth hour of life in predicting the development of significant hyperbilirubinemia during the first 5 days of life.

high (94.5%) and the positive predictive value was 39.7% (Table 3). Of the 63 newborns who had a serum total bilirubin level of ≥4 mg/dL at the sixth hour of life, 25 (39.7%) subsequently developed significant hyperbilirubinemia, whereas only 4 of the 73 newborns (5.5%) who had a serum total bilirubin level of <4 mg/dL at the sixth hour developed significant hyperbilirubinemia later during the first 5 days of life (Fig 2, Table 3).

During the study period, 6 of the 29 newborns who underwent phototherapy as a result of significant hyperbilirubinemia had increasing serum bilirubin levels despite phototherapy, and these newborns were administered additional treatment modalities: intense phototherapy and intravenous immunoglobulin (n = 5) and plus exchange transfusion (n = 1). All of these newborns had higher bilirubin levels and reticulocyte counts than the other newborns; all had a positive direct antiglobulin test, and 5 of 6 had a sibling with neonatal jaundice. These newborns thus were deemed to have severe hemolytic disease as a result of ABO incompatibility. Of the 119 newborns who had a serum bilirubin level of <6 mg/dL at the sixth hour of life, 14 underwent phototherapy for developing significant hyperbilirubinemia, and none of these required any of the additional treatment modalities. In contrast, of the 17 newborns who had a serum bilirubin level of ≥6 mg/dL at the sixth hour of life, only 2 newborns did not develop significant hyperbilirubinemia, and of the 15 newborns who underwent phototherapy, 6 required at least 1 of the additional treatment modalities. At the mean serum bilirubin level of 6 mg/dL at the sixth hour of life, the sensitivity, specificity, and negative and positive predictive values were 100%, 91.5%, 100%, and 35.3%, respectively, in diagnosing severe hemolytic disease of the newborn as a result of ABO incompatibility.

In an additional assessment of the predictive ability of the sixth-hour serum bilirubin value in determining the development of significant hyperbilirubinemia on an hour (age)-specific percentile-based

TABLE 3. Sensitivity, Specificity, and Positive and Negative Predictive Values of Various Serum Bilirubin Levels at the Sixth Hour of Life in Predicting the Development of Significant Hyperbilirubinemia*

Serum Bilirubin Level at the Sixth Hour	False-Negatives (*n* [%])	True-Positives (*n* [%])	True-Negatives (*n* [%])	False-Positives (*n* [%])	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
4 mg/dL	4 (2.9) (0.1–5.7)	25 (18.4) (11.9–24.9)	69 (50.7) (42.3–59.1)	38 (27.9) (20.3–35.4)	86.2	64.5	39.7	94.5
5 mg/dL	12 (8.8) (4.0–13.5)	17 (12.5) (16.9–18.1)	97 (71.3) (63.7–78.9)	10 (7.4) (3.0–11.8)	58.6	90.7	62.9	89.0
6 mg/dL	14 (10.3) (5.2–15.4)	15 (11.0) (5.7–16.3)	105 (77.2) (70.1–84.2)	2 (1.5) (0–3.5)	51.7	98.1	88.2	88.2

* Values in parantheses indicate the lower and upper bounds of the 95% confidence interval.

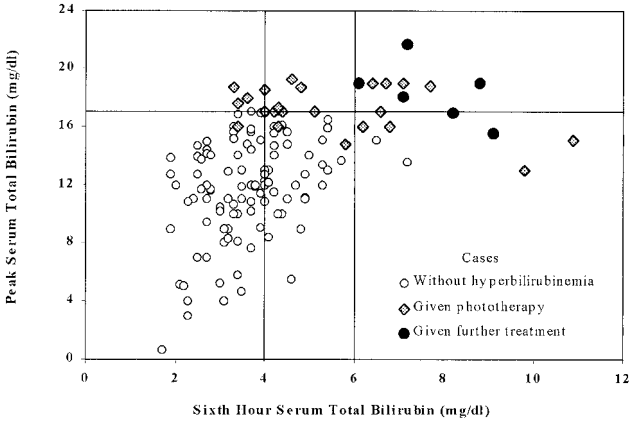

Fig 2. The schematic representation of the relationship between the sixth-hour critical serum bilirubin levels of 4 mg/dL and 6 mg/dL and the development of significant hyperbilirubinemia requiring phototherapy and an additional treatment modality.

nomogram, the 35th, 60th, and 90th percentile tracks determined by means of the highest sensitivity, specificity, and negative and positive predictive values were used as risk zone demarcators (Fig 3, Table 4). Serum total bilirubin levels of ≥10.7 mg/dL at 24 hours, ≥14.2 mg/dL at 48 hours, and ≥16.5 mg/dL at 72 hours of age were above the 90th percentile for postnatal age in hours.

The critical serum total bilirubin levels of 3.3 mg/dL and 6.5 mg/dL at the sixth hour of life had the highest (100%) sensitivity and specificity, respectively, thus approximating the 35th and 90th percentiles on the nomogram, respectively (Fig 3, Table 4).

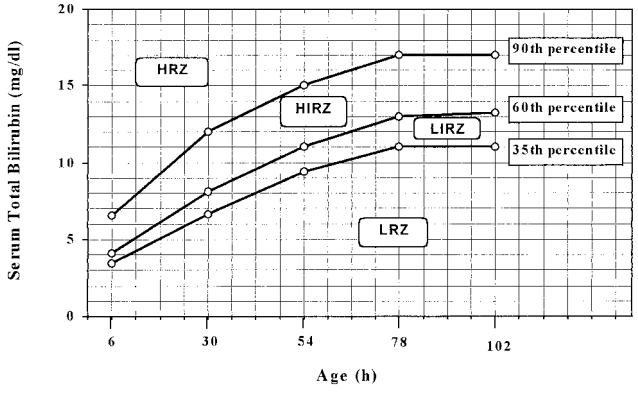

Fig 3. Risk designation of newborns according to the percentile tracks based on the age-specific serum bilirubin values. HRZ, high-risk zone designated above the 90th percentile track; HIRZ, high intermediate-risk zone between the 60th and 90th percentiles; LIRZ, low intermediate-risk zone between the 60th and 35th percentiles; LRZ, low-risk zone below the 35th percentile track.

DISCUSSION

Considering that severe jaundice and kernicterus can occur in even some full-term healthy newborns with no apparent hemolysis or jaundice in the first 24 hours of life,[20,21] the prediction of a probable future hyperbilirubinemia in newborns discharged from the hospital in the era of early discharge gains much more importance than ever. Although various parameters, including cord blood bilirubin and antiglobulin test and maternal isoimmune antibody titers, have been studied to predict the clinical course of a newborn with ABO incompatibility,[22,23] the development and severity of a subsequent hyperbilirubinemia or isoimmune disease remain difficult to anticipate because there is no test that is of high predictive value.[24] We therefore aimed in this study to determine prospectively the critical serum total bilirubin level to predict significant hyperbilirubinemia and severe hemolytic disease in healthy term newborns with ABO incompatibility on the basis of a serum bilirubin measurement made at a postnatal age at which all newborns are at the hospital before discharge and at which any therapeutic intervention, if necessary, could be started as early as possible or appropriate follow-up programs could be implemented in the high-risk groups in the absence of possibility of early treatment modalities.

The incidences of ABO incompatibility (14.8%), significant hyperbilirubinemia in ABO incompatibility (21.3%), and severe hemolytic disease of the newborn as a result of ABO incompatibility (4.4%) in this study population of infants with type O-A and type O-B incompatibility were reportedly in accordance with the incidence and epidemiology of ABO incompatibility.[16,25] The incidence of significant hyperbilirubinemia in our study (21.3%) is much higher than that reported in the general population.[13–15] This may be attributable to the ethnic and geographic characteristics of our population, because a previous study performed on healthy term Turkish newborns[12] also showed a higher incidence of significant hyperbilirubinemia (12.05%) than that reported in other parts of the world. In that previous study performed in Ankara,[12] 498 full-term newborns were followed prospectively during the first 5 days of life, and the critical serum bilirubin level of 6 mg/dL

TABLE 4. Sensitivity, Specificity, and Positive and Negative Predictive Values of the Percentile Tracks as Risk Demarcators in Predicting the Development of Significant Hyperbilirubinemia*

Percentile Track as Risk Demarcator	False-Negatives (*n* [%])	True-Positives (*n* [%])	True-Negatives (*n* [%])	False-Positives (*n* [%])	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
90th percentile	17 (12.5) (6.9–18.0)	12 (8.8) (4.0–13.6)	106 (77.9) (70.9–84.9)	1 (0.7) (0–2.1)	41.4	99.0	92.3	86.2
60th percentile	6 (4.4) (0.9–7.8)	23 (16.9) (10.6–23.2)	78 (57.4) (49.1–65.7)	29 (21.3) (14.4–28.2)	79.3	72.9	44.2	92.9
35th percentile	0 (0) (0–0)	29 (21.3) (14.4–28.2)	43 (31.6) (23.8–39.4)	64 (47.1) (38.7–55.5)	100	40.2	31.2	100

* Values in parantheses indicate the lower and upper bounds of the 95% confidence interval.

measured in the first 24 hours (6.2–21.4) of life had the highest sensitivity (90%) and negative predictive value (97.9%) in determining the newborns who would have significant hyperbilirubinemia and the newborns who would require phototherapy treatment. When we compared the newborns with significant hyperbilirubinemia in the 2 studies conducted in the same region of Turkey, the critical serum bilirubin level that had the highest sensitivity and negative predictive value in the present study was lower than that in the previous study (4 mg/dL vs 6 mg/dL), although the first serum bilirubin measurement was not made at a uniform hour in that study. This difference must be attributable to the higher incidence of significant hyperbilirubinemia in the present study (21.3% vs 12.05%) resulting from the risk of ABO incompatibility. When we compared the newborns who did not have significant hyperbilirubinemia in these 2 studies, the first 5 days' mean serum bilirubin levels (5.04 ± 1.79 mg/dL, 7.85 ± 2.41 mg/dL, 10.09 ± 1.13 mg/dL, 11.37 ± 2.82 mg/dL, 12.46 ± 2.03 mg/dL, respectively) in the previous study[12] were very similar to those in the present study. Nevertheless, the mean serum bilirubin levels of the newborns with significant hyperbilirubinemia and of the newborns without significant hyperbilirubinemia in both studies performed in Central Anatolia were significantly higher than those reported in other regions of the world, further confirming the possible role of ethnic and geographic characteristics of the population in the development of hyperbilirubinemia. Bhutani et al,[13] in their first study, prospectively followed 1097 newborns during the first 5 days of life and reported an incidence of 4.6% for significant hyperbilirubinemia (≥17 mg/dL). According to the serum bilirubin levels measured at 20 to 28 hours of life, the critical serum bilirubin levels of 5 mg/dL and 6 mg/dL had the highest sensitivity (100%) and specificity (80.1%), respectively.

In the present study, 6 newborns were considered to have severe ABO hemolytic disease because they met several of the hemolysis criteria, such as early onset hyperbilirubinemia, a positive direct antiglobulin test, and reticulocytosis, and because they did not respond to initial phototherapy treatment. However, if we defined ABO hemolytic disease with a single criterion, jaundice in the first 24 hours, reportedly being as one of the most important hallmarks of hemolytic disease of the newborn as a result of ABO incompatibility,[26] then we would have a total of 17 cases with ABO hemolytic disease, although not all of them were severe, because they all had a serum bilirubin level of ≥6 mg/dL at the sixth hour of life.

Seidman et al[14] also followed 1177 term newborns during the first 5 days of life by measuring serum bilirubin levels daily. Their first bilirubin measurement time was between 8 and 24 hours of life, and their threshold levels for defining significant hyperbilirubinemia were similar (total serum bilirubin of >10 mg/dL on day 2, >14 mg/dL on day 3, and >17 mg/dL on days 4 and 5 of life) to the criteria that we used in our study. In their study, the risk of significant hyperbilirubinemia was 5.1% and the critical serum bilirubin level of 5 mg/dL was reported to have the sensitivity and specificity of 63.1% and 94.2%, respectively, for detecting significant hyperbilirubinemia. According to our findings, 86.2% of the newborns who later developed significant hyperbilirubinemia had a sixth-hour serum bilirubin level of ≥4 mg/dL and 64.5% of newborns who later did not develop significant hyperbilirubinemia had a sixth-hour serum bilirubin level of <4 mg/dL.

In a previous study that constructed a similar percentile-based nomogram in 2840 newborns,[15] significant hyperbilirubinemia was defined as the presence of any total serum bilirubin level reaching into the high-risk zone (≥95th percentile track), and the predictive ability of the 40th percentile track as the risk demarcator had the highest (100%) sensitivity and negative predictive value. To define risk groups for hyperbilirubinemia according to the percentiles of the study population, to make it possible making an instantaneous evaluation of the risk status on an age-specific basis without the need to follow any newborn for respective days, and to detect the critical serum bilirubin levels that had the highest (100%) sensitivity and specificity, we constructed an age (hour)-specific percentile-based bilirubin nomogram from our data. On this age-specific nomogram, the 35th percentile (serum bilirubin of 3.3 mg/dL at the sixth hour of life) and 90th percentile (serum bilirubin of 6.5 mg/dL at the sixth hour of life) had the highest (100%) sensitivity and negative predictive value, and the highest (99%) specificity, respectively. These findings indicate that newborns who will later develop significant hyperbilirubinemia have serum bilirubin levels above the 35th percentile track (≥3.3 mg/dL at the sixth hour of age), and most newborns with serum bilirubin levels below the 35th percentile track (<3.3 mg/dL at the sixth hour of age) will not have significant hyperbilirubinemia.

Two findings of hemolysis (reticulocytosis and a

positive direct antiglobulin test) and the history of a sibling who had jaundice in the neonatal period were significantly more prominent in the newborns who later required phototherapy treatment in the present study. In analysis of the consecutive pregnancies of 230 primigravid mothers whose first offspring had hemolytic disease of the newborn as a result of ABO incompatibility, ABO hemolytic disease recurred in 88% of their next offspring who had incompatibility, and 62% of these required treatment.[27]

The reticulocyte count, a positive direct antiglobulin test, and the presence of a sibling with neonatal jaundice were determined to be the good predictors for the development of significant hyperbilirubinemia and severe hemolytic disease of the newborn in a selective high-risk population of full-term healthy newborns with ABO incompatibility in this study. A serum bilirubin measurement and the use of the critical bilirubin levels of 4 mg/dL and 6 mg/dL at the sixth hour of life will predict nearly all newborns who will have significant hyperbilirubinemia and those who will develop severe hemolytic disease of the newborn, respectively. To make a more sensitive and more specific evaluation considering the percentile distribution of serum bilirubin levels for postnatal age, an hour (age)-specific percentile-based nomogram constructed from daily serum bilirubin values of newborns followed during the first 5 days of life can be used to predict which newborn is at high risk (≥90th percentile), intermediate risk (35th–90th percentiles), and low risk (<35th percentile) for developing significant hyperbilirubinemia. According to age-specific nomogram determined in this study, 35th and 90th percentile tracks, approximating the serum bilirubin levels of 3.3 mg/dL and 6.5 mg/dL at the sixth hour of life, respectively, can be used as safe risk demarcators in deciding about the time of discharge of ABO-incompatible newborns from the hospital. However, results of the present study should be confirmed in additional studies that include larger numbers of newborns with significant hyperbilirubinemia and hemolytic disease of the newborn.

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