

The Value of First-Day Bilirubin Measurement in Predicting the Development of Significant Hyperbilirubinemia in Healthy Term Newborns

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ABSTRACT. *Objective.* The recognition, follow-up, and early treatment of neonatal jaundice has become more difficult, since the earlier discharge of newborns from hospitals has become common practice. This prospective study was undertaken to identify the newborns at risk for developing significant hyperbilirubinemia later during the first days of life by measuring the serum bilirubin levels of the first 5 days of life to determine the critical predictive serum bilirubin value on the first day of life.

Methodology. A total of 498 healthy term newborns were followed with daily serum total bilirubin measurements for the first 5 days of life, and cases with serum bilirubin levels of ≥ 17 mg/dL after 24 hours of life were defined to have significant hyperbilirubinemia.

Results. No newborns had a serum total bilirubin level of ≥ 17 mg/dL in the first 72 hours of life. Sixty of 498 cases (12.05%) had significant hyperbilirubinemia after 72 hours of life, and these cases had significantly higher bilirubin levels than those who did not develop significant hyperbilirubinemia on each of the first 5 days' measurements. Of the 206 newborns who had a serum bilirubin level of ≥ 6 mg/dL in the first 24 hours, 54 (26.21%) developed significant hyperbilirubinemia, whereas only 6 of the 292 newborns (2.05%) who had a serum bilirubin level of < 6 mg/dL on the first day developed significant hyperbilirubinemia. A mean serum bilirubin level of ≥ 6 mg/dL on the first day had the highest sensitivity (90%). At this critical serum bilirubin value, the negative predictive value was very high (97.9%) and the positive predictive value was fairly low (26.2%). Furthermore, because no cases with a serum bilirubin level of < 6 mg/dL in the first 24 hours of life required a subsequent phototherapy treatment and because all of those infants requiring a phototherapy treatment with serum bilirubin levels of ≥ 20 mg/dL were just among the cases whose first-day bilirubin levels were ≥ 6 mg/dL, the critical bilirubin level of 6 mg/dL on the first day made it possible, with the highest (100%) sensitivity and negative predictive value, to definitely predict all of the infants who would have a bilirubin level of > 20 mg/dL, requiring a phototherapy treatment later during the first days of life.

Conclusions. A serum bilirubin measurement and the use of the critical bilirubin level of 6 mg/dL in the first 24 hours of life will predict nearly all of the term newborns

who will have significant hyperbilirubinemia and will determine all those who will require a phototherapy treatment later during the first days of life. *Pediatrics* 2000;106(2). URL: <http://www.pediatrics.org/cgi/content/full/106/2/e16>; early discharge, jaundice, newborn, prediction, significant hyperbilirubinemia.

ABBREVIATION. ROC, receiver operating characteristic.

Early discharge of healthy term newborns after delivery has become a common practice because of medical and social reasons and economic constraints.¹⁻⁴ However, an association between the decreased length of stay and the risk of readmission to the hospital has previously been shown,^{5,6} and it is significant that the most common cause for readmission during the early neonatal period is hyperbilirubinemia.⁵⁻⁷ Thus, the recognition, follow-up, and early treatment of jaundice has become more difficult as a result of earlier discharge from the hospital. Severe jaundice, and even kernicterus, can occur in some full-term healthy newborns discharged early with no apparent early findings of hemolysis.⁸ Therefore, it is difficult to predict which infants are at increased risk for significant and relatively late hyperbilirubinemia, and there is an obvious need to implement follow-up programs or to develop predictive guidelines that will enable the physicians to predict or to identify which of the early discharged newborns will develop significant hyperbilirubinemia.

In this study, we aimed to identify the newborns at risk for developing significant hyperbilirubinemia later during the first days of life by measuring serum bilirubin levels daily for the first 5 days of life to determine the critical predictive serum bilirubin value on the first day of life.

METHODS

This study was performed at the Department of Pediatrics of Gülhane Military Medical Academy between December 1997 and May 1998. All healthy full-term (≥ 38 weeks of gestation) newborns born at this hospital during this period were prospectively enrolled in the study. Infants with blood group system of groups A, AB, B, and O or Rhesus blood factor incompatibility and a positive direct antiglobulin test result or a glucose-6-phosphate dehydrogenase deficiency were not included in the study.

Complete blood, reticulocyte and differential counts; blood group including Rhesus; a direct antiglobulin test; glucose-6-phosphate dehydrogenase activity; hepatic and renal function; serum direct and indirect bilirubin levels; and C-reactive protein deter-

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minations were performed routinely in all cases. Serum total bilirubin measurements were initially made within the first 24 hours of life (mean: 17.1 hours; range: 6.2–21.4 hours) and were repeated daily for the next 4 days, performing each measurement just 24 hours after the previous measurement. Newborns with serum total bilirubin levels of ≥ 17 mg/dL after 24 hours of life were defined to have significant hyperbilirubinemia, and these cases underwent phototherapy treatment if their bilirubin levels exceeded 20 mg/dL on follow-up. Serum total bilirubin levels at entry into and during the study were measured with direct spectrophotometry (Bilirubin Analyser Bil Micro Meter, Kohsoku Denki Co, Ltd, Tokyo, Japan) in capillary blood samples obtained by a heel stick. In all cases, gender, birth weight, gestational age, delivery route, feeding pattern, maternal age, Apgar scores, whether the mother had smoked or acquired any chronic diseases (hypertension, diabetes mellitus, etc) during gestation, and whether there were any siblings with neonatal jaundice and neonatal enclosed hemorrhage or abnormal weight loss were recorded. Informed consent was obtained from all parents of the newborns enrolled 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 level measured in the first 24 hours of life having the highest sensitivity was determined with the receiver operating characteristic (ROC) curve analysis.

RESULTS

A total of 525 newborns were initially enrolled in the study, but 27 of these were excluded during the study because of various diagnoses, such as hypothyroidism, neonatal hepatitis, duodenal atresia, direct hyperbilirubinemia, and infection or sepsis, or because some of the parents did not want to continue participating in the study.

No newborns had a serum total bilirubin level of ≥ 17 mg/dL in the first 72 hours of life. Sixty of 498 newborns (12.05%) followed for 5 days had serum total bilirubin levels of ≥ 17 mg/dL after 72 hours of life. When the first 5 days' mean bilirubin levels of the cases who did and who did not develop significant hyperbilirubinemia were compared, the cases who later developed significant hyperbilirubinemia had significantly higher bilirubin levels on each day (Table 1).

With ROC analysis, a mean serum bilirubin level of ≥ 6 mg/dL in the first 24 hours of life was determined to have the highest sensitivity (90%) to predict the newborns who would develop significant hyperbilirubinemia (Fig 1). At this critical mean serum bilirubin level, the negative predictive value was very high (97.9%) and the positive predictive value was fairly low (26.2%; Table 2). Of the 206 newborns who had a serum total bilirubin level of ≥ 6 mg/dL in the first 24 hours of life, 54 (26.21%) developed significant hyperbilirubinemia after 72 hours of life, whereas only 6 of the 292 newborns (2.05%) who had

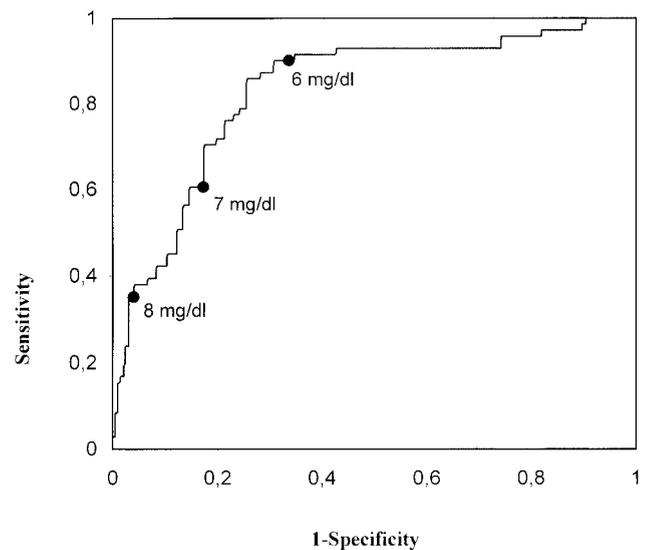


Fig 1. The ROC analysis of the various serum bilirubin levels on the first day of life in predicting the development of subsequent significant hyperbilirubinemia.

a serum total bilirubin level of < 6 mg/dL on the first day developed significant hyperbilirubinemia later on the fourth and fifth days of life (Fig 2; Table 2).

There were no significant differences between the cases who did and who did not develop significant hyperbilirubinemia with respect to various factors that may be associated with the risk of hyperbilirubinemia, such as hemoglobin level, gender, gestational age, birth weight, delivery route, feeding pattern, and maternal smoking (Table 3).

There were also no significant differences between the clinical characteristics of the cases who had a serum total bilirubin of ≥ 6 mg/dL and of < 6 mg/dL in the first 24 hours of the study (Table 4).

On follow-up, a total of 14 newborns had serum bilirubin levels exceeding 20 mg/dL on the fourth and fifth days of life. Of the 292 newborns who had a serum bilirubin level of < 6 mg/dL in the first 24 hours of life, 6 developed significant hyperbilirubinemia, but none of these cases had peak bilirubin levels of > 20 mg/dL. In contrast, of the 54 cases who developed significant hyperbilirubinemia among the 206 newborns with a serum bilirubin level of ≥ 6 mg/dL in the first 24 hours of life, 14 had peak serum bilirubin levels exceeding 20 mg/dL, and these cases received phototherapy treatment (Fig 2). At the mean serum bilirubin level of 6 mg/dL in the first 24 hours of life, the sensitivity and negative predictive value

TABLE 1. The First Five Days' Bilirubin Levels of the Cases Who Did and Who Did Not Develop Significant Hyperbilirubinemia (≥ 17 mg/dL) After 72 Hours of Age*

	Day 1	Day 2	Day 3	Day 4	Day 5
Significant hyperbilirubinemia (<i>n</i> = 60)	7.17 \pm 1.57 (6.76–7.58)	10.95 \pm 1.78 (10.42–11.35)	13.7 \pm .81 (13.31–14.14)	18.86 \pm 1.79 (18.14–19.58)	18.75 \pm 1.94 (18.06–19.44)
Insignificant hyperbilirubinemia (<i>n</i> = 438)	5.04 \pm 1.79 (4.87–5.22)	7.85 \pm 2.41 (7.62–8.08)	10.09 \pm 1.13 (9.79–10.38)	11.37 \pm 2.82 (10.91–11.83)	12.46 \pm 2.03 (11.95–12.97)
<i>P</i> Value	$<.01$	$<.01$	$<.01$	$<.01$	$<.01$

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

TABLE 2. Sensitivity, Specificity, and Positive and Negative Predictive Values of Various Serum Bilirubin Levels in the First 24 Hours of Life in Predicting the Development of Significant Hyperbilirubinemia

Serum Bilirubin Level in the First 24 Hours	False-Negatives <i>n</i> (%)	True-Positives <i>n</i> (%)	True-Negatives <i>n</i> (%)	False-Positives <i>n</i> (%)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
≥6 mg/dL	6 (1.2)	54 (10.9)	286 (57.4)	152 (30.5)	90	65.3	26.2	97.9
≥7 mg/dL	24 (4.8)	36 (7.2)	363 (72.9)	75 (15.1)	60	82.9	32.4	93.8
≥8 mg/dL	39 (7.9)	21 (4.2)	413 (82.9)	25 (5.0)	35	94.3	45.7	91.4

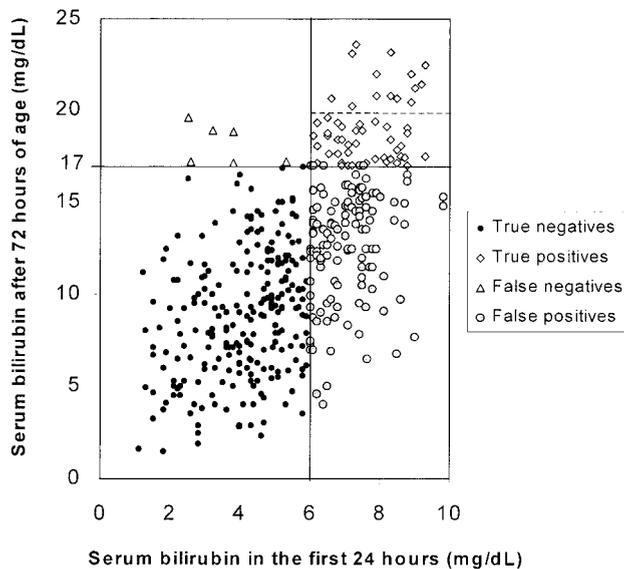


Fig 2. The schematic representation of the relationship between the first day critical bilirubin level of 6 mg/dL and the development of significant hyperbilirubinemia. (The true positives above the dashed line indicate the cases requiring a phototherapy treatment.)

were very high in predicting the subsequent need of a phototherapy treatment (Table 5).

DISCUSSION

Although there has been a decrease in the length of postdelivery hospital stays for newborns and their mothers in recent years, there is still much controversy about when, early (<48 hours after delivery) or late (>72 hours after delivery), a mother-child dyad should be discharged. Opponents of the early discharge suggest that various risks, such as hyperbilirubinemia; breast-feeding difficulties and feeding problems leading to dehydration and malnutrition; missed identification of congenital anomalies and newborn screening; readmission, and maternal postpartum cognitive deficits, are all associated with early discharge.⁹⁻¹² In contrast, proponents of the early discharge regard it as safe and advantageous because of various medical, social, and economic reasons.^{1-4,13} Although an influencing effect of early discharge on morbidity and mortality of the newborns has not been established yet, and first studies have not demonstrated any adverse outcomes or any increased readmission risks of early discharge,^{7,14,15} more recent studies suggest that newborns discharged early are at increased risk for rehospitalization during the neonatal period.^{5,6,16,17} The current guidelines of the American Academy of Pediatrics recommend a follow-up for newborns discharged

before 48 hours of life at 2 to 3 days postnatally.¹⁸ However, a complete follow-up is not always possible because of the geography and climate of the area, personal safety, or patient incompletion, and thus, there is a need to identify newborns who are at risk for developing significant hyperbilirubinemia as early as possible. We aimed, in this study, to prospectively determine the critical serum total bilirubin level to predict significant hyperbilirubinemia in healthy term newborns based on serum bilirubin measurements made within 24 hours of life.

The incidence of significant hyperbilirubinemia depends on regional variations, ethnic makeup of the population, laboratory variability in the measurement of bilirubin, and the incidence of breastfeeding.¹⁹ In our study group, there were no significant differences between the cases who did and the cases who did not develop significant hyperbilirubinemia with respect to these and other factors (such as hemoglobin level, gender, delivery route, birth weight, gestational age, and maternal smoking) that may be associated with the risk of hyperbilirubinemia. In 4 studies from 3 different countries investigating the predictive value of first-day serum bilirubin measurement on predicting the later development of significant hyperbilirubinemia, the incidence of significant hyperbilirubinemia has been reported to be between 1.7% and 12%.²⁰⁻²³ The 60 cases with significant hyperbilirubinemia in our study group of 498 newborns represented an incidence of 12.05%. These minor differences may be attributable to ethnic and geographic variations in different populations. In our study, the cases who developed significant hyperbilirubinemia also had significantly higher bilirubin levels on days 2 through 5 in addition to the first-day values, compared with cases who did not develop significant hyperbilirubinemia.

Bhutani et al²⁰ have prospectively followed term newborns over the first 5 days of life by measuring serum bilirubin levels daily. In their series of 1097 newborns, no infant who had a bilirubin level of <5 mg/dL at 20 to 28 hours of life developed significant hyperbilirubinemia (≥17 mg/dL), whereas 33% of those whose serum bilirubin level at the same hours was at least 8 mg/dL developed significant hyperbilirubinemia. In our study, of the 206 newborns who had a bilirubin level of ≥6 mg/dL in the first 24 hours of life, 26.21% developed significant hyperbilirubinemia, whereas only 2.05% of the 292 newborns whose bilirubin level was <6 mg/dL on the first day of life developed significant hyperbilirubinemia.

In a similar study by Seidman et al,²¹ the risk of significant hyperbilirubinemia was 1.6% in cases whose bilirubin level was <5 mg/dL at 24 hours of

TABLE 3. Demographic Characteristics of Cases Who Did and Who Did Not Develop Significant Hyperbilirubinemia (≥ 17 mg/dL) After 72 Hours of Life

Demographics	Cases With Significant Hyperbilirubinemia (n = 60)	Cases Without Significant Hyperbilirubinemia (n = 438)	P Value
Hemoglobin (g/dL)*	16.8 \pm 1.7	17.2 \pm 1.4	.541
Gender (male/female)	37/23	229/209	.175
Gestational age (wk)*	39.4 \pm 1.5	39.9 \pm 1.2	.722
Birth weight (g)*	3275 \pm 375	3302 \pm 429	.646
Delivery mode (vaginal/cesarean)	34/26	234/204	.711
Feeding pattern			
Breast milk	43	345	
Formula milk	3	34	.276
Partially breast milk	14	59	
Maternal gestational smoking (present/absent)	13/47	92/346	.890

* Values are given as mean \pm standard deviation.

TABLE 4. Demographic Characteristics of Cases Who Had a Serum Total Bilirubin Level of < 6 mg/dL and ≥ 6 mg/dL in the First 24 Hours

Demographics	Cases With a Serum Bilirubin Level of < 6 mg/dL (n = 292)	Cases With a Serum Bilirubin Level of ≥ 6 mg/dL (n = 206)	P Value
Gender (male/female)	150/142	115/91	.613
Birth weight (g)*	3310 \pm 305	3240 \pm 340	.551
Gestational age (wk)*	39.1 \pm 1.7	39.9 \pm 1.6	.716
Maternal gestational smoking (present/absent)	64/228	43/163	.493
Delivery mode (vaginal/cesarean)	159/133	115/91	.088
Maternal age (y)*	25.76 \pm 4.82	26.23 \pm 4.96	.094
Apgar score*	8.1 \pm .4	8.4 \pm .5	.662
Feeding pattern			
Breast milk	241	172	.110
Formula milk	19	11	
Partially breast milk	32	23	
Maternal gestationally acquired chronic disease (present/absent)	10/282	11/195	.095
Enclosed hemorrhage (present/absent)	4/288	3/203	.414
Any sibling with neonatal jaundice (present/absent)	26/266	16/190	.312
Abnormal ($\geq 10\%$) weight loss at the end of first 5 d (present/absent)	6/286	4/202	.618

* Values are given as mean \pm standard deviation.

TABLE 5. Sensitivity, Specificity, and Predictive Values of the First-Day Serum Bilirubin Level of 6 mg/dL in Determining the Subsequent Need of Phototherapy Treatment

Serum Bilirubin Level in the First 24 Hours of Life	Cases With a Peak Bilirubin Level of < 20 mg/dL After 72 Hours of Age (n)	Cases Requiring Phototherapy Treatment With a Peak Bilirubin Level of ≥ 20 mg/dL After 72 Hours of Age (n)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
< 6 mg/dL (n = 292)	292	0	100	60	6.7	100
≥ 6 mg/dL (n = 206)	192	14				

life, whereas that risk was 6.6% in cases whose bilirubin level was ≥ 5 mg/dL at 24 hours of life. In their series of 1075 newborns, this critical bilirubin level (5 mg/dL) was reported to have a high specificity (91.9%) and a low sensitivity (45.5%) for detecting significant hyperbilirubinemia; the positive predictive value was very low (8.9%) and the negative predictive value was very high (99.0%). In their next study, Bhutani et al²² followed 2840 newborns, although not daily, during the first postnatal week,

and they investigated the predictive value of a pre-discharge hour-specific serum bilirubin measurement in determining the development of postdischarge significant hyperbilirubinemia. According to their percentile-based bilirubin nomogram constructed from hour-specific pre-discharge and post-discharge total serum bilirubin values of newborns, significant hyperbilirubinemia was defined as the presence of a postdischarge total serum bilirubin level reaching into the high-risk zone (≥ 95 th percen-

tile track), and the predictive ability of the 40th percentile track as the risk demarcator was the highest (100% sensitivity and 100% negative predictive value) in detecting the 126 of 2840 cases who developed a subsequent significant hyperbilirubinemia. In our study, the bilirubin level of 6 mg/dL on the first day had the highest sensitivity (90%), and this critical bilirubin level had a very high (97.9%) negative predictive value and fairly low (26.2%) positive predictive value. According to our findings, a critical cutoff level of 6 mg/dL in the first 24 hours of life predicted 90% of the newborns who developed jaundice. However, the bilirubin level of <6 mg/dL did not completely exclude the development of significant hyperbilirubinemia; only 2.05% of the newborns with bilirubin levels of <6 mg/dL developed jaundice. A 97.9% negative predictive value in the present study suggests that measurement of serum bilirubin in the first 24 hours of life can help identify those newborns who are unlikely to require further evaluation and intervention. Furthermore, because no cases with a serum bilirubin level of <6 mg/dL in the first 24 hours of life required a subsequent phototherapy treatment and because all of those infants requiring a phototherapy treatment with serum bilirubin levels of ≥ 20 mg/dL were just among the cases whose first-day bilirubin levels were ≥ 6 mg/dL, the critical bilirubin level of 6 mg/dL on the first day made it possible, with the highest (100%) sensitivity and negative predictive value, to definitely predict all the infants who would have a bilirubin level of >20 mg/dL, requiring a phototherapy treatment later in the first days of life.

To target limited health care resources more effectively toward high-risk newborns after the era of early discharge of newborns from hospitals, there is an obvious need to develop practical guidelines to predict which newborns will develop significant hyperbilirubinemia or will require further and close follow-up or intervention. From our particular experience, we conclude that a serum bilirubin measurement and the use of the critical bilirubin level of 6 mg/dL in the first 24 hours of life will predict nearly all healthy term newborns who will have significant hyperbilirubinemia and will determine all of those infants who will require a phototherapy treatment later during first days of life. However, results of the present study are applicable only to healthy term newborns, and further studies including larger numbers of newborns should be conducted to establish more sensitive and more predictive guidelines.

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