

## Correlation between cord blood bilirubin level and incidence of hyperbilirubinemia in term newborns

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### Abstract

**Background** Discharging healthy term newborns from the hospital after delivery at increasingly earlier postnatal ages has recently become a common practice due to medical, social, and economic reasons, however it contributes to readmission because of jaundice.

**Objective** To investigate the correlation between level of cord blood bilirubin and development of hyperbilirubinemia among healthy term newborns.

**Methods** Prospective observational study was performed on 88 healthy term newborns. Cord blood was collected for the total bilirubin, conjugated bilirubin, unconjugated bilirubin level measurement and blood group test. Measurements of total bilirubin, conjugated bilirubin, and unconjugated bilirubin were repeated on the 5<sup>th</sup> day with serum sampling, or as soon as the newborn appeared to be jaundice.

**Results** Subjects were categorized into hyperbilirubinemia and non-hyperbilirubinemia newborns. There was a correlation between cord blood and the 5<sup>th</sup> day bilirubin level. By ROC analysis, cord blood bilirubin level of  $\geq 2.54$  mg/dL was determined to have high sensitivity (90.5%), specificity of 85%, and accuracy of 86.4%.

**Conclusions** There is a correlation between cord blood bilirubin level and hyperbilirubinemia in healthy term newborns. Cord blood bilirubin level at or greater than 2.54 mg/dL can predict the development of hyperbilirubinemia. [Paediatr Indones. 2009;49:349-54].

**Keywords:** cord blood, hyperbilirubinemia, early detection, newborn, jaundice

Jaundice is a clinical condition that is often present and constitutes one of the major issues during neonatal period due to transient bilirubin conjugation deficiency, including hepatic uptake and intracellular transport deficiency, and increased enterohepatic circulation.<sup>1,2</sup> Although jaundice affects nearly all newborns, 5% to 6% of healthy term newborns develops significant hyperbilirubinemia ( $> 12.9$  mg/dL).<sup>3</sup> This condition can cause cellular damage, especially brain neuron damage resulting in neurological problems after several years or even death.<sup>4</sup> American Academy of Pediatrics (AAP) reports that kernicterus has at least 10% mortality and 70% long-term morbidity if total serum bilirubin (TSB) level is higher than 20 mg/dL.<sup>5</sup>

Discharging healthy term newborns from the hospital after delivery at increasingly earlier postnatal ages has recently become a common practice due to medical, social, and economic reasons. Association between an early discharged newborn and the risk of readmission to the hospital has previously been reported, and it was most commonly caused by hyperbilirubinemia.<sup>6</sup> A study by Seidman et al<sup>6</sup> In United States showed that 0.36%

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## Methods

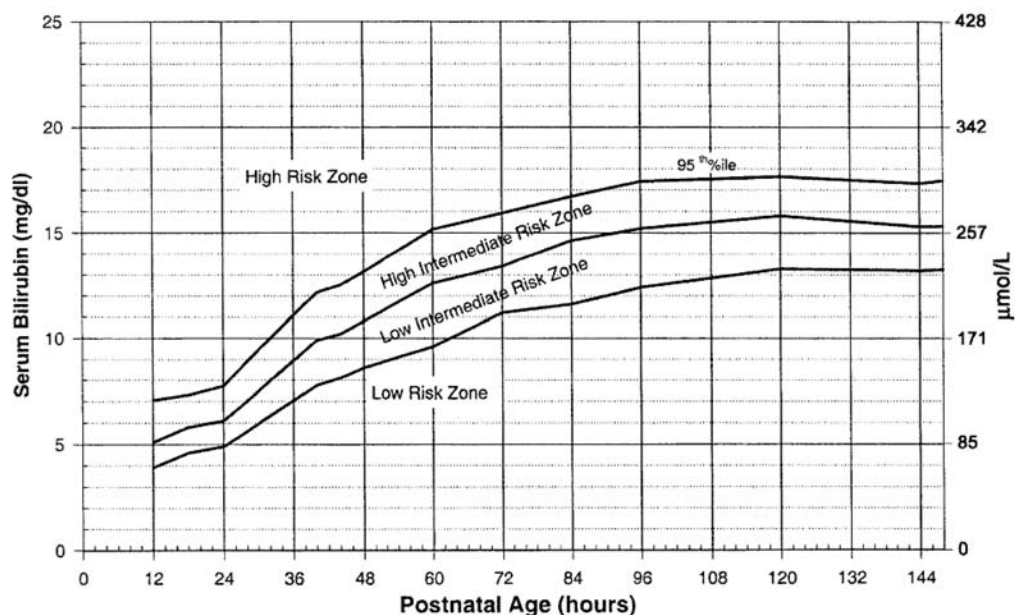
of healthy term newborns developed severe neonatal hyperbilirubinemia in the first postnatal week and had to be readmitted to the hospital.<sup>6</sup> The problem is the recognition of jaundice becomes more difficult. Severe jaundice, and even kernicterus, can occur in some full-term healthy newborns with no apparent hemolysis, jaundice in the first 24 hours, or any causes other than breastfeeding hyperbilirubinemia.

Early detection and recognition of risk factors before discharging newborns from the hospital are the primary prevention of severe hyperbilirubinemia development. Some studies use the first 24 hours of newborns total serum bilirubin (TSB) as a predictor of hyperbilirubinemia development, while others try to find another methods such as transcutaneous bilirubinometry and cord blood bilirubin measurement. Venipuncture, which is performed to get the blood sample for TSB examination, is an invasive procedure and has a risk of injury or infection, is not a practical procedure to be done as a routinely. Examination of newborns' cord blood bilirubin level is a non-invasive procedure and can increase early detection coverage to prevent severe hyperbilirubinemia.<sup>7,8</sup> We investigated the correlation between level of cord blood bilirubin at birth and the development of hyperbilirubinemia in the first week of life among healthy term newborns.

This was a prospective cohort study, carried out at Perinatology Division, Department of Child Health, Hasan Sadikin Hospital, Bandung, during the period January to February 2009. We enrolled healthy full-term newborns (37-42 weeks of gestation as determined by New Ballard Score), both genders, delivered by vaginal delivery or cesarean section with birth weight  $\geq 2500$  g and Apgar score  $\geq 7$  at 5 minutes. Newborns with ABO incompatibility were excluded.

All subjects were cared with the rooming-in method to ensure the practice of exclusive breastfeeding. Informed consent was obtained from all parents. The study was approved by the The Health Research Ethics Committee, Medical School, Padjadjaran University, Bandung.

History taking was performed to the mother, including mother's age, ethnic, medical history, pregnancy history, drug, sibling's history of jaundice, and parents' blood group. Cord blood samples were collected from all newborns that complied with the inclusion criteria protocol at the delivery. An amount of 2 ml cord blood was required and sent to clinical laboratory of Hasan Sadikin Hospital for the measurement of total bilirubin, conjugated bilirubin,



**Figure 1.** Nomogram of risk determination in well newborns at 36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values

unconjugated bilirubin level (referred as TB<sub>0</sub>, CB<sub>0</sub>, UB<sub>0</sub> thereafter) and blood group test. The newborns were then followed up according to the routine neonatal unit admission procedure. Measurement of total bilirubin, conjugated bilirubin, unconjugated bilirubin level were repeated on day 5 (TB<sub>5</sub>, CB<sub>5</sub>, UB<sub>5</sub>) with serum sampling, or as soon as the newborn appeared to be jaundice. Newborns whose parents were discharged early, were suggested to visit the perinatology clinic in the outpatient department on day 5, or as soon as the newborns appeared to be jaundiced. Total bilirubin (TB) level was measured using Vitros 250 Chemistry System Spectrophotometer (Ortho-Clinical Diagnostics, Johnson & Johnson Company) at room temperature. Subjects with TB level of  $\geq 12.9$  mg/dL on the 5<sup>th</sup> day or when the newborns appeared to be jaundice were defined as having hyperbilirubinemia and they had to undergo phototherapy.

Non-physiologic hyperbilirubinemia was defined as level of TSB above the 95<sup>th</sup> percentile based on the normogram (Figure 1).<sup>9,10</sup> Blood group incompatibility was defined as a newborn with non-O blood group who was delivered by O blood group mother; or rhesus-positive newborns who were delivered from rhesus-negative mother.<sup>11</sup>

The correlation between cord blood bilirubin level and TSB on day 5 or when the newborns appeared to be jaundice was determined by the linear regression analysis. The correlation strength of these variables was determined using Pearson correlation coefficient. The cut-off point of total cord blood bilirubin level was determined using the receiver operating characteristic (ROC) curve analysis, then sensitivity, specificity, and accuracy were obtained. Cord blood bilirubin level and confounding risk factors were analyzed with logistic regression, and P values with significance of less than 0.05 were considered statistically significant.

## Results

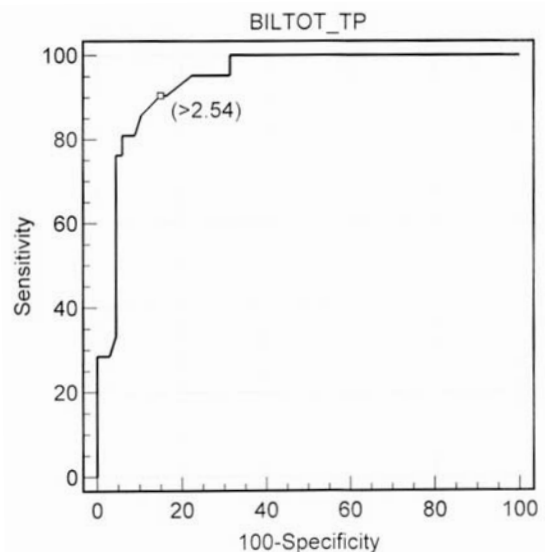
A total of 88 newborns was enrolled, 50 (57%) were male and 38 (43%) female. Mean gestational age was 38.9 weeks, and mean birth weight was 3057 grams. Sixty-six newborns (75%) were delivered vaginally, the rest were delivered by cesarean section. Twenty-one newborns (24%) developed significant

**Table 1.** Characteristics of subjects

Characteristics	Hyperbilirubinemia		P
	Yes (n=21)	No (n=67)	
Gender - n			
Male	16	34	0.040
Female	5	33	
Delivery mode - n			
Vaginal	16	50	0.885
Cesarean	5	17	
Subject's blood group - n			
A	8	23	0.956
B	4	16	
O	7	23	
AB	2	5	
Mother's blood group - n			
A	11	29	0.587
B	5	15	
O	5	18	
AB	0	5	
Feeding pattern - n			
Breast milk	8	39	0.08
Partially breast milk	13	24	
Formula milk	0	4	
Gestational age - weeks			
Mean (SD)	38.7 (1.42)	39 (1.30)	0.287§
Range	37-42	37-42	
Birth weight - g			
Mean (SD)	2981(326)	3080(428.3)	0.402§
Range	2500-3600	2500-4170	
Maternal age - yr			
Mean (SD)	27.76(7.6)	27.43(5.74)	0.833¶
Median	27.0	27.0	
Range	17-40	17-39	
Parity - n			
Mean (SD)	0.86 (1.24)	1.01(1.39)	0.439§
Interval	0-4	0-9	

§T test analysis

¶Mann-Whitney test analysis



**Figure 2.** ROC curve analysis

**Table 2.** Bilirubin level in subjects' cord blood

Bilirubin in cord blood	Hyperbilirubinemia		Z <sub>M-W</sub>	P value
	Yes (n=21)	No (n=67)		
Total bilirubin (mg/dL)				
Mean (SD)	3.77(1.07)	2.14(0.58)	6.084	<0.001
Median	3.50	2.03		
Interval	2.34-6.60	0.90-4.22		
Conjugated bilirubin (mg/dL)				
Mean (SD)	0.23(0.31)	0.18(0.28)	0.659	0.51
Median	0.0	0.0		
Interval	0.0-0.86	0.0-0.87		
Unconjugated bilirubin (mg/dL)				
Mean (SD)	3.53(1.20)	1.94(0.60)	5.564	<0.001
Median	3.40	1.90		
Interval	1.71-6.60	0.80-3.93		

SD=Standard deviation; Z<sub>M-W</sub>= Mann-Whitney test

hyperbilirubinemia (total serum bilirubin  $\geq$  12.9 mg/dl on day 5). There was a significant difference in sex between newborns who developed and did not develop significant hyperbilirubinemia (P=0.04). Characteristics of subjects are presented in **Table 1**.

Statistical analysis with Mann-Whitney test showed that conjugated and unconjugated bilirubin level in cord blood was significantly different (P<0.001) between both groups (**Table 2**). Regression analysis was used to determine correlation between total bilirubin in cord blood and on day 5 with equation:  $y = 6.825 + 1.160x$  ( $r = 0.710$ ;  $P < 0.001$ ).

By ROC analysis (**Figure 2**), it was determined that total bilirubin level in cord blood of  $\geq$  2.54 mg/dL had a high sensitivity (90.5%), high specificity

(85%), and accuracy of 86.4% (**Table 3**). Reliability was determined with Kappa Index (K) of 0.668 (substantial agreement).

Logistic regression analysis was used to determine risk factors involved in the development of significant hyperbilirubinemia, and sex that in bivariables showed significant association (**Table 4**).

## Discussion

There is a concern about increasing incidence of kernicterus in healthy term neonates, and hyperbilirubinemia is one of the most common causes for readmission of the newborns. The need for early detection of hyperbilirubinemia in early discharged newborns from the hospital is therefore important. Knowledge of infants at risk of developing jaundice allows simple bilirubin reducing methods to be implemented before bilirubin levels reach critical levels.<sup>13</sup>

This study showed a significant correlation between total bilirubin level in cord blood and incidence of significant hyperbilirubinemia (P<0.001) and critical level of 2.54 mg/dL could predict the development of significant hyperbilirubinemia in the first week of life with sensitivity of 90.5%, specificity of 85%, and accuracy of 86.4%.

Bernaldo and Segre<sup>14</sup> found that the critical bilirubin level of  $\geq$  2.0 mg/dL indicated 53% probability of the need for further treatment by phototherapy, and when the level was 3.0 mg/dL, the probability of needing treatment was 86%. If it was 3.5 mg/dl, the

**Table 3.** Sensitivity, specificity, and accuracy of total bilirubin critical level in cord blood on development of significant hyperbilirubinemia

Total Bilirubin Critical Level in Cord Blood (mg/dL)	Hyperbilirubinemia		Total
	Yes (n=21)	No (n=67)	
$\geq$ 2.54	19	10	29
<2.54	2	57	59
Total	21	67	88

**Table 4.** Logistic regression analysis

Variable	B Coefficient	SE(B)	P value	OR (95%CI)
Cord total bilirubin ( $\geq$ 2.54 mg/dL)	4.473	0.925	<0.001	87.60 (14.3 to 536.68)
Gender (♀ to ♂)	-2.026	0.826	0.014	0.132 (0.026 to 0.665)
Constanta	-0.824	-	-	

Model Accuracy: 90.9%

SE: standard error



probability went up to 93% ( $P < 0.001$ ). Sun et al<sup>15</sup> found that cord blood bilirubin level could predict the development of significant hyperbilirubinemia in healthy term newborns. This study show the bilirubin in cord blood critical level of  $\geq 35 \mu\text{mol/l}$  (2 mg/dl) had positive predictive value of 45.68% and sensitivity of 68.27 ( $P < 0.001$ ).

Rataj et al<sup>16</sup> carried out a study in 800 healthy term newborns and the results showed a similarity with the current study as reported that critical bilirubin level in cord blood of  $> 2.5 \text{ mg/dL}$  had a probability of 89% for the development of significant hyperbilirubinemia in newborns.

Knudsen,<sup>17</sup> in 1989, carried out a study to demonstrate that jaundiced newborns presented higher umbilical cord blood bilirubin levels than newborns without clinical jaundice. In addition, the number of jaundiced newborns undergoing phototherapy was significantly higher when these levels were higher than 2.3 mg/100 dL, in comparison with number of jaundiced newborns with no need for treatment whose bilirubin levels were lower than or equal to 2.3 mg/100 dL. This proved the possibility of defining a newborn risk group for developing neonatal hyperbilirubinemia at birth.

There are conflicting reports of the predictability of cord blood bilirubin of later hyperbilirubinemia. A study in Iran, concluded that cord bilirubin levels could not identify newborn infants who were at risk for developing significant hyperbilirubinemia.<sup>18</sup> A total of 634 healthy term and exclusively breast-fed newborns were enrolled in this study. Seventy-six newborns (11.8%) had significant hyperbilirubinemia ( $\geq 14 \text{ mg/dL}$ ) with mean level of bilirubin in cord blood of 37.4 (SD 17)  $\mu\text{mol/L}$  (2.2 (SD 1.0) mg/dL) and mean level of bilirubin in cord blood was 34 (SD 16)  $\mu\text{mol/L}$  (2.0 (SD 0.9) mg/dL) in newborns who did not develop significant hyperbilirubinemia. Based on the data there was no significant difference between two groups.

Critical level of bilirubin in cord blood found was 4 mg/dL with sensitivity of 7.9%, specificity of 97.7%, positive predictive value of 31.6%, and negative predictive value of 88.8%. Based on the data, it was found that bilirubin level in cord blood could not predict the development of significant hyperbilirubinemia in newborns.

We found that male newborns had higher risk of developing significant hyperbilirubinemia ( $P = 0.04$ ).

AAP had reported male gender as one of the minor risk factor;<sup>12</sup> this was in agreement with previous studies.<sup>18,19</sup> Fourteen subjects were dropped out from our follow-up and this condition could influence statistical analysis in this study. Limited period of follow up, also not daily total and unbound bilirubin measurements were also considered as the weakness of our study.

We conclude that bilirubin level in cord blood has a correlation with the incidence of significant hyperbilirubinemia in term newborns. Bilirubin level of  $\geq 2.54 \text{ mg/dL}$  could predict the development of significant hyperbilirubinemia in term newborns.

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