"EVALUATION OF CORD BLOOD ALBUMIN, BILIRUBIN, NUCLEATED RBC AND RETICULOCYTE COUNT AS EARLY PREDICTORS IN NEONATAL HYPERBILIRUBINEMIA"

BY

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UNDER THE GUIDANCE

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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. Each year, approximately 60% of the 4 million newborns in the United States are believed to become clinically jaundiced.[1] Such data is not available for India.

When the newborn stays at the hospital for a 72-hour post-delivery period, it is possible to observe the peaking of the physiological jaundice, thus allowing medical intervention, if necessary. However, in cases of early discharge from the hospital, the newborn may be subject to readmission for phototherapy treatment, because of high levels of unconjugated bilirubin and this is the most common cause of readmission to NICU in early neonatal period. Such readmission, besides involving extra expenses for both the 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.[2]

In India, financial pressures have influenced the shortening of hospital stays for mothers and their babies, whether born via vaginal delivery or caeserean section. Early discharge of healthy term newborns after delivery has become a common practice because of medical and social reasons and economic constraints.[3] The American Academy of Pediatrics recommends that newborns discharged within 48 hours should have a follow-up visit after 2-3 days to detect significant jaundice and other problems[4]. This recommendation is not possible in our country due to

limited follow up facilities in the community. However, so far, no standardized procedure has been laid down in our country either for predicting neonatal jaundice or for following up these early discharged newborns, thus increasing the risk of readmission and the possibility of brain damage due to kernicterus. A reliable, clinically evaluated method for estimation of the risk of bilirubin dependent brain damage is still lacking.[5,6] Physical examination is not a reliable measure of the serum bilirubin.[7] Under these circumstances 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 concept of prediction of jaundice offers an attractive option to pick up babies at risk of neonatal hyperbilirubinemia. Concern regarding early discharge and hyperbilirubinemia in newborns has led to frequent discussions and many controversies. Early hospital discharge has had the implication of reexamining the approach towards neonatal jaundice, now taking into consideration the bilirubin levels presented in the first 24 to 48 hours 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.

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]

The present study was conducted to evaluate the predictive value of cord albumin, bilirubin, nRBC and reticulocyte level for identifying term infants at risk for subsequent hyperbilirubinemia.

OBJECTIVE:

Evaluation and statistical correlation of umbilical cord albumin, bilirubin, nucleated RBC and reticulocyte count in early prediction of neonatal hyperbilirubinemia.

AIMS:

1. To estimate serum albumin, bilirubin, nRBC and reticulocyte count in umbilical cord blood of healthy term neonates.
2. To follow up these healthy term neonates clinically for 72hrs.
3. To re estimate serum bilirubin of these neonates after 72hrs.
4. To compare serum albumin, bilirubin, nRBC and reticulocyte count of umbilical cord blood of the neonates with that estimated after 72hrs.
5. To find out the incidence of neonates developing significant hyperbilirubinemia.

REVIEW OF LITERATURE

Jaundice and Hyperbilirubinemia in the Newborn[10]

Hyperbilirubinemia is a common and, in most cases, benign problem in neonates. Jaundice is observed during the 1st week of life in approximately 60% of term infants and 80% of preterm infants. The yellow color usually results from the accumulation of unconjugated, nonpolar, lipid-soluble bilirubin pigment in the skin. This unconjugated bilirubin (designated indirect-acting by nature of the Van den Bergh reaction) is an end product of heme-protein catabolism from a series of enzymatic reactions by heme-oxygenase and biliverdin reductase and nonenzymatic reducing agents in the reticuloendothelial cells. It may also be due in part to deposition of pigment from conjugated bilirubin, the end product from indirect, unconjugated bilirubin that has undergone conjugation in the liver cell microsome by the enzyme uridine diphosphoglucuronic acid (UDP)– glucuronyl transferase to form the polar, water-soluble glucuronide of bilirubin (direct-reacting). Although bilirubin may have a physiologic role as an antioxidant, elevations of indirect, unconjugated bilirubin are potentially neurotoxic. Even though the conjugated form is not neurotoxic, direct hyperbilirubinemia indicates a potentially serious hepatic disorder or a systemic illness.[10]

Albumin is synthesized by liver and helps in transport of uncongugated bilirubin. Plasma albumin limits the toxicity of bilirubin by reducing the unbound bilirubin concentration and thereby competing tissue for bilirubin binding. Extremely avid binding to albumin maybe detrimental however, because it limits the rate of hepatic removal of unconjugated bilirubin from the plasma. Thus, the affinity of albumin for unconjugated bilirubin may reflect a compromise between the need to prevent excessive binding to tissue and the need for efficient hepatic elimination.[10]

Nucleated red blood cells are sometimes called erythroblasts, normoblasts, or normocytes. For this review, the term "normoblasts" will be used to refer to the cells when they are in the bone marrow and "nRBCs" when they are in circulating blood. Nucleated red blood cells (nRBCs) are rarely found circulating in older children, they are commonly seen in the blood of newborns. They are primarily produced in the fetal bone marrow in response to erythropoietin and are stored in the marrow as precursors to reticulocytes and mature erythrocytes. Many acute and chronic stimuli cause increases in the number of circulating nRBCs from either increased erythropoietic activity or a sudden release from the marrow storage pools. It emphasizes the effects of acute, subacute, and chronic asphyxia on nRBC counts. Increased numbers of circulating nRBCs are seen in association with long standing erythropoietin induced erythropoiesis, acute stress studies support the theory that mild, but prolonged, fetal hypoxia can induce erythropoiesis and increased nRBCs. Blood loss and hemolysis are potent

stimulants of erythropoietin and increased nRBCs. Although hemolysis from any cause can result in an increase in circulating nRBCs, ABO isoimmunization is most common.[60,61]

Reticulocytes are the erythroid cells in the peripheral blood that are in a discrete, penultimate phase of maturation. The nucleus has been removed, usually before the red cells enter the peripheral blood. However, some of the extranuclear RNA remains. This residual RNA generally is lost progressively during the 24 hours after the cell enters the circulation Reticulocytes thus represent a distinctive cohort of cells, those most recently entering the peripheral blood. Reticulocytes differ from other red cells in that they have a more convoluted shape, and are about 8% larger than the more mature cells. These latter two distinctions are not so clear-cut as is the presence of residual RNA. With the typical Wright's stain used for routine examination, only the earliest reticulocytes with the most residual RNA will be "polychromatophil" (i. e., more bluish than the mature erythrocytes).[63]

It is assumed that the normal red cell life span is 120 days and that the duration of a reticulocyte in the peripheral blood is 1 day. It follows that reticulocytes at a random time, in a normal subject at a steady state, will be 1/120, or 0 .8% of all red cells. The reticulocyte percentage in the peripheral blood is an indication of the rapidity of red cell turnover if the patient is in a steady state. However, the number of reticulocytes released into the blood reflects the amount of erythropoiesis on a given day. Increased reticulocyte percentages are seen in hemolytic disorders, whether intrinsic (e.g.,

hemoglobinopathy or enzymopathy) or extrinsic (e.g., traumatic, heart valve, acquired immune hemolytic anemia). As long as the hemolytic cause is not corrected, the reticulocyte count will remain elevated. low reticulocyte percentage or count reflects a marrow unable to compensate for anemia. A high reticulocyte percentage or count reflects a marrow that is attempting to compensate for red cell destruction, or recovering from anemia.[64]

Etiology[10]

During the neonatal period, metabolism of bilirubin is in transition from the fetal stage, during which the placenta is the principal route of elimination of the lipid-soluble, unconjugated bilirubin, to the adult stage, during which the water-soluble conjugated form is excreted from hepatic cells into the biliary system and gastrointestinal tract. Unconjugated hyperbilirubinemia may be caused or increased by any factor that

(1) Increases the load of bilirubin to be metabolized by the liver.

(2) Damages or reduces the activity of the transferase enzyme or other related enzymes.

(3) Competes for or blocks the transferase enzyme.

(4) Leads to an absence or decreased amounts of the enzyme or to reduction of bilirubin uptake by liver cells.

The toxic effects of elevated serum concentrations of unconjugated bilirubin are increased by factors that reduce the retention of bilirubin in the circulation (hypoproteinemia, displacement of bilirubin from its binding sites on albumin by competitive binding of drugs such as sulfisoxazole and moxalactam, acidosis, and increased free fatty acid concentration secondary to hypoglycemia, starvation, or hypothermia). Neurotoxic effects are directly related not only to the permeability of the blood-brain barrier and nerve cell membranes but also to

neuronal susceptibility to injury, all of which are adversely influenced by asphyxia, prematurity, hyperosmolality, and infection. Early and frequent feeding decreases, whereas breast-feeding and dehydration increase, serum levels of bilirubin. Delay in passage of meconium, which contains 1 mg bilirubin/dL, may contribute to jaundice by enterohepatic recirculation after deconjugation by intestinal glucuronidase (Fig. 1). Drugs such as oxytocin (in the mother) and chemicals used in the nursery such as phenolic detergents may also produce unconjugated hyperbilirubinemia. Risk factors for unconjugated hyperbilirubinemia are listed in Table 1 Additional risk factors include polycythemia, infection, prematurity, and having a diabetic mother.

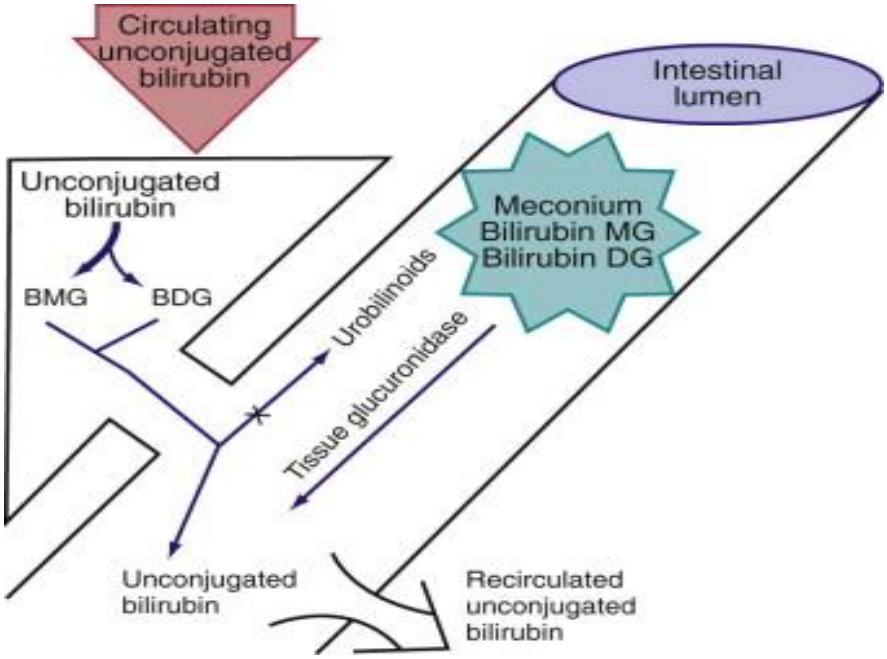


Figure 1 The neonatal production rate of bilirubin is 6-8 mg/kg/24 hr (in contrast to 3-4 mg/kg/24 hr in adults). Water-insoluble bilirubin is bound to albumin. At the plasma-hepatocyte interface, a liver membrane carrier (bilitranslocase) transports bilirubin to a cytosolic binding protein (ligandin or Y protein, now known to be glutathione S-transferase), which prevents back-absorption to plasma. Bilirubin is converted to bilirubin monoglucuronide (BMG). Neonates excrete more BMG than adults do. In the fetus, conjugated lipid-insoluble BMG and bilirubin diglucoronide (BDG) must be deconjugated by tissue β-glucuronidases to facilitate placental transfer of lipid-soluble unconjugated bilirubin across the placental lipid membranes. After birth, intestinal or milk-containing glucuronidases contribute to the enterohepatic recirculation of bilirubin and possibly to the development of hyperbilirubinemia.

Table 1 -- RISK FACTORS FOR DEVELOPMENT OF SEVERE HYPERBILIRUBINEMIA IN INFANTS ≥35 WEEKS OF GESTATION (IN APPROXIMATE ORDER OF IMPORTANCE)[11]

MAJOR RISK FACTORS
Predischarge TSB or TcB level in the high-risk zone [12,13]
Jaundice observed in the first 24 hr[14]
Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (glucose-6-phosphate dehydrogenase deficiency), elevated end-title CO concentration
Gestational age 35-36 wk[15,16]
Previous sibling received phototherapy[16,17]
Cephalohematoma or significant bruising[15]
Exclusive breast-feeding, particularly if nursing is not going well and weight loss is excessive[15,16]
East Asian race*[15]
MINOR RISK FACTORS
Predischarge TSB or TcB level in the high intermediate-risk zone[12,13]
Gestational age 37-38 wk[15,16]

Jaundice observed before discharge[16]
Previous sibling with jaundice[16,17]
Macrosomic infant of a diabetic mother[18,19]
Maternal age ≥25 yr[15]
Male gender[15,16]
DECREASED RISK (these factors are associated with decreased risk of significant jaundice, listed in order of decreasing importance)
TSB or TcB level in the low-risk zone [12,13]
Gestational age ≥41 wk[15,16]
Exclusive bottle-feeding[15,16]
Black race*[20]
Discharge from hospital after 72 hr[16,21]

TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

*Race as defined by mother's description.

Clinical Manifestations[10]

Jaundice may be present at birth or may appear at any time during the neonatal period, depending on etiology. Jaundice usually becomes apparent in a cephalocaudal progression, starting on the face and progressing to the abdomen and then the feet, as serum levels increase. Dermal pressure may reveal the anatomic progression of jaundice (face, ≈5 mg/dL; mid-abdomen, ≈15 mg/dL; soles, ≈20 mg/dL), but clinical examination cannot be depended on to estimate serum levels. Jaundice to the mid-abdomen, signs or symptoms, high-risk factors that suggest nonphysiologic jaundice, or hemolysis must be evaluated further (Tables 1 and 2). Noninvasive techniques for transcutaneous measurement of bilirubin (TcB) that correlate with serum levels may be used to screen infants, but determination of serum bilirubin level is indicated in patients with elevated age-specific transcutaneous bilirubin measurement, progressing jaundice, or risk for either hemolysis or sepsis. Whereas jaundice from deposition of indirect bilirubin in the skin tends to appear bright yellow or orange, jaundice of the obstructive type (direct bilirubin) has a greenish or muddy yellow cast. Infants with severe hyperbilirubinemia may present with lethargy and poor feeding and, without treatment, can progress to acute bilirubin encephalopathy (kernicterus).

Table 2 -- LABORATORY EVALUATION OF THE JAUNDICED INFANT ≥35 WEEKS OF GESTATION

INDICATIONS	ASSESSMENTS
Jaundice in first 24 hr	Measure TcB and/or TSB
Jaundice appears excessive for infant's age	Measure TcB and/or TSB
Infant receiving phototherapy or TSB rising rapidly (i.e., crossing percentiles [see Fig. 96-8]) and unexplained by history and physical examination	Blood type and Coombs test, if not obtained with cord blood Complete blood count and smear Measure direct or conjugated bilirubin It is an option to perform reticulocyte count, G6PD, and $ETCO_c$, if available Repeat TSB in 4-24 hr depending on infant's age and TSB level
TSB concentration approaching exchange levels or not responding to phototherapy	Perform reticulocyte count, G6PD, albumin, $ETCO_c$, if available
Elevated direct (or conjugated) bilirubin level	Do urinalysis and urine culture Evaluate for sepsis if indicated by history and physical examination
Jaundice present at or beyond age 3 wk, or sick infant	Total and direct (or conjugated) bilirubin level

INDICATIONS	ASSESSMENTS
	If direct bilirubin elevated, evaluate for causes of cholestasis Check results of newborn thyroid and galactosemia screen, and evaluate infant for signs or symptoms of hypothyroidism

$ETCO_c$, end tidal carbon monoxide concentration; G6PD, glucose-6-phosphate dehydrogenase; TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

Differential Diagnosis[10]

Jaundice present at birth or within the 1st 24 hr of life requires immediate attention and may be due to erythroblastosis fetalis, concealed hemorrhage, sepsis, or congenital infections, including syphilis, cytomegalovirus, rubella, and toxoplasmosis.

Jaundice that first appears on the 2nd or 3rd day is usually physiologic but may represent a more severe form,Familial nonhemolytic icterus (Crigler-Najjar syndrome) and early-onset breast-feeding jaundice.

Jaundice appearing after the 3rd day and within the first week suggests bacterial sepsis or urinary tract infection; it may also be due to other infections, notably syphilis, toxoplasmosis, cytomegalovirus, and enterovirus. Jaundice secondary to extensive ecchymosis or blood extravasation may occur during the 1st

day or later, especially in premature infants. Polycythemia may also lead to early jaundice.

Jaundice first recognized after the 1st wk of life, including breast milk jaundice, septicemia, congenital atresia or paucity of the bile ducts, hepatitis, galactosemia, hypothyroidism, cystic fibrosis, and congenital hemolytic anemia crises related to red blood cell morphology and enzyme deficiencies (Fig. 2).

Persistent jaundice during the first month of life includes hyperalimentation-associated cholestasis, hepatitis, cytomegalic inclusion disease, syphilis, toxoplasmosis, familial nonhemolytic icterus, congenital atresia of the bile ducts, galactosemia, and inspissated bile syndrome following hemolytic disease of the newborn. Rarely, physiologic jaundice may be prolonged for several weeks, as in infants with hypothyroidism or pyloric stenosis.

If direct hyperbilirubinemia is present, hepatitis, congenital bile duct disorders (atresia, paucity, Byler disease), cholestasis, inborn errors of metabolism, cystic fibrosis, and sepsis are diagnostic possibilities

Full-term, low-risk, asymptomatic infants with jaundice may be evaluated by monitoring of total serum bilirubin (TSB) levels. Regardless of gestation or time of appearance of jaundice, patients with significant hyperbilirubinemia and those with symptoms or signs require a complete diagnostic evaluation, which includes determination of direct and indirect bilirubin fractions, hemoglobin, reticulocyte count, blood type, Coombs test, and examination of a peripheral blood smear.

Indirect hyperbilirubinemia, reticulocytosis, and a smear with evidence of red blood cell destruction suggest hemolysis (see Table 2). In the absence of blood group incompatibility, nonimmunologically induced hemolysis should be considered. If the reticulocyte count, Coombs test result, and direct bilirubin value are normal, physiologic or pathologic indirect hyperbilirubinemia may be present (see Fig. 2).

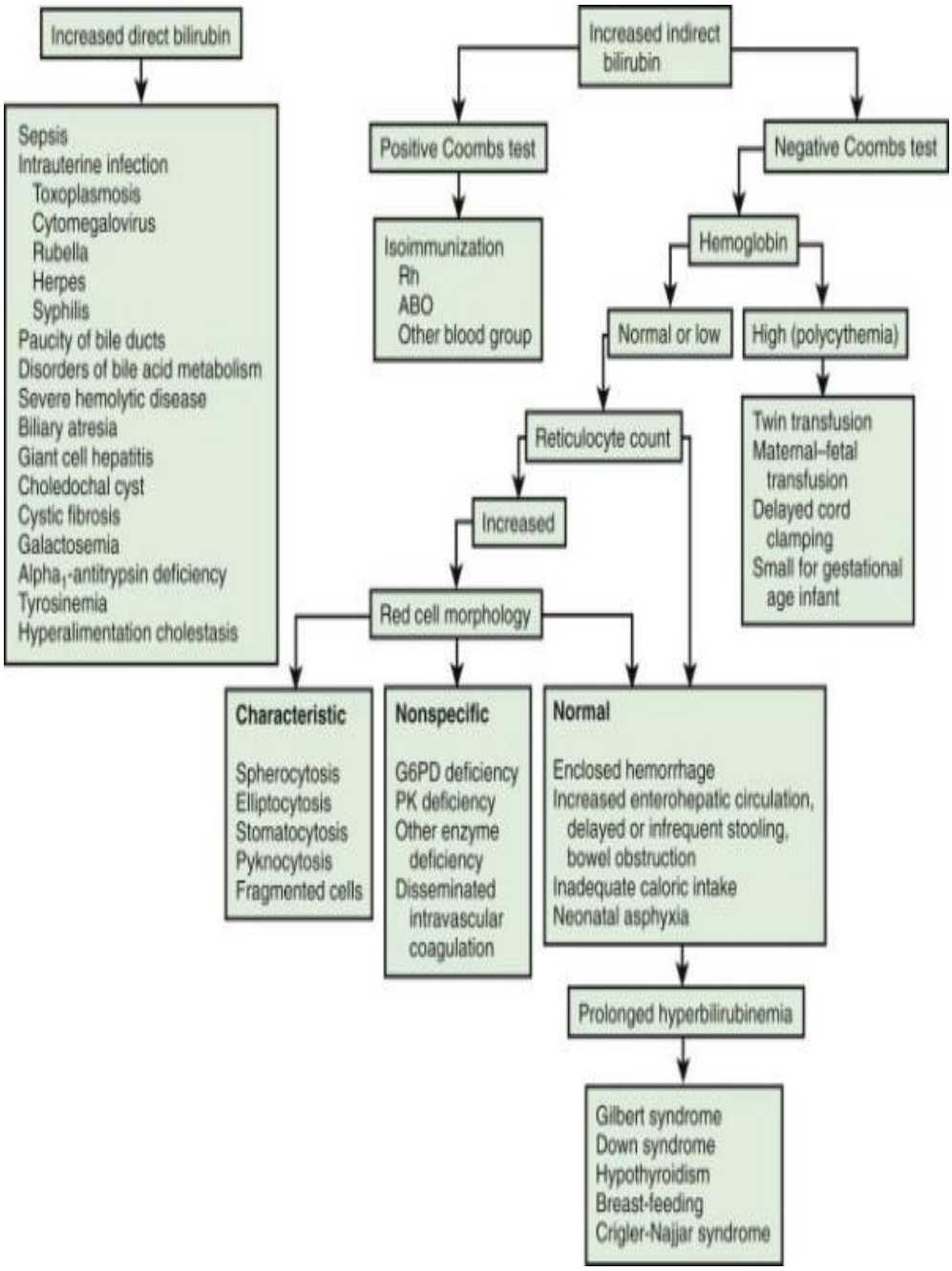


Figure 2 - Schematic approach to the diagnosis of neonatal jaundice. G6PD, glucose-6-phosphate dehydrogenase; PK, pyruvate kinase.

Physiologic Jaundice (Icterus Neonatorum)[10]

Under normal circumstances, the level of indirect bilirubin in umbilical cord serum is 1-3 mg/dL and rises at a rate of <5 mg/dL/24 hr; thus, jaundice becomes visible on the 2nd or 3rd day, usually peaking between the 2nd and 4th days at 5-6 mg/dL and decreasing to <2 mg/dL between the 5th and 7th days of life. Jaundice associated with these changes is designated physiologic and is believed to be the result of increased bilirubin production from the breakdown of fetal red blood cells combined with transient limitation in the conjugation of bilirubin by the immature neonatal liver.

Overall, 6-7% of full-term infants have indirect bilirubin levels >13 mg/dL and less than 3% have levels >15 mg/dL. Risk factors (Table 1). In infants without risk factors, indirect bilirubin levels rarely rise above 12 mg/dL, whereas infants with several risk factors are more likely to have higher bilirubin levels(Table 1). A combination of breast-feeding, variant-glucuronosyl transferase activity (1A1), and alterations of the organic anion transporter 2 gene increases the risk in Asian children. Predicting which neonates are at risk for exaggerated physiologic jaundice can be based on hour-specific bilirubin levels in the first 24-72 hr of life (Fig. 3). Transcutaneous measurements of bilirubin are linearly correlated with serum levels and can be used for screening. Indirect bilirubin levels in full-term infants decline to adult levels (1 mg/dL) by 10-14 days of life. Persistent indirect hyperbilirubinemia beyond 2 wk suggests hemolysis, hereditary glucuronyl transferase deficiency, breast milk jaundice, hypothyroidism, or intestinal obstruction. Jaundice associated

with pyloric stenosis may be due to caloric deprivation, deficiency of hepatic UDP-glucuronyl transferase, or an increase in the enterohepatic circulation of bilirubin from the ileus. In premature infants, the rise in serum bilirubin tends to be the same or somewhat slower but of longer duration than in term infants. Peak levels of 8-12 mg/dL are not usually reached until the 4th-7th day, and jaundice is infrequently observed after the 10th day, corresponding to the maturation of mechanisms for bilirubin metabolism and excretion.

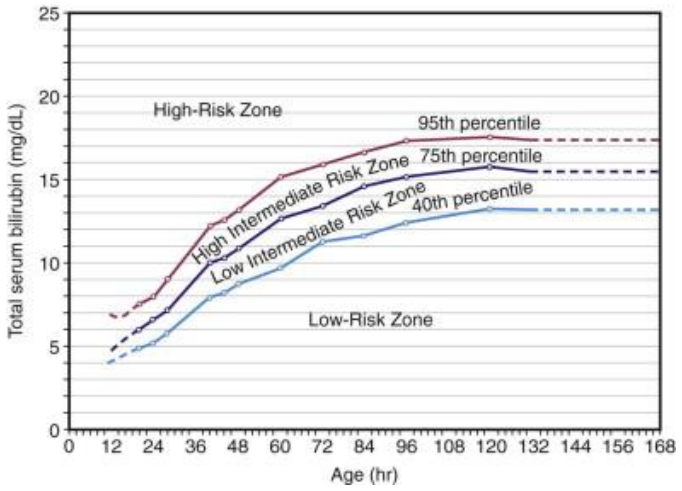


Figure 3 Risk designation of term and near-term well newborns based on their hour-specific serum bilirubin values. The high-risk zone is subdivided by the 95th percentile track. The intermediate -risk zone is subdivided into upper and lower risk zones by the 75th percentile track. The low-risk zone has been electively and statistically defined by the 40th percentile track.[13]

The diagnosis of physiologic jaundice in term or preterm infants can be established only by excluding known causes of jaundice on the basis of the history, clinical findings, and laboratory data (Table 3).

Table 3 -- DIAGNOSTIC FEATURES OF THE VARIOUS TYPES OF NEONATAL JAUNDICE.[22]

DIAGNOSIS	NATURE OF VAN DEN BERGH REACTION	JAUNDICE		PEAK BILIRUBIN CONCENTRATION		BILIRUBIN RATE OF ACCUMULATION (mg/dL/day)	REMARKS
		Appears	Disappears	mg/dL	Age in Days		
"Physiologic jaundice":							Usually relates to degree of maturity
Full-term	Indirect	2-3 days	4-5 days	10-12	2-3	<5	
Premature	Indirect	3-4 days	7-9 days	15	6-8	<5	
Hyperbilirubinemia due to metabolic factors:							Metabolic factors: hypoxia, respiratory distress, lack of carbohydrate
Full-term	Indirect	2-3 days	Variable	>12	1st wk	<5	Hormonal influences: cretinism, hormones, Gilbert syndrome
Premature	Indirect	3-4 days	Variable	>15	1st wk	<5	Genetic factors: Crigler-Najjar syndrome,

DIAGNOSIS	NATURE OF VAN DEN BERGH REACTION	JAUNDICE		PEAK BILIRUBIN CONCENTRATION		BILIRUBIN RATE OF ACCUMULATION (mg/dL/day)	REMARKS
		Appears	Disappears	mg/dL	Age in Days		
							Gilbert syndrome Drugs: vitamin K, novobiocin
Hemolytic states and hematoma	Indirect	May appear in 1st 24 hr	Variable	Unlimited	Variable	Usually >5	Erythroblastosis: Rh, ABO, Kell Congenital hemolytic states: spherocytic, nonspherocytic Infantile pyknocytosis Drugs: vitamin K Enclosed hemorrhage—hematoma
Mixed hemolytic and	Indirect and direct	May appear in	Variable	Unlimited	Variable	Usually >5	Infection: bacterial sepsis,

DIAGNOSIS	NATURE OF VAN DEN BERGH REACTION	JAUNDICE		PEAK BILIRUBIN CONCENTRATION		BILIRUBIN RATE OF ACCUMULATION (mg/dL/day)	REMARKS
		Appears	Disappears	mg/dL	Age in Days		
hepatotoxic factors		1st 24 hr					pyelonephritis, hepatitis, toxoplasmosis, cytomegalic inclusion disease, rubella, syphilis Drugs: vitamin K
Hepatocellular damage	Indirect and direct	Usually 2-3 days; may appear by 2nd wk	Variable	Unlimited	Variable	Variable, can be >5	Biliary atresia; paucity of bile ducts, familial cholestasis, galactosemia; hepatitis and infection

In general, a search to determine the cause of jaundice should be made if

(1) it appears in the first 24-36 hr of life,

(2) serum bilirubin is rising at a rate faster than 5 mg/dL/24 hr,

(3) serum bilirubin is >12 mg/dL in a full-term infant (especially in the absence of risk factors) or 10-14 mg/dL in a preterm infant,

(4) jaundice persists after 10-14 days of life, or

(5) direct bilirubin fraction is >2 mg/dL at any time.

Other factors suggesting a nonphysiologic cause of jaundice are family history of hemolytic disease, pallor, hepatomegaly, splenomegaly, failure of phototherapy to lower the bilirubin level, vomiting, lethargy, poor feeding, excessive weight loss, apnea, bradycardia, abnormal vital signs (including hypothermia), light-colored stools, dark urine positive for bilirubin, and signs of kernicterus.

Pathologic Hyperbilirubinemia[10]

Jaundice and its underlying hyperbilirubinemia are considered pathologic if the time of appearance, duration, or pattern varies significantly from that of physiologic jaundice or if the course is compatible with physiologic jaundice but other reasons exist to suspect that the infant is at special risk for neurotoxicity. It may not be possible to determine the precise cause of an abnormal elevation of

unconjugated bilirubin, but many infants with this finding have associated risk factors such as Asian race, prematurity, breast-feeding, and weight loss. Frequently, the terms exaggerated physiologic jaundice and hyperbilirubinemia of the newborn are used in infants whose primary problem is probably a deficiency or inactivity of bilirubin glucuronyl transferase (Gilbert syndrome) rather than an excessive load of bilirubin for excretion. The combination of glucose-6-phosphate dehydrogenase (G6PD) deficiency and a mutation of the promoter region of UDP-glucuronyl transferase-1 produces indirect hyperbilirubinemia in the absence of signs of hemolysis. Nonphysiologic hyperbilirubinemia may also be caused by mutations in the gene for bilirubin UDP-glucuronyl transferase.

The greatest risk associated with indirect hyperbilirubinemia is the development of bilirubin-induced neurologic dysfunction, which typically occurs with high indirect bilirubin levels. The development of kernicterus (bilirubin encephalopathy) depends on the level of indirect bilirubin, duration of exposure to bilirubin elevation, the cause of jaundice, and the infant's well-being. Neurologic injury including kernicterus may occur at lower bilirubin levels in preterm infants and in the presence of asphyxia, intraventricular hemorrhage, hemolysis, or drugs that displace bilirubin from albumin. The exact serum indirect bilirubin level that is harmful for VLBW infants is unclear.

Jaundice Associated with Breast-Feeding[10]

Significant elevation in unconjugated bilirubin (breast milk jaundice) develops in an estimated 2% of breast-fed term infants after the 7th day of life, with

maximal concentrations as high as 10-30 mg/dL reached during the 2nd-3rd week. If breast-feeding is continued, the bilirubin gradually decreases but may persist for 3-10 wk at lower levels. If nursing is discontinued, the serum bilirubin level falls rapidly, reaching normal range within a few days. With resumption of breast-feeding, bilirubin seldom returns to previously high levels. Phototherapy may be of benefit. Although uncommon, kernicterus can occur in patients with breast milk jaundice. The etiology of breast milk jaundice is not entirely clear but may be attributed to the presence of glucuronidase in some breast milk.

This syndrome should be distinguished from an early-onset, accentuated unconjugated hyperbilirubinemia known as breast-feeding jaundice, which occurs in the 1st week of life in breast-fed infants, who normally have higher bilirubin levels than formula-fed infants (Fig. 4). Hyperbilirubinemia (>12 mg/dL) develops in 13% of breast-fed infants in the 1st wk of life and may be due to decreased milk intake with dehydration and/or reduced caloric intake. Prophylactic supplements of glucose water to breast-fed infants are associated with higher bilirubin levels, in part because of reduced intake of the higher–caloric density breast milk. Frequent breast-feeding (>10/24 hr), rooming-in with night feeding, and ongoing lactation support may reduce the incidence of early breast-feeding jaundice. Even when breast-feeding jaundice develops, breast-feeding should be continued if possible. It is an option to temporarily interrupt breast-feedings and substitute formula for a day or two. In addition, frequent feeding and supplementation with formula or expressed breast milk is appropriate if the intake seems inadequate, weight loss is excessive, or the infant appears dehydrated.

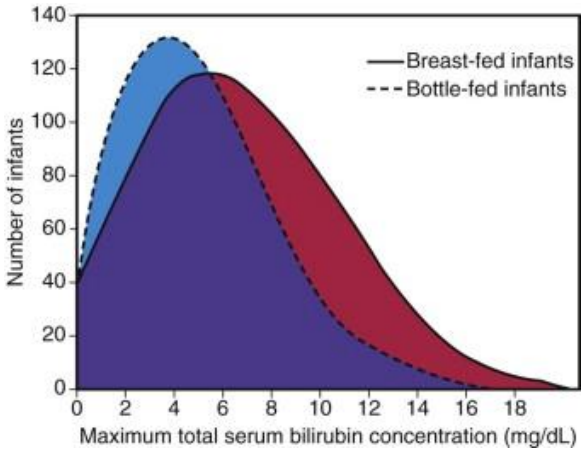


Figure 4 Distribution of maximal bilirubin levels during the first wk of life in breast-fed and formula-fed white infants weighing more than 2,500 g.[23]

Kernicterus[10]

Kernicterus, or bilirubin encephalopathy, is a neurologic syndrome resulting from the deposition of unconjugated (indirect) bilirubin in the basal ganglia and brainstem nuclei. The pathogenesis of kernicterus is multifactorial and involves an interaction between unconjugated bilirubin levels, albumin binding and unbound bilirubin levels, passage across the blood-brain barrier, and neuronal susceptibility to injury. Disruption of the blood-brain barrier by disease, asphyxia, and other factors and maturational changes in blood-brain barrier permeability affect risk.

The precise blood level above which indirect-reacting bilirubin or free bilirubin will be toxic for an individual infant is unpredictable, but in a large series,

kernicterus occurred only in infants with a bilirubin >20 mg/dL. Ninety percent of the infants in whom kernicterus developed were in previously healthy, predominantly breast-fed term and near-term infants.[10] The duration of exposure to high bilirubin levels needed to produce toxic effects are unknown. The more immature the infant is, the greater the susceptibility to kernicterus.

Clinical Manifestations[10]

Signs and symptoms(Table 4) of kernicterus usually appear 2-5 days after birth in term infants and as late as the 7th day in premature infants, but hyperbilirubinemia may lead to encephalopathy at any time during the neonatal period. The early signs may be subtle and indistinguishable from those of sepsis, asphyxia, hypoglycemia, intracranial hemorrhage, and other acute systemic illnesses in a neonate. Lethargy, poor feeding, and loss of the Moro reflex are common initial signs. Subsequently, the infant may appear gravely ill and prostrate, with diminished tendon reflexes and respiratory distress. Opisthotonos with a bulging fontanel, twitching of the face or limbs, and a shrill high-pitched cry may follow. In advanced cases, convulsions and spasm occur, with affected infants stiffly extending their arms in an inward rotation with the fists clenched . Rigidity is rare at this late stage.

TABLE – 4 CLINICAL FEATURES OF KERNICTERUS.[23]

ACUTE FORM
Phase 1 (1st 1-2 days): poor suck, stupor, hypotonia, seizures Phase 2 (middle of 1st wk): hypertonia of extensor muscles, opisthotonos, retrocollis, fever Phase 3 (after Table the 1st wk): hypertonia
CHRONIC FORM
1st year: hypotonia, active deep tendon reflexes, obligatory tonic neck reflexes, delayed motor skills After 1st yr: movement disorders (choreoathetosis, ballismus, tremor), upward gaze, sensorineural hearing loss

Many infants who progress to these severe neurologic signs die; the survivors are usually seriously damaged but may appear to recover and for 2-3 mo show few abnormalities. Later in the 1st yr of life, opisthotonos, muscle rigidity, irregular movements, and convulsions tend to recur. In the 2nd yr, the opisthotonos and seizures abate, but irregular, involuntary movements, muscle rigidity, or, in some infants, hypotonia increase steadily. By 3 yr of age, the complete neurologic syndrome is often apparent; it consists of bilateral choreoathetosis with involuntary muscle spasms, extrapyramidal signs, seizures, mental deficiency, dysarthric speech, high-frequency hearing loss, squinting, and defective upward eye movements. Pyramidal signs, hypotonia, and ataxia occur in a few infants. In mildly affected infants, the syndrome may be characterized only by mild to moderate neuromuscular incoordination, partial deafness, or “minimal brain dysfunction,”

occurring singly or in combination; these problems may be inapparent until the child enters school .

Incidence and Prognosis[10]

By pathologic criteria, kernicterus develops in 30% of infants (all gestational ages) with untreated hemolytic disease and bilirubin levels >25-30 mg/dL. The incidence at autopsy in hyperbilirubinemic premature infants is 2-16%. Reliable estimates of the frequency of the clinical syndrome are not available because of the wide spectrum of manifestations. Overt neurologic signs have a grave prognosis; more than 75% of infants die, and 80% of affected survivors have bilateral choreoathetosis with involuntary muscle spasms. Mental retardation, deafness, and spastic quadriplegia are common.

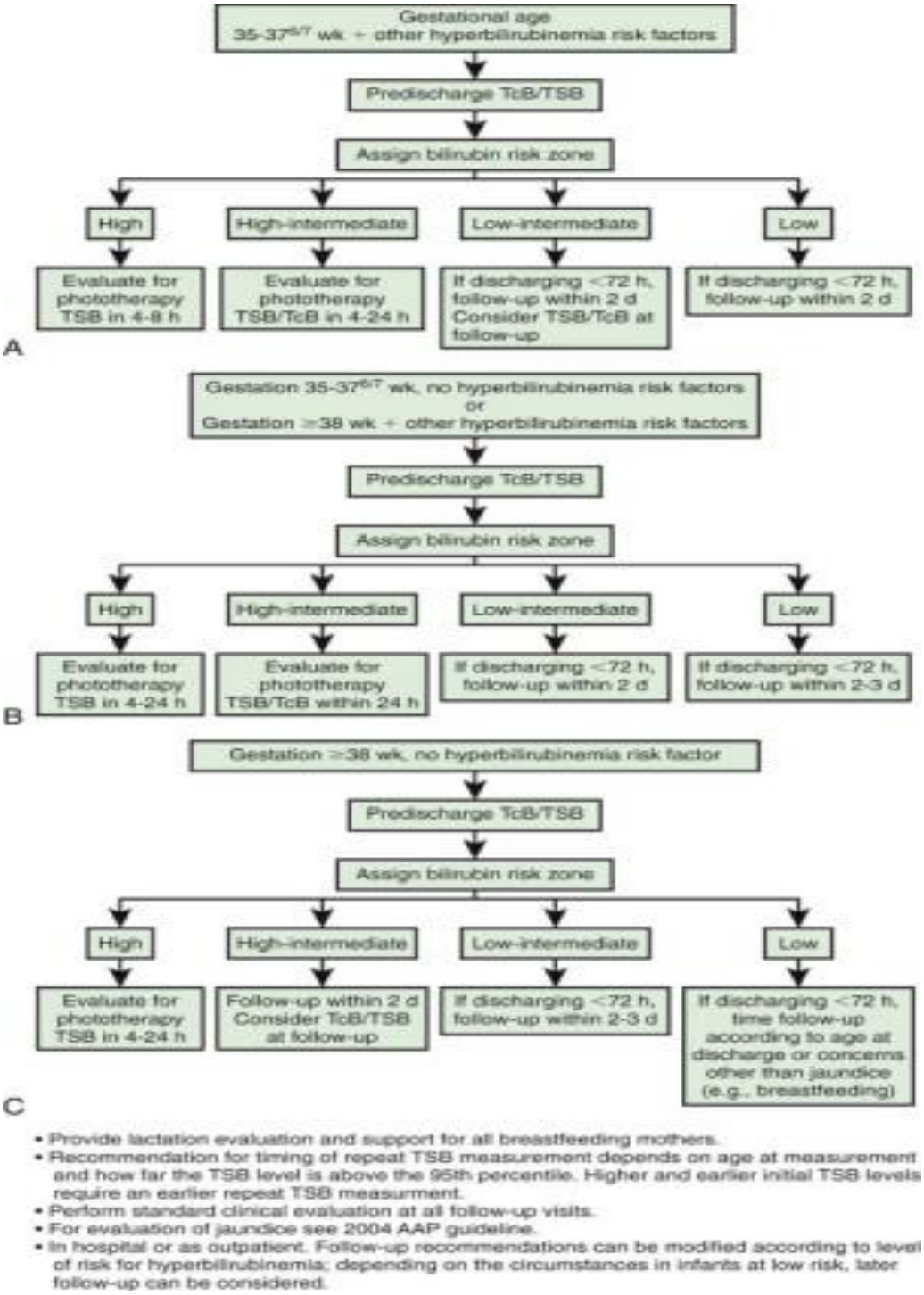


Figure 5 Algorithm providing recommendations for management and follow-up according to predischarge bilirubin measurements, gestation, and risk factors for subsequent hyperbilirubinemia

MANAGEMENT OF HYPERBILIRUBINEMIA[11]

The following are the key elements of the recommendations provided by AAP guidelines.

1. Promote and support successful breastfeeding.
2. Establish nursery protocols for the identification and evaluation of hyperbilirubinemia.
3. Measure the total serum bilirubin (TSB) or trans-cutaneous bilirubin (TcB) level on infants jaun- diced in the first 24 hours.
4. Recognize that visual estimation of the degree of jaundice can lead to errors, particularly in darkly pigmented infants.
5. Interpret all bilirubin levels according to the infant's age in hours.
6. Recognize that infants at less than 38 weeks' gestation, particularly those who are breastfed,are at higher risk of developing hyperbilirubinemia and require closer surveillance and monitoring.
7. Perform a systematic assessment on all infants before discharge for the risk of severe hyperbilirubinemia.
8. Provide parents with written and verbal information about newborn jaundice.
9. Provide appropriate follow-up based on the time of discharge and the risk assessment.
10. Treat newborns, when indicated, with phototherapy or exchange transfusion.

PRIMARY PREVENTION

Clinicians should advise mothers to nurse their infants at least 8 to 12 times per day for the first several days.[25] Poor caloric intake and/or dehydration associated with inadequate breastfeeding may contribute to the development of hyperbilirubinemia.[26,27,28] Increasing the frequency of nursing decreases the likelihood of subsequent significant hyperbilirubinemia in breast- fed infants.[29,30,31] Providing appropriate support and advice to breastfeeding mothers increases the likelihood that breastfeeding will be successful.

The AAP recommends against routine supplementation of nondehydrated breastfed infants with water or dextrose water. Supplementation with water or dextrose water will not prevent hyperbilirubinemia or decrease TSB levels.[32,33]

SECONDARY PREVENTION

An evidence-based management algorithm for infants is shown in (Figure 5). In addition, it is recommended to determine before discharge each infant's risk factors from established protocols (Table 1).

Clinicians should perform ongoing systematic assessments during the neonatal period for the risk of an infant. developing severe hyperbilirubinemia.

Blood Typing

All pregnant women should be tested for ABO and Rh (D) blood types and have a serum screen for unusual isoimmune antibodies. If a mother has not had prenatal blood grouping or is Rh-negative, a direct anti- body test (or

Coombs' test), blood type, and an Rh (D) type on the infant's (cord) blood are strongly recommended. If the maternal blood is group O, Rh-positive, it is an option to test the cord blood for the infant's blood type and direct antibody test, but it is not required provided that there is appropriate surveillance, risk assessment before discharge, and follow-up.[34]

Clinical Assessment

Clinicians should ensure that all infants are routinely monitored for the development of jaundice, and nurseries should have established protocols for the assessment of jaundice. Jaundice should be assessed whenever the infant's vital signs are measured but no less than every 8 to 12 hours. Protocols for the assessment of jaundice should include the circumstances in which nursing staff can obtain a TcB level or order a TSB measurement.

Laboratory Evaluation

A TcB and/or TSB measure- ment should be performed on every infant who is jaun- diced in the first 24 hours after birth (Fig 6 and Table 2).[14] The need for and timing of a repeat TcB or TSB measurement will depend on the zone in which the TSB falls (Fig 3) the age of the infant, and the evolution of the hyperbilirubinemia.

Recommendations for TSB measurements after the age of 24 hours are provided in Fig 6 and Table 2.

A TcB and/or TSB measure- ment should be performed if the jaundice appears excessive for the infant's age. If there is any doubt about the degree of jaundice,

the TSB or TcB should be measured. Visual estimation of bilirubin levels from the degree of jaundice can lead to errors, particularly in darkly pigmented infants.

All bilirubin levels should be interpreted according to the infant's age in hours (Fig 3).

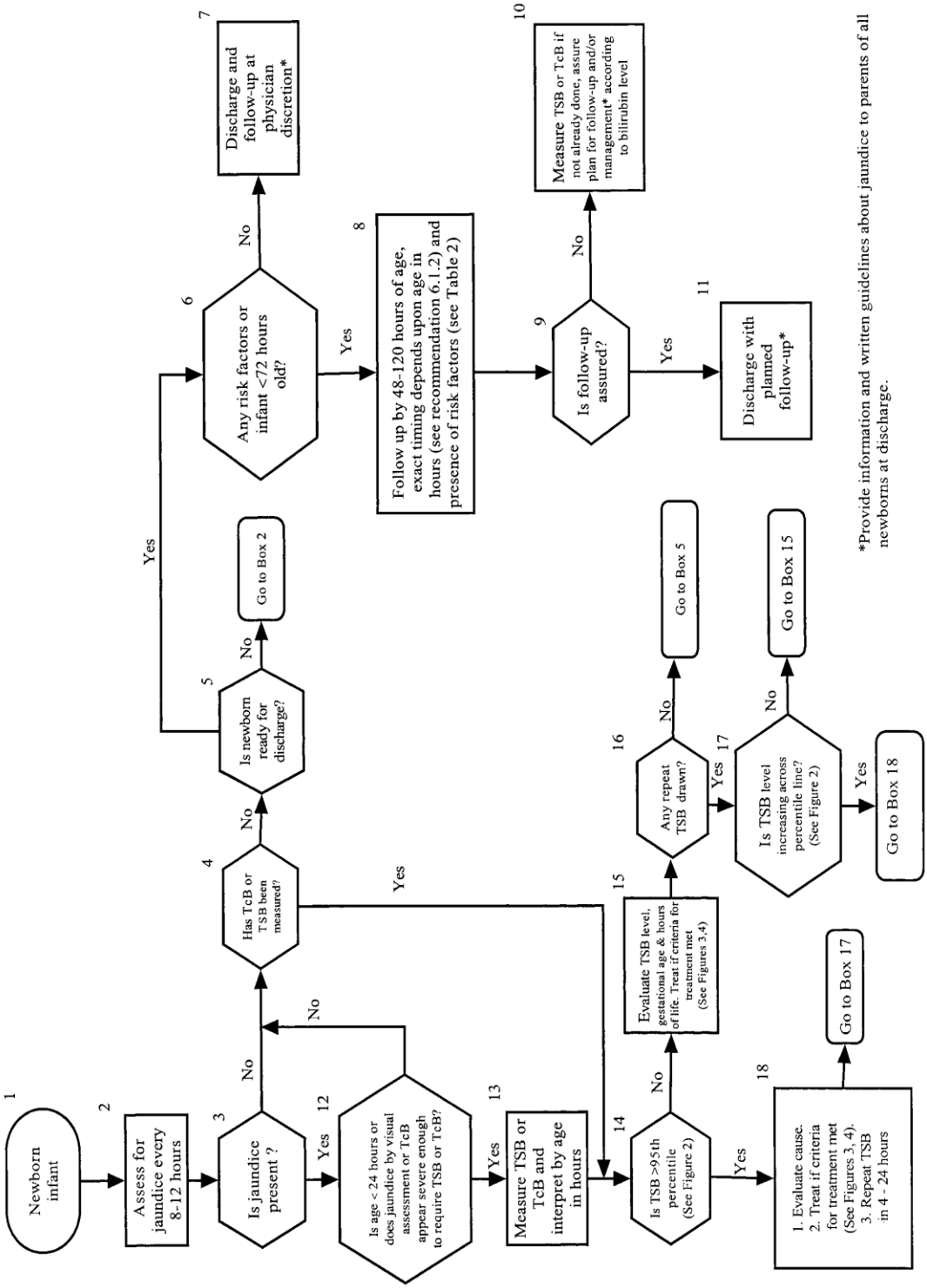


Figure 6:Algorithm for management of jaundice in the newborn nursery

Cause of Jaundice

The possible cause of jaundice should be sought in an infant receiving phototherapy or whose TSB level is rising rapidly (ie, crossing percentiles [Fig 3]) and is not explained by the history and physical examination.

Infants who have an elevation of direct-reacting or conjugated bilirubin should have a urinalysis and urine culture.[35] Additional laboratory evaluation for sepsis should be performed if indicated by history and physical examination.

Sick infants and those who are jaundiced at or beyond 3 weeks should have a measurement of total and direct or conjugated bilirubin to identify cholestasis (Table 2). The results of the newborn thyroid and galactosemia screen should also be checked in these infants.

If the direct-reacting or conjugated bilirubin level is elevated, additional evaluation for the causes of cholestasis is recommended.

Measurement of the glucose-6-phosphate dehydrogenase (G6PD) level is recommended for a jaundiced infant who is receiving phototherapy and whose family history or ethnic or geographic origin suggest the likelihood of G6PD deficiency or for an infant in whom the response to phototherapy is poor.

Before discharge, every newborn should be assessed for the risk of developing sever hyperbilirubinemia, and all nurseries should establish protocols for assessing this risk. Such assessment is particularly important in infants who are

discharged before the age of 72 hours

The AAP recommends 2 clinical options used individually or in combination for the systematic assessment of risk: predischarge measurement of the bilirubin level using TSB or TcB and/or assessment of clinical risk factors.

Whether either or both options are used, appropriate follow-up after discharge is essential

Hospital Policies and Procedures

All hospitals should provide written and verbal information for parents at the time of discharge, which should include an explanation of jaundice, the need to monitor infants for jaundice, and advice on how monitoring should be done.

Follow-up

All infants should be examined by a qualified health care professional in the first few days after discharge to assess infant well-being and the presence or absence of jaundice. The timing and location of this assessment will be determined by the length of stay in the nursery, presence or absence of risk factors for hyper-bilirubinemia (Table 1 and Fig 3), and risk of other neo- natal problems.

Timing of Follow-up

Follow-up should be pro- vided as follows.

Timing of Follow up	
Infant Discharged	Should be Seen by Age
Before age 24 hrs	72 h
Between 24 and 47.9 hrs	96 h
Between 48 and 72 hrs	120 h

For some newborns discharged before 48 hours, 2 follow-up visits may be required, the first visit between 24 and 72 hours and the second between 72 and 120 hours. Clinical judgment should be used in determining follow- up. Earlier or more frequent follow-up should be provided for those who have risk factors for hyperbilirubinemia (Table 1), whereas those discharged with few or no risk factors can be seen after longer intervals.

If appropriate follow-up cannot be ensured in the presence of elevated risk for developing severe hyperbilirubinemia, it may be necessary to delay discharge either until appropriate follow-up can be ensured or the period of greatest risk has passed (72-96 hours).

Follow-up Assessment

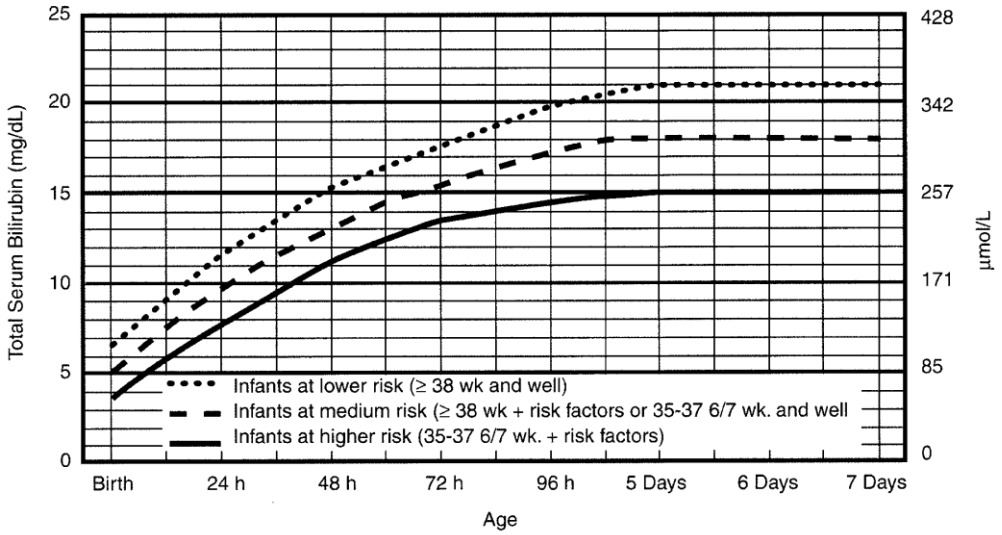
The follow-up assessment should include the infant's weight and percent change from birth weight, adequacy of intake, the pattern of void- ing and stooling,

and the presence or absence of jaundice. Clinical judg- ment should be used to determine the need for a bilirubin measurement. If there is any doubt about the degree of jaundice, the TSB or TcB level should be measured. Visual estimation of bilirubin levels can lead to errors, particularly in darkly pigmented infants.

TREATMENT: Phototherapy and Exchange Transfusion

Recommendations for treatment are given in Figs 6 and 7 In using the guidelines for phototherapy and exchange transfusion, the direct-reacting (or conjugated) bilirubin level should not be subtracted from the total.

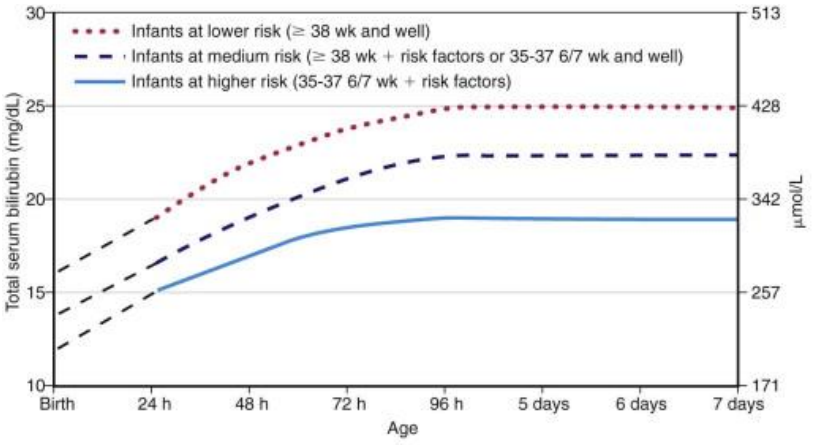
Regardless of the cause, the goal of therapy is to prevent neurotoxicity related to indirect-reacting bilirubin while not causing undue harm. Phototherapy and, if it is unsuccessful, exchange transfusion remain the primary treatment modalities used to keep the maximal total serum bilirubin below pathologic levels (Figs.7 and 8;). The risk of injury to the central nervous system from bilirubin must be balanced against the potential risk of treatment. When identified, underlying medical causes of elevated bilirubin and physiologic factors that contribute to neuronal susceptibility should be treated, with antibiotics for septicemia and correction of acidosis (Table 6).



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin < 3.0g/dL (if measured)
- For well infants 35-37 6/7 wk can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 wks and at higher TSB levels for those closer to 37 6/7 wk.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50mmol/L) below those shown but home phototherapy should not be used in any infant with risk factors.

Figure 7: Guidelines for phototherapy in hospitalized infants of ≥35 weeks of gestation. *Note:* These guidelines are based on limited evidence, and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy, which should be used when the total serum bilirubin (TSB) exceeds the line indicated for each category. Infants are designated as "higher risk" because of the potential negative effects of the conditions listed on albumin binding of bilirubin,[36-38] the blood-brain barrier,[39] and the susceptibility of the brain cells to damage by bilirubin.[39] "Intensive phototherapy" implies irradiance in the blue-green spectrum (wavelengths approximately 430-490 nm) of at least 30 µW/cm^2/nm (measured at the infant's skin directly below the center of the phototherapy unit) and delivered to as much of the infant's skin surface area as possible. Note that irradiance measured below the center of the light source is much greater than that measured at the periphery. Measurements should be made with a radiometer specified by the

manufacturer of the phototherapy system. If TSB levels approach or exceed the exchange transfusion line , the sides of the bassinette, incubator, or warmer should be lined with aluminum foil or white material, to increase both the surface area of the infant exposed and the efficacy of phototherapy. The presence of hemolysis is strongly suggested if the TSB does not decrease or continues to rise in an infant who is receiving intensive phototherapy. Infants who receive phototherapy and have an elevated direct-reacting or conjugated bilirubin value (cholestatic jaundice) may inconsistently have the bronze-baby syndrome. G6PD, glucose-6-phosphate dehydrogenase.



- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥ 5 mg/dL (85 μmol/L) above these lines.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Measure serum albumin and calculate B/A ratio (see legend).
- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- If infant is well and 35-37 6/7 wk (median risk), can individualize TSB levels for exchange based on actual gestational age.

Figure 8- Guidelines for exchange transfusion in hospitalized infants of ≥35 weeks of gestation. *Note:* These suggested levels represent a consensus of most of the committee but are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if the total serum bilirubin (TSB) rises to these levels despite

intensive phototherapy. In a readmitted infant, if the TSB level is above the exchange level, TSB measurement should be repeated every 2-3 hr; exchange transfusion should be considered if the TSB remains above the levels indicated after intensive phototherapy for 6 hr. The following B/A ratios can be used together with, but not in lieu of, the TSB level as an additional factor in determining the need for exchange transfusion. G6PD, glucose-6-phosphate dehydrogenase.

Phototherapy

Clinical jaundice and indirect hyperbilirubinemia are reduced by exposure to a high intensity of light in the visible spectrum. Bilirubin absorbs light maximally in the blue range (420-470 nm). Broad-spectrum white, blue, and special narrow-spectrum (super) blue lights have been effective in reducing bilirubin levels. Bilirubin in the skin absorbs light energy, causing several photochemical reactions. One major product from phototherapy is a result of a reversible photo-isomerization reaction converting the toxic native unconjugated 4Z,15Z-bilirubin into an unconjugated configurational isomer, 4Z,15E-bilirubin, which can then be excreted in bile without conjugation. The other major product from phototherapy is lumirubin, which is an irreversible structural isomer converted from native bilirubin that can be excreted by the kidneys in the unconjugated state. It is an option to measure the serum albumin level and consider an albumin level of less than 3.0 g/dL as one risk factor for lowering the threshold for phototherapy use (see Fig 3)

Complications associated with phototherapy include loose stools, erythematous macular rash, purpuric rash associated with transient porphyrinemia, overheating, dehydration (increased insensible water loss, diarrhea), hypothermia

from exposure, and a benign condition called bronze baby syndrome (which occurs in the presence of direct hyperbilirubinemia; see later). Phototherapy is contraindicated in the presence of porphyria. Before phototherapy is initiated, the infant's eyes should be closed and adequately covered to prevent light exposure and corneal damage. Body temperature should be monitored, and the infant should be shielded from bulb breakage. Irradiance should be measured directly. In infants with hemolytic disease, care must be taken to monitor for the development of anemia, which may require transfusion. Anemia may develop despite lowering of bilirubin levels.

The term bronze baby syndrome refers to a sometimes-noted dark, grayish brown skin discoloration in infants undergoing phototherapy. Almost all infants observed with this syndrome have had significant elevation of direct-reacting bilirubin and other evidence of obstructive liver disease. The discoloration may be due to photo-induced modification of porphyrins, which are often present during cholestatic jaundice and may last for many months. Despite the bronze baby syndrome, phototherapy can continue if needed.

Table 5 -- EXAMPLE OF A CLINICAL PATHWAY FOR MANAGEMENT OF THE NEWBORN INFANT READMITTED FOR PHOTOTHERAPY OR EXCHANGE TRANSFUSION

TREATMENT
Use intensive phototherapy and/or exchange transfusion as indicated in Figs. 96-11 and 96-12
LABORATORY TESTS
TSB and direct bilirubin levels Blood type (ABO, Rh) Direct antibody test (Coombs) Serum albumin Complete blood cell count with differential and smear for red cell morphology Reticulocyte count End-tidal CO concentration (if available) Glucose-6-phosphate dehydrogenase if suggested by ethnic or geographic origin or if poor response to phototherapy Urine for reducing substances If history and/or presentation suggest sepsis, perform blood culture, urine culture, and cerebrospinal fluid for protein, glucose, cell count, and culture
INTERVENTIONS
If TSB ≥25 mg/dL (428 μmol/L) or ≥20 mg/dL (342 μmol/L) in a sick infant or infant <38 wk gestation, obtain a type and crossmatch, and request blood in case an exchange transfusion is necessary.

	In infants with isoimmune hemolytic disease and TSB level rising in spite of intensive phototherapy or within 2-3 mg/dL (34-51 µmol/L) of exchange level (Fig. 96-12), administer intravenous immunoglobulin 0.5-1 g/kg over 2 hr and repeat in 12 hr if necessary. If infant's weight loss from birth is >12% or there is clinical or biochemical evidence of dehydration, recommend formula or expressed breast milk. If oral intake is in question, give intravenous fluids.
FOR INFANTS RECEIVING INTENSIVE PHOTOTHERAPY:	
	Breast-feed or bottle-feed (formula or expressed breast milk) every 2-3 hr If TSB ≥25 mg/dL (428 µmol/L), repeat TSB within 2-3 hr If TSB 20-25 mg/dL (342-428 µmol/L), repeat within 3-4 hr. If TSB <20 mg/dL (342 µmol/L), repeat in 4-6 hr. If TSB continues to fall, repeat in 8-12 hr. If TSB is not decreasing or is moving closer to level for exchange transfusion or the TSB/albumin ratio exceeds levels shown in Fig. 96-12, consider exchange transfusion (see Fig. 96-12 for exchange transfusion recommendations). When TSB is <13-14 mg/dL (239 µmol/L), discontinue phototherapy. Depending on the cause of the hyperbilirubinemia, it is an option to measure TSB 24 hr after discharge to check for rebound.

Intravenous Immunoglobulin

The administration of intravenous immunoglobulin is an adjunctive treatment for hyperbilirubinemia due to isoimmune hemolytic disease. Its use is recommended when serum bilirubin is approaching exchange levels despite maximal interventions including phototherapy.[40] Intravenous immunoglobulin (0.5-1.0 g/kg/dose; repeat in 12 hr) has been shown to reduce the need for exchange transfusion in both ABO and Rh hemolytic disease, presumably by reducing hemolysis.[40]

Metalloporphyrins

A potentially important alternative therapy is the use of metalloporphyrins for hyperbilirubinemia.[41-44] The metalloporphyrin Sn-mesoporphyrin (SnMP) offers promise as a drug candidate. The proposed mechanism of action is competitive enzymatic inhibition of the rate-limiting conversion of heme-protein to biliverdin (an intermediate metabolite in the production of unconjugated bilirubin) by heme-oxygenase. A single intramuscular dose on the 1st day of life may reduce the need for subsequent phototherapy. Such therapy may be beneficial when jaundice is anticipated, particularly in patients with ABO incompatibility or G6PD deficiency or when blood products are objected to, as with Jehovah's Witness patients. Complications from metalloporphyrins include transient erythema if the infant is receiving phototherapy. Administration of SnMP may reduce bilirubin levels and decrease both the need for phototherapy and the duration of hospital stay; however, it remains unclear whether treatment with metalloporphyrins for unconjugated hyperbilirubinemia will alter the risk of kernicterus or long-term neurodevelopment

impairment. Data on efficacy, toxicity, and long-term benefit are currently being evaluated.

Exchange Transfusion

If the TSB is at a level at which exchange transfusion is recommended (Fig 7) or if the TSB level is 25 mg/dL (428 mol/L) or higher at any time, it is a medical emergency and the infant should be admitted immediately and directly to a hospital pediatric service for intensive phototherapy. These infants should not be referred to the emergency department, because it delays the initiation of treatment[45]

Exchange transfusions should be performed only by trained personnel in a neonatal intensive care unit with fu If an exchange transfusion is being considered, the serum albumin level should be measured and the bilirubin/albumin (B/A) ratio used in conjunction with the TSB level and other factors in dete mining the need for exchange transfusion monitoring and resuscitation capabilities.

Double-volume exchange transfusion is performed if intensive phototherapy has failed to reduce bilirubin levels to a safe range and if the risk of kernicterus exceeds the risk of the procedure. Potential complications from exchange transfusion are not trivial and include metabolic acidosis, electrolyte abnormalities, hypoglycemia, hypocalcemia, thrombocytopenia, volume overload, arrhythmias, NEC, infection, graft versus host disease, and death.

Material & Methods

- Study design: Prospective observational study.
- Place: Neonatology unit in BLDEU Shri B.M. Patil Medical College, Hospital and Research Centre, Vijayapur
- Duration: November 1st 2015 to April 2017.
- Subjects: Newborn babies born in this hospital

Selection criteria

Inclusion criteria:

Term babies, both genders, both normal and lower segment caesarean-section deliveries, birth weight ≥ 2500 gm and APGAR score > 7/10 at 1 min.

Exclusion criteria:

1) Rh incompatibility
2) ABO incompatibility
3) Neonatal sepsis
4) Instrumental delivery
5) Birth asphyxia
6) Meconium stained amniotic fluid
7) Pathological jaundice
8) Any NICU admission [other than observation]
9) Any significant congenital malformations and
10) Denial of consent

METHODOLOGY

In this prospective observational analytical study, a sample of 123 healthy full term newborns delivered in Shri B.M. Patil Medical College, Hospital and Research Centre with birth weight of ≥ 2500 gm was included.

Cord blood was taken from umbilical cord at birth for analysis of albumin, bilirubin, nRBC and reticulocyte levels. Then newborns, will be monitored in terms of developing jaundice using Krammer index every morning after birth. Serum bilirubin was done on 3rd day and whenever it is ≥12 mg/dl (as per Krammer index), babies was followed up clinically in the ward till discharge or seventh day of life. If baby had clinically significant jaundice then treatment and follow up was done as per NICU protocol. Those babies who are discharged early they were called on 3rd day and clinical findings was noted. In case of significant jaundice serum bilirubin estimates was done and managed according to protocol.

All neonates included in the study had the following done:

1. Detailed maternal history like age, parity, gestational age was noted.
2. Details of labour, mode of delivery was recorded.
3. Details of baby like: sex, date of birth, time of birth, Apgar scores was noted.
4. Thorough clinical examination of the neonates was done.
5. All investigations was done at the haematology and biochemistry department of Shri B.M Patil Medical College, Hospital and Research Center, Vijayapur.

STATISTICAL ANALYSIS

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries. The difference of the means of analysis variables between two independent groups was tested by unpaired t test. The difference of the means of analysis variables between more than two independent groups was tested by ANOVA and F test of testing of equality of Variance. Bivariate correlation analysis using Pearson's correlation coefficient (r) was used to test the strength and direction of relationships between the interval levels of variables. ROC analysis for Sensitivity- specificity was done to check relative efficiency. If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23.0. and Microsoft office.

RESULTS

The total number of neonates estimated with cord bilirubin levels were 200. A total of 77 Neonates who were discharged early from the hospital, the ones who did not turn up for the followup for re-estimation of serum bilirubin at 72 hours were excluded from the study. The total no. of neonates included in the study was 123.

TOTAL No. OF NEONATES IN THE STUDY

TABLE 6

No. of neonates estimated with cord albumin, bilirubin, nRBC and reticulocyte levels	200
No. of neonates lost follow up	77
No. of neonates included in the study	123

MATERNAL CHARACTERISTICS

TABLE:7 DISTRIBUTION OF CASES ACCORDING TO MODE OF DELIVERY

MOD	N	%
CS	28	22.8
NV	95	77.2
Total	123	100

FIGURE:9 DISTRIBUTION OF CASES ACCORDING TO MODE OF DELIVERY

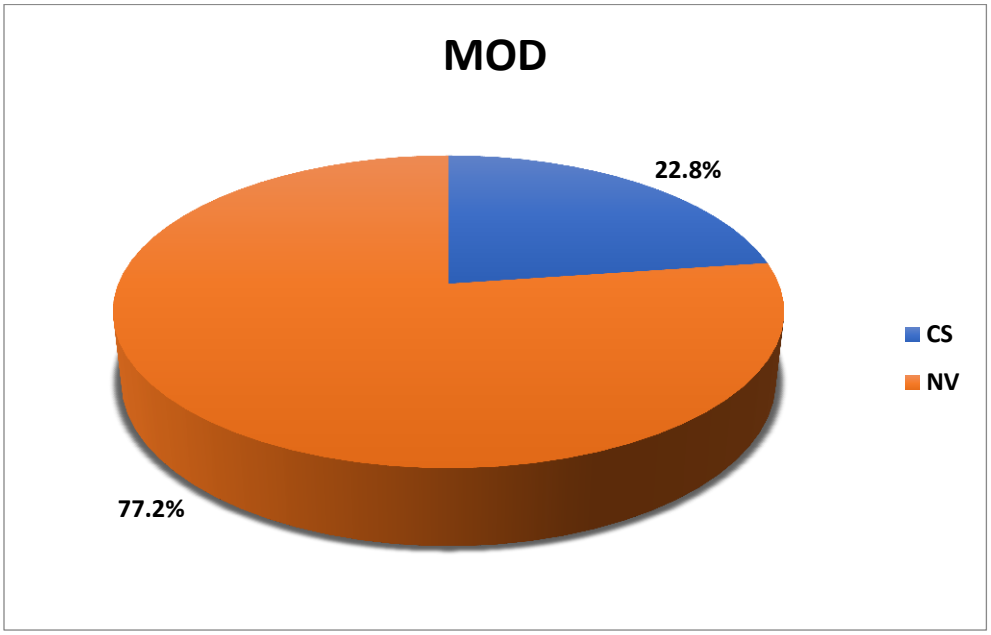
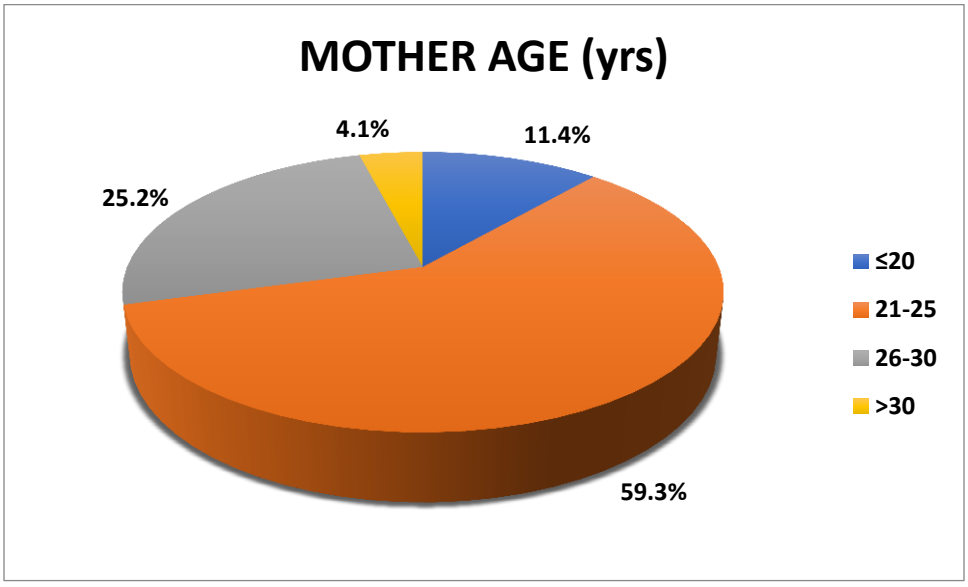


TABLE:8 DISTRIBUTION OF CASES ACCORDING TO MOTHER'S AGE

MOTHER AGE (yrs)	N	%
≤20	14	11.4
21-25	73	59.3
26-30	31	25.2
>30	5	4.1
Total	123	100

FIGURE:10 DISTRIBUTION OF CASES ACCORDING TO MOTHER'S AGE



NEONATAL CHARACTERISTICS

TABLE:9 DISTRIBUTION OF CASES ACCORDING TO SEX

SEX	N	%
Male	71	57.7
Female	52	42.3
Total	123	100

FIGURE:11 DISTRIBUTION OF CASES ACCORDING TO SEX

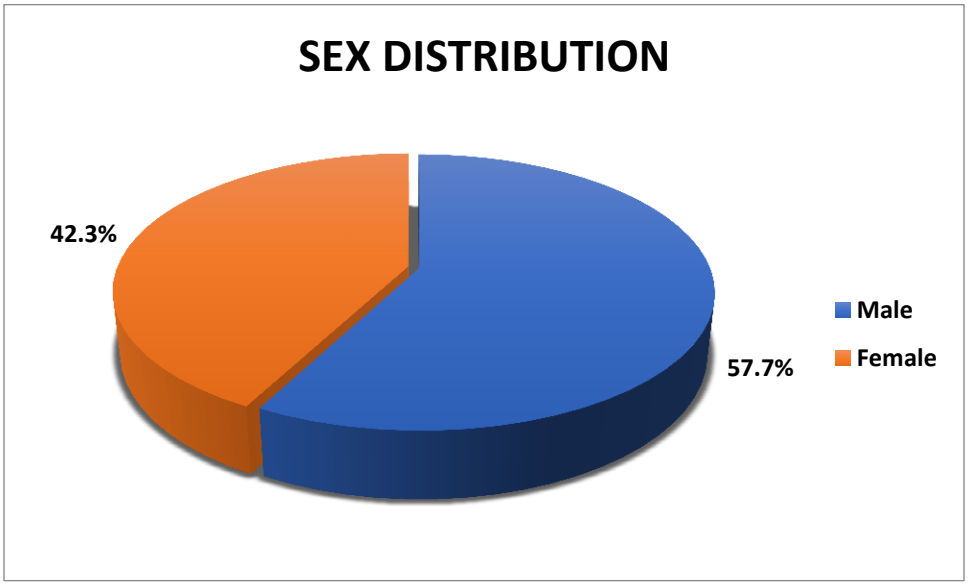


TABLE:10 DISTRIBUTION OF CASES ACCORDING TO BIRTHWEIGHT

BIRTHWEIGHT (gm)	N	%
2.5	5	4.1
>2.5-3.0	70	56.9
>3.0	48	39
Total	123	100

FIGURE:12 DISTRIBUTION OF CASES ACCORDING TO BIRTHWEIGHT

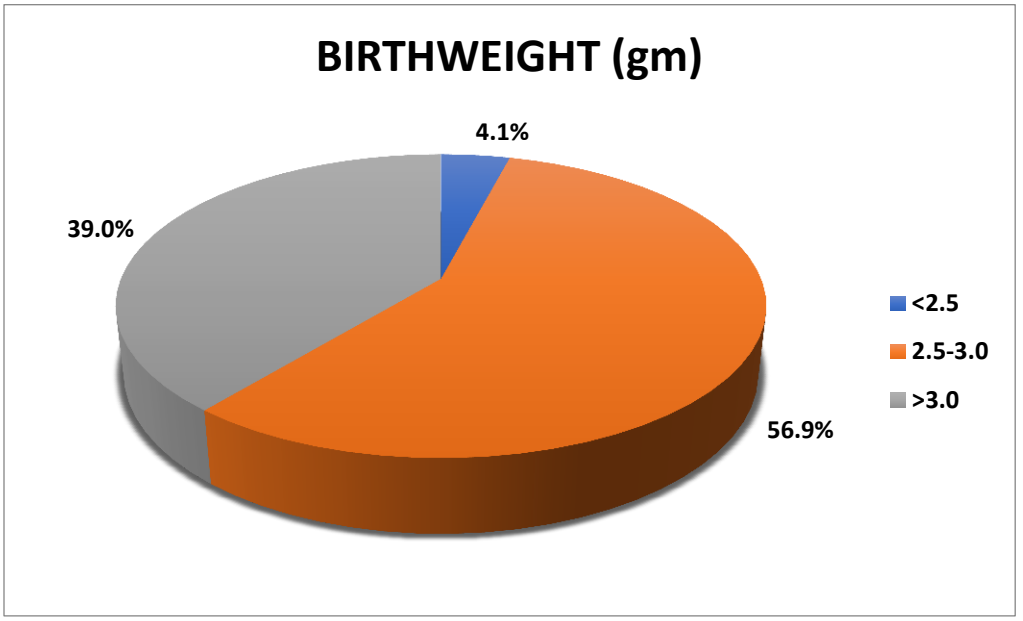


TABLE:11 BIRTHWEIGHT OF CASES ACCORDING TO HYPERBILIRUBINEMIA (≥12MG/DL) AFTER 72HRS

Variables	Serum bilirubin (≤12mg/dl) after 72hrs		Serum bilirubin (>12mg/dl) after 72hrs		p value
	Mean	SD	Mean	SD	
BIRTHWEIGHT (gm)	2894.8	273.4	2942.7	288.8	0.417

TABLE:12 MOTHER AGE OF CASES ACCORDING TO HYPERBILIRUBINEMIA (≥12MG/DL) AFTER 72HRS

MOTHER AGE (yrs)	Serum bilirubin (≤12mg/dl) after 72hrs		Serum bilirubin (>12mg/dl) after 72hrs		p value
	Mean	SD	Mean	SD	
≤20	11	11.7	3	10.3	0.987
21-25	55	58.5	18	62.1	
26-30	24	25.5	7	24.1	
>30	4	4.3	1	3.4	
Total	94	100.0	29	100.0	

TABLE:13 SEX OF CASES ACCORDING TO HYPERBILIRUBINEMIA (≥12MG/DL) AFTER 72HRS

SEX	Serum bilirubin (≤12mg/dl) after 72hrs		Serum bilirubin (>12mg/dl) after 72hrs		p value
	Mean	SD	Mean	SD	
Male	51	54.3	20	69.0	0.161
Female	43	45.7	9	31.0	
Total	94	100.0	29	100.0	

TABLE:14 MODE OF DELIVERY OF CASES ACCORDING TO HYPERBILIRUBINEMIA (≥12MG/DL) AFTER 72HRS

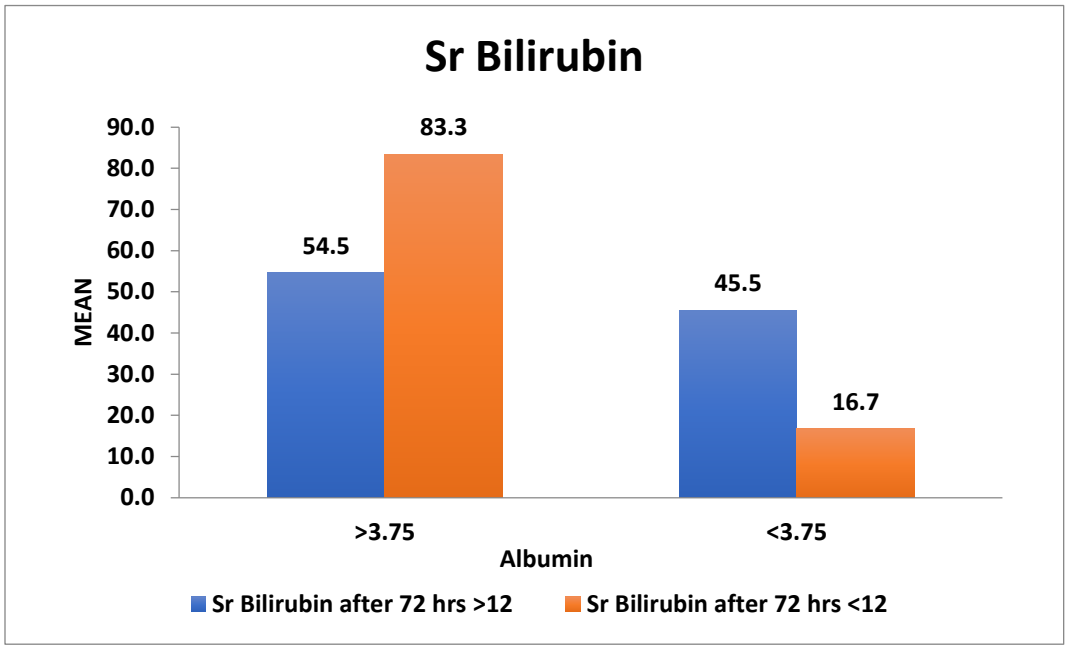
MOD	Serum bilirubin (≤12mg/dl) after 72hrs		Serum bilirubin (>12mg/dl) after 72hrs		p value
	Mean	SD	Mean	SD	
CS	24	25.5	4	13.8	0.188
NV	70	74.5	25	86.2	
Total	94	100.0	29	100.0	

There were no significant differences between the cases who had cord bilirubin level <1.75mg/dl and >1.75mg/dl with respect to various factors that may be associated with the risk of hyperbilirubinemia, such as gender, gestational age, birth weight and delivery route.

TABLE:15 DISTRIBUTION OF CORD ALBUMIN LEVELS

Albumin	Serum Bilirubin after 72 hrs >12(mg/dl)		Serum Bilirubin after 72 hrs <12(mg/dl)		p value
	N	%	N	%	
>3.75 (N=93)	18	54.5	75	83.3	0.001*
<3.75 (N=30)	15	45.5	15	16.7	
Total	33	100.0	90	100.0	

FIGURE:13 DISTRIBUTION OF CORD ALBUMIN LEVELS



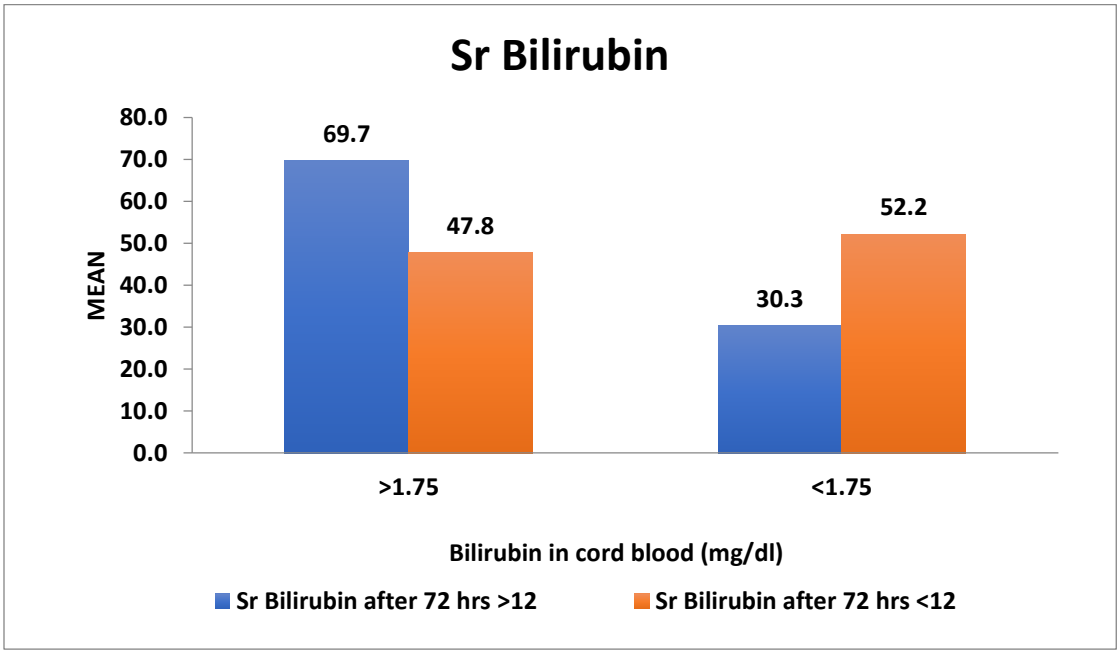
Relationship between cord albumin and serum bilirubin after 72hours

Of the 93 newborns who had cord albumin level >3.75 gm/dl, 18(19.35%) developed hyperbilirubinemia after 72 hours of life, whereas 15 of 30 newborns (50%) whose cord albumin is <3.75 gm/dl, developed hyperbilirubinemia after 72 hours of life.

TABLE:16 DISTRIBUTION OF CORD BILIRUBIN LEVELS

Bilirubin in cord blood (mg/dl)	Serum Bilirubin after 72 hrs >12(mg/dl)		Serum Bilirubin after 72 hrs <12(mg/dl)		p value
	N	%	N	%	
>1.75 (N=66)	23	69.7	43	47.8	0.031 *
<1.75 (N=57)	10	30.3	47	52.2	
TOTAL	33	100.0	90	100.0	

FIGURE:14 DISTRIBUTION OF CORD BILIRUBIN LEVELS



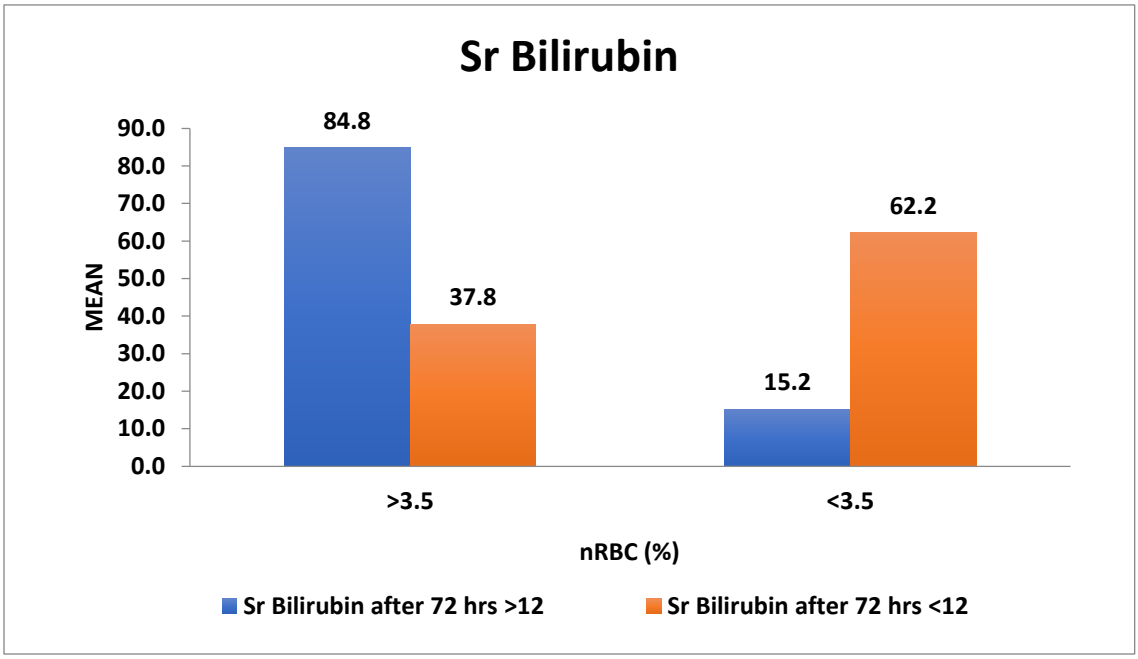
Relationship between cord bilirubin and serum bilirubin after 72hours

Of the 66 newborns who had cord bilirubin level >1.75 mg/dl, 23 (34.8%) newborns developed hyperbilirubinemia after 72 hours of life, whereas 10 of 57 newborns (17.5%) whose cord bilirubin level <1.75 mg/dl, developed hyperbilirubinemia after 72 hours of life.

TABLE:17 DISTRIBUTION OF CORD nRBC (%) LEVELS

nRBC (%)	Serum Bilirubin after 72 hrs >12(mg/dl)		Serum Bilirubin after 72 hrs <12(mg/dl)		p value
	N	%	N	%	
>3.5 (N=62)	28	84.8	34	37.8	<0.001*
<3.5 (N=61)	5	15.2	56	62.2	
Total	33	100.0	90	100.0	

FIGURE:15 DISTRIBUTION OF CORD nRBC(%) LEVELS



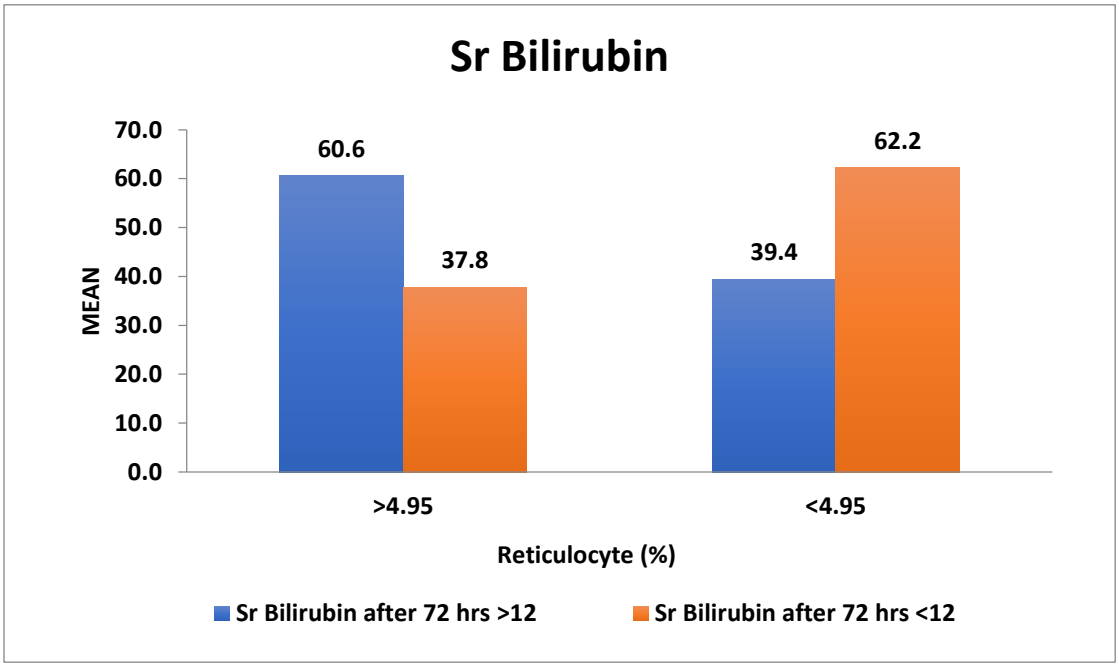
Relationship between cord nRBC and serum bilirubin after 72hours

Of the 62 newborns who had cord nRBC >3.5%, 28(45.16%) newborns developed hyperbilirubinemia after 72 hours of life, whereas 5 of 61 newborns (8.19%) whose cord nRBC <3.5%, developed hyperbilirubinemia after 72 hours of life.

TABLE:18 DISTRIBUTION OF CORD RETICULOCYTE (%) LEVELS

Reticulocyte (%)	Serum Bilirubin after 72 hrs >12(mg/dl)		Serum Bilirubin after 72 hrs <12(mg/dl)		p value
	N	%	N	%	
>4.95 (N=54)	20	60.6	34	37.8	0.024*
<4.95 (N=69)	13	39.4	56	62.2	
Total	33	100.0	90	100.0	

FIGURE:16 DISTRIBUTION OF CORD RETICULOCYTE (%) LEVELS



Relationship between cord reticulocyte count and serum bilirubin after 72hours

Of the 54 newborns who had cord reticulocyte >4.95%, 20 (37.03%) newborns developed hyperbilirubinemia after 72 hours of life, whereas 13 of 69 newborns (18.84%) whose cord reticulocyte level <4.95%, developed hyperbilirubinemia after 72 hours of life.

TABLE:19 CORRELATION OF BILIRUBIN AT DAY3 WITH OTHER PARAMETERS

	r value	p value
BIRTHWEIGHT (gm)	0.037	0.684
Albumin	-0.328	<0.001*
Bilirubin in cord blood (mg/dl)	0.243	0.007*
nRBC (%)	0.652	<0.001*
Reticulocyte (%)	0.341	<0.001*

Note: *means significant at 5% level of significance (p<0.05)

FIGURE:17 CORRELATION OF BILIRUBIN AT DAY3 WITH BILIRUBIN IN CORD BLOOD

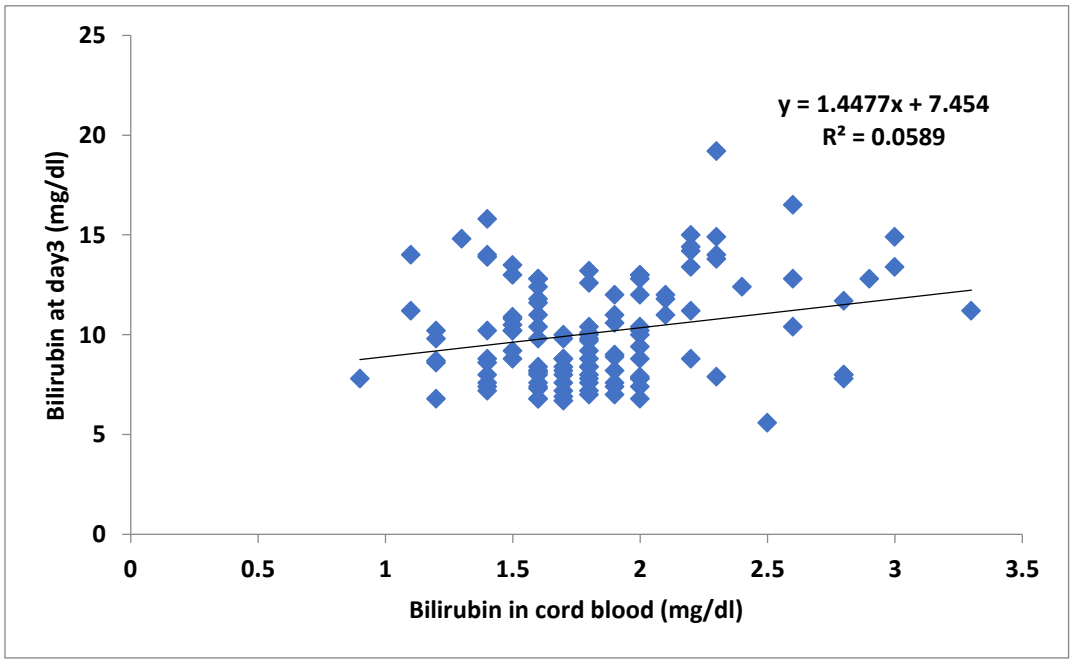


TABLE:20 COMPARISON OF MEAN VARIABLES ACCORDING TO HYPERBILIRUBINEMIA

Variables	Serum bilirubin (≤12mg/dl) after 72hrs		Serum bilirubin (>12mg/dl) after 72hrs		p value
	Mean	SD	Mean	SD	
Albumin	3.92	0.20	3.70	0.37	0.003*
Bilirubin in cord blood (mg/dl)	1.79	0.39	2.02	0.52	0.012*
nRBC (%)	2.84	2.30	8.55	4.77	<0.001*
Reticulocyte (%)	4.41	2.07	5.81	2.58	0.003*
Bilirubin at day3 (mg/dl)	8.95	1.54	13.91	1.45	<0.001*

Note: *means significant at 5% level of significance (p<0.05)

FIGURE:18 COMPARISON OF MEAN VARIABLES ACCORDING TO HYPERBILIRUBINEMIA

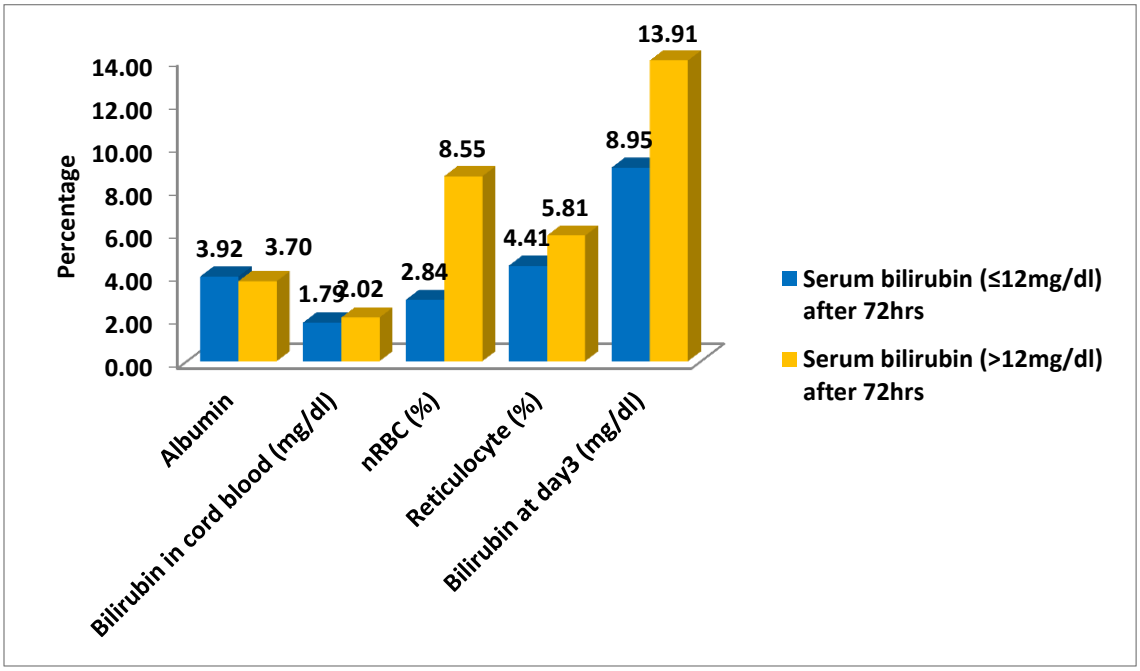


TABLE:21 ROC ANALYSIS OF VARIABLES IN PREDICTION OF NEONATAL HYPERBILIRUBINEMIA

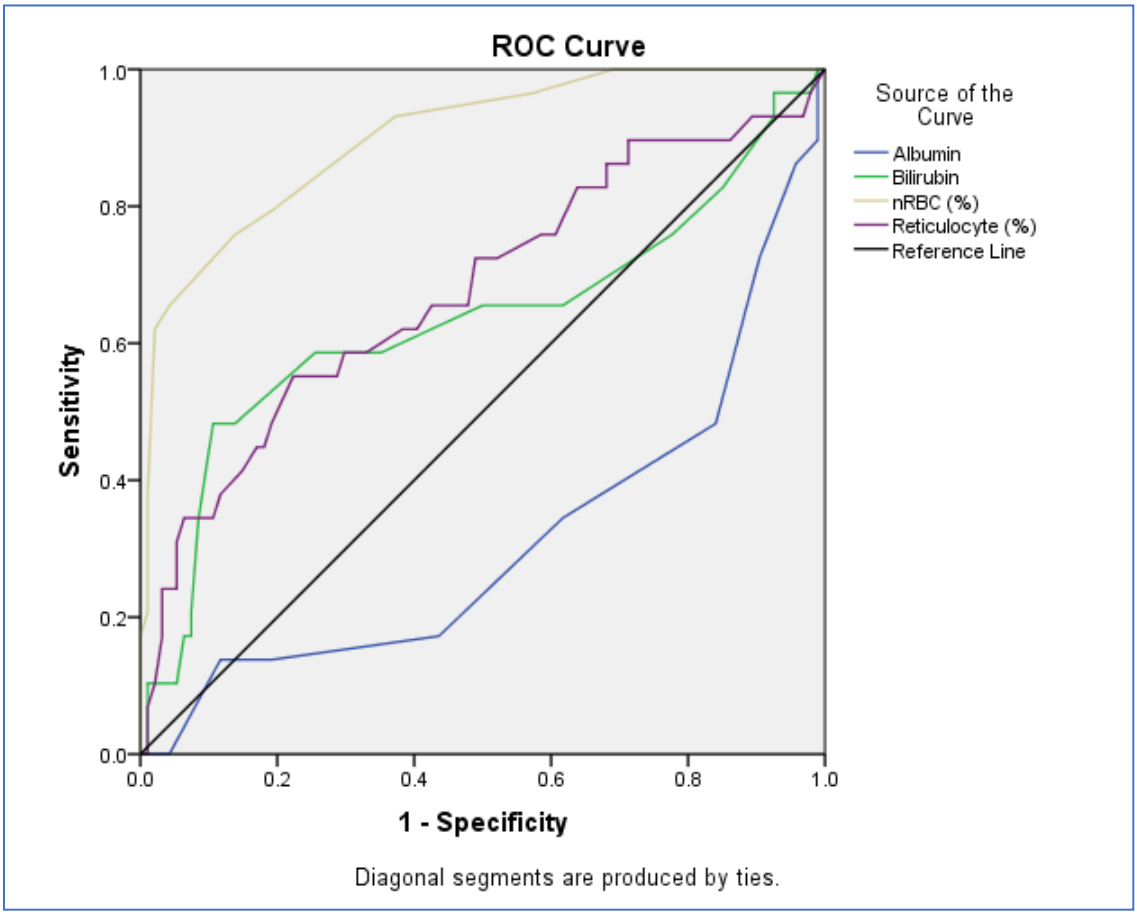
Test Result Variable	Area Under the Curve	Std. Error	p value
Albumin	0.312	0.061	0.002*
Bilirubin in cord blood (mg/dl)	0.632	0.069	0.031*
nRBC (%)	0.901	0.033	<0.001*
Reticulocyte (%)	0.676	0.062	0.004*

Note: *means significant at 5% level of significance ($p<0.05$)

TABLE:22 CUT OFF POINTS OF VARIABLES IN PREDICTION OF NEONATAL HYPERBILIRUBINEMIA

Score	Cutoff	Sensitivity	Specificity
Albumin	3.75	62.1%	54.9%
Bilirubin in cord blood (mg/dl)	1.75	65.5%	50.0%
nRBC (%)	3.5	93.1%	62.8%
Reticulocyte (%)	4.95	62.1%	61.7%

FIGURE:19 ROC CURVE



With Receiver operating characteristic (ROC) analysis, a cut off value of cord nRBC level of ≥3.5% was determined which has the highest sensitivity (84.8%) to predict the newborns who would develop hyperbilirubinemia.

RESULTS OF ANALYSIS

CORD ALBUMIN

Sensitivity	54.5%
Specificity	16.7%
PPV	19.4%
NPV	50.0%
Accuracy	26.8%

The probability that neonates with cord albumin lesser than 3.75gm/dl would later become hyperbilirubinemia (Positive Predictive Values) was 19.4%.

The negative predictive values, the probability of non-hyperbilirubinemia given a cord albumin higher or equal to 3.75 gm/dl was 50.0%.

If a neonate becomes hyperbilirubinemic, the probability that the cord albumin was lesser than 3.75gm/dl was 54.5% (Sensitivity).

Given a non-hyperbilirubinemic child, the probability that the cord albumin was higher or equal to 3.75 gm/dl was 16.7% (Specificity).

CORD BILIRUBIN

Sensitivity	69.7%
Specificity	52.2%
PPV	34.8%
NPV	82.5%
Accuracy	56.9%

The probability that neonates with cord bilirubin higher than 1.75mg/dl would later become hyperbilirubinemia (Positive Predictive Values) was 34.8%.

The negative predictive values, the probability of nonhyperbilirubinemia given a cord bilirubin lower or equal to 1.75mg/dl was 82.5%.

If a neonate becomes hyperbilirubinemic, the probability that the cord bilirubin was higher than 1.75mg/dl was 69.7%(Sensitivity).

Given a non-hyperbilirubinemic child, the probability that the cord bilirubin was lower or equal to 1.75mg/dl was 52.2%(Specificity).

CORD nRBC%

Sensitivity	84.8%
Specificity	62.2%
PPV	45.2%
NPV	91.8%
Accuracy	68.3%

The probability that neonates with cord nRBC higher than 3.5% would later become hyperbilirubinemia (Positive Predictive Values) was 45.2%.

The negative predictive values, the probability of nonhyperbilirubinemia given a cord nRBC lower or equal to 3.5% was 91.8%.

If a neonate becomes hyperbilirubinemic, the probability that the cord nRBC was higher than 3.5% was 84.8%(Sensitivity).

Given a non-hyperbilirubinemic child, the probability that the cord NRBC was lower or equal to 3.5% was 62.2%(Specificity).

CORD RETICULOCYTE%

Sensitivity	60.6%
Specificity	62.2%
PPV	37.0%
NPV	81.2%
Accuracy	61.8%

The probability that neonates with cord reticulocyte higher than 4.95% would later become hyperbilirubinemia (Positive Predictive Values) was 37.0%.

The negative predictive values, the probability of nonhyperbilirubinemia given a cord reticulocyte lower or equal to 4.95% was 81.2%.

If a neonate becomes hyperbilirubinemic, the probability that the cord reticulocyte was higher than 4.95% was 60.6%(Sensitivity).

Given a non-hyperbilirubinemic child, the probability that the cord reticulocyte was lower or equal to 4.95% was 62.2%(Specificity).

DISCUSSION

Jaundice in newborn is quite common affecting nearly 60% of term and 80% of preterm neonates during first week of life.[46] Higher cord bilirubin level levels among infants who later become jaundiced compared to cord bilirubin levels in non-jaundiced infants indicate that mechanisms of importance for the subsequent jaundice are already active in late fetal life. Nearly all fetal bilirubin is unconjugated, due to a limited ability of the fetal liver to conjugate bilirubin. In plasma, unconjugated bilirubin is tightly bound to albumin, which is the dominant bilirubin binding protein in plasma. Under normal circumstances no bilirubin deposition in fetal tissue takes place. Unconjugated bilirubin is rapidly transferred to the maternal circulation by the placenta, whereas only small quantities of conjugated bilirubin cross the placenta. Thus, bilirubin produced by the fetus is excreted by the mother, who presumably has a large reserve capacity for bilirubin excretion, and only minor differences in maternal bilirubin concentrations can be expected.[47] Raised cord blood bilirubin in ABO or non-ABO situation indicates ongoing in utero hemolysis. These babies are more likely to develop hyperbilirubinemia. A cord bilirubin level >2.5mg/dl predicts development of pathological jaundice.[48]

Alpay et al observed that a serum bilirubin >6mg/dl on the first day of life had 90% sensitivity of predicting a subsequent TSB >17mg/dl between 2nd and 5th day of life. At this critical serum bilirubin value, the negative predictive value was 97.9%. No cases with TSB of <6mg/dl in the first 24 hours required phototherapy treatment.[49]

Predictive value of measuring cord bilirubin concentration in ABO-incompatibility has been investigated by Riesenberg et al.[50] who found that all infants with cord bilirubin levels higher than 68µmol/l(4mg/dl), developed severe jaundice.

The study done by Seidman et al found that the risk of significant hyperbilirubinemia was 1.6% in cases whose bilirubin level was <5 mg/dL at 24 hours of life, whereas that risk was 6.6% in cases whose bilirubin level was >5 mg/dL at 24 hours of life.[51] The maternal and umbilical cord bilirubin concentration at delivery, a yellow skin colour on the first post-natal day, an increase in the yellow skin colour during the first 24 h of postnatal life, and carbon monoxide excretion are all associated with the later development of neonatal jaundice in the healthy, mature newborn infant.[52]

Rosenfeld J reported that infants with cord bilirubin levels less than 2.0 mg/dL have only a 4 percent chance of developing hyperbilirubinemia and a 1.4 percent chance of needing phototherapy. However, if serum cord bilirubin levels are more than 2.0 mg/dL, the infant has a 25 percent chance of developing subsequent hyperbili-rubinemia.[53]

Rataj J et al reported that if cord bilirubin was under 1 mg% jaundice occurred in 2.4% newborns, where as 89% of the infants with cord bilirubin above 2.5 mg% became jaundiced.[54]

Knudsen A found that if cord bilirubin was below 20 µmol/l(1.17mg/dl), 2.9% became jaundiced as opposed to 85% if cord bilirubin was above 40 µmol/l(2.34mg/dl). Furthermore, 57% of jaundiced in-fants with cord bilirubin above 40 µmol/l(2.34mg/dl) required phototherapy, but only 9% if cord bilirubin was 40 µmol/l(2.34mg/dl) or lower (p less than 0.003).[55]

Amar Taksande et a1.[56] observed that infants with cord bilirubin level <2mg/dl had only 1.28% chances of developing significant hyperbilirubinemia. However, if serum cord bilirubin level is >2mg/dl, the neonate had 38.63% chances of developing significant hyperbilirubinemia (sensitivity 89.5%, specificity 85.1%, positive predictive value 38.6% and negative predictive value 98.7%)

In our study, the cord bilirubin level of >1.75 mg/dL had the sensitivity (69.7%), and this critical bilirubin level had a high (82.5%) negative predictive value and fairly low (34.8%) positive predictive value. The cord bilirubin level of <1.75 mg/dL did not completely exclude the development of hyperbilirubinemia; only 17.5% of the newborns with cord bilirubin levels of <1.75mg/dL developed jaundice. A 82.5% negative predictive value in the present study suggests that measurement of cord serum bilirubin can help in

identify those newborns who are unlikely to require further evaluation and intervention.

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.

In our study group, there were no significant differences between the cases who did and the cases who did not develop significant hyper-bilirubinemia with respect to these factors (such as gender, delivery route, birth weight and gestational age) that may be associated with the risk of hyperbilirubinemia.

Sahu et al, showed that 70% newborn who developed significant Neonatal hyperbilirubinemia had cord albumin level <2.8 gm/dL, 30% newborn had cord albumin level 2.9-3.3 gm/dL and none of the newborns with cord albumin level >3.4 gm/dL developed hyperbilirubinemia.[57]

Gaurav aiyappa et al. observed the sensitivity of cord albumin <2.8gm/dl to detect hyperbilirubinemia in newborn was determined and found to be 71.8%, while specificity was 65.1%. The positive predictive value was found to be 38.9% and the negative predictive value was found to be 88.2%. The accuracy rate was 67.3%.[58]

Reshad M et al. observed in the term group, 61.2% newborns with CSA < 2.8 g/dL developed neonatal hyperbilirubinemia. 32.3% newborns had CSA level between 2.9- 3.3 g/dL, and only 6.5% of the newborns with CSA level ≥3.4 g/dL developed significant neonatal hyperbilirubinemia.[59]

In our study, the cord albumin level of <3.75 mg/dL had the sensitivity (54.5%), and this critical albumin level had a high (50.0%) negative predictive value and fairly low (19.4%) positive predictive value. The cord albumin level of >3.75 mg/dL did not completely exclude the development of hyperbilirubinemia; only 16.7% of the newborns with cord albumin levels of >3.75mg/dL developed jaundice. A 50.0% negative predictive value in the present study suggests that measurement of cord serum albumin can help in identify those newborns who are unlikely to require further evaluation and intervention.

Dr. Hermanson and his colleagues as the study of nRBC in fetuses and infants in the year of 2001 showed that increased amounts of nRBC and reticulocyte can be associated with cases such as nash stress, the use of oxytocin in labor, acute and chronic asphyxia, preeclampsia and diabetes mellitus, maternal smoking, types of anemia and embryonic hemolysis.[60]

Christianson et al. The presentation of NRBC baseline values in newborns In 2011, there was a significant correlation between elevated NRBC and reticulocyte and the presence of intracranial hemorrhage and premature neonate.[61]

Samiee Rad F et al. observed that NRBC values were higher than 5.5% with sensitivity of 66% and specificity of 90% and reticulocyte more than 5.6% with sensitivity of 73% and feature 60% can be used to identify high risk neonates for the development of jaundice.[62]

In our study, the cord nRBC of >3.5% had the sensitivity (84.8%), and this critical nRBC level had a high (91.8%) negative predictive value and fairly low (45.2%) positive predictive value. The nRBC of <3.5% did not completely exclude the development of hyperbilirubinemia; only 62.2% of the newborns with cord nRBC of <3.5% developed jaundice. A 91.8% negative predictive value in the present study suggests that measurement of cord nRBC can help in identify those newborns who are unlikely to require further evaluation and intervention.

In our study, the cord reticulocyte of >4.95% had the sensitivity (60.6%), and this critical reticulocyte level had a high (81.2%) negative predictive value and fairly low (37.0%) positive predictive value. The reticulocyte of <4.95% did not completely exclude the development of hyperbilirubinemia; only 62.2% of the newborns with cord reticulocyte of <4.95% developed jaundice. An 81.2% negative predictive value in the present study suggests that measurement of cord reticulocyte can help in identify those newborns who are unlikely to require further evaluation and intervention.

CONCLUSION

Our study has shown that cut-off value of **cord albumin** level of 3.75gm/dL has sensitivity of 54.5%, specificity of 16.7%, positive predictive value of 19.4% and negative predictive value of 50.0%.

cut off value of **cord bilirubin** level of 1.75mg/dl has sensitivity of 69.7%, specificity of 52.2%, positive predictive value of 34.8% and negative predictive value of 82.5%.

cut off value of **cord nRBC** of 3.5% has sensitivity of 84.8%, specificity of 62.2%, positive predictive value of 45.2% and negative predictive value of 91.8% and

cut off value of **cord reticulocyte** of 4.95% has sensitivity of 60.6%, specificity of 62.2%, positive predictive value of 37.0% and negative predictive value of 81.2% is useful in predicting those neonates who are at risk and those who are unlikely to develop hyperbilirubinemia.

As the positive predictive value was low with fairly high negative predictive value our cut off value of cord nRBC of 3.5% is more useful in detecting those neonates who are unlikely to develop hyperbilirubinemia.

In conclusion estimating cord albumin, bilirubin, nRBC and reticulocyte levels is a simple and non-invasive screening test to predict those neonates who are at least risk of developing hyperbilirubinemia and unlikely to require further evaluation and intervention.

SUMMARY

- Neonatal hyperbilirubinemia is the commonest cause of NICU admission in early neonatal period.
- Early detection and intervention could prevent serious complications like kernicterus.
- Cord albumin, bilirubin, nRBC and reticulocyte estimation is a simple and non-invasive test is to predict those neonates who are unlikely to develop significant hyperbilirubinemia.
- The study was done to compare cord albumin, bilirubin, nRBC and reticulocyte levels and serum bilirubin levels after 72 hours.
- A total of 123 heatlthy term neonates were included in the study for which cord albumin, bilirubin, nRBC and reticulocyte levels and serum bilirubin levels after 72 hours were done.
- By ROC curve analysis a cut-off value of 3.75gm/dL of cord albumin, 1.75mg/dl of cord bilirubin, 3.5% of cord nRBC and 4.95% of reticulocyte levels was determined.
- Of 123 neonates, 30 newborns who had a cord albumin level of <3.75gm/dL, 15(50%) developed significant hyperbilirubinemia after 72 hours of life. Of the 93 newborns who had cord albumin level >3.75 gm/dl, 18(19.35%) developed hyperbilirubinemia after 72 hours of life.
- Of the 66 newborns who had cord bilirubin level >1.75 mg/dl, 23 (34.8%) newborns developed hyperbilirubinemia after 72 hours of life, whereas 10 of

57 newborns (17.5%) whose cord bilirubin level <1.75 mg/dl, developed hyperbilirubinemia after 72 hours of life.

- Of the 62 newborns who had cord nRBC >3.5%, 28(45.16%) newborns developed hyperbilirubinemia after 72 hours of life, whereas 5 of 61 newborns (8.19%) whose cord nRBC <3.5%, developed hyperbilirubinemia after 72 hours of life.

- Of the 54 newborns who had cord reticulocyte >4.95%, 20 (37.03%) newborns developed hyperbilirubinemia after 72 hours of life, whereas 13 of 69 newborns (18.84%) whose cord reticulocyte level <4.95%, developed hyperbilirubinemia after 72 hours of life.
- Estimation of cord nRBC levels in predicting hyperbilirubinemia had highest sensitivity of 84.8% and specificity of 62.2%
- Positive and negative predictive value of 45.2% and 91.8% respectively.
- Estimation of cord albumin levels in predicting hyperbilirubinemia had lowest sensitivity of 54.5% and specificity of 16.7%
- Positive and negative predictive value of 19.4% and 50% respectively.

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ANNEXURES

ETHICAL CLERANCE CERTIFICATE

B.L.D.E.UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR – 586103
INSTITUTIONAL ETHICAL COMMITTEE

NO/55/2015
20/11/15

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 17-11-2015 *at* 03 pm *scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.*

Title "Evaluation of cord blood albumin, bilirubin, Nucleated RBC & reticulocyte count as early predictors in neonatal hyperbilirubinemia"

Name of P.G. Student : Dr Sadgunraju Chakrahari
Dept of pediatrics

Name of Guide/Co-investigator : Dr. M. M. Patil
Associate professor.

DR.TEJASWINI VALLABHA
CHAIRMAN

CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College,BIJAPUR-586103.

Following documents were placed before E.C. for Scrutinization
1)Copy of Synopsis/Research Project
2)Copy of informed consent form.
3)Any other relevant documents.

B.L.D.E.U. SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR-586103

RESEARCH INFORMED CONSENT FORM

TITLE OF THE PROJECT: EVALUATION OF CORD BLOOD ALBUMIN, BILIRUBIN, nRBC AND RETICULOCYTE COUNT IN EARLY PREDICTION OF NEONATAL HYPERBILIRUBINEMIA.

PRINCIPAL INVESTIGATOR : Dr. SADGUNRAJU CHAKRAHARI
P.G. DEPARTMENT OF
PAEDIATRICS

P.G.GUIDE : Dr. MM PATIL$_{MD}$
ASSOCIATE PROFESSSOR
DEPARTMENT OF
PAEDIATRICS

PURPOSE OF RESEARCH:

I have been informed that this study will help in early prediction of neonatal hyperbilirubinemia

PROCEDURE:

I am aware that in addition to routine care received, I will be asked series of questions by the investigator. I have been asked to undergo the necessary investigations which will help the investigator in this study.

RISK AND DISCOMFORTS:

I understand there is no risk involved and that the baby may experience some pain and discomforts during the examination. This is mainly the result of the condition and the procedures of this study are not expected to exaggerate these feelings which are associated with the usual course of treatment.

BENEFITS:

I understand that participation in the study will help the investigator to help in the early prediction of neonatal hyperbiliruninemia and early treatment.

CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of hospital records and will be subject to the confidentiality. Information of sensitive personal nature will not be part of the medical record, but will be stored in the investigations research file.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs will be used only with special written permission. I understand that I may see the photograph before giving the permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time; Dr. Sadgunraju Chakrahari at the department of pediatrics is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL FOR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice. I also understand that Dr. Sadgunraju Chakrahari may terminate my participation in the study after he has explained the reasons for doing so.

INJURY STATEMENT:

I understand that in the unlikely event of injury to the baby resulting directly from participation in this study, if such injury were reported promptly, the appropriate treatment would be available to the baby. But, no further compensation would be provided by the hospital. I understand that by my agreements to participate in this study and not waiving any of my legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks to the best of my ability.

_____ _____

Dr. Sadgunraju Chakrahari Date

(Investigator)

PARENTS / GUARDIAN CONSENT STATEMENT:

We confirm that Dr.Sadgunraju Chakrahari is doing a study on Evaluation of cord blood albumin, bilirubin, nRBC and reticulocyte for early prediction of neonatal hyperbilirubinemia, has explained to us the purpose of research and the study procedure. We are willing to allow our baby to undergo investigations and the possible discomforts as well as benefits. We have been explained all the above in detail in our own language and we understand the same. Therefore we agree to give consent for our baby to participate as a subject in this research project.

_____ _____

(Parents / Guardian) Date

_____ _____

(Witness to signature) Date

PROFORMA

SCHEME OF CASE TAKING :

Name :

Sex : IP NO :

Religion : DOB :

Postal address: DOD :

Age of the mother : Education of mother :

Age of father : Education of father :

Occupation of mother : Occupation of father :

Antenatal registration (Yes/No):

Gravida : 1 / 2 / 3 / 4 / > 5

Gestational age :

Mode of delivery (Normal vaginal/Caesarean/Forceps/Vacum):

APGAR score :

Maternal obstetric history: significant /not significant ,if significant specify

GENERAL PHYSICAL EXAMINATION:

Birth weight…….gm

HR : RR : HC :

CFT : TEMP: LENGTH:

SYSTEMIC EXAMINATION:

CVS: Normal/Abnormal, if abnormal specify :

RESPIRATORY SYSTEM:

GASTRO – INTESTINAL SYSTEM:

CNS:

Clinical evaluation of jaundice (Kramer index):

Skin of	DAY 3	DAY 4	DAY5	DAY6	DAY7
FORE HEAD 4-6 mg/dl					
CHEST 6-8 mg/dl					
ABDOMEN 8-12m g/dl					
LEGS 12-14mg/dl					
PALMS AND SOLES.> 15mg/dl					

INVESTIGATIONS:

Cord blood Albumin	
Cord blood Bilirubin	
nRBC	
Reticulocyte count	

FOLLOW UP

DATE	BILIRUBIN LEVEL mg/dl	ACTION

Final diagnosis :

BIO DATA

GUIDE

NAME : Dr .M.M PATIL

DOB : 22/07/75

QUALIFICATIONS– : M.B.B.S - KIMS Hubli

M.D – KIMS Hubli

KMC REGISTER NO : KMC 52830

WORK EXPERIENCE : UG Teacher – 9 YEARS

PG Teacher – 3 YEARS

MEMBERSHIP : IAP L2007 p1100

PRESENTLY WORKING AS: ASSOCIATE PROFESSOR

DEPARTMENT OF PEDIATRICS

SHRI B.M.PATIL MEDICAL COLLEGE,

HOSPITAL AND RESEARCH CENTRE,

BLDE UNIVERSITY

VIJAYAPUR -586103

INVESTIGATOR BIODATA

NAME : Dr.SADGUNRAJU CHAKRAHARI

DOB : 11| 02| 1989

QUALIFICATIONS : MBBS - JIUJIANG UNIVERSITY, PR CHINA

APMC REG NO : 90169

PRESENTLY

WORKING AS : POST GRADUATE/JUNIOR RESIDENT

DEPARTMENT OF PEDIATRICS

SHRI B.M.PATIL MEDICAL COLLEGE,

HOSPITAL AND RESEARCH CENTRE,

BLDE UNIVERSITY

VIJAYAPUR -586103

MASTER CHART

SL. No	NAME	MOTHER AG	SEX	IP No	MOD	Birthwt	Albumin	Bilirubin	nRBC	Reticulocyte	3rd day Bil
1	Reshma	24	Female	41911	nv	2680gm	3.9	1.5	2/100	5.00%	10.5
2	Ashwiini	21	male	41873	nv	3120gm	3.7	1.1	6/100	9	14
3	Laxmi	25	male	42163	cs	2900gm	3.6	1.5	3/100	0.3	13.5
4	Laxmi guru	25	male	232	nv	2600gm	4.2	1.6	4/100	0	12.8
5	savitha	22	male	239	nv	3600gm	4.2	1.4	26/100	3.1	15.8
6	Laxmi goni	23	male	248	nv	2500gm	3.9	2.8	4/100	5.2	8
7	Bhuvaneshwari	22	female	246	nv	3160gm	4.2	2	2/100	0	8.8
8	Tejaswini	28	female	455	nv	3100gm	3.8	2.6	5/100	4.3	10.4
9	mahananda	22	female	484	nv	2560gm	3.8	1.8	6/100	2	9.8
10	Rekha	22	female	379	nv	3300gm	4.2	1.8	4/100	5.4	12.6
11	Raeshwari	26	female	503	nv	2580gm	3.8	2.6	15/100	10	12.8
12	Beby	24	female	10386	nv	2620gm	4	1.3	8/100	8.4	14.8
13	Bhagyasree	22	male	10376	cs	2700gm	3.8	1.4	2/100	6	10.2
14	manjula	28	female	10158	nv	3200gm	3.5	1.2	3/100	5	9.8
15	ayesha	26	female	10126	nv	2700gm	4.5	2.6	8/100	8	16.5
16	chandrakala	20	female	8657	cs	2920gm	4.5	2.5	3/100	4	5.6
17	ashwini	28	male	6925	nv	2914gm	3.8	1.6	8/100	5.9	9.8
18	ratna	22	male	4955	cs	2500gm	3.9	2.2	4/100	5	8.8
19	javeda	21	female	4692	nv	3280gm	3.8	2.8	6/100	6	11.7
20	vidyasree	24	male	4428	nv	3100gm	3.3	1.8	4/100	8.3	8.4
21	basamma	30	male	11935	nv	3420gm	3.4	2.4	7/100	8.4	12.4
22	kasturi	26	female	10984	nv	2500gm	3.7	1.6	6/100	6	11
23	sushmitha	26	male	10979	nv	2620gm	3.9	1.2	7/100	4.8	10.2
24	anitha	23	male	10944	cs	2850gm	4	2	3/100	6.4	12
25	bismilla	23	male	13119	nv	3560gm	4	2.1	4/100	3.6	11.8
26	taslim	25	female	13142	nv	2900gm	3.5	1.6	6/100	5.6	10.4
27	ashwini	20	female	14884	nv	2510gm	3.8	2	5/100	6.1	10.4
28	surekha	25	male	14635	nv	2800gm	3.8	1.8	13/100	3	8
29	shruthi	35	male	15372	nv	3000gm	4.2	1.2	3/100	2	8.6
30	renuka	26	male	15404	nv	2900gm	3.9	1.8	3/100	4	8.8
31	anjanna	26	male	15325	nv	2800gm	3.9	3	12/100	9.4	13.4

32	bibifathima	26	male	15536	nv	2600gm	4	1.5	2/100	4.6	10.8
33	bismilla	36	male	15527	nv	2740gm	4.3	1.7	3/100	4.9	8.8
34	meenaxi	20	female	15972	nv	3000gm	4.3	1.1	4/100	2.2	11.2
35	rekha	18	male	15414	nv	2560gm	4.2	1.8	3/100	4.6	10
36	bagamma	21	male	15393	nv	3200gm	4.2	3.3	4/100	4.1	11.2
37	laxmi	25	female	16049	nv	2800gm	3.9	2	9/100	4.2	13
38	renuka	20	female	14954	nv	2920gm	4.2	1.4	8/100	6.6	14
39	sunanda	22	female	15124	nv	3420gm	3.9	1.6	4/100	6	12.4
40	jayashree	19	female	15113	nv	2910gm	4.1	1.2	3/100	3.4	8.7
41	parvati	24	female	15151	nv	3200gm	3.8	0.9	2/100	4	7.8
42	supritha	21	male	16139	nv	3180gm	4.8	1.6	15/100	2.1	12.8
43	gurudevi	25	female	16157	nv	3106gm	3.9	1.9	2/100	5.8	7.6
44	pushpa	24	female	16151	nv	2810gm	3.8	1.5	10/100	4.5	13
45	savithri	20	female	16527	nv	2800gm	4	1.5	6/100	4.3	10.2
46	mahananda	20	female	16637	nv	2600gm	3.8	1.4	4/100	6.2	8.6
47	geeta	25	female	16370	cs	2940gm	3.8	1.4	0/100	6.4	7.6
48	pooja	24	male	15574	cs	2846gm	4	1.4	0/100	2.2	7.4
49	sudha	26	female	14941	nv	3016gm	4.2	1.6	2/100	1.7	6.8
50	nagamma	24	male	16161	nv	2765gm	3.6	2.2	9/100	6.4	15
51	madevi	22	male	17083	nv	3016gm	4	1.6	0/100	3.9	8.2
52	riyana	24	male	16034	cs	2716gm	3.6	2	8/100	4.5	13
53	shabana	21	male	15182	nv	2642gm	4	1.4	0/100	1.5	7.2
54	laxmi	23	male	15492	cs	2650gm	3.9	1.7	3/100	2.1	7.2
55	akshata	26	male	16590	nv	2780gm	3.9	1.2	0/100	2.1	6.8
56	dilshad	28	female	16686	nv	3124gm	4	1.6	1/100	1.4	7.4
57	husainabee	26	male	16642	nv	2643gm	3.8	1.8	4/100	4.2	10.4
58	reshma	30	male	16663	nv	2821gm	3.8	1.6	0/100	4.6	8.2
59	akkubai	23	female	16381	nv	2520gm	3.7	1.9	4/100	4.1	11
60	surekha	25	female	15910	nv	3020gm	3.9	1.8	0/100	2.4	7.2
61	jyothi	21	male	16798	nv	2800gm	4	1.6	0/100	1.4	6.8
62	veena	28	male	17074	nv	2680gm	3.8	1.4	1/100	4.2	8
63	komal	20	female	17124	nv	2508gm	3.9	1.4	3/100	4.4	8.8
64	madhuri	23	female	16248	nv	2600gm	3.6	2.2	7/100	3	11.2
65	rekha	24	female	16270	nv	3100gm	4	1.6	0/100	5.4	8

66	savitha	25	male	12709	nv	3160gm	4	1.8	3/100	3.9	7.6
67	shilpa	22	male	22952	nv	3060gm	3.6	2	2/100	8	12.8
68	parvati	23	female	12692	nv	3110gm	3.8	1.8	2/100	3.9	7.8
69	ashwini	22	female	13900	nv	2670gm	4	1.6	0/100	2.2	7.6
70	neelama	24	male	12125	cs	2760gm	4	1.8	3/100	4.5	7
71	bandakka	28	male	12707	cs	2840gm	3.7	1.6	3/100	3	8.4
72	sunanda	21	male	12117	nv	3010gm	3.8	2.2	10/100	4	13.4
73	shridevi	22	male	12977	nv	2760gm	3.9	1.8	3/100	4.2	9.2
74	shwetha	26	male	11228	nv	2840gm	4.1	2	0/100	2.6	6.8
75	deepa	22	female	12180	nv	3010gm	4	1.7	0/100	2.5	8
76	shadbee	27	male	13507	cs	2768gm	3.9	1.7	0/100	2.8	6.7
77	jyoti	24	male	17110	nv	2970gm	4.1	1.6	0/100	3.2	7.3
78	mumtaz	22	female	17081	nv	3051gm	3.8	2	4/100	2.8	10
79	rekha	25	female	16900	nv	3017gm	4	1.8	1/100	2.8	8.4
80	nitha	23	male	16678	nv	3007gm	3.8	2	1/100	4.2	7.8
81	shilpa	28	female	16405	cs	2870gm	4.1	1.6	1/100	4.6	8.1
82	roopa	32	male	16227	nv	3172gm	4	2	0/100	2.8	7.4
83	shabhana	26	male	15777	cs	2620gm	4.2	1.7	0/100	4.2	6.9
84	kasturibai	28	male	15844	nv	3015gm	3.7	1.9	0/100	4.6	7.4
85	lakshmi	28	male	16179	nv	2580gm	3.7	2.2	8/100	4.8	14.4
86	mahadevi	22	female	15590	cs	2500gm	4	2	3/100	4.9	9.4
87	siddama	24	male	16060	nv	2760gm	3.7	2.3	6/100	7.2	13.8
88	shoba	24	male	16530	nv	3012gm	3.8	2.3	13/100	6.1	14
89	roopa	24	female	16501	nv	3076gm	4	1.9	5/100	4.8	10.6
90	rakambai	22	male	16536	nv	2580gm	4.1	1.7	3/100	4.2	9.8
91	kavita	27	male	16908	nv	2524gm	4	1.9	0/100	6.7	8.9
92	geeta	25	female	17029	nv	2876gm	3.9	2.1	3/100	7.1	12
93	mahadevi	24	female	17871	nv	3042gm	4.1	2	0/100	6.6	7.9
94	channamma	24	female	20408	nv	3042gm	3.8	1.9	4/100	5.9	8.2
95	nikitha	21	female	20557	cs	2589gm	3.6	1.7	4/100	3.2	8.8
96	gourabai	25	male	22208	nv	2876gm	3.4	2.3	9/100	6.5	14.9
97	pallavi	24	male	33112	cs	2620gm	4	2.8	12/100	0.3	7.8
98	chandrabag	30	male	33139	cs	2800gm	4.2	1.9	0/100	0.4	7
99	deepa	27	male	33165	cs	3400gm	3.9	1.8	5/100	5	13.2

100	geeta	20	female	33217	cs	2900gm	3.6	2.1	6/100	5.6	11
101	aishwarya	27	male	33147	cs	2850gm	3.4	2.3	4/100	6	19.2
102	laxmi	35	male	33525	nv	2840gm	4.6	3	8/100	3.5	14.9
103	pooja	20	female	33734	nv	2840gm	4.6	2.9	13/100	4	12.8
104	priyanka	19	female	33831	nv	2910gm	3.8	1.5	4/100	9	10.9
105	laxmi	22	female	33824	nv	3520gm	3.8	2	6/100	12	7.8
106	tarabai	21	male	33995	cs	2800gm	4.3	1.7	0/100	2.5	8.2
107	sumitra	22	male	33974	cs	3414gm	4	1.5	5/100	6.5	10.2
108	sarojini	30	female	34231	nv	252ogm	4	1.5	2/100	6.5	8.8
109	manhananda	25	male	34227	nv	2920gm	3.9	1.8	4/100	8.5	9.7
110	rajashree	35	male	34341	cs	34190gm	3.5	1.8	5/100	6.5	10.1
111	tejaswini	24	female	34343	cs	3200gm	3.7	2.3	2/100	7	7.9
112	banadevi	26	female	34428	nv	3140gm	3.9	1.7	3/100	5	8.4
113	akshata	21	male	347111	nv	2910gm	4	1.7	4/100	5	7.6
114	pooja	23	male	34749	nv	2780gm	4.4	2	4/100	5.2	10.2
115	ashwini	20	male	35157	nv	2580gm	3.9	1.4	6/100	8.5	13.9
116	prema	23	male	35155	nv	3280gm	4.1	1.5	3/100	7.2	9.2
117	ambawwa	30	male	35131	nv	3220gm	3.6	1.6	0/100	8.2	11.8
118	ashwini	21	male	35162	nv	3280gm	3.7	2.2	8/100	8.5	14.2
119	surekha	19	male	244	cs	3400gm	3.9	2.8	4/100	5.2	8
120	Sukanya	22	male	3610	nv	2860gm	3.8	1.6	6/100	2.1	11.6
121	Rajashree	21	female	2840	nv	2840gm	3.8	1.9	2/100	0	12
122	Balabai	22	male	3310	cs	3310gm	3.9	1.9	6/100	6.9	9
123	Bharathi	20	male	3400	cs	3400gm	3.6	1.7	1/100	5.6	10