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Effect of Instituting a Hospital Pre-discharge Bilirubin Screening on Subsequent Significant Hyperbilirubinemia in Term and Near Term Newborn

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Authors' contributions

This work was carried out in collaboration between all authors. Authors MR and AN were responsible for the coordination of the overall study, including: the study design, collaboration amongst investigators, data analysis, and manuscript preparation. Author GS wrote the first draft of the manuscript. Authors AN and GS managed the analyses of the study and the literature searches. Authors MR, AN and GS contributed to the study design and selection of cognitive biobehavioral instruments. Authors ZN and ASN assisted with staff training, manuscript review, and study design. All authors read and approved the final manuscript.

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ABSTRACT

Background: Neonatal Jaundice is a common disorder worldwide. Early identification and proper management is needed to prevent the serious neurological complications associated with it.
Objective: The aim of this study is to assess the predictive ability of a pre-discharge serum bilirubin measurement to screen for subsequent significant hyperbilirubinemia in the term and near-term newborn.
Materials and Methods: This is a historic cohort study conducted at Makassed General Hospital during two periods of time: January 2011 till December 2011, versus January 2013 till December 2013. A bilirubin screening program, instituted in February 2012, called for a total serum bilirubin to be performed on every neonate before discharge regardless of whether clinical jaundice was observed. For non-jaundiced neonates, the nursery staff was encouraged to obtain the screening

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total serum bilirubin at the sametime they obtained the hospital-mandated newborn screen for inborn errors of metabolism. Bilirubin values were plotted on an hour-specific nomogram. This study compared mean total serum bilirubin and hospital readmission data for two different periods before and after implementing the program.

Results: The study involved 1200 neonates: 601 in period one and 599 in period two. After initiating the program, the mean peak of total serum bilirubin fell from 14.76 mg/dl to 11.03 mg/dl. Also the rate of hospital readmission with a primary diagnosis of jaundice fell from 10% in period one to 1.8% in period two.

Conclusion: A pre-discharge total serum bilirubin applied as a policy in hospitals would facilitate targeted intervention and follow-up for indirect hyperbilirubinemiaina safe, cost-effective manner.

Keywords: Indirect hyperbilirubinemia; neonates; pre-discharge bilirubin screening program; Neonatal Intensive Care Unit; Newborn Nursery.

1. INTRODUCTION

Hyperbilirubinemia is a common and, in most cases, benign problem in neonates. Jaundice is observed during the first 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 is an end product of heme-protein catabolism from a series of enzymatic reactions by heme-oxygenase and biliverdin reductase and non-enzymatic reducing agents in the reticuloendothelial cells [1].

Neonatal hyperbilirubinemia remains a public health concern as documented by recent reports of kernicterus in otherwise healthy term and near-term newborns born and cared for all over the world [2,3]. Kernicterus in such newborns is preventable, provided excessive hyperbilirubinemia for age is promptly identified and appropriately treated [4,5]. With the intent to facilitate such identification and treatment, universal screening for severity of hyperbilirubinemia before hospital discharge may predict that extraordinary segment of the neonatal population that is at risk for excessive hyperbilirubinemia during the first week after birth. By identifying at-risk infants, these strategies provide an opportunity for preventive interventions to be initiated in a timely manner. They, therefore, have the potential to reduce the number of infants who develop damaging levels of bilirubin responsible for inducing neurologic injury in “healthy” term and near-term newborn infants.

Although the threshold concentration of bilirubin and/or the duration of hyperbilirubinemia have not been clearly delineated, the early detection of hyperbilirubinemia and the timely initiation of therapy offer some margin of safety for the prevention of bilirubin-induced brain injury [6]. However, the results of several studies indicate that hyperbilirubinemia is the most common cause of readmission to the hospital in the first two weeks of life [7-9]. As a risk-reduction strategy, we implemented a system wide pre-discharge bilirubin screening program in February 2012 at Makassed General Hospital, Beirut, Lebanon (MGH). The primary objective of the present study is to determine if this program was associated with reduction in the proportion of neonates with significant hyperbilirubinemia and in the proportion readmitted to the hospital with the diagnosis of hyperbilirubinemia. To our knowledge, our study is the first screening pre-discharge bilirubin level study to be conducted in Lebanon and neighboring countries.

2. MATERIALS AND METHODS

This is a historic cohort study that is carried out at Makassed General Hospital, Beirut, Lebanon, a tertiary referral medical center. This study was approved by the hospital’s Institutional Review Board. Neonates delivered at ≥35 weeks gestation during two periods of time January 2011 till December 2011, and January 2013 till December 2013 were enrolled in the study. A bilirubin screening program, instituted in February 2012, called for a total serum bilirubin (TSB) to be performed on every neonate regardless of whether clinical jaundice was observed. Bilirubin values were plotted on an hour-specific bilirubin nomogram (Fig. 1) [10]. If a bilirubin value above the 40th percentile curve, the care provider was notified and intervention, evaluation, and follow-up was arranged as deemed necessary. Newborns with indirect hyperbilirubinemia received phototherapy according to guidelines for phototherapy in hospitalized infants of 35 or more weeks’ gestation (Fig. 2) [11].

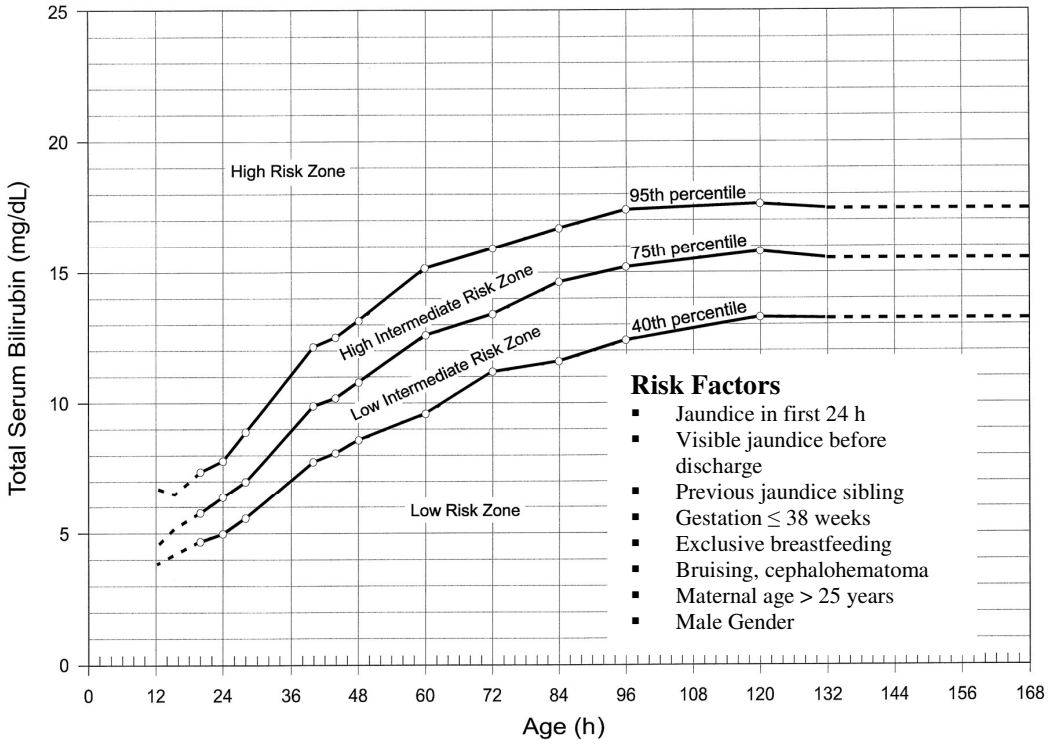

Fig. 1. Risk designation of term and near-term well newborns based on their hour-specific serum bilirubin values

Exclusion criteria consisted of all neonates born < 35 weeks gestation, newborns who were first admitted to neonatal intensive care unit (NICU) and then transferred to nursery, and babies discharged against medical advice from nursery before initiating the laboratory bilirubin test.

Fresh blood for enrolled newborns was collected at the nursery after birth mostly between 12 and 24 hours of age in microtainer tubes and sent to the hospital laboratory. Bilirubin level was performed by automated method, using dry chemistry, an end point colorimetric test based on Malloy and Evelyn [12].

2.1 Data Collection

Medical records for the newborns enrolled during the two periods were subjected to thorough review and analysis. The following data for the newborns enrolled: birth weight, gestational age, gender, maternal and baby's blood group, direct coombs test, mode of delivery, type of feeding, postnatal age at TSB measurement, phototherapy, and the likely cause of jaundice were all documented in the medical records.

2.2 Statistical Analysis

Data are reported as frequency (percent) or mean (standard deviation). Chi-square test and t-test were used to evaluate any significant difference between the two study periods. Multivariate logistic regression was done to assess the effect of taking pre-discharge bilirubin on readmission. P-value <0.05 is considered significant.

3. RESULTS

3.1 Compliance with the Program

In the first period of the study conducted from the first of January 2011 till the end of December 2011, before the bilirubin screening program was introduced, 30.4% of neonates born in MGH had a TSB level measured before hospital discharge. In contrast, after the program was introduced, the number increased rapidly such that by December 2013, 99.5% of neonates born in MGH had at least one pre-discharge bilirubin level measured.

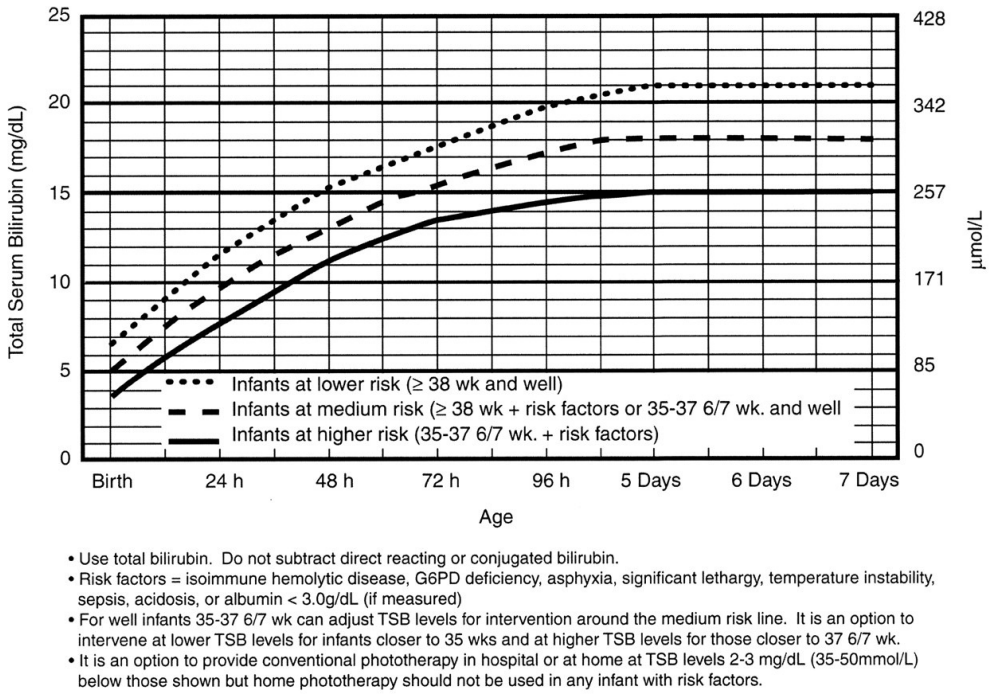

Fig. 2. Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation

3.2 Demographic Characteristics of the Study Population

In the first period 601 newborns, delivered at our hospital, were randomly selected and enrolled in the study, and in the second period 599 newborns were enrolled. There was no statistically significant difference in the demographic characteristics concerning the birth weight, gender, gestational age and mode of delivery between the 2 studied groups (Table 1). Concerning the birth weight, newborns were grouped into three categories: small, appropriate, and large for gestational age [13]. During both periods it was noted that <5 percent of babies were exclusively breastfed.

3.3 Incidence of Indirect Hyperbilirubinemia and Hospital Readmission

In the first period, 60 of 601 neonates (10%) were readmitted to the hospital for treatment of indirect hyperbilirubinemia. As shown in Table 2, during the second period after implementing the pre-discharge TSB program, the proportion of neonates readmitted fell to 11 of 599 (1.8%; P-value< 0.0001), thus decreasing the rate of hospital readmission significantly (odds ratio: 5.298). In the first period, 41 of 601 newborns (6.8%) were readmitted to NICU, whereas in period 2, this number declined to 9of 599 newborns (1.5%; P-value< 0.0001). A trend toward reducing the proportion of neonates readmitted to NICU after discharge from hospital for management of indirect hyperbilirubinemia.

3.4 Characteristics of Hospital Readmitted Newborns with Indirect Hyperbilirubinemia

The mean peak TSB for newborns readmitted in 2011 was 14.76 mg/dl, whereas in period 2, this mean level fell to 11.03 mg/dl (P-value<0.0001). However, there was no statistically significant difference regarding age of newborns at hospital readmission and at hospital discharge between period 1 and period 2 (P-value= 0.13 and P-value= 0.24 respectively). But newborns with indirect hyperbilirubinemia, who were readmitted to NICU during the period of bilirubin screening program implementation, tend to present earlier approximately at day 3 of life when compared to those who were readmitted during the period before program implementation, who presented with indirect hyperbilirubinemia at approximately day 5 of life, despite this, P-value was insignificant.

On the other hand, newborns with indirect hyperbilirubinemia received same duration of phototherapy during the two study periods (P-value= 0.332) (Table 3).

3.5 Causes of Indirect Hyperbilirubinemia in Hospital Readmitted Newborns

In the first period, 60 newborns were readmitted to the hospital for indirect hyperbilirubinemia.

Nineteen patients (31.7%) had ABO incompatibility (mother usually blood group O, infant blood group "A" or "B"), 13 (21.6%) had breastfeeding jaundice, 4(6.7%) had Rh sensitization, 4 (6.7%) had breast milk jaundice, and two (3.3%) had jaundice due to Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency) (Table 4). Hypothyroidism was the cause for jaundice in two cases; one (1.7%) patient in addition to ABO incompatibility had cephalohematoma. Sepsis, urinary tract infection and cephalohematoma were the cause for indirect hyperbilirubinemia in three patients respectively. A specific cause of the indirect hyperbilirubinemia was not identified in nine patients.

In the second period when the pre-discharge TSB program was conducted, 4 of 11(36.4%) patients had ABO incompatibility as a cause of readmission for jaundice, 3(27.3%) had breastfeeding jaundice, one (9.1%) had urinary tract infection, one (9.1%) had both hypothyroidism and ABO incompatibility, another newborn was late premature, and a specific cause for jaundice was undetermined in one patient. During these two periods clinical signs of acute bilirubin encephalopathy (ABE) were not observed in any of the patients. They all received phototherapy, whereas, exchange transfusion was not required for any of the patients.

Table 1. Newborns' demographic characteristics

	Period 1 2011 (n=601)	Period 2 2013 (n=599)	P-value
Birth weight			
Small for gestation	5(0.8%)	4(0.7%)	
Appropriate for gestation	528(87.9%)	499(83.3%)	
Large for gestation	68(11.3%)	96(16%)	0.058
Gender			
Male	294(48.9%)	310(51.8%)	
Female	307(51.1%)	289(48.2%)	0.326
Gestational age			
[35-36[	13(2.2%)	15(2.5%)	
[36-37[	32(5.3%)	30(5%)	
[37-38[	117(19.5%)	110(18.4%)	
[38-39[	219(36.4%)	240(40.1%)	
[39-40[	206(34.3%)	180(30.1%)	
40+	14(2.3%)	24(4%)	0.330
Mode of delivery			
Vaginal	515(85.7%)	493(82.3%)	
C-section	86(14.3%)	106(17.7%)	0.110

Data are presented as number of patients (%)

Table 2. Hospital Readmission frequency over the two study periods

Hospital Readmission	Period 1 2011 (n=601)	Period 2 2013 (n=599)	P-value	Odds ratio	95% confidence Interval
Readmission					
Readmitted	60(10%)	11(1.8%)			
Not admitted	541(90%)	588(98.2%)	<0.0001	5.928	[3.085-11.394]
Place of readmission					
NICU	41(6.8%)	9(1.5%)			
Nursery	19(3.1%)	2(0.3%)	<0.0001		

Data are presented as number of patients (%)

Table 3. Characteristics of hospital readmitted newborns with hyperbilirubinemia

Characteristics of hospital readmitted newborns	Period 1 2011 (n=601)	Period 2 2013 (n=599)	P-value
Peak TSB, mean ± SD	14.76±3.23	11.03±2.80	<0.0001
Age at readmission (days), mean ± SD	5.0±2.68	3.56±1.74	0.13
Age at discharge (days), mean ± SD	7.8±2.695	6.67±2.17	0.243
Duration of phototherapy (days), mean ± SD	2.05±0.8	2.33±0.70	0.332

Data are presented as number of patients (%) or mean (standard deviation)

Table 4. Likely causes of indirect hyperbilirubinemia in the two study periods

Causes of hyperbilirubinemia	Period 1 2011	Period 2 2013	P-value
Likely cause of hyperbilirubinemia for newborns before discharge			
ABO incompatibilty	22(62.9%)	15(53.6%)	
ABO/Rh isoimmunization	1(2.9%)	0(0%)	
Rh isoimmunization	3(8.6%)	3(10.7%)	
Undetermined	9(25.7%)	10(35.7%)	0.520
Likely cause of hyperbilirubinemia for readmitted newborns			
ABO incompatibilty	19(31.7%)	4(36.4%)	
ABO/cephalohematoma	1(1.7%)	0(0%)	
ABO/hypothyroidism	0(0%)	1(9.1%)	
ABO/UTI	1(1.7%)	0(0%)	
Breast feeding	13(21.6%)	3(27.3%)	
Breast milk	4(6.7%)	0(0%)	
Cephalohematoma	1(1.7%)	0(0%)	
G6PD	2(3.3%)	0(0%)	
Hypothyroidism	2(3.3%)	0(0%)	
Late premature	0(0%)	1(9.1%)	
Low birth weight	2(3.3%)	0(0%)	
Rh isoimmunization	4(6.7%)	0(0%)	
Sepsis	1(1.7%)	0(0%)	
UTI	1(1.7%)	1(9.1%)	
Undetermined	9(15%)	1(9.1%)	0.592

Data are presented as number of patients (%), ABO incompatibility (mother usually blood group O, infant blood group "A" or "B"), Urinary tract infection (UTI), Glucose-6-phosphate dehydrogenase deficiency (G6PD)

4. DISCUSSION

Jaundice occurs in most newborn infants. Most jaundice is benign, but because of the potential toxicity of bilirubin, newborn infants must be monitoredto identify those who might develop severe indirect hyperbilirubinemia and, in rare cases, acute bilirubin encephalopathy or kernicterus [11]. In the 1990s, the United States and other developed countries noted a reemergence of kernicterus amongterm and near-term infants [2,14]. Increased breastfeeding and shorter hospital stays were suggested as contributing to the reemergence [7,15] as was the advocacy of a less aggressive approach to jaundiced neonates without hemolysis [13,16,17]. Variability in the time of appearance of jaundice from newborn to newborn and in the ability of the professionals to see jaundice and estimate its severity, coupled with the considerable range of TSB values associated with its cephalo-caudal progression, have been the subject of articles spanning nearly 60 years [18,19].Additionally, in most of the recently reported healthy term newborns who developed kernicterus, significant jaundice was almost certainly present before the first hospital discharge, judging from the height of TSB for age in hours at readmission [2,20]. In February 2012, we implemented in MGH a system wide hospital pre-discharge bilirubin screening program aimed at reducing severe indirect hyperbilirubinemia. Associated with the implementation of this program, we have documented a reduction in the proportion of

neonates with significant indirect hyperbilirubinemia and in the proportion readmitted to the hospital with the primary diagnosis of jaundice. Our program guidelines called for a TSB measurement on all term and near-term newborn infants before discharge. The bilirubin value was plotted on an hour-specific bilirubin nomogram to assess the hyperbilirubinemia in the context of postnatal age [11]. Bhutani et al. [14] showed the importance of interpreting neonatal bilirubin values in the context of postnatal age in hours. Based on a pre-discharge bilirubin level; they used this predictive nomogram to guide evaluation, therapy, and/or follow-up [10]. Other potentially predictive tools have been developed to aid in the identification of infants at risk fordeveloping significant indirect hyperbilirubinemia. In a retrospective study, Newman and colleagues identified eight clinical predictors of indirect hyperbilirubinemia using amultivariate logistic-regression model [21]. The predictors included early onset of jaundice, a sibling who had jaundice, exclusive breast feeding, bruising, East Asian parents, cephalohematoma, maternal age and earlier gestation. These features were used to create a bilirubin risk index for predicting TSB ≥25 mg/dl. Some of Newman's clinical risk factors were taken into consideration in our study, but the bilirubin nomogram was used as our primary predictive instrument.

In our study, we used the TSB as a screening tool for indirect hyperbilirubinemia. However, Noninvasive transcutaneous bilirubin (TcB) levels can be used as a screening tool for total serum bilirubin (TSB) levels [22]. Transcutaneous bilirubin measurements are immediate and permit screening at any age in the first few days of life. Some error is acknowledged, thus it seems reasonable to use TcB values when they are consistent with low risk. However, some degree of inaccuracy becomes more problematic at higher values that could place patients in medium or higher risk levels. It is generally recommended that TcBs in the high intermediate risk zone or higher for babies that fit the Bhutani curve or approaching the phototherapy curve for babies with risk factors should be validated with serum values [23]. In a study done on 74 term and near term newborns from September 2007 to October 2008, TSB confirmation was recommended when TcB cutoff values greater than 9, 12, 13, 15 mg/dL at 24 (TSB:8 mg/dL), 36 (TSB: 10 mg/dL), 48 (TSB: 12 mg/dL) and 72 (TSB: 15 mg/dL) hours' postnatal age, respectively [22].In any case, a serum bilirubin should be drawn before initiating phototherapy as it will not be possible to use TcB once the phototherapy has begun, and it will be important to have an initial value to compare laboratory results that are drawn later to determine therapeutic efficacy. Therefore in our study we used the TSB for all patients.

It has been estimated that approximately 1 in 70 term and near-term newborn infants develop severe indirect hyperbilirubinemia (≥20 mg/dl), 1 in 700 develop extreme indirect hyperbilirubinemia (≥25 mg/dl), and 1 in 10 000 develop hazardous hyperbilirubinemia(≥30 mg/dl) [15,24]. In the period before we initiated the bilirubin screening program, the mean for peak TSB was 14.76 mg/dl, but after initiating the program in MGH, the level declined to 11.0 mg/dl (P-value<0.001), thus leading to less complications from indirect hyperbilirubinemia. Extreme hyperbilirubinemia (≥25 mg/dl) in our population was not reported in any case in the two periods, which is less than the rate reported by Bhutani et al. [14] and Newman et al [24]. Despite the P-value was not statistically significant in the two periods of the study concerning the age of newborns who were readmitted to the hospital for management of indirect hyperbilirubinemia, the newborns after initiating the pre-discharge bilirubin level were readmitted earlier to the hospital by approximately one and a half day leading to less duration of exposure for high bilirubin levels and earlier management.

The results of several studies indicate that indirect hyperbilirubinemia is the most common cause of readmission to the hospital in the first 2 weeks of life [15,8,9]. Published rates of readmission range from 0.17 to 3.02 per 100 live births [14]. Before our program, readmission rate for jaundice was 10 percent, but after implementing the pre-discharge TSB program, the readmission rate dropped to 1.8 percent. In the study conducted within Intermountain Health Care's (IHC's) 18-hospital system during 2 periods of time: March 1, 2001, to December 31, 2002, and January 1, 2003, to December 31, 2004, the rate of readmission decreased from 0.5 percent to 0.43 percent [25].

ABO incompatibility (mother usually blood group O, infant blood group "A" or "B"), is the most common cause for hemolytic disease in newborn in the UK and occurs in 15% of pregnancies [26]. In our study it was obvious that the most common cause for jaundice was ABO

incompatibility in both groups of newborns who received pre-discharge phototherapy in the nursery or babies who were readmitted for management of indirect hyperbilirubinemia during the two periods (31.7% and 36.4% respectively). Our results were higher compared to the study conducted in pediatric unit, Lady Reading Hospital, Peshawar where out of 200 neonates presented with clinical jaundice, prevalence of ABO incompatibility was found to be 22.5% [27]. But it was similar to a study in Sgro in Canada, where ABO incompatibility was most common cause in newborns admitted for severe hyperbilirubinemia [28]. In a study conducted in Vali-e-Asr Hospital in Zanjan City, Iran, the percentage of newborns who were found to have G6PD and Rhisoimmunization admitted for indirect hyperbilirubinemia (2.1% and 2.1% respectively) was lesser than those newborns enrolled in our study and found to have G6PD and Rh isoimmunization (3.3% and 6.7% respectively), but there was a significant difference between our study and Iranian study concerning the newborns who developed jaundice due to sepsis with a higher percentage in the study conducted in Iran (1.7% and 15.7% respectively) [29].

5. CONCLUSION

This study is the first study conducted on the pre-discharge total serum bilirubin in Lebanon and neighboring countries. The results of our study demonstrate that pre-hospital discharge bilirubin screening, across a large hospital corporation; coupled with the evaluation of serum bilirubin concentrations using a percentile based nomogram, can identify neonates who are at risk for indirect hyperbilirubinemia, decrease the rate of readmission to the hospital for management of jaundice leading to a better outcome. Therefore every newborn should be assessed for the risk of developing severe indirect hyperbilirubinemia, and all nurseries should implement protocols for bilirubin measurement to be taken before discharge with the neonatal screening regardless of whether clinical jaundice was observed. 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.

CONSENT

Not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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