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Early Term Gestation - An important risk factor for significant hyperbilirubinemia in Neonates.

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ABSTRACT

Significant hyperbilirubinemia (HB) is observed in 8-11% of neonates and if severe, it may result in acute bilirubin encephalopathy, kernicterus, and subtle neurodevelopmental disorders. This study aimed to look for the risk factors for readmission with significant HB among late preterm and term babies who are discharged home without prior phototherapy. The objective was to analyze the areas of quality improvement in discharge and follow up of such babies in our institution. We performed a retrospective data review of all babies who are 35 weeks or more, born in our hospital between January 2017 and December 2018, and readmitted due to jaundice with a TSB>300 micro mols/L . We also compared the baseline data to that of the total population of babies who were born during the same period. During the period, 16498 babies were born at 35 weeks or more gestational age. 150 babies qualified the inclusion criteria. 46% of these babies had underlying risk factors. When compared to the general birth cohort, Vaginal birth (P < 0.001, OR 3.09, 95% CI 1.96 to 4.87),instrumental delivery (P <0.001, OR 3.018, 95% CI 2.02 to 4.49) and gestational age below 39 weeks(P <0.001) were significantly higher in the study group. We identified a gap between our current practice and the actual need for follow up. In addition to late prematurity, early-term gestations, namely 37 and 38 weeks, are significant risk factors of HB. Combining pre-discharge bilirubin with gestational age and risk factors enhances the chances of identifying babies with subsequent risk for significant and severe HB.

KEYWORDS: Bhutani nomogram, Early term gestation, Kernicterus, Neonatal hyperbilirubinemia, Transcutaneous bilirubin.

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I. INTRODUCTION

The majority of newborns develop physiological jaundice due to combined effects of high red cell turn over, immature hepatic conjugation, and enterohepatic circulation. Significant HB in infants ≥35 weeks gestational age is defined as a TSB level >95th percentile on the hour-specific Bhutaninomogram [1] This occurs in 8-11 % of neonates [2],[3].

The major risk factors for severe HB include pre-discharge Total serum bilirubin (TSB) or Transcutaneous bilirbun (TcB) level in the high-risk zone, jaundice observed in the first 24 h [4], blood group incompatibility with the positive direct anti-globulin test, other known hemolytic disease (e.g., Glucose -6-Phosphate Dehydrogenase deficiency), elevated end-tidal carbon dioxide, Gestational age 35–36 weeks[5],[6], previous sibling received phototherapy[6],[7] cephalohematoma or significant bruising[5] exclusive breastfeeding, (particularly if nursing is not going well and weight loss is excessive[5],[6] and East Asian race [5].The minor risk factors include pre-discharge TSB or TcB level in the high intermediate-risk zone[8],[9]. Gestational age 37–38 wk[5],[6], Jaundice observed before discharge[6], macrosomic infant of a diabetic mother[10],[11], Maternal age ≥ 25 y[5] and male gender[5],[6].

Acute bilirubin encephalopathy and kernicterus are the deadly complications of neonatal HB. Although no specific bilirubin threshold level can predict the onset of

acute bilirubin encephalopathy, population-based studies[12,13] showed that almost all babies with total bilirubin more than 35 mg/dL (599 micromol/L) Developed kernicterus. The incidence was 6% in patients with bilirubin level between 25 -30 mg/dL (428 -513 micromol/L). Some studies have observed an association between HB and more subtle neurodevelopmental effects[14]-[17], [29]. These may include developmental delay, cognitive impairment, disordered executive function, and behavioral and psychiatric disorders. Bhutani et al.[8] showed that pre-discharge TSB is useful in identifying babies who are at risk for significant HB. Babies who have pre-discharge bilirubin in the high risk or high intermediate risk zones of Bhutani nomogram are more likely to have TSB>95th centile upon follow up. Several clinical studies show that combining clinical risk factor analysis with a pre-discharge measurement of TSB or TcB significantly improves the prediction of subsequent HB risk.[18],[19],[20].

Timely follow up might be helpful in early tackling of neonatal jaundice related to breastfeeding. Phototherapy should be used judiciously. Some recent studies have pointed out the possibility of long term adverse effects for phototherapy like seizure during the first six years of life[21],[22] childhood cancer[23],[24] and melanocyte nevi [25],[26]. The existing safety nets for prevention and early management of significant HB in our institution include antenatal screening for blood group antigens and antibodies, administration of anti D to Rh-negative mothers, universal blood type screening and direct agglutination test for neonates, cord blood CBC and bilirubin for babies born to Rh-negative mothers, effective promotion and support of breast feeding, postnatal transcutaneous bilirubin screening for all neonates with more frequent TcB in high risk babies, use of American Academy of Pediatrics (AAP) guidelines for phototherapy availability of highly effective phototherapy and facility for exchange transfusion. Babies with risk factors or high pre-discharge bilirubin are followed up in the well-baby jaundice clinic or Pediatric emergency department. We frequently encounter neonates who are readmitted for phototherapy in the Pediatric Emergency Department (PED).

Objectives :

Primary objective: To look for the areas of quality improvement in discharge and follow up of late preterm and term neonates who are later readmitted with significant HB.

Secondary objectives: to study underlying the risk factors and management of significant HB in those neonates.

Inclusion criteria: babies who are 35 weeks or more, born at AWH between January 2016 and December 2018, and readmitted to AWH within 28 days of life due to indirect hyperbilirubinemia>300 micromol/L. The cut off value of 300 micromol/L is at or above the 95th centile of Bhutaninomogram for late preterm (35 weeks or more) and term neonates during the first week of life

Exclusion criteria: Babies who were born in other hospitals, Preterm < 35 weeks, those who received phototherapy before initial discharge, direct HB, incompletely documented file.

II. MATERIALS AND METHODS

This was a retrospective data review. We reviewed the files of all babies who developed HB more than 300 micromol /L and treated at Al Wakra Hospital (AWH) during the period from Jan 2016 to Dec 2018 (36 months). The health card numbers of all such babies were collected from Medical Records department. The files were examined for the baseline characteristics, risk factors for jaundice, peak bilirubin level, management, discharge, and follow up. To compare the baseline characteristics, baseline data of all live births during the corresponding three years were obtained from the Labor room register. For comparison of the discharge age, we obtained a random sample of healthy postnatal neonates who were born during the study period.

III. STATISTICAL ANALYSIS and GRAPHICAL PRESENTATION

Descriptive statistics was used to summarize the risk factors for jaundice. Data were compared as per the nature. For comparison of categorical data, Chi square test / Fisher exact test were applied and for continuous data Independent Sample T test / Mann – Whitney U test were used. All P values presented were two-tailed, and P values <0.05 was considered as statistically significant . Confidence interval was calculated with 95% confidence limit. All Statistical analyses were done using statistical packages SPSS 22.0 (SPSS Inc. Chicago, IL) software.

Baseline data

Table: 1 Baseline data in comparison to the birth cohort of the corresponding years

S.N0			Babies with bilirubin >300 micro mols/L (35 weeks or more) N=150 No (%)	All live births at 35 weeks or more (Jan 2016-Dec2019 N =16498 No (%)	P-value	OR	95% CI
1	Birth year	2016	58 (38%)	5192(31%)	0.1612		
		2017	46(30%)	5733(34.8%)			
		2018	46(30%)	5573(33.8%)			
2.	Sex	Male	82(54%_	8338 (50.5%)	0.056	1.383	0.98 to 1.94
		Female	68(46%)	8160 (49.5%)			
3.	Mode of delivery	Vaginal	128(85%)	10796(65.4%)	<0.0001	3.09	1.96 to 4.87
		LSCS	22(25%)	5702 (34.6%)			
4.	Instrumental vaginal birth		31(21%)	1330(8.6%)	<0.0001	3.018	2.02 to 4.49
5.	Nulliparous mother		54 (36%)	4887 (29.6%)	0.085	1.34	0.95 to 1.87
6.	Gestational age	35 weeks	5(3.3%)	226 (1.37%)	0.055	2.51	1.02 to 6.19
		36 weeks	15(10%)	494 (3%)	0.0001	3.681	2.14 to 6.32
		37 weeks	25(16.7%)	1325 (8.03%)	<0.0001	2.315	1.50 to 3.57
		38 weeks	44(29.3%)	3509(21.27%)	0.016	1.538	1.08 to 2.19
		>38 weeks	63(42%)	10944(66.3%)	<0.0001	0.363	0.26 to 0.50
7.	Birth weight	<2.5 kg	8(5.3%)	778 (4.72%)	0.71	1.139	0.55 to 2.33
		2.5 -2.99kg	36(24%)	3517 (21.31%)	0.42	1.167	0.80 to 1.70
		3 -3.99kg	100(65%)	11170 (67.7%)	0.337	0.851	0.61 to 1.18
		4 kg or more	6 (4%)	1033 (6.27%)	0.25	0.62	0.27 to 1.41
8.	Babies born in peak summer (Jun-Aug)		38 (25%)	4038 (24.5%)	0.806	1.047	0.72 to 1.51
9.	Babies born in peak winter (Dec – Feb)		38(25%)	3692 (22.4%)	0.402	1.177	0.81 to 1.70

Figure 1: Gestational age proportions-comparison with the birth cohort

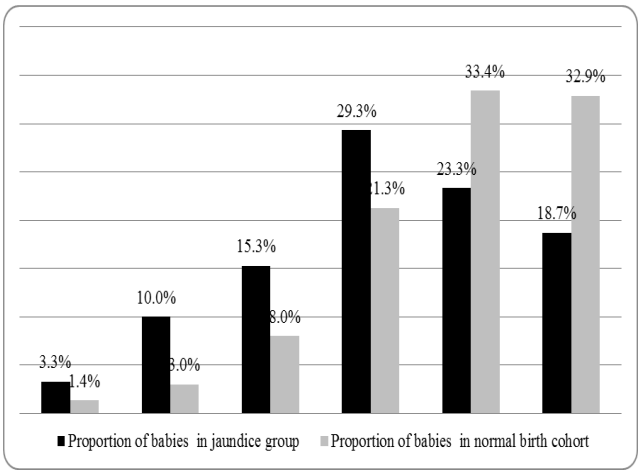

Figure 2 : Peak bilirubin level

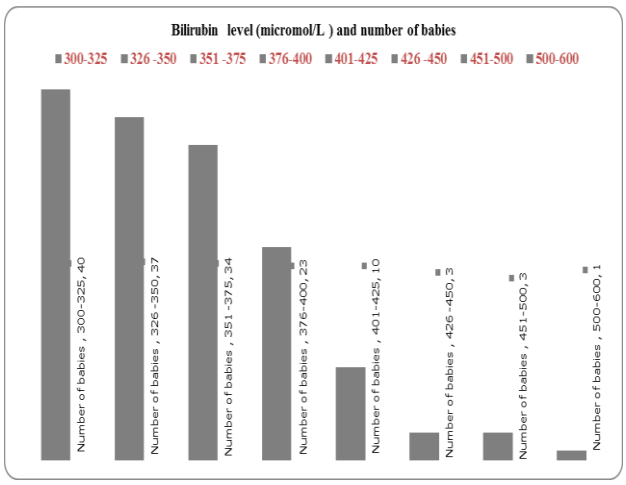

Table 2: Age upon discharge – comparison with healthy neonates who were not readmitted.

Age upon discharge	Babies readmitted with bilirubin >300 (LSCS and NICUadmissions excluded) N=120	Healthy babies –not readmitted with jaundice (random sample, matched to the time period of birth, gestational age and mode of delivery)N=120
<24 hours	27	25
24-35 hours	44	44
36 -48 hours	29	37
49-72 hours	20	14
>72 hours	0	0

Table.3: Pre - discharge bilirubin and risk factors

Risk level based on Bhutani nomogram (based on discharge TcB and age in hours)	No (%)	Additional risk factors (ABO, Rh, G6PD, Cephal) No
High risk	10(6.6%)	4
High intermediate	33 (22%)	15
Low intermediate	71(47%)	25
Low risk	36(24%)	18

Table 4. Risk factors for jaundice

Risk factor	Number of babies	Percentage
Babies with at least one predisposing factor	69	46%
ABO/Rh DAT positive	11	7.30%
ABO/Rh DAT negative	25	16.70%
G6PD deficiency	8	5.30%
Late preterm 35 - 36weeks	20	13%
Cephalhematoma, Subgalleal bleed, Polycythemia	8	5.30%
Total	**150**	**100%**

Fig 3. Pre-discharge bilirubin, gestational age and risk factors combined

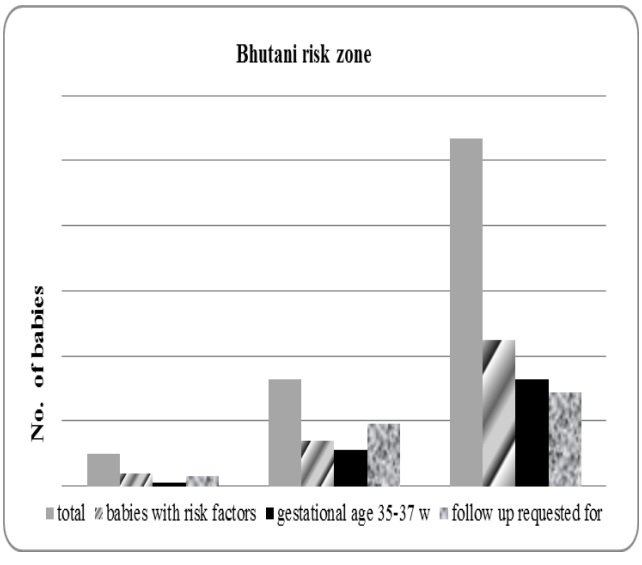

Table 5: Prediction of hyperbilirubinemia based on gestational age, risk factors or predischarge bilirubin

Bilirubin cut off level	Total no	Babies who are 35-37 weeks OR discharge bilirubin >75th centile OR with risk factors.No(%)
>300 micro mols/L (17.6 mg%)	150	110 (73%)
>342 micro mols/L (20 mg%)	87	65(75%)
>427 micromo/L (25 mg%)	8	7(87.5%)

IV. RESULTS

During the study period, 239 babies with bilirubin >300 were treated at AWH. Of them, five were born outside AWH. From the remaining 234 babies, three were excluded due to prematurity <35 weeks, and 84 excluded because of receiving phototherapy before initial discharge.

The final population consisted of 150 neonates. Our center had 16837 live births during the study period. Of them, 16498 babies were 35 weeks, or more were at birth. The baseline characteristics of the study population were compared with those of this birth cohort (Table 1).

Male babies were proportionately more, but this was not statistically significant when compared to the birth cohort. (P = 0.056) (Table 1). Vaginal births (P 0.001, OR 3.09 95% CI 1.96 to 4.87) and instrumental vaginal births (P <0.001, OR 3.018, 95% CI 2.02 to 4.49) were more frequent in the study sample. Compared to the birth cohort, the proportions of each gestational week before 39 were significantly more in the study group (Fig 1). The birth weight distribution of the study group was similar to that of the birth cohort. The incidence did not vary in peak of summer(P = 0.806) or winter (P =0.402).

The peak bilirubin (Fig 2) ranged from 301 to 590 micromol/L (354.6 ±6.7) on the mean age of 5.54 ±0.42 days.

Early discharge from hospital and inadequate follow up are potential contributing factors for subsequent significant HB[38]

To estimate the length of stay of healthy neonates, we collected the discharge data of 120 normal neonates who were discharged from the postnatal ward during the study period. This was a computerized random sample from all the postnatal babies born between Jan 2016 and Dec 2018. Babies with gestational age <35 weeks, born by LSCS and those babies who needed NICU admission or phototherapy were excluded from this control group (Table 2). Age upon initial discharge was similar in healthy babies and in those who were readmitted with jaundice.

The two important factors considered while deciding the need for further follow up are bilirubin upon discharge and the underlying risk factors. We plotted the discharge bilirubin in the Bhutani nomogram to stratify the subsequent risk of significant HB (Table 3).

Only 43 babies (28.6%) had their predischarge bilirubin in the high risk or high intermediate risk zones. This showed that a low pre-discharge bilirubin alone was not much predictive of future Hb in these neonates. 69 babies (46%) had at least one major risk factor for subsequent HB (Table 4) The major risk factors included ABO or Rh isoimmunization (n=36,24%), G6PD deficiency (n=8, 5.3%), Scalp hematomas and polycythemia (n= 8, 5.3%). 20 babies (13%) were late preterm,35-36 weeks.

To assess how was the overall eligibility for follow up at the time of discharge, we combined the gestational age, risk factors and risk zone and plotted them together (Fig 3)

When pre-discharge bilirubin, risk factors, and gestational age were combined; 110 babies (73%) had risk for subsequent HB above 300 micromol/L. But follow up for reassessing the jaundice was requested only for 57 babies (52%).(Table 5)

All the babies were initially treated by phototherapy in PED, and 66 (44%) were admitted to Pediatric inpatient or intensive care units for continuing phototherapy. None of the babies received Intravenous immune globulin. One baby with ABO incompatibility required exchange transfusion on day 12 (Peak bilirubin 590 mmol/L).

96 babies were 18 months or older at the time of the study. Of them, the developmental status was documented in 89 babies. Except for one baby with severe autistic features neurologic status was normal, among others.

V. DISCUSSION

The primary objective of our study was to explore the areas of quality improvement in discharge and follow up of neonates who were later readmitted to our Pediatric Emergency Department with significant HB. For data collection, we selected a cut off value of 300 micromol/L. This value is at or above the 95th centile of Bhutani nomogram [28] for any neonates during the first week of life.

150 babies qualified for the inclusion criteria. During the study period, our hospital recorded 16838 live births. Among them, 16498 babies were born at 35 weeks or more gestational age. Although some of the jaundiced babies are likely to attend other hospitals in the country, the sample is reflective of our hospital birth cohort. Male babies were proportionately more, but this was not significant when compared to the birth cohort. (P = 0.056) (table 6).Previous studies have demonstrated higher bilirubin in male neonates.[5],[6]

When compared to the birth cohort, vaginal births were more common in the study sample (P 0.001, OR 3.09 95% CI 1.96 to 4.87) (Table 1)[27],[28] Even though previous studies have observed the association between vaginal birth and jaundice, the higher incidence in our study could be partially explained by the fact that babies born by LSCS are mostly discharged after 72 hours of age, thus facilitating early recognition and treatment of jaundice. The incidence of instrumental vaginal births were also higher in the study group (P<0.001, OR 3.018, 95% CI 2.02 to 4.49). Vacuum extraction can increase the incidence of cephalhematoma and bruise. 1 gram of Hb can produce 35 mg of bilirubin. Nulliparous mothers are more likely to experience prolonged labor, instrumental births, and problems related to breastfeeding. All these may increase the chances of HB. But the proportion of nulliparous mothers in this study group was similar to that of the birth cohort (P =0.08).

Compared to the birth cohort, the proportions of each gestational weeks from 35 to 38 weeks were significantly higher in the study group (Table 1, Fig 1). Apart from hemolysis, the single most important factor associated with subsequent risk of significant jaundice is the decreasing gestational\age[5],[19]. Newman et al[5] calculated the risk for each decreasing week of gestation below 40 weeks. For each decreasing week, the risk of developing jaundice >25 mg % increases by 1.6 times. Compared to full term (40 weeks) babies, infants who are 35 weeks are 13 times more likely to get readmitted because of severe jaundice.[6].

The birth weight distribution of the study population was similar to that of the birth cohort. The difference was not statistically significant. (Table 1).

A Cochrane analysis observed that, delayed cord clamping is associated with an increased incidence of jaundice needing phototherapy [30] The delayed cord clamping practice was implemented in our institution since 2017 and was well established in 2018. When compared to 2016, the number of jaundice readmissions were not different in 2018, after adjusting to the number of live births.

Since many of the babies developed jaundice with no apparent risk factors, we looked for any possible variation in the incidence in relation to peaks of summer or winter. There was no significant seasonal variation in the incidence. Some authors have noted a higher rate of neonatal jaundice during summer.[31], [32].

69 babies (46%) had at least one risk obvious factor for neonatal jaundice. These included ABO or Rh incompatibility (24%), late prematurity (13%), G6PD deficiency (5.3%), and scalp hematoma or polycythemia (5.3%).

Of the 81 babies (54 %) without any distinct risk factors for developing jaundice, 47 (58%) were early term (37 and 38 weeks). AAP classifies early-term gestation as a minor risk factor for developing neonatal jaundice[5],[6] .

Being retrospective in nature, our study could not quantify the breastfeeding practice and family history of a sibling with neonatal jaundice. Multiple studies have demonstrated the association between breastfeeding and increased incidence of jaundice[33]. Less effective breastfeeding, rather than breastfeeding or breast milk per se , is more likely to be the culprit(34). Recent evidences show that genetic defects in the uridine diphosphate gluconurate glucuronosyl transferase (UGT1A1) like Gilbert syndrome, CrigglerNajjar syndrome, organic anion transporter protein-2 (OATP-2) defects maybe responsible for defective conjugation among a significant proportion of patients[35],[36].

Discharge before 48 hours of age is a significant risk factor for readmission with jaundice[37]. We compared the discharge age of the study population with that of healthy neonates who were discharged from the postnatal ward, excluding the Cesarean born neonates (Table.2). The number of babies who were discharged before 48 hours of age was less in the study population (83% Vs. 88%), indicating that early discharge was not a significant risk factor in these babies.

Bhutani et al. [1] showed that pr-discharge TSB is useful in identifying babies who are at risk for significant HB. Babies who have pre-discharge bilirubin in the High-risk zone of Bhutani nomogram are more likely to have TSB>95th centile upon follow up.

All our babies had a TcB or TSB performed before discharge. We plotted this on the hour specific Bhutani nomogram.(table 3)

Only 43 babies (28.6%) had their pre-discharge bilirubin in the high risk or high intermediate risk zones. This showed that pre-discharge bilirubin alone was not sufficient to predict the future risk of HB in these neonates. To assess how was the overall eligibility for follow up at the time of discharge, we combined the gestational age, risk factors, and risk zone and plotted them together (Fig 3). Previous studies have shown that combining pre-discharge measurement of TSB or TcB with clinical risk factors and gestational age significantly improved the prediction of subsequent HB risk [18],[19],[20]. When these were combined, 110 babies required early follow up. But follow up was requested only for 52% of them. This identified an area for quality improvement among our population.

VI. CONCLUSION

This study confirms the fact that early term gestation (37 and 38 weeks) is an important risk factor for subsequent risk of developing significant HB. The approach by combining gestational age, risk factors, and pre-discharge bilirubin significantly improves our ability to identify babies with future risk of HB. The study also identified a gap between the actual need and the current practice of follow up in our institution.

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