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TRANSCUTANEOUS BILIRUBIN NOMOGRAM IN LATE PRETERM FOR PREDICTION OF SIGNIFICANT HYPERBILIRUBINAEMIA

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ABSTRACT

AIMS: To construct transcutaneous bilirubin (TcB) nomogram for late preterm babiesover the first 120 hours of .To construct a regression equation to predict serum bilirubin from transcutaneous bilirubin level in late preterm babies.

MATERIALS AND METHODS : This Prospective observational study conducted in the Vijay Marie Hospital over a period of 1-year (January 2023- January 2024). All babies born between 34 weeks to 36 weeks + 6 day delivered in Vijay Marie Hospital were included in the study. Transcutaneous bilirubin was estimated at regular intervals till 120 hours or till discharge.

RESULTS AND CONCLUSION: A total 270 babies were recruited for the study to obtain a minimum of 143TcBvalues in each epoch. Transcutaneous bilirubin nomogram was constructed for a cohort of late preterm babies. The 5^{th}, 10^{th}, 25^{th}, 50^{th},75^{th},90^{th},95^{th} percentiles TcB charts were created. Rate of rise of bilirubin more than 0.25 mg/dl/h (which is a predictor of hyperbilirubinemia) was noticed for the first 24 hours in ≥ 75th percentile and in values ≥90th percentile till the 36th hour of life. There is no significant difference between the nomogram for boys and girls and also not much variability was noted in the rate of rise of bilirubin for 34,35and 36 weeks babies hence they may be taken as a single group in the construction of TcB nomogram. There exists a good correlation between the TcB value and the paired TSB obtained though the agreement is not very good.

Key words: Late Preterm ,Bilirubin, Nomogram,Transcutaneous,Hyperbilirubinemia.

INTRODUCTION

Jaundice is the clinical manifestation of hyperbilirubinemia (1). Neonatal hyperbilirubinemia is very common with an incidence of 60 % in healthy term babies and most preterm babies(2). Preterm babies are more prone for hyperbilirubinemia compared to term babies. Late preterm babies have approximately 8 times increased risk of developing total serum bilirubin(TSB)more than 20 mg/dl as compared to term babies born(3). Most neonatal guidelines including the AAP guidelines regarding management of neonatal hyperbilirubinemia considers newborn more than 35 weeks in a single group and treating late preterm as a separate entity is not considered. Different methods of assessment of hyperbilirubinemia are clinical assessment, serum bilirubin estimation and by transcutaneous bilirubin (TcB) estimation. Many studies have shown that clinical estimation of serum bilirubin as a screening tool is not reliable and may fail to detect significant neonatal hyperbilirubinemia before discharge and may lead to inadequate follow up(4).Hour specific serum total bilirubin nomogram by Bhutani et al (5) is used Widely to predict the risk of significant hyperbilirubinemia and also for identifying the need for additional evaluation (6). The problem with serum bilirubin estimation is it is an invasive procedure. To circumvent the problem of invasive procedure, transcutaneous bilirubin estimation was introduced. Transcutaneous bilirubin estimation is a better screening method when compared to visual estimate. Study. Currently transcutaneous bilirubin nomograms are available for different regions of the world covering different populations. None of the nomograms differentiated late preterm as a separate entity while constructing nomograms. Our study was done with the intention of constructing a transcutaneous bilirubin nomogram exclusively for late preterm babies as a first step in seeing the normal trend of bilirubin rise in late preterm babies.

AIMS AND OBJECTIVES

1. To construct a nomogram for TcB values in late preterm babies over the first 120 hours of life.
2. To assess the correlation and agreement between the transcutaneous bilirubin and serum bilirubin values. To construct a regression equation to predict serum bilirubin from transcutaneous bilirubin level in late preterm babies.

MATERIALS AND METHODS

Study design: Prospective observational study.

The study was done over a period of 1-year (January 2023- January 2024) Vijay Marie Hospital.

Inclusion Criteria:

All late preterm babies born in Vijay Marie Hospital.

Exclusion Criteria:

- Rh isoimmunization, ABO incompatibility
- Major congenital malformation
- Feeds not initiated within 48 hours of birth.
- Lack of parental consent

METHODS AND METHODOLOGY

The study was an observational cohort study. Late Preterm babies who fit into the study criteria were identified and parents approached for informed consent. A proforma was maintained which contained the basic information of the mother and the baby along with any predisposing factors for the development of hyperbilirubinemia. This also contained the feeding history of the baby. Transcutaneous bilirubin measurement was done at 6 hours intervals in the first 24 hours of life (6,12,18 ,24 hours) and then 12th hourly till 120 hours or till discharge of the baby. For all time frames, bilirubin was done at hour 1 If babies were commenced on phototherapy, only pre- phototherapy treatment values were considered. All babies who were evaluated for jaundice as per unit policy were screened for pathological causes of jaundice. If this revealed the presence of haemolytic hyperbilirubinemia, baby was excluded from the study. Similarly, any condition likely to cause cholestatic jaundice (sepsis, intrauterine infections) was excluded. The decision to start phototherapy was according to the unit protocol and those babies requiring exchange transfusion were excluded from the study. Hour specific transcutaneous bilirubin nomogram was constructed in the 5th 10th 25th 50th 75th 90th and 95th percentile. As part of secondary outcome, those babies whose serum bilirubin was estimated as part ofunit policy (for clinical jaundice) had a corresponding TcB estimated and the correlation between these values was estimated

Sample size:

For every time frame,Considering the number of late preterm deliveries, we opted for absolute precision of 0.9 with 95% confidence interval and the sample size was found to be 143 – 150 TcB values in each time period.

Statistical methods:

Transcutaneous bilirubin levels would be obtained for designated times (6th hourly till 24 hours and then 12th hourly till 10 hours of life) and 5th, 10th, 25th, 50th,75th,90th,95th percentiles TcB values will be obtained and the nomogram will be plotted.

OBSERVATIONS AND RESULTS

During the study period from January 2023- January 2024, 270 babies satisfying the inclusion criteria were recruited in the study. The graph below gives the course of the study. A total 270 babies were recruited for the study to obtain a minimum of 143TcBvalues in each epoch. About 50 % of babies could not be followed up to 120 hours of life because of variable reasons- major causes being starting of phototherapy for hyperbilirubinemia as per the unit protocol and early discharge before the completion of 120 hour.The mean gestational age of babies recruited was 35.6 weeks with a standard deviation of 0.8 weeks . Babies with a wide range of birth weight were recruited to the study and the birth weight ranged from 1140g to 3500g. There was almost equal distribution of boys and girls in the study. Only around 57 % of babies were on exclusive breast feeding the other 47% being on supplementary feeds. Supplementary feeds were banked breastmilk . The indication for supplementary feeds was mainly due to non availability of mother in the first 48 hours or lack of breastmilk. Those babies not started on feeds by 48 hours of life was not included in the study. As shown in Table1, about 20.3 % of the babies recruited for the study were 34 weeks, 27.8% was 35 weeks gestational age and majority of the babies (51.9%) were 36 weeks gestational age.

TABLE 1: GESTATIONAL AGE DISTRIBUTION

Gestational age	Number of Babies	
34 - 34 weeks 6 days	55	20.3 %
35 - 35 weeks 6 days	75	27.8 %
36 - 36 weeks 6 days	140	51.9 %

TABLE 2: **DETAILS OF NUMBER OF TCB MEASUREMENTS TAKEN DURING THE STUDY PERIOD.**

Total number of babies recruited for the study	270			
Total TcB value obtained	N = 2109			
TcB Value	No. of Values	34 weeks	35 weeks	36 weeks
6 hours of life	251	50	71	130
12hours of life	252	52	68	132
18hours of life	248	51	68	129
24hours of life	247	51	68	128
36 hours of life	241	49	68	124
48hours of life	247	50	69	128
60 hours of life	207	38	58	111
72 hours of life	206	40	56	110
84 hours of life	188	36	51	101
96 hours of life	172	30	49	93
108 hours of life	135	29	40	66
120 hours of life	131	28	38	65

Table 2 shows that a total of 270 babies were recruited for the study and the total number of TcB measured over time was 2109. There was a fairly proportional representation for TcB measurements between the various gestational ages in each time epoch. As can be seen, we could not achieve sample size (143 measurements) at 108 and 120 hours.

Figure 1: TRANSCUTANEOUS NOMOGRAM FOR PRETERM BABIES TILL 120 HOURS OF LIFE

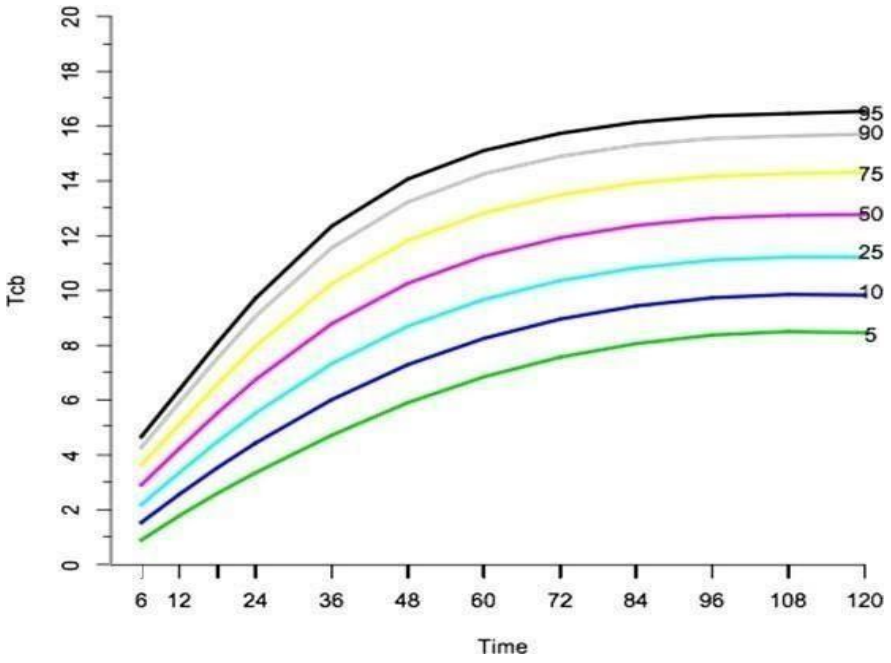


Figure 1 The 5th 10th 25th 50th 75th 90th and 95th percentile nomograms were constructed from the data's available. The chart shows a marked rise in the first 36 hours followed by a gradual rise of bilirubin till 72-84 hours of life after which the bilirubin rise is negligible

TABLE 3 RISE OF MEAN BILIRUBIN IN DIFFERENT TIME PERIOD

Percentile	**Increase in TcB Level, mg/dl per h**

	6-12	12-24	24-36	36-48	48-60	60-72	72-84	84-96	96-108	108-120
Th 5	0.033	0.075	0.025	0.01	-0.017	-0.05	-0.067	-0.075	-0.11	0.14
Th 10	0.05	0.117	.075	0.03	0.017	0.017	-0.33	-0.033	-0.79	0.116
Th 25	0.117	0.175	0.108	0.075	0.050	0.025	0.019	0.008	-0.033	0.060
Th 50	0.217	0.217	0.15	0.108	0.100	0.058	0.05	0.033	0.017	0.017
Th 75	0.3	0.258	0.216	0.15	0.133	0.100	0.083	0.075	0.058	0.041
Th 90	0.42	0.338	0.33	0.2	0.167	0.167	0.117	0.141	0.138	0.100
Th 95	0.43	0.383	0.41	0.217	0.278	0.221	0.15	0.167	0.188	0.117
Mean	0.225	0.217	0.176	0.108	0.094	0.067	0.05	0.043	0.018	-0.011

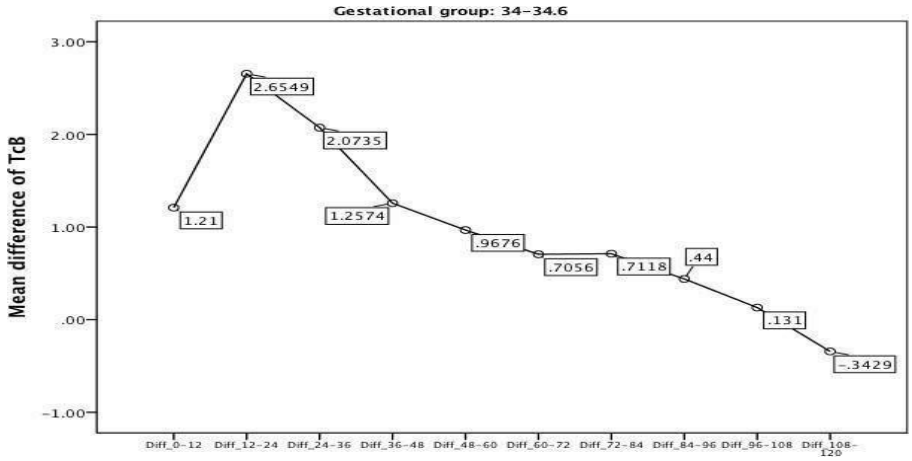
Table 3 shows the mean rate of rise of bilirubin is maximum at 6 to 12 hours and is 0.225 mg/dl/hour. Rate of increase bilirubin remains high (0.217) in the next 12 hours. After 108 hours bilirubin starts falling as evident by negative mean TcB rise. The table also shows that the rate of rise of bilirubin is more than 0.25 mg/dl/hour in the babies ≥75 th percentile during the first 24 hours and ≥90th percentile at 24-36 hours.

TABLE 4: RATE OF RISE OF MEAN TCB IN DIFFERENT GESTATIONAL AGE

Time	34 weeks		35weeks		36 weeks		P value
	Mean	SD	Mean		Mean	SD	
6 hours	2.69	0.97	2.91	0.8	2.84	0.98	0.327
12 hours	3.88	1.47	4.4	1.29	4.1	1.37	0.69
18 hours	5.2	1.47	5.8	1.43	5.4	1.43	0.233
24 hours	6.58	2.27	6.8	1.86	6.89	1.75	0.673
36 hours	8.6	2.1	8.78	2.08	8.95	2.13	0.783
48 hours	9.8	2.03	10.2	2.48	10.34	2.05	0.547
60 hours	10.3	2.9	10.9	2.56	11.44	2.33	0.088
72hours	11.1	2.28	11.71	2.26	12.22	2.21	0.082
84hours	11.6	2.03	11.87	2.27	12.67	2.2	0.047
96 hours	11.7	2.03	12.52	1.94	13.24	2.5	0.023
108ho ur s	11.9	1.8	13.03	1.79	13.24	2.8	0.042
120ho ur s	11.4	2.09	12.98	2.13	12.98	2.3	0.02

Table 4 shows the rate of rise of bilirubin for each percentile in different time period as noted in the table maximum rise of bilirubin is noted at 12 to 24 hours interval and then the bilirubin rise slows down and it very minimal after 72 hours and the bilirubin level tends to fall after 108 hours.

Figure 2: Rise of mean bilirubin in different time period for 34-34.6 weeks



As shown in the figure 2 maximum rate of rise of bilirubin is seen in first 24 hours and there is a gradual increase after 24 hrs till 72 hours after which the rate of rise of bilirubin is minimal ,figure shows a decline of bilirubin after 108 hours of life.

Figure 3: Graph showing correlationship between Tcb and Serum bilirubin values

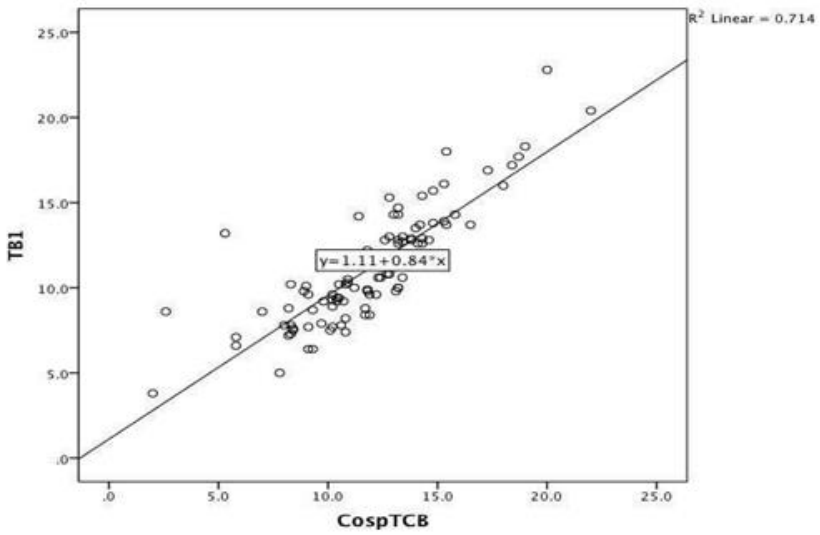


Figure 3 shows the graph depicting a linear relationship between the Total serum bilirubin estimated and the corresponding TcB. A total of 102 paired samples were obtained for comparison

REGRESSION FORMULA From the paired serum and transcutaneous bilirubin values, we tried to construct a regression equation to estimate serum bilirubin level from any given TcB level. We derived the f3ollowing equation:

Y= 1.11+0.84 X, where y represents serum bilirubin level and x represents TcB

DISCUSSION

Serum bilirubin estimation for assessing the risk of hyperbilirubinemia needs invasive technique and in order to circumvent the invasiveness of serum bilirubin estimation, TcB measurement was introduced. To assess the risk of hyperbilirubinemia using TcB values, TcB nomogram is a necessity as the nomogram using TSB cannot be applied for TcB values. Most nomogram assessing the risk of future hyperbilirubinemia considers new born babies more than 35 weeks as a single group .A literature search did not reveal any nomogram exclusively for late preterm babies. There are also very few nomograms for Indian populations. Hence the need to do the current study. One published nomogram from Indian population was by Satish Mishra et al from the Department of Pediatrics, All India Institute of Medical Sciences, New Delhi. the authors made it clear that the need for phototherapy was higher for late preterm as compared to term neonates and the difference was statistically significant with the proportion of preterm babies needing phototherapy amounting to 29 % and term babies needing phototherapy being 10 %.The study had only 10 % of babies in the late preterm group and the authors have raised their concern that with increasing rate of late preterm births, predictive ability of their nomogram would change .The study would differ from other studies in that we would recruit only late preterm babies, who constituted a small fraction of babies evaluated for constructing nomograms for newborn 35 weeks or above. During the study period, we recruited a total of 270 babies and followed them with serial TcB monitoring at 6-hour intervals in the first 24 hours and then 12th hourly till 120 hours. A total of 2109TcB values were obtained. Other studies involved in the construction of nomogram included all babies more than 35 weeks as a single group. In the study by Sathish Misra et al,of the 625 babies evaluated, only 10% were late preterm. Only one study by Daniele De Luca et al constructed nomogram in babies more than 35 weeks recruiting a total of 2198 babies of whom 27% were 35 and 36 weeks. The issue with their nomogram was that, though they constructed a separate nomogram for babies born at 35 and 36 weeks, they did not include 34 weeks babies in their study. As shown in Table 4, among the late preterm babies assessed, more than half (51 % of babies) were born at 36 weeks, 27 % at 35 weeks and 23 % of babies at 34 weeks. We could not get an adequate representation for each gestation to construct nomograms for each gestation if necessary. This may alter the nomogram in favour of 36 weeks babies. A total of 140 TcB values was needed as sample size for each epoch, but we could get only 130 TcB values at 120 hours of life because of time constraint and as many babies were discharged between 72 and 96 hours of life. A large number of babies were also taken off the study because they were started on phototherapy. Even with a sample size of 130, the confidence limit was 95% with an unit precision of 1 which is acceptable. Of the babies, about 20 % were 34 weeks 28% were 35 weeks and 52 % were 36 weeks. We separately analysed the gestational age distribution in each time epoch to see any marked difference in each time period but found almost the same proportion of representation were from each gestational age in each time epoch. We longitudinally followed up the babies recruited in the study till 120 hours of life. In our study those babies started on phototherapy the pre phototherapy values were included in the study. This is in contrast to some of the earlier studies constructing TcB nomogram like the TcB nomogram by Satish Mishra et al, Sanpavat et al where they excluded the TcB values of babies

started on phototherapy.We included the babies without haemolytic anemia in our study and we included the pre phototherapy value of babies started on phototherapy as we believed it represents the actual normative data and excluding the pre phototherapy value may lead to falsely low normative value. In constructing the nomogram, we opted to longitudinally follow up babies at 12th hourly interval till 120 hours of life with more frequent assessment in the first 24 hours. Most of the previous studies like the one by Maisels et al and Deluca et al constructed bilirubin nomogram till 96 hours of life and the one by Satish Mishra et al TcB nomogram was constructed till 72 hours of life 72 only. These studies involved a predominant number of term babies for whom nomogram till 96 hours of life is sufficient since studies have shown that in term babies serum bilirubin peaks by day 3 and then falls, but for preterm babies the bilirubin peaks by around 5th day and then falls. As bilirubin peak was expected in preterm babies by day 5 of life, we decided to follow up babies till 120 hours of life Our nomogram did not show any marked increase in bilirubin after 72 hours and in fact, a fall in bilirubin was seen after 108 hours of life. This may be attributed to the actual natural history of bilirubin rise in late preterm babies or may be because the babies in the higher percentiles being taken out of study due to start of phototherapy and babies in the lower percentiles being followed up till 120 hours.

Table 5 shows comparison of the centiles between our study and the two other studies showed almost similar mean TcB levels in each epoch until 72 hours. However, the 95th centile showed higher values in the CMCH study as compared to the studies by Misra et al and De Luca et al. This may be understandable given that late preterm were likely to have higher bilirubin levels as compared to term babies.

Table 5 : COMPARISION OF TCB VALUES OF OUR STUDIES WITH PREVIOUS STUDIES:

Study	24 hours		36 hours		48 hours		60 hours		72 hours	
	th 50	th 95	th 50	th 90	th 50	th 90	th 50	th 90	th 50	th 90
CMCH Study	6	10.1	8.3	13.2	9	14.2	10	14.5	10.8	14
Daniele De Luca et al(35 &36 weeks)	5.8	9	6.7	10.8	8	13.8	8	14	8.8	15.4
Satish Mishra et al(97th percentile)	5.8	9.2	7.8	11.5	9	12.3	9.8	14	14	10.2

CONCLUSION

- Transcutaneous bilirubin nomogram was constructed for a cohort of late preterm babies. The 5th, 10th, 25th, 50th,75th,90th,95th percentiles TcB charts were created.
- Rate of rise of bilirubin is maximum during the first 24 hours of life after which there is a gradual decrease in rate of rise. Peak bilirubin level in this cohort is at 72 hours of life.
- Rate of rise of bilirubin more than 0.25 mg/dl/h (which is a predictor of hyperbilirubinemia) was noticed for the first 24 hours in ≥75th percentile and in values ≥90th percentile till the 36th hour of life.
- There is no significant difference between the nomogram for boys and girls and also not much variability was noted in the rate of rise of bilirubin for 34,35and 36 weeks babies hence they may be taken as a single group in the construction of TcB nomogram.
- There exists a good correlation between the TcB value and the paired TSB obtained though the agreement is not very good.

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