

STUDY PROTOCOL

EFFECTIVENESS OF TRANSCUTANEOUS BILIRUBIN (TCBR) MEASUREMENT IN HIGH RISK NEONATES AND TO EVALUATE THE VALIDITY OF TRANSCUTANEOUS BILIRUBIN (TCBR) WITH TOTAL SERUM BILIRUBIN (TSBR) LEVELS IN BOTH LOW AND HIGH RISK NEONATES AT A TERTIARY CARE CENTER OF A DEVELOPING COUNTRY

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ABSTRACT

Objective: To evaluate the utility of a Transcutaneous Bilirubin nomogram in high risk neonates and to evaluate the validity of Transcutaneous Bilirubin and Total serum bilirubin in both low and high-risk neonates.

Study Design: Cross-sectional study.

Place and Duration of Study: Postnatal Ward, Aga Khan University Hospital, Karachi, from May to Oct 2019.

Methodology: The participants will include all neonates born and admitted in the well baby nursery with jaundice. All neonates with gestational age of <35 weeks, requiring admission in Neonatal intensive care unit, and neonates with conjugated hyperbilirubinemia will be excluded. We will stratify our neonates into high and low risk population based on predefined criteria. Eighty five neonates in low risk group and 122 neonates in high risk group will be included.

Results: We aim to assess the effectiveness of Transcutaneous Bilirubin nomogram in high risk neonates as an effective and non-invasive tool in the management of neonatal jaundice in high risk neonates. We will also assess the sensitivity and specificity of Transcutaneous Bilirubin and Total serum bilirubin measurements and the analysis would be performed separately for high risk and low risk neonates to evaluate the validity of Transcutaneous Bilirubin independently in both groups.

Conclusion: We hope to establish a validated phototherapy guideline based on the Transcutaneous Bilirubin nomogram, as a cost effective and noninvasive tool in the management of neonatal jaundice in both high and low risk groups in Pakistan.

Keywords: High Risk Neonates, Hyperbilirubinemia, Transcutaneous bilirubin, Total serum bilirubin.

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INTRODUCTION

Neonatal hyperbilirubinemia, is one of the most common problems encountered in the clinical practice and remains an issue of interest and discussion¹. Hyperbilirubinemia is defined as a total serum bilirubin (TB) level >95th percentile on the hour specific nomogram². Increase in TB produces neonatal jaundice which is yellow discoloration of the skin and/or sclera caused by bilirubin deposition. Worldwide, 60% of term and 80% of preterm neonates develop jaundice⁴. Neonatal jaundice is one of the most common causes of hospital admissions in neonates, especially in

Asia⁵, therefore the timely identification and treatment is necessary to avoid serious complications including bilirubin induced brain damage (BIND) and mental retardation⁷.

Serum bilirubin measurement is the gold standard method to evaluate neonatal jaundice accurately but it involves an invasive and painful venipuncture and is time consuming and resource intensive¹³. Transcutaneous bilirubinometry, first introduced in 1980, is increasingly being used in health care settings mostly in developed world as an alternate and cost effective screening tool for the measurement of bilirubin concentration in neonates¹⁴. It reduces the complications of TsBR method, becoming a reliable yet non-invasive screening tool for hyperbilirubinemia in both term and preterm neonates¹⁵. Recent studies

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have shown 40-79% fall in venipuncture in premature neonates, after the use of TcBR method².

Studies suggest a strong correlation between TcBR and TsBR measurements¹⁶, and a screening protocol utilizing TcBR nomogram for low risk babies has been published from our center¹⁷. To the best of our knowledge, no study has been performed using TcBR nomogram in Pakistan for high risk neonates. The aim of our study is to evaluate the effectiveness of TcBR nomogram in high risk neonates. This will also help in reducing the number of blood sampling in high risk babies. We also aim to assess the validity of TcBR and TsBR in both high and low risk neonates.

The objective of this study is to evaluate the utility of a Transcutaneous Bilirubin (TcBR) nomogram in high risk neonates and to evaluate the validity of Transcutaneous Bilirubin (TcBR) and Total serum bilirubin (TsBR) in both low and high-risk neonates.

Operational Definitions:

- Clinical Jaundice:

Yellow discoloration of skin reaching up to abdomen assessed by physician or nursing staff.

- Low Risk Babies:

1. All healthy neonates with gestational age of 37 weeks and above.
2. All healthy neonates with birth weight of 2.5kgs and above.
3. All healthy neonates with no risk factors associated with development of significant jaundice.

- High Risk Neonates:

1. Neonates with gestational age 35 weeks to 36+6 weeks
2. Rhesus isoimmunization: when Mother's blood group is negative and baby's blood group is positive.
3. ABO isoimmunization: when mother's blood group is O and baby's blood group is A or B or AB.
4. History of G6PD deficiency in family

5. Jaundice within the first 24 hours

6. History of Neonatal jaundice in siblings treated with phototherapy or Exchange transfusion or ending up in kernicterus.

METHODOLOGY

This cross-sectional study conducted at Postnatal Ward of Aga Khan University Hospital (AKUH), Karachi, from May to Oct 2019. In this study, around 5500 neonates are delivered per year out of which about 85% are term and around 15% are preterm births. Currently, all neonates admitted in well baby nursery are assessed by Neonatologist / Fellow/ Resident/ nursing staff. All neonates admitted in well baby nursery with jaundice, at Aga Khan Hospital will be included in the study.

Neonates with gestational age of <35 weeks, requiring NICU admission, who are on phototherapy or have received phototherapy in the past, neonates with conjugated hyperbilirubinemia and neonates who develop clinical jaundice after 7 days of life will be excluded.

If jaundice appears within 24 hours of birth, then TsBR is sent and the jaundice is managed according to AAP guidelines¹⁹ which are followed in our unit. If jaundice appears after 24 hours, then risk assessment is performed and in low risk babies TcBR is checked and plotted on the TcBR nomogram for low risk babies (fig-1, Hussain *et al*¹⁷). If TcBR level falls on or above red line, TsBR is sent, and phototherapy initiated. If TcBR level falls on the blue line, then TsBR is sent and phototherapy is started only if TsBR falls on or above red line.

All babies with TcBR level below the blue line are followed with TcBR every 8 hourly until resolution of clinical jaundice or discharge. For high risk babies TsBR is sent for all and managed according to AAP guidelines for management of neonatal jaundice¹⁹.

In this study, all the babies that meet the inclusion criteria, will be recruited. Basic demographic and anthropometric data will be recorded including gestational age, mother's blood

group, baby's blood group and other risk factors for jaundice. Two Dräger JM-105 bilirubinometry will be used for monitoring of TCBR, one for each

medical department. Mean of three readings will be taken on the sternum and plotted on the TcBR nomogram for low-/high-risk respectively.

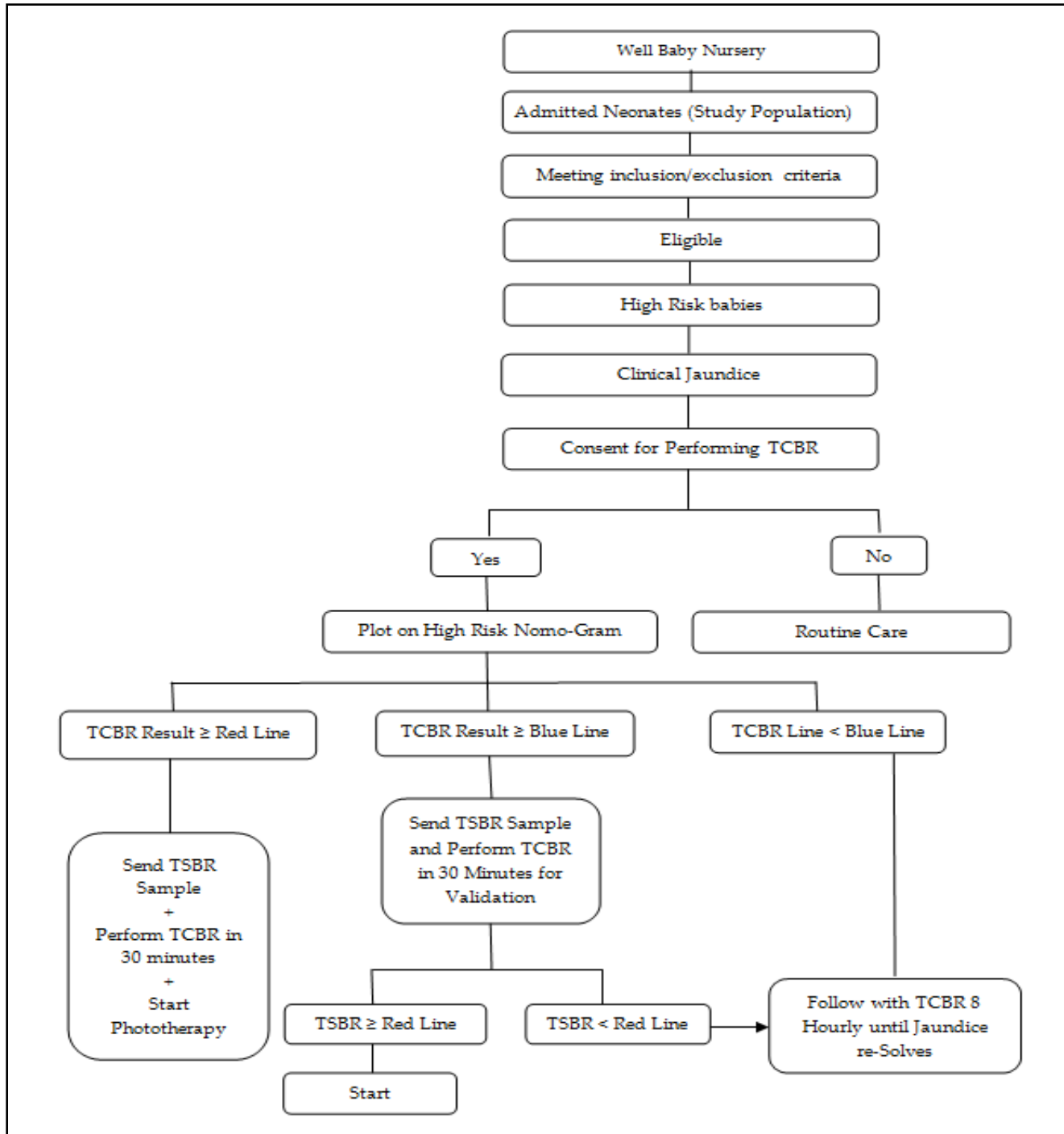


Figure-1: Process flow for high risk babies.

well baby nursery. Both devices will be regularly calibrated and serviced by our hospitals biome-

TsBR will be performed by venipuncture, by the nurse in the neonatal ward/phlebotomist

when indicated as per protocol, and sample will be sent to the laboratory for analysis. Prior to the implementation of the project, training will be carried out for competency certification for all neonatal healthcare providers. During this training; all providers will be trained on stratification of newborns to high and low risk; familiarization and training on the plotting of the nomogram and study protocol details and how to perform Transcutaneous bilirubinometry. Protocol flow chart (fig-1) and TcBR nomogram will be handed over to all postnatal nurses and physicians, also pasted in all postnatal ward areas for reference.

Establishing TcBR Nomogram and process flow for high risk babies:

TcBR nomogram for high risk babies will be made using American Academy of Pediatrics (AAP) guidelines as reference for phototherapy threshold. A new line will be drawn 1 mg/dL (34.2 μmol/L) below the phototherapy line (red line) for high risk babies and will be named as TcBR line (blue line) because literature review reveals a variation of ± 1 mg/dL (17.1 μmol/L) in results of TcBR and TsBR¹¹. For simplification, the intermediate and low risk lines are removed from the chart since those babies are not the study population and their management is being done according to the hospitals jaundice protocol. The lines are color coded. Phototherapy line is of red color, whereas TcBR line is blue colored. This modification in the AAP nomogram will be called as High risk TcBR nomogram. Attached is the sample of our high risk TcBR nomogram (fig-2).

For high risk babies, on appearance of clinical jaundice consent will be taken for TcBR. The study will be explained to the parents of babies who fulfill the eligibility criteria, by the health care provider and consent will be taken in a pre-designed consent form (fig-3). TcBR will be then plotted on TcBR nomogram for high risk babies (fig-2). If TcBR level falls on or above red line, TsBR will be sent and a second TcBR will be done within 30 minutes for validation purpose. An effort will be made to repeat TcBR within 30

minutes for validation purpose, however if it is delayed we will exclude the baby from the study.

If TcBR level falls on blue line, then TsBR will be sent, TcBR will be done within 30 minutes for validation and phototherapy will be started only if TsBR falls on or above red line. All babies with TcBR level below blue line will be followed with TcBR every 8 hourly until resolution of clini-

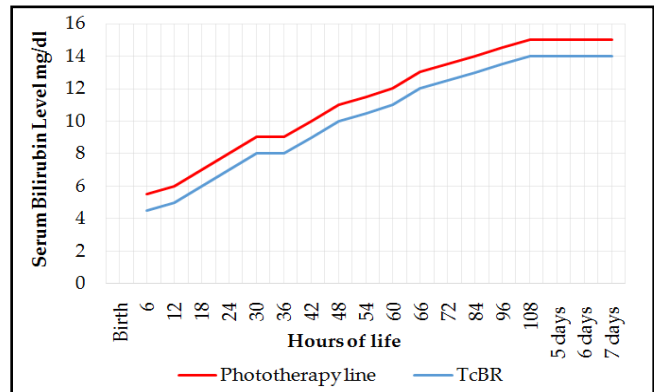


Figure-2: TcBR Nomogram for high risk babies.

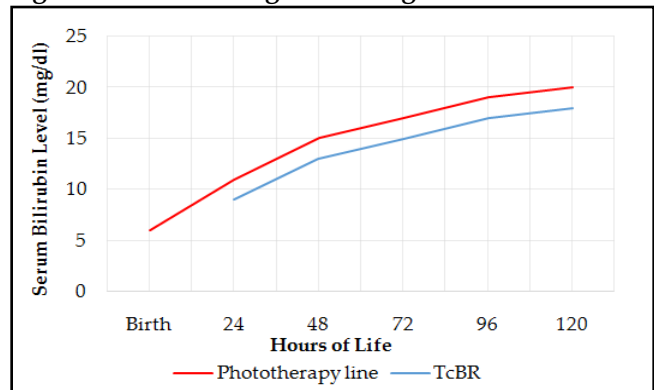


Figure-3: TcBR Nomogram for low risk babies.

cal jaundice or discharged. The values of TsBR and TcBR will be recorded in pre-designed pro-forma for validation.

No biological specimen specific for this study will be collected. No patient identifier will be collected and the data will only be used for the publication and research purposes. Confidentiality will be assured by keeping all the data in a locked cabinet, and will be accessible only by the PI and co-investigator. No other ethical concerns are identified.

TcBR Nomogram and Process Flow for Low Risk Babies:

TcBR nomogram for low risk babies (fig-4), is already in use for our low risk babies and is made

of serum sampling for TsBR using this nomogram¹⁷. It is similar to the high risk nomogram and also has two color coded lines, a red line (phototherapy line) which shows the pho-

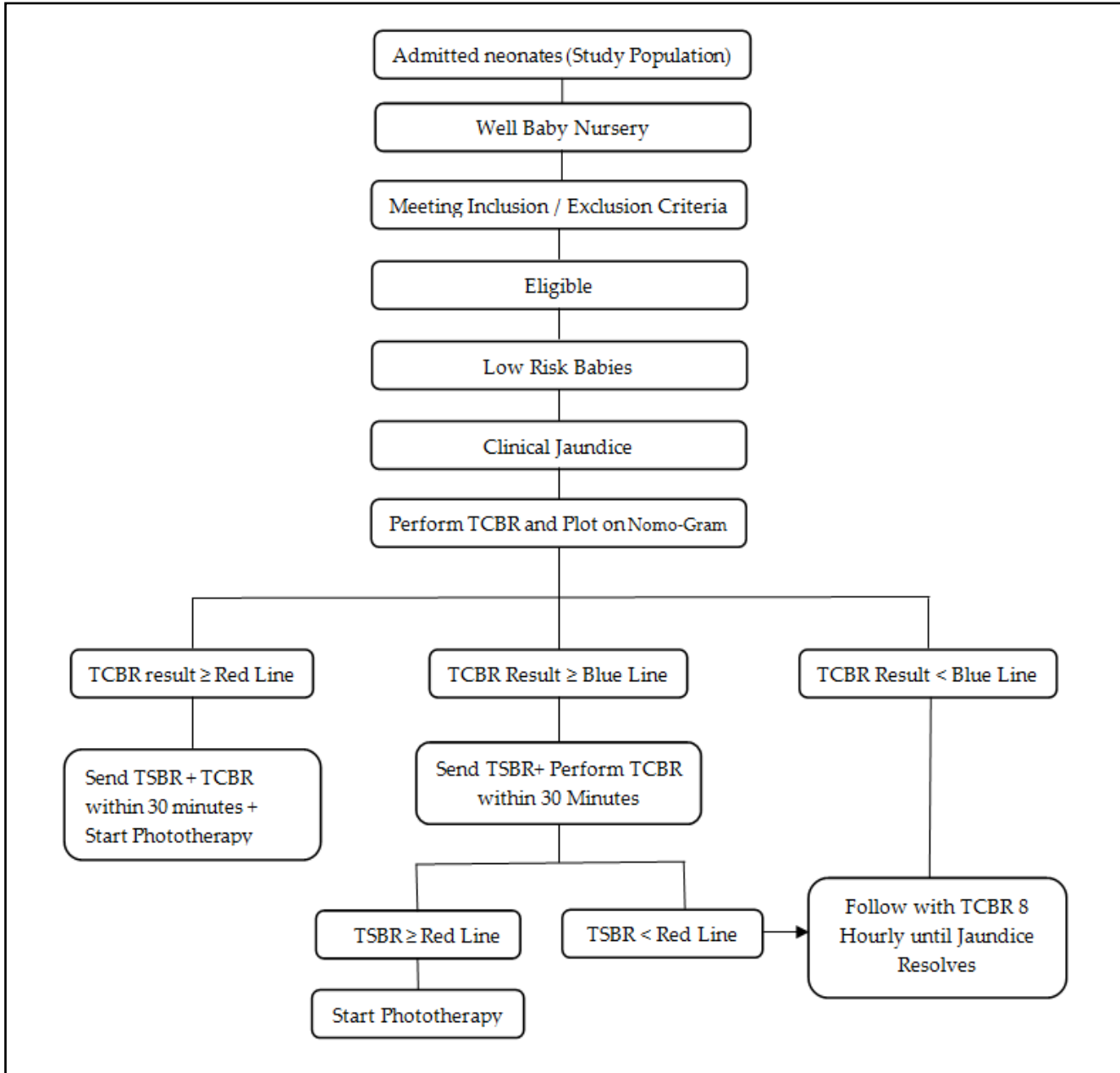


Figure-4: Process flow for low risk babies.

using American Academy of Pediatrics (AAP) guidelines for phototherapy threshold for low risk babies. It was incorporated into the hospitals guideline for the management of neonatal jaundice after we found a 70% reduction in the freq-

uency of serum sampling for TsBR using this nomogram¹⁷. It is similar to the high risk nomogram and also has two color coded lines, a red line (phototherapy line) which shows the pho-

TcBR and TsBR. For simplification, the high and intermediate risk lines are removed from the AAP nomogram. This modification in the AAP nomogram is called as TcBR nomogram for low risk babies. Attached is the sample of our TcBR nomogram for low risk babies.

For all low risk babies, on appearance of clinical jaundice TcBR will be done and plotted on TcBR nomogram. If TcBR level falls on or above red line, TsBR will be sent (according to departmental protocol in practice already), a repeat TcBR will be done within 30 minutes for validation and phototherapy will be started. If TcBR level falls on blue line, then TsBR will be sent, TcBR will be done within 30 minutes for validation and phototherapy will be started only if TsBR falls on or above red line. All babies with TcBR level below blue line, will be followed with TcBR every 8 hourly until resolution of clinical jaundice.

RESULTS

Descriptive analysis will be performed on SPSS-19, using mean, standard deviation for normally distributed and median (IQR) for non-normally distributed continuous variables. Frequency and percentages will be reported for categorical variables.

Bland Altman plots will be constructed to depict relationship between TcBR and TsBR measurements. Correlation coefficients will be calculated using Pearson correlation (parametric test) or Spearman rank correlation (nonparametric test) based on normal/non-normal distribution of data as appropriate. We will also assess the sensitivity and specificity of TcBR and TsBR measurements.

Sample size calculated separately for low risk and high risk neonates using Bland-Altman procedure to assess agreement between two methods. Literature reported mean difference among two methods for low risk group 0.08 ± 0.5 (ref: Mansouri *et al*) and high risk 0.98 ± 0.3 (ref: Amruta *et al*). Using 0.05 level of significance and 80% power we would need 85 neonates in low risk group and 122 neonates in high risk group.

The analysis would perform separately for high risk and low risk infants to assess the validity of TcBR independently in both groups.

CONCLUSION

We anticipate that establishing a validated phototherapy guideline for low and high risk babies using modified AAP nomogram will be effective and safe in reducing serum sampling for babies and can be used at a larger scale in our country and instances where serum bilirubin cannot be performed. Using TcB in high risk babies with jaundice after screening can be referred promptly from community/PHC/level-2 hospitals to tertiary care hospital for adequate management.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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