Reliability of Visual Assessment for Diagnosis of Neonatal Jaundice Among Neonates of Black Descent: A Cross-Sectional Study From Tanzania.

Ikunda Dionis (dionisikunda@gmail.com)

Department of Physiology and Biochemistry, College of Health Science, (CHS), The University of Dodoma.

Omary Chillo

Department of Physiology, School of medicine, Muhimbili University of Health and Allied Sciences.

George M Bwire

Department of Pharmaceutical microbiology, School of Pharmacy, Muhimbili University of Health and Allied Sciences.

Manase Kilonzi

Department of Clinical Pharmacy and Pharmacology, School of Pharmacy, Muhimbili University of Health and Allied Sciences.

Calvin Ulomi

Department of Physiology, School of medicine, Muhimbili University of Health and Allied Sciences.

Emmanuel Balandya

Department of Physiology, School of medicine, Muhimbili University of Health and Allied Sciences.

Research Article

Keywords: Diagnosis, Neonatal jaundice, TSB

Posted Date: February 24th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-228372/v1

Authors- Ikunda Dionis[1, 4]*, Omary Chillo[1], George M Bwire[2], Calvin Ulomi[1], Manase Kilonzi[3*], Emmanuel Balandya[1]

Affiliation

[1]Department of Physiology, School of medicine, Muhimbili University of Health and Allied Sciences, P O Box 65001 Dar es Salaam, Tanzania.

[2]Department of Pharmaceutical microbiology, School of Pharmacy, Muhimbili University of Health and Allied Sciences, P O Box 65013 Dar es Salaam, Tanzania.

[3]Department of Clinical Pharmacy and Pharmacology, School of Pharmacy, Muhimbili University of Health and Allied Sciences, P O Box 65013 Dar es Salaam, Tanzania.

[4]Department of Physiology and Biochemistry, College of Health Science, (CHS), The University of Dodoma, P.O. Box 259, Dodoma. Tanzania.

***Corresponding author**; dionisikunda@gmail.com

Authors' emails and Zip code

ID:dionisikunda@gmail.com,

EB:ebalandya@yahoo.com,

GMB: georgebwire@gmail.com,

OC:omarychillo@googlemail.com,

MK:manasekilonzi@gmail.com,

CU:calvinulomi@gmail.com,

Title: Reliability of Visual Assessment for Diagnosis of Neonatal Jaundice among neonates of black descent: A cross-sectional study from Tanzania.

Abstract

Background: Jaundice is common among neonates and if untreated can lead to kernicterus. Diagnosing of jaundice in neonates using Kramer's method (visual assessment) is considered user friendly in resource limited areas. However, there are conflicting finding on reliability of the Kramer's method in diagnosis of neonatal jaundice (NJ) particularly of black descent. Therefore, this study aimed to determine diagnostic accuracy of Kramer's method in comparison with total serum bilirubin (TSB) test in diagnosis of NJ among neonates of black descent in Tanzania.

Methods: A cross-sectional study was conducted between June and July 2020 at Muhimbili National Hospital (MNH) in Dar es Salaam Tanzania. A total of 315 neonates were recruited consecutively. In each neonates' jaundice was assessed by using Kramer's method and TSB test. A 2 X 2 table was created for determination of sensitivity, specificity, positive predictive values (PPV), negative predictive value (NPV), positive and negative likelihood ratios (+LR/-LR) and diagnostic accuracy (effectiveness). Cohen kappa (κ) was used to analyze the agreement between Kramer's method and TSB. Association between independent variables and presence of jaundice were assessed using chi-square test and the $p < 0.05$ was considered to be statistical significance.

Results: The prevalence of NJ was 49.8% by Kramer's method and 63.5% by TSB. The Sensitivity, Specificity, PPV, and NPV of the Kramer's method were 70.5%, 86.1%, 88.8%, and 62.6%, respectively. The +LR and –LR were 5.07 and 0.34 respectively. The diagnostic accuracy of the Kramer's method was 76.1%. There was a moderate agreement between Kramer's method and TSB results ($\kappa = 0.524$, $P<0.001$). No significance relationship between the independent variables and presence of NJ.

Conclusion: Kramer's method was found to be inefficient in detecting NJ among neonates of black descent. However, it can be used as a predictor of NJ and whenever available invasive techniques should be applied.

Background

Neonatal jaundice (NJ) affects one in two neonates worldwide (1) and the problem is much bigger in sub-Saharan Africa and South Asia. About 60% of the term and 80% of the preterm babies suffers jaundice during the first 7 days of life and is the major reasons why neonates attend emergency department (2, 3). Neonates with jaundice are prone to bilirubin encephalopathy and kernicterus which contribute to neonatal morbidity and mortality (4).

Early detection/diagnosis and appropriate management of NJ are very crucial in order to prevent its complications. Visual assessment (Kramer's rule), transcutaneous bilirubinometry (TcB), and TSB are the approaches used for the detection of NJ (5). Kramer's method is user friendly because is non-invasive, doesn't require any machine so it can be used as a screening and diagnosing tool in resource limited areas. The technique was introduced by Kramer, and showed a positive correlation between progressions of skin discoloration and serum bilirubin levels (5, 6) due to skin thickness differences. According to Kramer, the assessment should begin from the head towards the feet which portray the five zones of the cephalic-caudal progression of jaundice. It is important to examine all zones because studies reported that bilirubin concentration differ significantly between each dermal zone.

Controversial findings on reliability of this user friendly method for detecting NJ have been reported worldwide. Studies conducted in Pakistan (2010) and Indonesia (2017) reported that Kramer's method is reliable in detection of NJ and being black is not a matter of concern (7, 8). However, a study conducted in United State of America (USA) reported that Kramer's method alone is not reliable in detecting NJ especially in darkly pigmented neonates (9). Besides, study conducted in South Africa reported that Kramer's method was able to peak only 17% out of the 52% neonates with hyperbilirubinemia (1).

Despite those conflicting results Kramer's method is the backbone in diagnosis in most of the low-level health facilities in low-middle income countries like Tanzania. Therefore, this study aimed to determine sensitivity, specificity and accuracy of Kramer's method in detecting NJ in comparison with TSB test in Tanzania setting.

Methods

Study design, period and setting

A hospital-based cross-sectional study aimed on assessing the reliability of the Kramer's method in detecting NJ was conducted between June and July 2020 at MNH, Tanzania. MNH is a national hospital located in Dar es Salaam center, receiving patients from different parts of the city and regions of Tanzania. MNH neonatal unit is one the big unit serving up to 500 neonates per month. The unit have adequate numbers of skilled pediatricians, medical doctors and nurses. In addition, MNH has well equipped central laboratory with capacity of performing several tests.

Study population and eligibility criteria

Black descent neonates aged less than 28 days admitted at MNH and their mothers/guardians provided written consent to participate in the study were enrolled. Neonates with rashes and those who were severely sick (in life support, in oxygen masks) were excluded because Kramer's method cause physical discomfort to the babies.

Sample size, sample size calculation and sampling technique

A total of 315 neonates were recruited into this study. The formula for 'diagnostic sample size calculation' was used to calculate the sample size (10) (i.e. n= $\frac{Z^2 \text{ x Specificity x (1-specificity)}}{e^2 \text{ x (1-prevalence)}}$). Specificity of Kramer's method of 89% from a study conducted in Indonesia (8), prevalence of NJ of 50% in Tanzania (unpublished article), precision of 5% and 95% (z=1.96) confidence interval were used to obtain 283.5. Considering 10% non-respondent rate a total of 315 neonates were obtained. Participants were recruited consecutively.

Data collection procedure

Data were collected using case report form (CRF) comprises of 3 sections; demographic information (age, gender, birthweight, gestational age, and delivery mode), Kramer scores and TSB results. The CRF was developed following literature review and experts' consultation. Each neonate was subjected to visual assessment using Kramer's method and TSB test.

Visual assessment using Kramer's rule

Two Doctors and 1 pediatrician with experience in neonatal assessment performed the visual assessment. For each neonate visual assessment using Kramer's method was performed by the 2 doctors separately and discrepancies were resolved by the pediatrician. Visual assessment of the 5 dermal zones were scored as no jaundice =0, jaundiced at level of head and neck = 1, jaundiced at upper trunk (above umbilicus) =2, jaundiced at lower trunk and things (below umbilicus) =3, jaundiced at arms and lower legs =4, jaundiced palms and soles= 5 (11). The discrepancy of one value in Kramer score was acceptable. Discrepancies of more than one value in Kramer score were resolved by consulting a pediatrician. Kramer score recorded for each neonate was the average score of the two examiners. During assessment, the neonate was fully undressed and assessment was conducted under blue fluorescent light. Besides, by using the thumb, the skin of neonate was blanched to observe the underlying skin color from the head to toes following standard procedure described by Devi et al (6).

Laboratory measurements

About 2-2.5 mls of blood sample was withdrawn from each neonate femoral vein using 2.5 cc syringe into a green topped heparinized vacutainer tube. The collected sample was transported to the laboratory for processing within 2 hours using a cooler box containing ice packs. In the laboratory, the sample was centrifuged using a centrifuging machine to obtain serum. The obtained serum was analyzed for bilirubin concentration using the spectrophotometric chemistry analyzer (Architect chemistry analyzer, USA). Bilirubin determination was based on the run of bilirubin with diazotized sulfanilic acid. Azobilirubin concentration was measured at an absorbance of 500-600nm which is proportionate to bilirubin concentration.

Data analysis

Data was entered and analyzed by SPSS version 23 software. Frequencies and percentages were used to summarize categorical variables and continuous variables were summarized by using median (interquartile ranges (IQR)). For Kramer's method, those who scored 0 were grouped as no jaundice while 1-5 were considered to have jaundice. TSB test of ≥ 85µmol/l were considered to have jaundice and below that as not jaundice. Sensitivity, specificity, predictive values and

diagnostic effectiveness (accuracy) were obtained by contingency tables (2 x 2 table for diagnostic test) (12). Diagnostic accuracy results were defined as very weak (> 50%–60%), weak (> 60%–70%), moderate (>70%–80%), good (> 80%–90%), or very good (> 90%–100%). Positive likelihood ratio (+LR) >10 and negative likelihood ratio (-LR) < 0.1 was considered to be a good test (13). Cohen kappa statistic (κ) was used to determine agreement of Kramer's method and TSB results, with (κ) of 0.21 - 0.40, 0.41 - 0.60, 0.61 - 0.80 and 0.81 - 1.00 being fair, moderate, good and very good agreement respectively (12). Association of independent variables and NJ was done using the chi-square test (X^2 test) and $p < 0.05$ was considered to be statistically significant.

Results

580 neonates were admitted at the MNH neonatal unit during the study period. 247 were not eligible because written consent was not obtained as mothers were left at health facilities where they gave birth due to obstetric complications/management and 333 were enrolled. Out 333, 18 were excluded because blood sample were not taken (13) and TSB test results were misplaced (5), therefore a total of 315 were subjected to analysis. *Figure 1*.

Figure 1: Schematic of participants' enrolment.

Socio-demographic characteristics of the participants

Of 315 respondents with complete data, 182 (57.8%) were males with the median (IQR) age of 4 (2-8) days. More than half (58.4%) of the neonates were delivered by spontaneous vaginal delivery and half of the neonates 158 (50.2%) were born at preterm with median (IQR) birth weight of 2500 (1700 - 3000) grams. *Table 1*.

Table 1: Social-demographic characteristics of the participants (n=315)

Magnitude of NJ by Kramer's method, TSB and associated factors.

The prevalence of NJ was 63.5% by TSB and 49.8% by Kramer's method (*Figure 2*). The median (IQR) TSB for neonates who were clinically not jaundiced was 65(40-106) µmol/l and 178 (121-238) µmol/l for neonates who were clinically jaundiced. Following chi-square test all variables include; age (p = 0.46), gender (p=0.77), delivery mode (p=0.13), birthweight (p=0.19) and gestational age (0.78) were not statistical significantly associated with occurrences of NJ.

Figure2: The prevalence of neonatal jaundice

Diagnostic accuracy of the Kramer's method.

Kramer's method had a Sensitivity-70.5%, Specificity-86.1%, PPV-89.9%, and NPV-62.7% in detecting NJ. It has 5.07 LR of detecting jaundice and 0.34 LR of not detecting jaundice among neonates with a diagnostic accuracy of 0.761. Kramer's method had moderate agreement with TSB test ($\kappa = 52.4$, $P < 0.01$). *Table 2*.

Table 2: Diagnostic accuracy of the Kramer' method.

Diagnostic performance of Kramer's method based on Term, Preterm, and birthweight.

For neonates born at term, the Kramer test had 75.3 % sensitivity, 82.8% specificity, 86.4% PPV, 69.7 % NPV and 56.4% Cohen kappa in comparison to 66.4% sensitivity, 82.8% specificity, 93.0% PPV, 56.0NPV and 48.8% Cohen kappa for preterm neonates, $P < 0.001$. *Table 3*.

Table 3: Diagnostic performance of visual assessment based on Term, Preterm, and birthweight.

Discussion

The study aimed at determining the reliability of Kramer's method for diagnosis of NJ among neonates of black descent. Our study found the diagnostic effectiveness (accuracy) of Kramer's method to be moderate (76%), sensitivity moderate (70.5%), and specificity good (86.1%). Besides, Kramer's method found to have good (89.9%) ability of predicting presence of NJ but poor ability to predict those with no jaundice.

Our findings are consistence with the study conducted in Indonesia, in which sensitivity, and specificity of Kramer's method reported to be 76.92% and 89.47% respectively. This study was conducted among neonates of black descent and the diagnostic accuracy found to be moderate which is in line with findings in various studies which reported that the diagnostic accuracy of Kramer's method is poor for neonates of black ethnicity compared to other groups (14). Hence, our study emphasize that Kramer's method may be used as a predictor (PPV =89.8%) of NJ and should be used as confirmatory test only in absence of invasive techniques when diagnosing NJ. In contrast to our finding the Indonesian study reported a good (86.27%) diagnostic accuracy (8).

The observed discrepancy could be due to difference in sample size and characteristics of study participants, our study involved neonates of black descent only while their study includes black and white neonates. In addition, our finding is similar to what reported in Switzerland, in which the diagnostic accuracy of Kramer's method was found to be moderate (73%) (14).

Our study also demonstrated slightly increases in sensitivity of Kramer's method when detecting jaundice among term (75.3%) and normal birthweight (80%) neonates and specificity in neonates with low birthweight (89. 4%).The findings are comparable to what reported in Denmark and Switzerland where sex, birthweight and gestational age were demonstrated to be the determinants of the diagnostic accuracy of the visual assessment technique (14, 15). These findings suggest the consideration of gestational age and birthweights when using Kramer's method in screening and diagnosis of NJ.

Lastly this study showed that occurrences of NJ is independently of age, gender, delivery mode, birthweight and gestational age. The findings are comparable to a study done by Aprillia et al (2017) who reported that gender, skin color and gestational age were not determinants of occurance of NJ. However, the findigs are inconsistance with a review conducted in USA (2011) reported that physiological jaundice is expected to reach maximum between 3- 5 days of life (16). Additionally, study conducted in India showed that hyperbilirubinemia is much common in female than male neonates because albumin concentration differ between gender (15). The observed difference might be due to different in study population (USA study recruited neonates of less than 5 days of life and India study recruited only those neonates with low birthweight).

The fact that this study was conducted at the tertiary referral hospital implies that the prevalence of NJ might have been overestimated. Also, Kramer method could be affected by intra- observer variability which was tacked by reconciling individual observations to the level of one-unit difference in scores, and computing Cohen kappa statistics for reliability during data analysis.

Conclusions

Kramer's method was found to be inefficient in detecting NJ among neonates of black descent. However, Kramer's method can be used as a predictor of NJ and whenever available invasive techniques should be applied as confirmatory tests. In addition, gestational age, mode of delivery,

age and gender found not to be determinants of occurrences of jaundice among neonates. Our study recommends a robust study to investigate determinants of NJ among neonates of black descent.

Abbreviations

CI: confidence interval; CRF: case report form; CS: cesarean section; GA: gestational age; IQR: Interquartile range; LBWT: low birth weight; LR: Likelihood ratio; MNH: Muhimbili national hospital; MUHAS:Muhimbili university and allied sciences; NBWT: Normal birth weight; NJ: Neonatal Jaundice; NPV: Negative predictive value; PPV: Positive predictive value; SPSS: Statistical product and service solution; SVD: spontaneous vaginal delivery ;TcB: Transcutaneous bilirubinometry; TSB: total serum bilirubin; USA: United states of America.

Keywords: Neonatal jaundice, black descent, Kramer, total serum bilirubin, diagnostic accuracy, Tanzania, sensitivity and specificity.

DECLARATION

Ethical approval

Ethical clearance was obtained from Muhimbili University of Health and Allied Sciences (MUHAS) institutional' review board with reference number **DA.287/298/01A/** .All procedures performed in studies involving human participants were in accordance with the Helsinki declaration .Permission to conduct this study at MNH was obtained from the Office of Research and Publications. Informed consent was obtained from all mothers/guardians before enrollment of their neonates into the study. Participants' numbers and codes were used instead of names during data collection, analysis and presentation to ensure confidentiality.

Consent for publication

Non applicable

Availability of data and materials.

The datasets analyzed during this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interest.

Funding

None

Authors' contribution.

ID perceived the study and wrote the manuscript. ID, MK and GMB analyzed the data.OC, CU and EB critically reviewed the manuscript for its Intellectual content. All authors read and approved the final version of the manuscript for publication.

Acknowledgement.

We thank all the staff members of the neonatal unit at MNH for their tireless support during this study. We acknowledge the MUHAS physiology department members for their contributions, critics and inputs to this work. In addition, we acknowledge management of University of Dodoma for supporting the study. Special thanks to all parents and guardians who allowed their neonates to be involved in this study.

REFERENCES

1. Brits H, Adendorff J, Huisamen D, Beukes D, Botha K, Herbst H, et al. The prevalence of neonatal jaundice and risk factors in healthy term neonates at National District Hospital in Bloemfontein. African journal of primary health care & family medicine. 2018;10(1):1-6.
2. Ekwochi U, Osuorah CD, Ndu IK. Correlation between total serum bilirubin and clinico-laboratory parameters of babies admitted for neonatal jaundice in a resource-limited setting. International Journal of Clinicopathological Correlation. 2018;2(2):21.
3. Cohen RS, Wong RJ, Stevenson DK. Understanding neonatal jaundice: a perspective on causation. Pediatrics & Neonatology. 2010;51(3):143-8.
4. Kulkarni S, Dolas A, Doibale M. Risk factors of neonates with indirect hyperbilirubinemia in a tertiary care hospital. International Journal of Basic and Applied Medical Sciences. 2014;4(1):395-9.
5. Wan A, Daud SM, Teh S, Choo Y, Kutty FM. Management of neonatal jaundice in primary care. Malaysian family physician: the official journal of the Academy of Family Physicians of Malaysia. 2016;11(2-3):16.
6. Devi S, Dash M, Chitra F. Detection of Neonatal Jaundice among the Newborn Using Kramer's Criteria. Epidemiology (Sunnyvale). 2018;8(355):2161-1165.1000355.
7. Hatzenbuehler L, Zaidi AK, Sundar S, Sultana S, Abbasi F, Rizvi A, et al. Validity of neonatal jaundice evaluation by primary health-care workers and physicians in Karachi, Pakistan. Journal of perinatology. 2010;30(9):616.
8. Aprillia Z, Gayatri D, Waluyanti FT. Sensitivity, Specificity, and Accuracy of Kramer Examination of Neonatal Jaundice: Comparison with Total Bilirubin Serum. Comprehensive child and adolescent nursing. 2017;40(sup1):88-94.
9. Keren R, Tremont K, Luan X, Cnaan A. Visual assessment of jaundice in term and late preterm infants. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2009;94(5):F317-F22.
10. Negida A, Fahim NK, Negida Y. Sample size calculation guide-part 4: how to calculate the sample size for a diagnostic test accuracy study based on sensitivity, specificity, and the area under the roc curve. Advanced journal of emergency medicine. 2019;3(3):e33-e.
11. Kramer LI. Advancement of dermal icterus in the jaundiced newborn. American Journal of Diseases of Children. 1969;118(3):454-8.

12. Florkowski CM. Sensitivity, specificity, receiver-operating characteristic (ROC) curves and likelihood ratios: communicating the performance of diagnostic tests. The Clinical Biochemist Reviews. 2008;29(Suppl 1):S83.
13. Šimundić A-M. Measures of diagnostic accuracy: basic definitions. Medical and biological sciences. 2008;22(4):61.
14. Szabo P, Wolf M, Bucher H, Haensse D, Fauchere J, Arlettaz R. Assessment of jaundice in preterm neonates: comparison between clinical assessment, two transcutaneous bilirubinometers and serum bilirubin values. Acta Paediatrica. 2004;93(11):1491-5.
15. Knudsen A, Ebbesen F. Cephalocaudal progression of jaundice in newborns admitted to neonatal intensive care units. Neonatology. 1997;71(6):357-61.
16. Dennery PA, Seidman DS, Stevenson DK. Neonatal hyperbilirubinemia. New England Journal of Medicine. 2001;344(8):581-90.

Figures

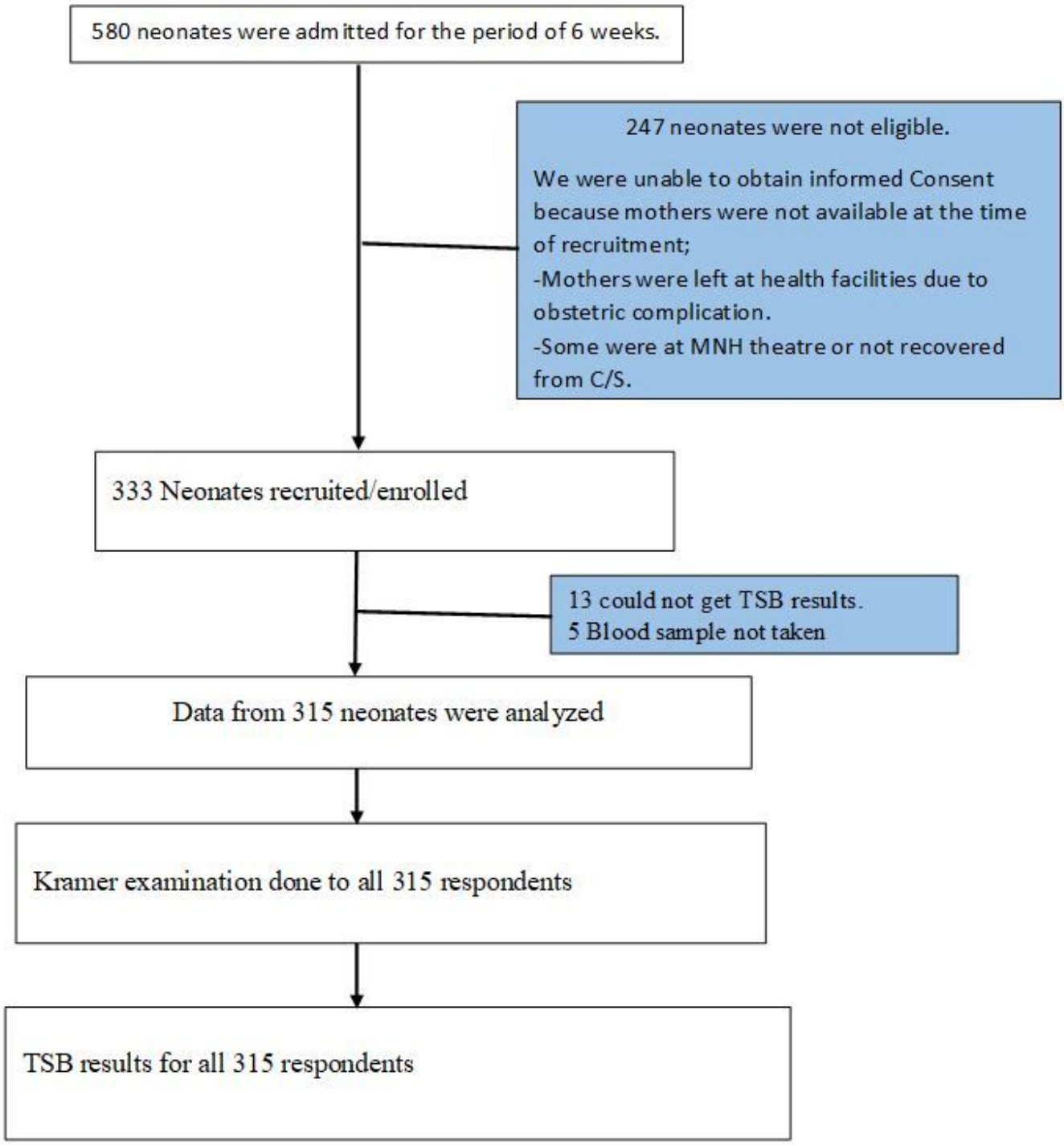

Figure 1

Schematic of participants' enrolment.

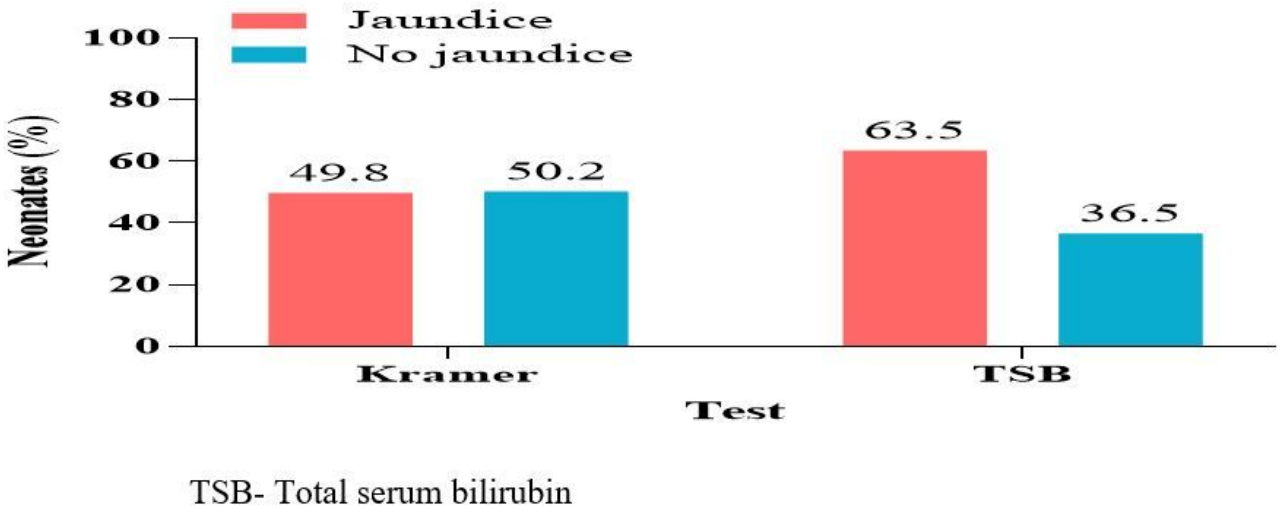

Figure 2

The prevalence of neonatal jaundice

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table2.jpg