

CLINICAL STUDY

Association Between Kramer Visual Jaundice Grade and Total Serum Bilirubin in Neonates: A Cross-Sectional Study From Venezuela

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ABSTRACT

BACKGROUND:

Kramer visual staging is a rapid bedside method for estimating the cephalocaudal extent of neonatal jaundice, but visual assessment is imprecise and should not substitute for objective bilirubin measurement. This study evaluated the association between Kramer grade and total serum bilirubin (TSB) in neonates with jaundice at a Venezuelan maternity hospital.

METHODS:

This single-center cross-sectional clinical study prospectively collected data from 80 neonates with clinically recognized jaundice at Hospital Materno Infantil Dr. Jose Maria Vargas, Valencia, Venezuela, from January through June 2020. Kramer grade and TSB were recorded using a standardized study form. Mean TSB across Kramer grades was compared using one-way analysis of variance (ANOVA), and the monotonic association between Kramer grade and TSB was assessed using Spearman rank correlation.

RESULTS:

Kramer grade 2 was most frequent (32/80, 40.0%), followed by grades 1 (28.8%), 3 (20.0%), and 4 (11.3%); no infant was classified as grade 5. Overall mean TSB was 10.69 ± 0.37 mg/dL (mean $\pm$ standard error). Mean TSB increased from 9.43 mg/dL at grade 1 to 14.06 mg/dL at grade 4, with a significant overall between-grade difference (ANOVA $P = 0.0019$). Kramer grade showed a moderate positive correlation with TSB (Spearman $\rho = 0.42$; $P = 0.0006$).

CONCLUSIONS:

Higher Kramer grade was associated with higher TSB, but the association was only moderate and bilirubin ranges overlapped across grades. Kramer staging may provide a preliminary bedside cue in resource-constrained settings, but quantitative transcutaneous or serum bilirubin measurement remains necessary for risk stratification and treatment decisions.

KEYWORDS

neonatal jaundice; hyperbilirubinemia; Kramer scale; total serum bilirubin; Venezuela

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The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Andres Efrain de San Jose Betancourt Sosa: Conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing-original draft, and writing-review and editing. Juan Jesus Arvelo C.: Conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing-original draft, and writing-review and editing. Rodolfo Moreno: Conceptualization, methodology, supervision, validation, and writing-review and editing. All authors reviewed and approved the final manuscript and agree to be accountable for the work.

DATA AVAILABILITY

The de-identified data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to applicable institutional and ethical requirements

ETHICS

The study protocol was reviewed and approved through the Research and Bioethics Committee process of Hospital Materno Infantil Dr. Jose Maria Vargas, Valencia, Venezuela. Separate institutional authorization by the Medical Directorate was documented on February 13, 2020. An approval number was not available in the archived documentation. The requirement for informed consent was formally waived by the approving body.

CONSENT

Not applicable.

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ABSTRACT

Background: Kramer visual staging is a rapid bedside method for describing the cephalocaudal extent of neonatal jaundice, but visual assessment is imprecise and should not replace objective bilirubin measurement. We evaluated the association between Kramer grade and total serum bilirubin (TSB) in neonates with jaundice at a Venezuelan maternity hospital.

Methods: This single-center cross-sectional study prospectively collected data from 80 neonates with clinically recognized jaundice at Hospital Materno Infantil Dr. José María Vargas, Valencia, Venezuela, from January through June 2020. Kramer grade and TSB were recorded using a standardized study form. Spearman rank correlation was the primary analysis; one-way ANOVA was used as a secondary overall comparison of mean TSB across Kramer grades. Postnatal age at assessment was not captured and could not be included as a covariate.

Results: Kramer grade 2 was most frequent (32/80, 40.0%), followed by grades 1 (23/80, 28.8%), 3 (16/80, 20.0%), and 4 (9/80, 11.3%); no infant was classified as grade 5. Overall mean TSB was 10.69 ± 0.37 mg/dL (mean $\pm$ standard error). Mean TSB increased from 9.43 mg/dL at grade 1 to 14.06 mg/dL at grade 4 (overall ANOVA $P = 0.0019$). Kramer grade showed a moderate positive unadjusted correlation with TSB (Spearman $\rho = 0.42$; $P = 0.0006$).

Conclusions: Higher Kramer grade was associated with higher TSB, but the association was moderate and bilirubin ranges overlapped across grades. Because postnatal age was not recorded and no diagnostic threshold analysis was performed, these data do not establish diagnostic accuracy or clinical utility. Objective transcutaneous or serum bilirubin measurement remains necessary for clinical decision-making.

Keywords: neonatal jaundice; hyperbilirubinemia; Kramer scale; total serum bilirubin; Venezuela

INTRODUCTION

Neonatal jaundice is common, and clinically important hyperbilirubinemia requires timely recognition because excessive unconjugated bilirubin can cause acute bilirubin encephalopathy and kernicterus. For newborn infants at least 35 weeks of gestation, current American Academy of Pediatrics guidance emphasizes systematic

bilirubin surveillance using transcutaneous bilirubin (TcB) or total serum bilirubin (TSB), interpreted according to postnatal age and neurotoxicity risk factors.[1]

The Kramer method, first described in 1969, grades visible jaundice according to its cephalocaudal progression from the face and neck toward the palms and soles.[2] Because it is rapid, noninvasive, and requires no equipment, Kramer staging remains attractive where laboratory testing or TcB devices are not immediately available. However, visual assessment is influenced by ambient light, examiner experience, skin pigmentation, and the broad overlap of bilirubin concentrations within visually defined zones. A systematic review of noninvasive bilirubin methods found direct visual assessment to be the least accurate and least reliable approach compared with laboratory bilirubin measurement.[3]

Recent studies continue to show variable performance of visual Kramer assessment across settings and populations.[4-7] In resource-constrained clinical environments, visual staging may be attractive because it requires no equipment, but its diagnostic performance and clinical utility must be evaluated separately from simple correlation with TSB. Data from Venezuela remain limited. A prior Venezuelan study reported a strong correlation between Kramer index and serum bilirubin,[8] but correlation alone does not establish diagnostic accuracy, and observed associations may vary according to population, postnatal age, examiner technique, and the spectrum of jaundice severity.

The present study aimed to evaluate the unadjusted association between Kramer visual jaundice grade and TSB among neonates with clinical jaundice at a public maternal-child hospital in Valencia, Venezuela. We hypothesized that higher Kramer grades would be associated with higher TSB concentrations. The study was not designed to estimate sensitivity, specificity, receiver-operating-characteristic performance, treatment thresholds, or clinical utility.

METHODS

Study design and setting

This was a single-center, cross-sectional clinical study with prospective data collection at Hospital Materno Infantil Dr. José María Vargas in Valencia, Carabobo, Venezuela. Enrollment occurred from January through June 2020. The report was prepared in accordance with STROBE recommendations for cross-sectional observational studies.

Participants and sampling

The source population comprised newborns cared for at the study institution during the study period. The analytic sample consisted of 80 neonates with clinically recognized jaundice selected using nonprobability purposive sampling. Neonatal jaundice was the only explicit inclusion criterion documented in the study protocol, and no additional exclusion criteria were specified. Recorded gestational ages ranged from 37 to 41 weeks. No a priori sample-size calculation was documented.

Data collection and variables

Data were collected using structured direct observation and review of maternal and neonatal clinical records. Investigators used a standardized study record form capturing maternal characteristics, neonatal gestational age, sex, birth weight, length, Apgar scores, potential blood-group incompatibility, Kramer grade, and serum bilirubin values. Clinical assessments were performed under supervision of the clinical tutor or an attending clinician. Importantly, the original data-collection instrument did not include postnatal age in hours or days at Kramer assessment or TSB sampling. Therefore, postnatal age could not be reconstructed reliably or included in adjusted analyses. Study documentation also did not record the number of visual examiners, inter-rater reliability, ambient-light standardization, the exact interval between Kramer assessment and blood sampling, or the laboratory assay platform used for bilirubin measurement.

Kramer staging was recorded on the standard five-zone cephalocaudal scale: grade 1, face and neck; grade 2, upper extremities and upper trunk; grade 3, lower abdomen and thighs; grade 4, legs; and grade 5, palms and soles. No grade 5 neonates were observed in this cohort. TSB was the prespecified bilirubin outcome for this manuscript.

Statistical analysis

Statistical analyses were performed using SPSS version 17.0. Categorical variables were summarized as counts and percentages. Quantitative variables were summarized using the mean and standard error (SE), with medians

and ranges reported when available. Because Kramer grade is an ordinal variable and TSB is continuous, Spearman rank correlation was designated as the primary inferential analysis; this nonparametric measure evaluates the strength and direction of a monotonic association without treating Kramer grade as a continuous interval scale. A one-way analysis of variance (ANOVA), which was part of the original prespecified analysis, was retained as a secondary descriptive comparison of mean TSB across the observed Kramer groups. The ANOVA was interpreted only as an overall between-group comparison; no post hoc pairwise tests were available, and no claim was made that each adjacent grade differed significantly. A two-sided P value < 0.05 was considered statistically significant. No multivariable model adjusting for postnatal age was performed because postnatal age at assessment was not collected. The analyses were designed to evaluate association, not diagnostic accuracy; no prespecified TSB threshold, sensitivity, specificity, likelihood ratios, or receiver-operating-characteristic analysis was available.

Ethics

The study protocol was reviewed and approved through the Research and Bioethics Committee process of Hospital Materno Infantil Dr. José María Vargas, Valencia, Venezuela. Separate institutional authorization by the Medical Directorate was documented on February 13, 2020. An approval number was not available in the archived documentation. The requirement for informed consent was formally waived by the approving body.

RESULTS

Study population

Eighty neonates with clinically recognized jaundice were included, and Kramer grade and TSB were recorded for all 80 participants. Forty-five (56.3%) were male. Gestational age was most commonly 39 weeks (41.3%) or 38 weeks (36.3%). Mean birth weight was 3177.38 ± 36.18 g (mean ± SE), with a median of 3150 g and a reported range of 2300 to 4100 g. Baseline neonatal characteristics are summarized in Table 1.

Table 1. Baseline neonatal characteristics

Characteristic	Value
Gestational age, weeks	
37	2 (2.5%)
38	29 (36.3%)
39	33 (41.3%)
40	14 (17.5%)
41	2 (2.5%)
Male sex	45 (56.3%)
Female sex	35 (43.8%)
Birth weight, g, mean ± SE	3177.38 ± 36.18
Birth length, cm, mean ± SE	49.34 ± 0.18
Apgar score 9 at birth	72 (90.0%)
Apgar score 10 at 5 min	73 (91.3%)

Values are n (%) unless otherwise indicated. SE, standard error.

Kramer grade and total serum bilirubin

Kramer grade 2 was the most frequent classification (32/80, 40.0%), followed by grade 1 (23/80, 28.8%), grade 3 (16/80, 20.0%), and grade 4 (9/80, 11.3%). No infant was classified as Kramer grade 5. Overall mean TSB was 10.69 ± 0.37 mg/dL. Mean TSB increased across Kramer grades, from 9.43 mg/dL at grade 1 to 14.06 mg/dL at grade 4. As a secondary group comparison, the overall ANOVA was statistically significant (F = 5.44; P = 0.0019). This result indicates an overall difference among the observed group means but does not identify which specific Kramer grades differed from one another.

Table 2. Kramer grade distribution and total serum bilirubin

Kramer grade	n (%)	TSB, mg/dL, mean $\pm$ SE	95% CI for mean TSB
Overall	80 (100%)	10.69 $\pm$ 0.37	9.95-11.43
Grade 1	23 (28.8%)	9.43 $\pm$ 0.69	7.99-10.86
Grade 2	32 (40.0%)	10.28 $\pm$ 0.48	9.30-11.25
Grade 3	16 (20.0%)	11.44 $\pm$ 0.86	9.60-13.27
Grade 4	9 (11.3%)	14.06 $\pm$ 0.98	11.81-16.31

Overall one-way ANOVA: $F = 5.44$, $P = 0.0019$. CI, confidence interval; SE, standard error; TSB, total serum bilirubin. No pairwise post hoc comparisons were reported.

Correlation analysis

In the primary analysis, Kramer grade demonstrated a moderate positive unadjusted association with TSB (Spearman $\rho = 0.42$; $P = 0.0006$), indicating that higher visual grades tended to occur with higher TSB values. Because postnatal age at assessment was not recorded, this estimate could not be adjusted for age-related changes in bilirubin. The magnitude of association was insufficient to support quantitative bilirubin estimation from Kramer grade alone.

Table 3. Correlation between Kramer grade and total serum bilirubin

Variables	Spearman ρ	P value	Interpretation
Kramer grade vs TSB	0.42	0.0006	Moderate positive (unadjusted)

DISCUSSION

This study found a statistically significant but only moderate unadjusted relationship between Kramer visual jaundice grade and TSB in 80 neonates with clinically recognized jaundice. Mean TSB increased progressively from Kramer grade 1 through grade 4, and the secondary overall ANOVA was significant. Nevertheless, the 95% confidence intervals overlapped across adjacent grades, and the primary Spearman correlation coefficient was 0.42. These findings demonstrate a directional association within this cohort, but they do not establish that Kramer grade independently predicts TSB or that the visual scale has diagnostic accuracy or clinical utility.

Postnatal age is a particularly important potential confounder. Serum bilirubin changes substantially over the first days of life, and the visible cephalocaudal extent of jaundice may evolve over the same period. Consequently, both Kramer grade and TSB can vary with postnatal age, creating or modifying an observed association between them. The original study instrument did not record postnatal age at visual assessment or blood sampling, so an age-adjusted analysis cannot be performed retrospectively from the available study documentation. The reported Spearman coefficient should therefore be interpreted as an unadjusted association. This limitation also prevents age-specific interpretation of the observed bilirubin values against contemporary treatment or follow-up thresholds.

The magnitude of correlation was lower than that reported in the prior Venezuelan study by Acosta-Torres and colleagues, which described a correlation of approximately 0.93.[8] Differences may reflect study population, disease spectrum, postnatal age distribution, visual-assessment technique, examiner variation, or timing of serum measurement. Restricted spectrum may also have attenuated the present correlation because no infant reached Kramer grade 5 and only nine infants were classified as grade 4.

The present findings are consistent with the broader literature showing that visual jaundice assessment has variable performance. Aprillia and colleagues evaluated sensitivity and specificity against serum bilirubin,[4] while a Tanzanian study among neonates of Black African descent reported only moderate reliability and cautioned against use of Kramer assessment alone.[5] Other validation studies have likewise shown variation in diagnostic performance according to threshold and population.[6] These diagnostic-accuracy studies address a different question from the present analysis: the current dataset evaluated correlation and group-level differences, not sensitivity, specificity, predictive values, or discrimination at a prespecified clinically relevant bilirubin threshold. A 2021 review of noninvasive bilirubin methods concluded that direct visual assessment was the least accurate and least reliable modality when compared with laboratory bilirubin measurements.[3]

Current AAP guidance for infants at least 35 weeks of gestation relies on objective bilirubin measurement interpreted according to postnatal age and neurotoxicity risk factors, rather than visual staging alone.[1] More recent health-system evidence suggests that combining TcB with Kramer-based assessment may reduce blood sampling in some settings,[7] but the present study did not evaluate such a pathway, management decisions, treatment eligibility, readmission, or other clinical outcomes. Accordingly, no clinical-utility claim can be made from these data. The resource-constrained setting remains relevant as a context in which low-cost visual assessment is commonly used, but whether Kramer staging can safely function as a triage trigger requires prospective evaluation with age-specific bilirubin measurement and predefined clinical endpoints.

LIMITATIONS

The study has several limitations. First, postnatal age at Kramer assessment and TSB sampling was not recorded in the original data-collection instrument. This is a major source of potential confounding because both serum bilirubin concentration and visible jaundice evolve with time after birth; therefore, the observed correlation is unadjusted and cannot be interpreted as an age-independent relationship. Second, the exact interval between visual assessment and blood sampling was not documented. Third, this was a single-center nonprobability purposive sample of only 80 jaundiced neonates, which limits generalizability and introduces selection and spectrum bias; no Kramer grade 5 infants were included and only nine infants were classified as grade 4. Fourth, no a priori sample-size calculation was documented. Fifth, the study did not record examiner blinding, lighting standardization, inter-rater reliability, or the bilirubin assay platform. Sixth, no prespecified clinically relevant TSB threshold or patient-management endpoint was defined, and sensitivity, specificity, predictive values, likelihood ratios, receiver-operating-characteristic analysis, and decision-impact outcomes were not evaluated. The study therefore cannot establish diagnostic accuracy or clinical utility. Finally, no multivariable analysis could address postnatal age or other potential confounders, and data collection occurred during early 2020 with pandemic-related institutional-access limitations.

CONCLUSIONS

In this cohort, higher Kramer visual jaundice grade showed a moderate unadjusted association with higher TSB. Because postnatal age at assessment was not recorded, the association could not be adjusted for this important time-dependent confounder. The overlap in bilirubin ranges across Kramer grades, absence of a prespecified diagnostic threshold, and lack of sensitivity, specificity, or clinical-outcome analyses mean that these data should not be interpreted as evidence of diagnostic accuracy or clinical utility. Future prospective studies should record postnatal age in hours, standardize the timing and conditions of visual assessment and bilirubin measurement, and evaluate age-specific diagnostic thresholds and clinically relevant outcomes.

DECLARATIONS

Ethics approval and consent to participate: The study protocol was reviewed and approved through the Research and Bioethics Committee process of Hospital Materno Infantil Dr. José María Vargas, Valencia, Venezuela. Separate institutional authorization by the Medical Directorate was documented on February 13, 2020. An approval number was not available in the archived documentation. The requirement for informed consent was formally waived by the approving body.

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Author contributions: Author 1: Conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing - original draft, and writing - review and editing. Author 2: Conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing - original draft, and writing - review and editing. Author 3: Conceptualization, methodology, supervision, validation, and writing - review and editing. All authors reviewed and approved the final manuscript and agree to be accountable for the work.

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