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Comparing Kramer's rule with transcutaneous bilirubin vs. Kramer's rule only in reducing total serum bilirubin sampling among neonates with jaundice

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Abstract

Background In the Malaysian primary healthcare setting, neonatal jaundice (NNJ) screening uses either Kramer's Rule (KR), a visual assessment, or a combination with non-invasive transcutaneous bilirubin (TcB). However, data on the quantification of the need for total serum bilirubin (TSB) sampling between these approaches are limited. This study aimed to compare the frequency of blood draws required between the two cohorts, alongside investigating disparities in phototherapy initiation and severe hyperbilirubinemia occurrences.

Methods This multicentre retrospective cohort study enrolled neonates from six primary healthcare clinics, with three using KR plus TcB and three using KR only for NNJ screening. Neonates with a gestational age of ≥ 35 weeks and without prior phototherapy or exchange transfusion for hyperbilirubinemia were included in the study until reaching either day 10 of life or hospitalization for any reason, defining the study endpoint. The minimum sample size required was 379 neonates in each cohort. Generalized Poisson regression was used to compare the number of blood draws required for TSB sampling between the two cohorts.

Results Of 765 neonates included, the cohort using KR alongside TcB showed a 74% reduction in blood draw risk compared to KR alone cohort (IRR 0.26, 95% CI 0.23–0.39). There were no significant differences between cohorts in phototherapy initiation (25.5% vs. 24.4%), severe hyperbilirubinemia occurrence (0.0% vs. 0.0%) or rapid bilirubin level rise (0.3% vs. 0.8%).

Conclusion Incorporating TcB alongside KR for NNJ screening significantly reduces the need for TSB sampling without causing an escalation in phototherapy initiation or severe hyperbilirubinemia occurrences, suggesting the potential to optimize NNJ management in the local primary care setting.

Keywords Neonatal jaundice, Screening, Kramer's Rule, Transcutaneous bilirubin, Total serum bilirubin

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Background

Neonatal jaundice (NNJ) is the most common medical condition among neonates, with one in every ten neonates developing clinically significant jaundice, necessitating close monitoring and treatment [1]. Phototherapy is the mainstay of treatment for NNJ, and with prompt treatment, the prognosis for most NNJ is favourable [2]. However, neonates who progress to severe jaundice are at risk of developing serious complications such as Kernicterus Spectrum Disorder (KSD) [2, 3]. Hence, the 2004 American Academy of Pediatrics (AAP) Guidelines underscores the critical significance of timely jaundice screening, a measure poised to curtail the incidence of KSD [4].

The screening for NNJ encompasses various methods, each tailored to different clinical contexts and health systems [5]. In Malaysia, although both Kramer's rule (KR) and the combination of KR with transcutaneous bilirubin (TcB) measurements are recommended screening methods for NNJ, KR predominantly prevails in clinical practice [6]. This predominance is likely attributed to the high cost of TcB devices, which are approximately USD$5,000 each [7]. This requires a significant investment by the Malaysian healthcare system, making the routine implementation of TcB devices challenging. KR is based on Kramer's principle of cephalocaudal progression where clinicians evaluate jaundice intensity by comparing skin color across five dermal zones—head and neck, upper trunk, lower trunk and thighs, arms, and lower legs, and palms and soles [8]. Although visualization is a commonly used screening technique for NNJ, it only has a moderate correlation with actual total serum bilirubin (TSB) levels, and the correlation coefficient was substantially lower in preterm and dark skin tone neonates [9–11].

A recommended screening approach involves non-invasive TcB measurement, which assesses bilirubin levels by emitting light onto the neonate's skin and measuring the intensity of the reflected wavelength [12]. TcB is recommended for neonates with a gestational age of 35 weeks or more and a postnatal age of more than 24 h [6, 11]. Many studies have demonstrated that TcB has a good correlation with TSB and that it should be utilized as a screening tool when the detected level is less than 250 µmol/L [13]. Local guideline in Malaysia mandates TSB testing when TcB levels surpass 200 µmol/L, irrespective of TcB machine brand, in contrast to the AAP guidelines, which recommend TSB testing for TcB levels exceeding 250 µmol/L or TcB values < 50 µmol/L below the phototherapy level [6, 14].

Despite the availability of screening methods, TSB measurement remains the gold standard for NNJ diagnosis and the initiation of phototherapy [6, 14]. However, TSB involves obtaining blood samples from neonates via venepuncture or heel-prick, which is painful, time-consuming and requires trained medical personnel with laboratory support [15]. Due to the limitations of the visualization method in screening, TSB is frequently still required despite of all its associated challenges. Hence, TcB is put under extensive investigation and multiple studies have shown that TcB has potential benefits including enhanced accessibility, reduced reliance on TSB blood draws, parental acceptability and cost savings [16–20].

In Malaysia, while TcB is integrated into clinical practice guidelines as a screening tool for NNJ, there is a paucity of studies comparing the trends in the number of blood draws for TSB, need for phototherapy, and incidence of severe hyperbilirubinemia between neonates screened using KR with TcB versus KR alone. Researchers also aim to compare the number of blood draws for TSB, phototherapy initiation, and cases of severe hyperbilirubinemia in TcB cohorts when using AAP recommendations versus local guidelines. This comparison will explore the impact of different cut-off levels for TSB testing between the two guidelines. Addressing these research gaps is paramount in providing evidence-based recommendations to optimize the NNJ screening program locally.

Methods

Study design and population

This retrospective cohort study was conducted by reviewing and extracting clinical and laboratory data from medical records spanning from February 1st, 2023, to November 30th, 2023. The study consisted of two cohorts, each comprising three primary healthcare clinics. Each cohort utilized a different screening method: one cohort exclusively employed KR for screening, while the other cohort utilized KR alongside TcB measurements.

A consecutive sampling method was used in this study, where all eligible cases during the study period were included. Neonates were eligible for this study if they were 35 weeks of gestational age or more and had not undergone phototherapy or exchange transfusion for hyperbilirubinemia prior to their first clinic encounter. Exclusion criteria included neonates with major malformations, evidence of hemolysis, ongoing neonatal morbidity, and those screened using a different algorithm on more than one occasion from the original cohort. The exclusion of neonates who underwent different NNJ screening methods was aimed at preventing data contamination.

The study was approved by the Medical Research Ethics Committee of Ministry of Health, Malaysia (MREC) [KKM/NIHSEC/22-02554]. Informed consent was

waived as the study involved retrieving secondary data from medical records.

Standard NNJ screening algorithm and standard of care for managing NNJ

In Malaysia, each neonate is assigned to a designated primary health clinic for monitoring. A proactive postnatal care program is instituted to monitor the health of both neonates and mothers. Healthcare providers from the assigned clinic conduct regular home visits on days 1, 2, 3, 4, 5, 6, 8, and 10 during the first two weeks after birth to evaluate the health and well-being of both the mother and the neonate, including NNJ screening [21, 22]. As per the current Malaysia Clinical Practice Guidelines (CPG) for NNJ management [6], KR or KR alongside TcB can be used for NNJ screening. If TSB testing is deemed necessary based on the screening results, parents are guided to the designated clinic for further evaluation and management. The decision to initiate phototherapy is made based on the TSB levels [6, 23]. In instances where mothers observe clinical jaundice in the neonates outside of scheduled visits, they are encouraged to promptly bring the neonates to the designated clinic for NNJ screening. As primary health clinics are closed during weekends, all NNJ screenings are conducted at a nearby tertiary center, which may adopt either a similar or a distinct approach compared to the primary health clinics.

A) KR alongside TcB for NNJ screening

In clinics utilizing this screening algorithm, the decision to conduct a blood draw for TSB was determined through a combination of visual assessment using KR and TcB values. The Draeger JM-105 was utilized across all three clinics for TcB measurement on neonates, with a single TcB reading taken at the mid-sternum. If a neonate presented with a TcB value that exceeded phototherapy level or within 50μmol/L of the phototherapy level or TcB value exceeded 200 μmol/L, a blood sample was collected for TSB assay.

B) KR only for NNJ screening

In clinics utilizing this screening algorithm, the decision to conduct a blood draw for TSB assay was based on the physician's assessment using KR only.

Outcomes

The primary outcome of this study was comparing the number of blood draws needed for TSB assay between two cohorts utilizing different NNJ screening algorithms, upon reaching the study endpoint. The study endpoint was defined as either day 10 of life for the neonates or hospitalization for phototherapy or any other cause, whichever occurred first. Secondary outcomes were the initiation of phototherapy or exchange transfusion, the occurrence of severe hyperbilirubinemia (defined as TSB > 20 mg/dL or 342 μmol/L), and the presence of rapid rises in bilirubin levels (defined as TSB > 6 mg/dL per day or 103 μmol/L per day) [6].

Other covariates

Maternal demographic variables included age, ethnicity, and blood group, while neonatal demographic variables comprised of gestational age at birth, birth weight, gender, and Glucose-6-phosphate dehydrogenase (G6PD) status. Throughout the follow-up period, the study included data on TcB and TSB values at each screening or testing instances until reaching the study endpoint. Hospitalization duration, reasons for hospitalization (NNJ or other causes), and treatments administered (such as phototherapy, exchange transfusion, or other treatment) were also documented.

Statistical analysis

The sample size was determined by analyzing the mean difference in the number of TSB samples per neonate from a prior study [19] which involved a comparable population, with the assistance of the G-power calculator. Thus, the enrolment of 110 patients per group would provide the study with 80% power to detect an effect size of 0.38 for this outcome, with a two-sided type I error rate (alpha) of 0.05. However, considering the secondary endpoint supported by previous study findings [19], a sample size of 322 neonates per group was required to detect an absolute between-group difference of 8.6% for phototherapy, with a two-sided type I error rate (alpha) of 0.05. To accommodate potential missing data, the study aimed to enroll 379 patients per group.

All statistical analyses were performed using SPSS version 27.0.1.0 (IBM; SPSS Inc). Categorical variables were expressed as frequency and percentages, while continuous variables were reported as means with standard deviations or medians with interquartile ranges. Demographic, clinical characteristics and clinical outcomes were compared between the two cohorts. Continuous variables were analyzed using independent t-tests or Mann-Whitney U Test, while categorical data were analyzed using Pearson $\chi 2$ tests or Fisher's exact test. P values were considered statistically significant at $P < 0.05$ (two-tailed). The primary outcome was analysed using generalized Poisson regression where the number of blood draws required for each cohort were compared using incidence rate ratios (IRR) and 95% CIs while controlled for day of life upon first visit, ethnicity, gender, G6PD status, rapid rise of bilirubin level, initial bilirubin level, and neonate's birth weight.

One of the analysis of the seconday outcome focused on comparing the number of blood draws for TSB based on AAP and local guidelines within the cohort that

employed KR alongside TcB. The rationale for this comparison lies in the AAP guideline's criteria for TSB sampling, which stipulates that sampling is necessary if TcB levels exceed 250 μmol/L or if the TcB value falls below the phototherapy threshold by 50 μmol/L, as opposed to the different threshold for TSB sampling outlined in the local guideline.

Table 1 Demographic and clinical characteristics of mothers and neonates ($n=765$)

Characteristics	Overall ($n=765$)	KR with TcB ($n=384$)	KR ($n=381$)	*P* value
Mothers				
Maternal age, in years [mean (SD)]	30.7 (±5.4)	30.4 (±5.5)	31.0 (±5.3)	0.144
Maternal ethnicity [n (%)]				
Malay	595 (77.8)	295 (76.8)	300 (78.7)	0.675
Chinese	81 (10.6)	39 (10.2)	42 (11.0)	
Indian	67 (8.8)	38 (9.9)	29 (7.6)	
Others	22 (2.9)	12 (3.1)	10 (2.6)	
Maternal Blood Group [n (%)]				
A	216 (28.2)	119 (31.0)	97 (25.5)	0.104
B	211 (27.6)	99 (25.8)	112 (29.4)	
O	286 (37.4)	143 (37.2)	143 (37.5)	
AB	49 (6.4)	20 (5.2)	29 (7.6)	
Unknown	3 (0.4)	3 (0.8)	0 (0.0)	
Neonates				
Days of life during first encounter, in days [median (IQR)]	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.900[a]
Gender [n (%)]				
Male	403 (52.7)	206 (53.6)	197 (51.7)	0.591
Female	362 (47.3)	178 (46.4)	184 (48.3)	
Gestational age, in weeks [median (IQR)]	38.9 (38.0-39.9)	38.9 (38.0-39.9)	38.9 (38.0-39.9)	0.264[a]
Birth weight, in kg [mean (SD)]	3.01 (±0.39)	3.0 (±0.36)	3.03 (±0.41)	0.225
G6PD status [n (%)]				
Normal	756 (98.8)	379 (98.7)	377 (99.0)	0.334[b]
Deficiency	4 (0.5)	1 (0.3)	3 (0.8)	
Unknown	5 (0.7)	4 (1.0)	1 (0.3)	
Initial bilirubin level, in μmol/L [median (IQR)]	169.00 (140.00-198.00)	173.00 (140.25-205.75)	164.00 (140.00-193.00)	0.035[a]

KR: Kramer's Rule; TcB: Transcutaneous Bilirubin

[a] Mann-Whitney U test

[b] Fisher's exact test

Results

Table 1 presents the baseline characteristics of the 765 neonates included in this study, revealing no significant differences between the two cohorts. However, a noteworthy difference was observed in the initial bilirubin levels upon the first visit to the clinic, with the KR alongside TcB cohort exhibiting a significantly higher median bilirubin level of 173.00 μmol/L (140.25-205.75) compared to 164.00 μmol/L (140.00-193.00) in the KR cohort ($P=0.035$). Overall, the neonates had a median age of 2.0 days (1.0–3.0) at their first clinic encounter. A predominant proportion of neonates within the cohort were male, comprising 52.7% of the total. The median gestational age at birth was reported as 38.9 weeks (38.0-39.9), with a mean birth weight of 3.01 kg (±0.39 kg). Of the neonates, 98.8% had normal G6PD status, while 0.7% had an unknown G6PD status.

The median number of blood draws required to assay for TSB in the KR alongside TcB cohort was 1.0 (IQR, 0.0–1.0), compared to 4.0 (IQR, 2.0-5.5) in the KR cohort ($P<0.001$). Significantly fewer neonates in the KR alongside TcB cohort (8.6%) required more than two blood draws during the observation period compared to those in the KR cohort (74.0%). The mean highest bilirubin level during the study period was 199.9 (±50.7) for the KR alongside TcB cohort while this was 203.6 (±49.9) for the KR cohort. There was no significant difference in the proportion of neonates receiving phototherapy between the cohorts (25.5% vs. 24.4%). Likewise, there was no statistically significant difference between the cohorts when monitored for severe hyperbilirubinemia or rapid rise of bilirubin level. None of the neonates in either cohort underwent exchange transfusion (Table 2).

In the KR alongside TcB cohort of 384 neonates, a total of 1156 clinic visit episodes were observed and 386 blood samples for TSB were collected subsequent to NNJ screening, adhering to local guideline. In this same cohort, if the NNJ screening were based on the AAP guideline, where TcB level surpassing 250 μmol/L or less than 50 μmol/L from the threshold for phototherapy initiation were used, it would have prevented an additional 78 blood tests, representing an additional reduction of 6.8% ($P<0.001$, 95% CI: 3.06-10.51%). Furthermore, there were no statistically significant differences observed in terms of phototherapy and severe hyperbilirubinemia when comparing the utilization of local guideline versus the AAP guideline (Table 3).

Table 4 shows the generalized Poisson regression analysis results of the number of blood draws needed for TSB assay. Neonates screened with KR alongside TcB demonstrated a substantial 74% reduction in the risk of blood draws, with an Incidence Rate Ratio (IRR) of 0.26 (95% CI 0.23–0.39) in comparison with neonates who were screened using KR only, while controlling the effect of

Table 2 Comparison clinical outcome of neonates between KR with TcB cohort and KR cohort

Characteristics	No./total (%)			*P* value
	Overall	KR with TcB	KR	
	(*n* = 765)	(*n* = 384)	(*n* = 381)	
Number of blood sampling per neonate [median (IQR)]	2.0 (1.0–4.0)	1.0 (0.0–1.0)	4.0 (2.0-5.5)	< 0.001[a]
≤2	450 (58.8)	351 (91.4)	99 (26.0)	< 0.001
> 2	315 (41.2)	33 (8.6)	282 (74.0)	
*Highest bilirubin level, in µmol/L [mean (SD)]	201.78 (± 50.31)	199.94 (± 50.68)	203.62 (± 49.92)	0.312
Phototherapy				
Yes	191 (25.0)	98 (25.5)	93 (24.4)	0.723
No	574 (75.0)	286 (74.5)	288 (75.6)	
Severe hyperbilirubinemia				
Yes	1 (0.1)	0 (0.0)	1 (0.3)	0.498[b]
No	764 (99.9)	384 (100.0)	381 (99.7)	
**Rapid rise of bilirubin				
Yes	4 (0.5)	1 (0.3)	3 (0.8)	0.372[b]
No	761 (99.5)	383 (99.7)	378 (99.2)	
Duration of phototherapy, in days [median (IQR)] [*n* = 191]	2.0 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	< 0.001[a]

*Highest reading for each neonate

**More than 103 µmol/L from the previous TcB/TSB values over a 24-h period

[a] Mann-Whitney U test

[b] Fisher's exact test

Table 4 Generalized Poisson regression analysis of the number of blood draws needed for TSB assay

Variables	IRR	95% CI	*P* value
Screening method			
KR with TCB	0.26	0.23–0.29	**< 0.001**
KR	ref		
Day of life upon first visit	0.93	0.89–0.97	< 0.001
Ethnicity			0.648
Chinese	0.95	0.82–1.11	0.514
Indian	0.91	0.77–1.08	0.301
Other	1.06	0.81–1.38	0.665
Malay	ref		
Gender			
Male	1.12	1.03–1.23	0.012
Female	ref		
G6PD status			0.271
Normal	1.22	0.41–3.66	0.718
Unknown	1.71	0.81–3.61	0.161
Deficiency	ref		
Birth weight (in kg)	0.94	0.84–1.05	0.281
Rapid rise of bilirubin level			
No	1.05	0.58–1.90	0.883
Yes	ref		
Initial bilirubin level	1.00	1.00-1.01	< 0.001

Model was controlled for day of life upon 1st visit, ethnicity, gender, G6PD status, rapid rise of bilirubin level, initial bilirubin level, and baby's birth weight

IRR: Incidence Rate Ratio; KR: Kramer's Rule; TcB: Transcutaneous Bilirubin

day of life upon first visit, ethnicity, gender, G6PD status, rapid rise of bilirubin level, initial bilirubin level, and baby's birth weight.

Discussion

In our cohort of 765 neonates, we investigated the association between NNJ screening methods and the number of blood draws for TSB assay, while controlling for various confounding factors and demonstrated a significant decrease of 74% (IRR: 0.26; 95% CI 0.23–0.39) in the risk of blood draws comparing neonates who were screened with KR alongside with TcB to those screened using KR only. This emphasizes the efficiency of incorporating TcB alongside KR in NNJ screening protocols, as it significantly reduces the need for invasive blood draws. This would not only decrease discomfort and potential risks associated with frequent blood sampling but would also offer additional benefits of cost reduction and higher parental satisfaction [16–18].

Despite the notable difference in the number of blood draws between the cohorts, our study revealed no

Table 3 Requirement of TSB and clinical outcome based on different guidelines for KR alongside TcB cohort

Characteristics	KR with TcB (n = 1156 visits)		*P* value	95%CI
	Local guideline	AAP guideline		
Proceed with TSB [n (%)]				
Yes	386 (33.4)	308 (26.6)	< 0.001	3.06–10.51
No	770 (66.6)	848 (73.4)		
Phototherapy [n (%)]				
Yes	73 (6.3)	68 (5.9)	0.688	-1.57 to 2.37
No	1083 (93.7)	1088 (94.1)		
Severe hyperbilirubinemia [n (%)]				
Yes	0 (0.0)	0 (0.0)		
No	1156 (100.0)	1156 (100.0)		

KR: Kramer's Rule; TcB: Transcutaneous Bilirubin

KR: Kramer's Rule; TcB: Transcutaneous Bilirubin

significant disparities in the rates of phototherapy initiation and severe hyperbilirubinemia. This observation was noteworthy as it suggests that while KR alongside TcB-based screening may lead to a reduction in the number of blood draws, it did not compromise the safety of neonates in terms of identifying and managing clinically significant hyperbilirubinemia. Our findings provided reassurance with regard to the efficacy and safety of KR alongside TcB-based NNJ screening methods in clinical practice. Additionally, our study contributed to the existing body of evidence by quantifying the reduction in the number of blood draws. This may serve as a reference for policymakers when considering the implementation of this approach as a national clinical standard guideline. Furthermore, our findings may also facilitate others in assessing the cost-effectiveness of TcB implementation.

Our findings aligned with previous literature on this topic, which had reported reductions in blood draws for TSB ranging from 30 to 71% when using a transcutaneous device [16, 24–26]. However, our study diverged from prior reports regarding participant selection. We focused solely on healthy neonates with a gestational age of 35 weeks or more, while many prior studies included neonates with a gestational age of less than 35 weeks and some also included sick neonates. Furthermore, our study focused on NNJ screening in primary care settings, in contrast to previous studies primarily focusing on hospitalised neonates. Hence, the prior studies do not cover the complete scope of screening, management, and burden of neonatal hyperbilirubinaemia in a primary healthcare setting. Despite consistent results of reduced need for blood sampling when involving the use of transcutaneous device, it's noteworthy that in our study setting, there was a relatively higher blood sampling rate compared to previous studies.

According to the AAP guidelines, TSB measurement is recommended if the TcB exceeds the phototherapy level, is within 50μmol/L of the phototherapy level, or if the TcB exceeds 250 μmol/L [4]. Conversely, the Malaysia CPG guideline specifies that TSB measurement is indicated if the TcB exceeds the phototherapy level, is within 50μmol/L of the phototherapy level, or if the TcB exceeds 200 μmol/L [6]. Our study sought to assess the impact of adhering to the AAP guideline cut-off values compared to those outlined in the Malaysia CPG guideline on the number of blood tests performed for TSB measurement. We found that adopting the cut-off values as per the AAP guideline could have further prevented 78 blood tests, representing an additional reduction of 6.8% ($P<0.001$, 95% CI: 3.06-10.51%). Remarkably, this reduction did not lead to any discernible differences in the rates of phototherapy initiation or severe hyperbilirubinemia. By adhering to guidelines that advocate for a higher threshold for TSB measurement, clinicians can reduce the number of blood tests performed without compromising patient safety. The discrepancy between the AAP and Malaysia CPG guidelines highlights the need for ongoing evaluation and refinement of recommendations to ensure alignment with current evidence and local healthcare contexts. More studies should be conducted to justify the adoption of the cut-off values recommended by the AAP.

The ongoing STARSHIP trial in seven Dutch primary care birth centers is exploring the effectiveness of universal TcB screening versus visual inspection alone in preventing severe hyperbilirubinemia [27]. In the cohort where KR was incorporated alongside TcB measurements, no instances of severe hyperbilirubinemia were observed. However, in the cohort relying solely on KR, one case of severe hyperbilirubinemia was identified. Our study did not reveal a statistically significant difference in the prevention of severe hyperbilirubinemia between the two cohorts. The low occurrence of severe hyperbilirubinemia in our findings underscores the impact of the lower phototherapy level in Malaysia and the early detection and management of NNJ facilitated by the established postnatal care program.

One limitation of our study is the potential variability in clinical assessment and individual thresholds for ordering TSB measurements. However, we believe that this study design closely mirrors real-world clinical practice, where variations in the judgments of healthcare professionals are inevitable. Another limitation is that our study was conducted exclusively in the state of Perak, which may limit the generalizability of our findings to other states. However, given the nationwide adoption of the Malaysian CPG for NNJ management, we anticipate minimal variation in results across different states. Lastly, this study used TSB nomograms to interpret TcB values, which may not fully account for the differences between the two methods. Nonetheless, our findings showed no significant differences in safety outcomes, suggesting this limitation is unlikely to influence clinical decisions. Future research employing TcB-specific nomograms, such as the one developed in Myanmar [28], could offer deeper insights while accounting for potential inherent differences in measurement methods.

In light of our findings, which indicate that the integration of KR alongside TcB measurements not only substantially reduced the frequency of blood draws but also enabled a more targeted approach to NNJ management. Consequently, it could optimize resource allocation within healthcare facilities and uphold patient safety [20]. Moreover, the reduction in invasive procedures aligned with the principle of patient-centered care, leading to increased satisfaction for both caregivers and healthcare providers. Thus, healthcare stakeholders and policymakers should consider implementing KR alongside TcB as the primary screening method for NNJ in the country.

Although TcB has proven to be an effective and systematic approach for universal newborn screening in high-income countries, the financial barrier remains a significant obstacle to its broader implementation in low and middle-income countries like Malaysia [29]. Future studies focusing on the cost-effectiveness of NNJ screening incorporating TcB compared to traditional methods can provide valuable insights for policymakers and healthcare stakeholders. A cost-effectiveness analysis would evaluate the economic implications of incorporating TcB as part of the primary screening modality for NNJ, considering factors such as equipment costs, healthcare resource utilization, potential cost savings associated with reduced blood draws and clinical outcomes.

Conclusions

In conclusion, the NNJ screening with KR alongside TcB has yielded a significant reduction of over 74% in the necessity for blood draws for TSB assays. Importantly, this reduction was achieved without observing an increase in the incidence of phototherapy or severe hyperbilirubinemia. These findings underscored the efficacy of this integrated approach in minimizing invasive procedures while maintaining patient safety. Such outcomes hold promise for optimizing the NNJ screening and management without compromising patient care standards.

Abbreviations

NNJ	Neonatal Jaundice
KR	Kramer's Rule
TcB	Transcutaneous Bilirubin
TSB	Total Serum Bilirubin
AAP	American Academy of Pediatrics
G6PD	Glucose-6-Phosphate Dehydrogenase
IQR	Interquartile Range
IRR	Incidence Rate Ratio

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Author contributions

XJL: Responsible for the initial conceptualization of the study, developing the methodology, analyzing and interpreting the data, and writing the first draft of the manuscript. SA: Involved in the initial conceptualization of the study, interpreting the data, and revising the manuscript critically for important intellectual content. ELL: Involved in the initial conceptualization of the study, interpreting the data, and revising the manuscript critically for important intellectual content. JPN: Responsible for the initial conceptualization of the study, developing the methodology, interpreting the data, and revising the manuscript critically for important intellectual content. LZM, APP, FAH, SMNM, NIMA and PRD: Contributed to data curation, and participated in the review and editing of the manuscript. All authors have given their final approval of the version to be published.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Approval to conduct this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia with the protocol number NMRR ID-22-02554-BTL [KKM/NIHSEC/22-02554]. Informed consent was waived by MREC as the study involved retrieving secondary data from medical records. The study was adhere to the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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