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Delayed Cord Clamping and Hyperbilirubinemia Risk Across Racial and Ethnic Groups: A Single-Center Retrospective Review

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Abstract

Background and objective

Delayed cord clamping (DCC) improves neonatal iron stores and neurodevelopmental outcomes but may increase bilirubin levels. Historically, race was incorporated into the neonatal hyperbilirubinemia risk assessment as a proxy for underlying biologic and genetic risk factors; however, the removal of race-based risk stratification from clinical guidelines necessitates the development of alternative approaches to accurately identify at-risk populations. As DCC becomes standard practice, understanding subgroup-specific vulnerability is increasingly important. The objective of this study was to evaluate the incidence of hyperbilirubinemia requiring intervention among neonates of different racial/ethnic backgrounds following universal DCC.

Methods

A retrospective chart review was conducted at a tertiary care academic center using consecutive sampling of neonates ⩾36 weeks' gestation who received DCC for >30 seconds between June 2017 and August 2023. A total of 10,478 neonates met the inclusion criteria and were categorized by race. Multivariable logistic regression was used to evaluate the association between race and hyperbilirubinemia requiring phototherapy.

Results

Among 10,478 eligible neonates, 8,089 (77.2%) were White and 2,389 (22.8%) were non-White. Cord clamping duration was similar across racial groups. Non-White neonates had significantly higher 24-hour total serum bilirubin levels than White neonates ($p < 0.001$); however, the proportion of neonates requiring phototherapy was similar between groups. Racial subgroup analyses demonstrated substantial heterogeneity in the risk of hyperbilirubinemia: Asian neonates had the highest incidence of hyperbilirubinemia requiring intervention (n = 34, 12.2%). In multivariable models, the binary White vs. non-White race classification was not independently associated with hyperbilirubinemia requiring intervention; however, Asian race remained independently associated with increased risk in subgroup analyses.

Conclusions

Among neonates undergoing DCC, racial and ethnic background was not independently associated with hyperbilirubinemia requiring phototherapy, although Asian infants remained at increased risk. These findings support subgroup-specific risk stratification, including consideration of rapid glucose-6-phosphate dehydrogenase screening, to promote equitable neonatal care.

Categories: Pediatrics, Epidemiology/Public Health
Keywords: delayed cord clamping, jaundice neonatal, neonatal indirect hyperbilirubinemia, neonatal intensive care unit (nicu), race and ethnicity

Introduction

Delayed cord clamping (DCC) is a practice supported by strong evidence for improved outcomes, especially in the preterm population [1]. Term neonates benefit from enhanced iron stores for up to six months and improved neurodevelopmental outcomes at four years of age [2,3]. One potential risk associated with DCC is hyperbilirubinemia [4-6]. Historically, race has been incorporated into hyperbilirubinemia risk assessment as a proxy for underlying biologic and genetic risk factors, rather than as a direct biological determinant. This increased risk reflects differences in hepatic bilirubin uptake and clearance due to genetic variants in the UGT1A1 gene (e.g., Gly71Arg), UGT1A1 polymorphisms, or glucose-6-phosphate dehydrogenase (G6PD) deficiency, among other factors; G6PD deficiency is prevalent among individuals of East Asian descent [7-9].

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The revised 2022 American Academy of Pediatrics (AAP) guidelines removed race-based risk stratification, aiming to shift away from race-conscious medicine [10]. In response, some states are implementing statewide G6PD testing to identify at-risk neonates. However, a national consensus has not yet been established. As neonatal care guidelines evolve, a systematic evaluation of the clinical consequences of practice changes is warranted. We assessed outcomes following the implementation of universal DCC and the removal of race as a clinical risk factor by examining the incidence of hyperbilirubinemia requiring treatment among neonates from diverse racial/ethnic backgrounds.

Materials And Methods

Study design and setting

A retrospective chart review was conducted at a tertiary care academic center using consecutive sampling of neonates ⩾36 weeks' gestation who received DCC for >30 seconds between June 2017 and August 2023. A total of 10,478 neonates met the inclusion criteria and were categorized by race. The DCC protocol was implemented at the institution in early 2016.

Inclusion and exclusion criteria

The inclusion criteria were inborn neonates with a gestational age ⩾36 weeks who received DCC for >30 seconds. The exclusion criteria were no DCC performed, unrecorded DCC time, major congenital anomalies, no documented discharge bilirubin, and death within the first seven days of life.

Definitions

Hyperbilirubinemia was defined as a total serum bilirubin (TSB) concentration meeting or exceeding the age-specific phototherapy threshold according to the 2022 AAP guideline for infants ⩾35 weeks' gestation. High-risk hyperbilirubinemia at 24 hours was defined as a TSB concentration ⩾95th percentile for postnatal age (in hours) based on the Bhutani nomogram. Hyperbilirubinemia requiring intervention was defined as a TSB concentration meeting or exceeding the age-specific phototherapy threshold according to the 2022 AAP guideline for infants ⩾35 weeks' gestation. DCC was defined as a delay in cord clamping of >30 seconds. Hemolytic disease of the newborn was defined as immune-mediated hemolysis due to maternal-fetal blood group incompatibility (ABO or Rh), as documented in the medical record by a positive direct antiglobulin test and/or a clinical diagnosis by the treating neonatologist.

Data collection

Maternal self-reported race was used to classify the initial cohort as White or non-White. Subgroup categorization followed the 1997 Office of Management and Budget standards: Asian, African American (AA), American Indian or Pacific Islander (categorized as "Other"), and White. Although categorized as race in the electronic medical record, these groupings likely reflect a combination of social, cultural, and biologic factors and are therefore referred to as racial/ethnic groups.

We collected data for the first seven days of life. Neonatal and maternal characteristics included, but were not limited to, gestational age, birth weight, and sex; Down syndrome; polycythemia; ABO and Rh incompatibility; hemolytic disease of the newborn; and hospital discharge before 48 hours. Labor and delivery staff documented DCC time in both maternal and neonatal charts.

Clinical management of neonatal hyperbilirubinemia followed institutional protocols based on AAP guidelines (10). We used the 2004 AAP guideline until implementing the revised 2022 AAP guideline, which we adopted shortly after its release in August 2022. All neonates underwent a routine transcutaneous bilirubin (TcB) measurement once before hospital discharge. Infants whose TcB values plotted in the high-risk zone (⩾95th percentile for age in hours) on the Bhutani nomogram underwent confirmatory TSB testing. Thus, all infants had at least one TcB assessment, and a subset had an additional TSB measurement. Serum bilirubin testing was not routinely performed in all neonates at 24 hours of life.

Study outcomes

Primary Outcome

The primary outcome was the incidence of hyperbilirubinemia requiring intervention across racial/ethnic groups of neonates receiving DCC. We defined hyperbilirubinemia requiring intervention as receipt of phototherapy during the first seven days after birth. For outcome analyses, we classified infants dichotomously as having received or not received phototherapy, and each infant contributed only one event regardless of the number of phototherapy courses or treatment settings. We analyzed birth, readmission, and home phototherapy separately as treatment-location variables, and these categories were not mutually exclusive.

Secondary Outcome

The secondary outcome was the peak TSB level within the first 24 hours of life.

Statistical analysis

Categorical variables were compared using chi-square tests, whereas continuous variables were compared using Wilcoxon rank-sum or Kruskal-Wallis tests, as appropriate. We summarized distributions using additional descriptive statistics (frequencies, medians, first and third quartiles, minimum, and maximum). We reported means and standard deviations for continuous variables and percentages for categorical variables. We examined associations between hyperbilirubinemia and race using univariate and multivariate logistic regression. We entered covariates with $p < 0.25$ in the univariate analysis into the multivariate model; we retained race regardless of significance. We reported ORs and 95% CIs. We considered two-sided p-values <0.05 statistically significant. Analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethical considerations

The Joint Institutional Review Board of the University of Illinois College of Medicine Peoria and OSF HealthCare approved the study. The study complied with the principles of the Declaration of Helsinki and the U.S. Health Insurance Portability and Accountability Act (HIPAA).

Results

The initial cohort of 10,554 neonates was reduced to 10,478 after application of the predefined exclusion criteria (Figure *1*). The final cohort included 8,089 (77.2%) White and 2,389 (22.8%) non-White neonates. DCC time was consistent across groups. Most characteristics were comparable (Table *1*), except for maternal age >25 years, gestational age, and birth weight.

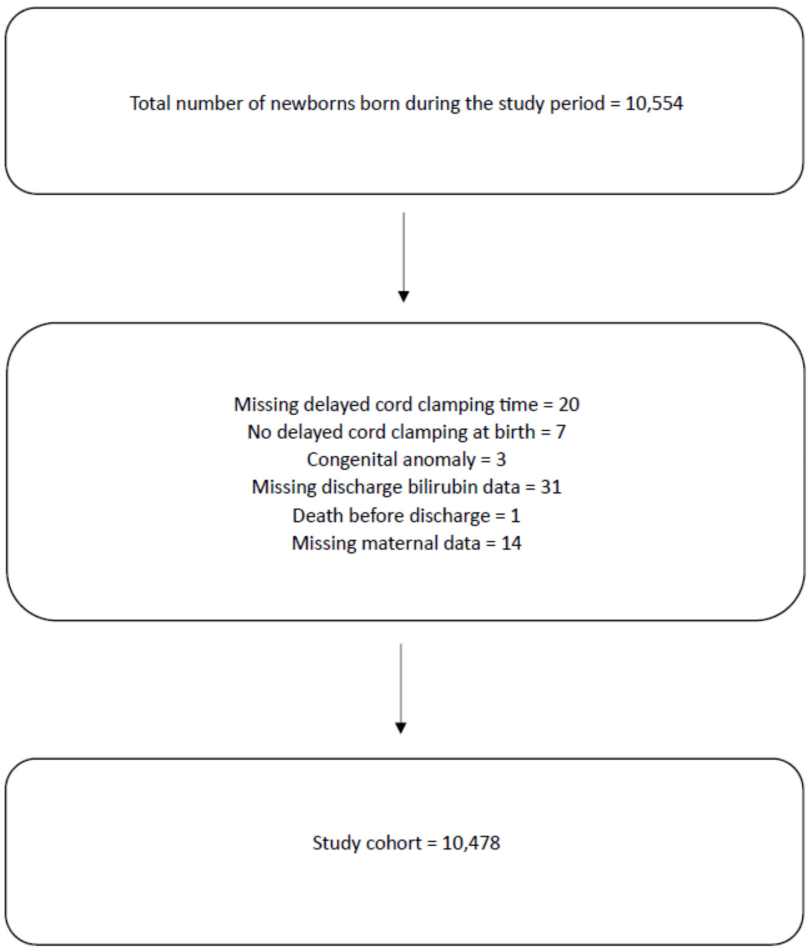


FIGURE 1: Study cohort selection flow diagram.

Characteristic	Non-White (N = 2,389), n (%)	White (N = 8,089), n (%)	Test statistic	p-value
Maternal age >25 years	1,449 (60.7)	6,247 (77.2)	259.83[c]	<0.001*
IDM	134 (5.6)	338 (4.2)	8.77[c]	0.003*
Instrumentation	71 (3.0)	256 (3.2)	0.23[c]	0.634
GA, median (Q25-Q75)	39.14 (38.43-39.86)	39.29 (38.71-40.00)	11,539,827[W]	<0.001*
BW (g), median (Q25-Q75)	3260 (2977-3572)	3487 (3175-3799)	9,912,100[W]	<0.001*
Male	1,177 (49.3)	4,140 (51.2)	2.70[c]	0.100
Abnormal birth weight				
SGA	111 (4.6)	178 (2.2)	85.52[c]	<0.001*
LGA	54 (2.3)	465 (5.7)		
Twin gestation	42 (1.8)	160 (2.0)	0.47[c]	0.492
Cord clamp time				
<60 seconds	1,433 (60.0)	4,838 (59.8)	0.02[c]	0.870
>60 seconds	956 (40.0)	3,251 (40.2)		

TABLE 1: Maternal and neonatal characteristics by race (non-White vs. White).

Values were rounded to the nearest whole number. Medians are presented with IQRs. * $p < 0.05$ was considered statistically significant.

BW, birth weight; [c], chi-square test; GA, gestational age; IDM, infant of a diabetic mother; LGA, large for gestational age; Q25-Q75, IQR (25th to 75th percentile); SGA, small for gestational age; W, Wilcoxon rank-sum test

Gestational age was higher in White neonates than in non-White neonates ($p < 0.001$). Birth weights were also higher among White neonates than among non-White neonates ($p < 0.001$). Exclusive breastfeeding rates were significantly higher in the White group than in the non-White group ($p < 0.001$; Table *2*).

Variable	Non-White (N = 2,389), n (%)	White (N = 8,089), n (%)	Test statistic	p-value
IUGR	13 (0.5)	35 (0.4)	0.50[c]	0.478
Exclusive breastfeeding	858 (36.1)	5,297 (65.6)	662.17[c]	<0.001*
Down syndrome	0 (0.0)	9 (0.1)	2.66[c+]	0.131
Polycythemia	4 (0.2)	9 (0.1)	0.47[c+]	0.506
Hospital discharge <48 hours	1,105 (46.3)	4,654 (57.5)	94.82[c]	<0.001*
ABO incompatibility	353 (14.8)	1,134 (14.0)	0.87[c]	0.352
Rh incompatibility	99 (4.1)	728 (9.0)	59.82[c]	<0.001*
Positive Coombs test	75 (3.1)	153 (1.9)	15.41[c]	<0.001*
Hemolytic disease of the newborn	58 (2.4)	116 (1.4)	11.15[c]	<0.001*
First TSB age (hours), median (Q25-Q75)	25.76 (25.01-37.78)	26.72 (25.10-44.58)	322,889.5[W]	<0.001*
Highest TSB at birth admission, median (Q25-Q75)	7.7 (5.8-9.9)	6.4 (4.8-8.5)	331,050.0[W]	0.013
TSB before discharge from birth admission, median (Q25-Q75)	9.6 (7.6-11.6)	9.8 (7.9-11.65)	342,518.0[W]	0.339

TABLE 2: Neonatal risk factors for hyperbilirubinemia by race (non-White vs. White).

Values were rounded to the nearest whole number. Medians are presented with IQRs. * p < 0.05 was considered statistically significant.

[c], chi-square test; [c+], exact chi-square test; IUGR, intrauterine growth restriction; Q25-Q75, IQR (25th to 75th percentile); TSB, total serum bilirubin; W, Wilcoxon rank-sum test

Early hospital discharge (less than 48 hours) was more common among White neonates than among non-White neonates (p < 0.001; Table 2). Non-White neonates had significantly higher 24-hour TSB levels than White neonates (p < 0.001); however, the proportion of neonates requiring phototherapy was similar between groups (Table 3).

Variable	Non-White (N = 2,389), n (%)	White (N = 8,089), n (%)	Test statistic	p-value
Hyperbilirubinemia requiring phototherapy	198 (8.3)	660 (8.2)	0.04[c]	0.840
Birth phototherapy	129 (5.4)	326 (4.0)	8.33[c]	0.004*
Readmission phototherapy	39 (1.6)	109 (1.3)	1.07[c]	0.300
Home phototherapy	56 (2.3)	288 (3.6)	8.59[c]	0.003*
Age (hours) at phototherapy, median (Q25-Q75)	35.38 (25.43-54.85)	45.32 (28.23-58.55)	23,988[W]	0.001*
High risk of TSB at 24 hours	145 (6.1)	172 (2.1)	97.47[c]	<0.001*

TABLE 3: Outcomes by race (non-White vs. White).

Values were rounded to the nearest whole number. Medians are shown with IQRs. * p < 0.05 was considered statistically significant.

[c], chi-square test; Q25-Q75, IQR (25th to 75th percentile); TSB, total serum bilirubin; W, Wilcoxon rank-sum test

In univariate analysis using a binary race classification, race was not significantly associated with the requirement for phototherapy (non-White vs. White: OR, 1.02; 95% CI, 0.86-1.20; p = 0.84). However, when race was examined using individual racial categories, Asian infants had higher odds of requiring phototherapy than White infants (OR, 1.84; 95% CI, 1.30-2.60), whereas Black infants had lower odds (OR, 0.70; 95% CI, 0.55-0.89) (Table 4).

Factor		OR	95% CI	Test statistic (Wald chi-square)	p-value
Race	-			27.71	<0.001*
	Asian vs. White	1.84	1.29-2.60	11.75	<0.001*
	Black vs. White	0.7	0.55-0.89	8.54	0.004*
	Other vs. White	1.34	1.05-1.71	5.33	0.021*
Race (two categories)	Non-White vs. White	1.02	0.86-1.20	0.04	0.840
IUGR	Yes vs. No	2.26	1.05-4.84	4.40	0.036*
Twin gestation	Yes vs. No	0.89	0.52-1.51	0.18	0.668
Abnormal birth weight	-			1.63	0.441
	LGA vs. AGA	1.18	0.87-1.59	1.12	0.289
	SGA vs. AGA	1.17	0.78-1.75	0.58	0.466
24-hour T bilirubin	High vs. Low	13.03	10.32-16.44	466.33	<0.001*
IDM	Yes vs. No	1.95	1.50-2.59	24.39	<0.001*
Down syndrome	Yes vs. No	3.22	0.69-15.59	2.13	0.144
Exclusive breastfeeding	Yes vs. No	0.62	0.54-0.71	43.92	<0.001*
Polycythemia	Yes vs. No	13.21	4.43-39.41	21.44	<0.001*
Sex	Male vs. Female	1.12	1.03-1.17	6.01	0.014*
Maternal age >25 years	Yes vs. No	1.26	1.07-1.49	7.83	0.005*
Hospital discharge <48 hours	Yes vs. No	0.34	0.29-0.39	199.50	<0.001*

TABLE 4: Univariate logistic regression for hyperbilirubinemia requiring intervention.

Values are ORs with 95% CIs and p-values. * $p < 0.05$ was considered statistically significant.

AGA, appropriate for gestational age; DAT, direct antiglobulin (Coombs) test; IDM, infant of a diabetic mother; IUGR, intrauterine growth restriction; LGA, large for gestational age; SGA, small for gestational age

The cohort was further categorized into the following subgroups: Asian, Black or AA, White, and Other. Asian neonates had the highest incidence of hyperbilirubinemia (12.2%), followed by neonates in the Other racial group (9.3%), Black or AA neonates (7.0%), and White neonates (6.4%) (Table 5).

Outcome	Asian (N = 278), n (%)	Black or AA (N = 1,367), n (%)	Other (N = 744), n (%)	White (N = 8,089), n (%)	DF	Test statistic	p-value
Hyperbilirubinemia requiring intervention	34 (12.2)	96 (7.0)	69 (9.3)	521 (6.4)	3	21.58[c]	<0.001*
Age at phototherapy (hours), median (IQR)	41.57 (26.17-63.08)	27.83 (24.85-49.88)	36.85 (26.07-57.52)	45.32 (28.23-58.55)	3	14.67[k]	0.002*
Readmission for phototherapy	10 (3.6)	14 (1.0)	15 (2.0)	109 (1.3)	3	13.20[c]	0.006*
Home phototherapy	12 (4.3)	16 (1.2)	28 (3.8)	288 (3.6)	3	22.65[c]	<0.001*

TABLE 5: Outcomes by race/ethnicity.

Values were rounded to the nearest whole number. * p < 0.05 was considered statistically significant.

AA, African American; [c], chi-square test; DF, degrees of freedom; [k], Kruskal-Wallis test

After adjusting for clinical risk factors, race remained significantly associated with hyperbilirubinemia requiring phototherapy. Compared with White infants, Asian infants had significantly higher odds of requiring phototherapy (OR, 1.55; 95% CI, 1.06-2.27; p = 0.024), whereas Black or AA infants had significantly lower odds (OR, 0.47; 95% CI, 0.36-0.63; p < 0.001) (Table *6*).

Factor	Comparison	OR	95% CI	Test statistic (Wald chi-square)	p-value
Race	-			35.56	<0.001*
	Asian vs. White or Caucasian	1.55	1.06-2.27	5.07	0.024*
	Black or AA vs. White or Caucasian	0.48	0.35-0.62	27.31	<0.001*
	Other vs. White or Caucasian	1.04	0.79-1.38	0.08	0.770
24-hour TSB	High vs. Low	10.6	8.19-13.73	321.14	<0.001*
IDM	Yes vs. No	1.63	1.26-2.27	12.13	<0.001*
Exclusive breastfeeding	Yes vs. No	0.82	0.67-0.96	6.27	0.013*
Polycythemia	Yes vs. No	7.92	2.14-29.27	9.63	0.002*
Sex	Male vs. Female	1.17	1.00-1.36	4.15	0.041*
Maternal age >25 years	Yes vs. No	1.16	0.96-1.39	2.60	0.100
Hospital discharge <48 hours	Yes vs. No	0.43	0.37-0.50	100.23	<0.001*

TABLE 6: Adjusted ORs for hyperbilirubinemia requiring intervention by racial subgroups and clinical risk factors.

Adjusted ORs with 95% CIs from multivariable logistic regression. For race, White is the reference group, and the p-value in the race header reflects the omnibus (overall) test across race categories. * p < 0.05 was considered statistically significant.

AA, African American; IDM, infant of a diabetic mother; TSB, total serum bilirubin

Discussion

The study found that non-White neonates had a significantly higher incidence of hyperbilirubinemia at discharge than White neonates, despite similar rates of phototherapy. Among racial subgroups, Asian neonates had the highest incidence of hyperbilirubinemia requiring intervention and remained at significantly increased risk after adjustment for known risk factors. Although the results largely confirm previously reported associations, they are not intended to introduce new risk factors but to underscore the importance of ongoing outcome evaluation as guidelines change. The evolution of medical practice necessitates continuous assessment of newly adopted policies and their real-world impact. A systematic

review by the International Liaison Committee on Resuscitation concluded that DCC provides low-certainty evidence of improved hemoglobin status in the neonatal period, with insufficient evidence of improved survival or neurodevelopment in early childhood [11]. In particular, as practices such as universal DCC and the removal of race as an explicit risk modifier are implemented, it is essential to examine whether these changes achieve their intended benefits and to identify any unintended consequences that might emerge in diverse clinical settings.

Castillo et al. reported higher rates of severe hyperbilirubinemia among neonates born to Asian mothers than among other groups [7]. Genetic contributors play a role; Yang et al. identified UGT1A1*6 as a major cause of breast milk jaundice (BMJ) in East Asian neonates [12], and Maruo et al. found that 51.8% of Japanese neonates with BMJ were homozygous for UGT1A1*6, with correspondingly higher serum bilirubin concentrations than those with other genotypes [9]. This study reinforces existing evidence that Asian race remains associated with an increased risk of severe hyperbilirubinemia. However, race is an imperfect surrogate for a complex interplay of genetic predispositions, environmental exposures, and social determinants of health rather than a direct biological variable. These findings suggest that, even as race-based risk stratification is de-emphasized, clinically meaningful differences across populations may persist and warrant careful, equity-focused evaluation.

Operationalizing current AAP guidance at discharge remains challenging. Risk stratification may be incomplete at discharge because key data (e.g., serum albumin or blood group incompatibility) are sometimes unavailable. Although the guideline emphasizes timely outpatient follow-up, access barriers, especially in underserved communities, can limit adherence and delay the detection of worsening jaundice. Historically, early postnatal discharge and delays in seeking care have contributed to increased readmission rates [13,14], and hyperbilirubinemia remains a common reason for readmission among otherwise healthy neonates [15-17].

Current clinical practice guidelines recommend G6PD testing in infants with a family history of neonatal hyperbilirubinemia; some jurisdictions (e.g., New York State) have mandated testing based on specified risk factors, including race/ethnicity. However, delayed turnaround times and a lack of standardized, age-appropriate reference ranges have been identified as barriers to timely identification and treatment [18,19]. Because G6PD status was not available in the present study, we could not evaluate the contribution of G6PD deficiency or other genetic factors to the observed associations. Although race/ethnicity is not a biological surrogate for genetic risk, Asian neonates in our cohort demonstrated higher adjusted odds of hyperbilirubinemia requiring phototherapy than White neonates. This finding is consistent with prior reports identifying variation in hyperbilirubinemia risk across populations [20]. However, the current study cannot determine the mechanisms underlying this association, which may reflect a combination of genetic, biological, environmental, and healthcare-related factors.

The findings align with existing knowledge but highlight the complexity of developing more effective and equitable risk-stratification methods that move beyond race/ethnicity while preserving patient safety. Future multicenter studies incorporating genetic testing, G6PD status, additional biological risk factors, and diverse patient populations may help clarify the contributors to hyperbilirubinemia risk and inform more individualized approaches to screening, follow-up, and management. Integrating electronic clinical decision support tools and interventions that address social determinants of health may further reduce outcome disparities.

Strengths

The study included a large cohort of neonates managed under a standardized DCC protocol at a single institution, reducing practice variation and providing a consistent clinical environment for evaluating outcomes. The study examined clinically relevant outcomes using contemporary definitions and treatment thresholds for hyperbilirubinemia. Including both binary race analyses and race/ethnicity-specific subgroup analyses allowed a more detailed assessment of potential differences in phototherapy risk across populations. Finally, the use of multivariable logistic regression enabled adjustment for established clinical risk factors, strengthening the evaluation of associations between race/ethnicity and hyperbilirubinemia requiring phototherapy.

Limitations

This study's retrospective design introduces potential selection and information biases. Additional limitations include reliance on parent-reported race/ethnicity, which may result in misclassification. Important factors that may influence hyperbilirubinemia risk, including socioeconomic conditions, access to post-discharge follow-up, social determinants of health, and genetic predisposition, were not available for analysis. In particular, G6PD status and other genetic contributors to bilirubin metabolism were not assessed, limiting the evaluation of potential biological mechanisms underlying the observed findings. The study was conducted at a single tertiary care center, which may limit the generalizability of the findings to other populations and practice settings. The absence of a comparison group without DCC precludes assessment of DCC's independent contribution to hyperbilirubinemia risk. Finally, the study period spanned evolving approaches to hyperbilirubinemia screening, management, and follow-up, and unmeasured

temporal changes in clinical practice may have influenced the observed outcomes.

Conclusions

In this cohort of neonates exposed to routine DCC, broad racial classification (non-White vs. White) was not associated with hyperbilirubinemia requiring intervention after adjustment for established risk factors. In contrast, Asian race remained independently associated with increased odds of phototherapy treatment. These findings highlight the limitations of using binary racial groupings when evaluating hyperbilirubinemia risk and suggest that risk may vary across specific racial and ethnic populations. Given the retrospective design and lack of genetic or G6PD data, additional studies are needed to clarify the factors contributing to the increased risk observed among Asian neonates.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Mehwish S. Sheikh, Shoji O. Samson

Acquisition, analysis, or interpretation of data: Mehwish S. Sheikh, Shoji O. Samson

Drafting of the manuscript: Mehwish S. Sheikh

Critical review of the manuscript for important intellectual content: Mehwish S. Sheikh, Shoji O. Samson

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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