ISSN: 2320-7159
IJMR
INTERNATIONAL JOURNAL OF MEDICAL RESEARCH

ORIGINAL RESEARCH ARTICLE

Cord Blood Alkaline Phosphatase as A Predictive Biomarker for Neonatal Jaundice in Term and Near-Term Neonate

Devyash Nagar[1*], Prashant shah[2]

[1,2]Department of Pediatrics, Krishna Vishwa Vidyapeeth "Deemed to Be University", Karad, Maharashtra, India

*Devyash Nagar (Email: Devyash94@gmail.com)

DOI: https://doi.org/10.55489/ijmr.1303202583

Citation: Nagar D, Shah P. Cord Blood Alkaline Phosphatase as A Predictive Biomarker for Neonatal Jaundice in Term and Near-Term Neonate. Intl J Med Res 2025;13(3):46-51. DOI: 10.55489/ijmr.1303202583

Received: March 23, 2025
Accepted: June 10, 2025
Published: July 01, 2025

Funding: Non-Declared.

Conflict of interests: The authors have declared that no conflict of interests exists.

Publisher: Medsci Publications, India

ABSTRACT

Background: Neonatal hyperbilirubinemia (NNHB) is a common condition that can lead to severe neurological complications if untreated, particularly in resource-limited settings where early detection is challenging. This study evaluates cord blood alkaline phosphatase (ALP) as a non-invasive biomarker for predicting neonatal jaundice.

Methods: A prospective observational study was conducted with 95 healthy term and near-term neonates (>35 weeks gestation) at Krishna Hospital, Karad, India, from May 2023 to November 2024. Cord blood ALP levels were analyzed at birth, with clinical follow-up for jaundice over 7 days. Neonates with conditions affecting liver or hematopoiesis or hematopoiesis were excluded. Data on demographic, clinical, and laboratory parameters, including hemoglobin and bilirubin levels, were collected. Statistical analysis was performed using chi-square tests and t-tests to assess associations with jaundice.

Results: Of 95 neonates, 44 (46.3%) developed jaundice. Jaundiced neonates had significantly higher cord blood ALP (345 ± 85 IU/L vs. 141 ± 37 IU/L, P <0.001) and lower hemoglobin (14.5 ± 3.2 g/dL vs. 16.5 ± 3.0 g/dL, P < 0.001) compared to non-jaundiced neonates. Parental consanguinity was more prevalent in jaundiced neonates (25% vs. 9.8%, P = 0.048). No significant associations were found with gestational age, birth weight, or breastfeeding.

Conclusion: Elevated cord blood ALP is a promising biomarker for early identification of neonates at risk of jaundice, particularly in resource-constrained settings. Future multicenter studies are needed to validate ALP thresholds and explore genetic factors linked to consanguinity for improved NNHB management.

Keywords: Neonatal Jaundice, Cord Blood, Alkaline Phosphatase, Hyperbilirubinemia, Hemolysis, Consanguinity

INTRODUCTION

Neonatal hyperbilirubinemia (NNHB) is a prevalent condition, affecting approximately 60% of term and 80% of preterm infants within the first week of life.[1] Characterized by elevated serum bilirubin levels, it manifests as jaundice, a benign condition in most cases. However, severe NNHB can lead to acute bilirubin encephalopathy or kernicterus, resulting in irreversible neurodevelopmental impairments, such as athetoid cerebral palsy and sensorineural hearing loss.[2,3] Early identification and management are critical to prevent these adverse outcomes, particularly in settings where follow-up care may be limited. The American Academy of Pediatrics (AAP) recommends predischarge bilirubin measurement and risk assessment for all newborns, with follow-up within 2-3 days for those discharged within 48 hours.[4,5]

However, in low-resource settings like parts of India, these guidelines are challenging to implement due to limited healthcare access and follow-up services [5]. Early discharge, driven by social, economic, and infection control considerations, further complicates timely detection of pathological hyperbilirubinemia.[6] Consequently, there is a pressing need for simple, cost-effective, and non-invasive biomarkers to identify neonates at risk of significant NNHB before discharge. Cord blood analysis offers a practical approach for early risk stratification, as it can be performed at birth without additional invasive procedures.

Among potential biomarkers, cord blood alkaline phosphatase (ALP) has shown promise. ALP, an intracellular hydrolase enzyme present in various cells, including red blood cells, is released into plasma during hemolysis, a key contributor to hyperbilirubinemia.[7] Elevated ALP levels may indicate increased red blood cell turnover, which can lead to bilirubin accumulation. Studies, such as those by Nalbantoglu et al. and Ahmadpour-Kacho et al., have reported higher cord blood ALP levels in neonates who later develop significant hyperbilirubinemia, suggesting its potential as a predictive tool.[8,9]

Despite these findings, the utility of cord blood ALP as a routine screening marker remains underexplored, particularly in resource-constrained settings. Establishing its validity could facilitate targeted follow-up for high-risk neonates, optimizing resource allocation and reducing the risk of bilirubin-induced neurological damage. This study addresses this gap by investigating the association between cord blood ALP levels and neonatal jaundice in a cohort of healthy term and near-term neonates.

The objectives are to determine whether cord blood ALP levels can predict early detection of neonatal jaundice and to evaluate the association between ALP levels and the occurrence of clinical jaundice.

MATERIALS AND METHODS

This hospital-based observational prospective study was conducted to explore the association between cord blood alkaline phosphatase (ALP) levels and neonatal jaundice over 18 months, from May 2023 to November 2024, at Krishna Hospital, a tertiary care facility affiliated with Krishna Vishwa Vidyapeeth, Karad, India.[10] The study was carried out in the Neonatal Department in collaboration with the Department of Gynecology and Obstetrics, ensuring access to a diverse neonatal population.

A sample size of 70 neonates was calculated using the formula: n = Z^2PQ/L^2 where Z = 1.96 (95% confidence interval), P = 16.8% (prevalence of birth asphyxia as a proxy for neonatal jaundice), Q = 83.2%, and L = 10% (allowable error).[11] To account for potential dropouts, 80 neonates were enrolled, with 95 ultimately included.

Neonates with gestational age >35 weeks (assessed by last menstrual period and New Ballard Score), Apgar scores ≥7 at 1 and 5 minutes, and healthy status were included.[12] Exclusion criteria comprised congenital anomalies affecting liver or hematopoiesis, prolonged rupture of membranes (>24 hours), sepsis, perinatal hypoxia, cephalohematoma, respiratory distress, intrauterine growth retardation, maternal diabetes, cholestatic jaundice, NICU admission, or parental refusal.[13]

Data collection involved clinical examinations by neonatologists, assessing vital signs, anthropometric measurements, and systemic health.[14] Maternal and neonatal histories were gathered through interviews and medical records, including maternal

demographics, obstetric details, and breastfeeding status.[15] Cord blood samples, collected aseptically post-delivery, were analyzed for ALP using a standardized enzymatic assay on a Roche Cobas c 311 analyzer, processed within 2 hours to prevent hemolysis.[7] Total and direct bilirubin levels were measured on days 3-5 or earlier if jaundice was evident, following American Academy of Pediatrics guidelines.[5] Neonates were monitored for 7 days, with daily jaundice assessments using Kramer's rule and transcutaneous bilirubin measurements when indicated.[16]

Data were stored in a secure, anonymized database, entered by trained staff, and verified for accuracy.[17] Statistical analysis using SPSS version 25.0 involved reporting continuous variables (e.g., ALP, bilirubin) as means ± standard deviation and categorical variables (e.g., jaundice presence) as percentages. Chi-square tests assessed associations between categorical variables, while t-tests or ANOVA compared continuous variables across groups.[18] A p-value <0.05 was considered significant.

The study was approved by the Institutional Ethics Committee of Krishna Vishwa Vidyapeeth. Informed written consent was obtained from parents in their preferred language, ensuring voluntary participation and data confidentiality.[19] No invasive procedures beyond routine care were performed, minimizing participant risk.

RESULTS

This prospective study evaluated 95 neonates to assess the association between cord blood alkaline phosphatase (ALP) levels and neonatal jaundice. Of the 95 neonates, 44 (46.3%) developed clinical jaundice, while 51 (53.7%) did not. Key findings are presented in two comprehensive tables, merging related variables to streamline the analysis, followed by a focused interpretation of significant results.

Table 1: Demographic and Clinical Characteristics of Jaundiced and Non-Jaundiced Neonates

Variable	Jaundiced (N=44)	Non-Jaundiced (N=51)	P-Value
Gestational Age			
<37 weeks	14 (31.8%)	7 (13.7%)	0.098
37 to <42 weeks	28 (63.6%)	40 (78.4%)	
≥42 weeks	2 (4.5%)	4 (7.8%)	
Mean ± SD (weeks)	38.5 ± 0.6	38.8 ± 0.5	
Birth Weight			
<2000 gm	3 (6.8%)	2 (3.9%)	0.536
2000-2500 gm	14 (31.8%)	11 (21.6%)	
2500-3000 gm	23 (52.3%)	34 (66.7%)	
>3000 gm	4 (9.1%)	4 (7.8%)	
Mean ± SD (gm)	2600 ± 420	2650 ± 430	
Sex			
Male	27 (61.4%)	29 (56.9%)	0.656
Female	17 (38.6%)	22 (43.1%)	
Parental Consanguinity	11 (25.0%)	5 (9.8%)	0.048
Previous Sibling Jaundice	6 (13.6%)	5 (9.8%)	0.561
Antenatal Care			
Received	37 (84.1%)	47 (92.2%)	0.221
Not Received	7 (15.9%)	4 (7.8%)	
Mode of Delivery			
Normal	31 (70.5%)	35 (68.6%)	0.847
Caesarean Section	13 (29.5%)	16 (31.4%)	
Oxytocin Use	15 (34.1%)	12 (23.5%)	0.256
Apgar Score at 1 min			
<7	1 (2.3%)	0 (0%)	0.476
7-8	9 (20.5%)	13 (25.5%)	
9-10	35 (79.5%)	38 (74.5%)	
Apgar Score at 5 min			
<7	0 (0%)	0 (0%)	0.764
7-8	7 (15.9%)	7 (13.7%)	
9-10	37 (84.1%)	44 (86.3%)	
Exclusive Breastfeeding	21 (47.7%)	29 (56.9%)	0.374

P-values calculated using chi-square test; P <0.05 indicates statistical significance.

Table 2: Laboratory and Clinical Outcomes in Jaundiced and Non-Jaundiced Neonates

Variable	Jaundiced (N=44)	Non-Jaundiced (N=51)	P-Value
Alkaline Phosphatase (IU/L) (Mean ± SD)	345 ± 85	141 ± 37	<0.001
Hemoglobin (g/dL) (Mean ± SD)	14.5 ± 3.2	16.5 ± 3.0	<0.001
WBC Count (/µL) (Mean ± SD)	5446 ± 936	5637 ± 1003	0.311
Platelet Count (/µL) (Mean ± SD)	250957 ± 52742	255942 ± 48462	0.624
ABO/Rh Incompatibility	8 (18.2%)	5 (9.8%)	0.236
Received Blood Transfusion	5 (11.4%)	3 (5.9%)	0.523
Positive Coombs Test	9 (20.5%)	6 (11.8%)	0.247

P-values for continuous variables calculated using unpaired t-test; for categorical variables, chi-square test. P <0.05 indicates statistical significance.

The study revealed a significant association between elevated cord blood ALP levels and neonatal jaundice, with jaundiced neonates exhibiting a mean ALP of 345 ± 85 IU/L compared to 141 ± 37 IU/L in non-jaundiced neonates (P <0.001).[8] This suggests that ALP is a promising biomarker for predicting neonatal hyperbilirubinemia, likely reflecting increased hemolysis, as ALP is released during red blood cell breakdown.[7] Similarly, hemoglobin levels were significantly lower in the jaundiced group (14.5 ± 3.2 g/dL vs. 16.5 ± 3.0 g/dL, P <0.001), supporting a link between hemolysis and jaundice.[20]

Parental consanguinity was significantly more prevalent in jaundiced neonates (25.0% vs. 9.8%, P = 0.048), indicating a potential genetic predisposition, possibly related to inherited hemolytic conditions.[10] Other variables, including gestational age, birth weight, sex, mode of delivery, oxytocin use, Apgar scores, exclusive breastfeeding, ABO/Rh incompatibility, and Coombs test results, showed no significant differences (P >0.05), suggesting these factors may not be major contributors to jaundice in this cohort.[5,15]

The lack of association with breastfeeding contrasts with some studies reporting prolonged jaundice in breastfed infants, possibly due to the short 7-day follow-up period.[21] Similarly, the non-significant association with ABO/Rh incompatibility and Coombs test results may reflect the study's exclusion of severe hemolytic cases.[14] These findings highlight cord blood ALP and hemoglobin as valuable predictors for early identification of neonates at risk of jaundice, enabling targeted interventions in resource-limited settings. The significant association with consanguinity underscores the need to consider genetic factors in neonatal care protocols.

Discussion

This study investigated the association between cord blood alkaline phosphatase (ALP) levels and neonatal jaundice among 95 neonates at Krishna Hospital, Karad, India, from May 2023 to November 2024. The findings confirm a significant association between elevated cord blood ALP levels (345 ± 85 IU/L in jaundiced vs. 141 ± 37 IU/L in non-jaundiced neonates, P <0.001) and the development of clinical jaundice, supporting ALP as a potential early biomarker for neonatal hyperbilirubinemia (NNHB).[8,9] This aligns with prior research by Ahmadpour-Kacho et al. and Al Assal et al., who reported ALP thresholds around 314 IU/L with high sensitivity (80-84%) for predicting significant NNHB requiring intervention.[9,22]

The elevated ALP likely reflects increased hemolysis, as ALP is released during red blood cell breakdown, a key contributor to bilirubin accumulation.[7] The significantly lower hemoglobin levels in jaundiced neonates (14.5 ± 3.2 g/dL vs. 16.5 ± 3.0 g/dL, P <0.001) further corroborate hemolysis as a mechanistic link.[20] This is consistent with Elgebaly et al., who noted lower hemoglobin in jaundiced neonates, suggesting that hemolysis-driven jaundice may be detectable through early cord blood markers.[23]

Parental consanguinity was also significantly associated with jaundice (25% in jaundiced vs. 9.8% in non-jaundiced, P = 0.048), aligning with El-Amin et al.'s findings (20% vs. 5.7%, P = 0.029) and indicating a genetic predisposition, possibly due to inherited hemolytic disorders like glucose-6-phosphate dehydrogenase deficiency [10,24]. No significant associations were found with gestational age, birth weight, sex, mode of

delivery, oxytocin use, Apgar scores, exclusive breastfeeding, or ABO/Rh incompatibility ($P > 0.05$).

The lack of association with gestational age ($P = 0.098$) contrasts with Watchko's observation that NNHB incidence decreases with gestational maturity, possibly due to the study's focus on near-term and term neonates (>35 weeks).[25] Similarly, the non-significant birth weight association ($P = 0.536$) aligns with Sally R. Eida et al.'s findings for term neonates but differs for preterm infants, where lower birth weight is a risk factor.[26] The absence of a breastfeeding effect ($P = 0.374$) contradicts Gartner's report of prolonged jaundice in breastfed infants, likely due to the 7-day follow-up missing late-onset cases.[21] The non-significant ABO/Rh incompatibility ($P = 0.236$) and Coombs test results ($P = 0.247$) may reflect the exclusion of severe hemolytic cases, reducing the prevalence of immune-mediated jaundice.[14]

The study's findings highlight the utility of cord blood ALP as a non-invasive, cost-effective screening tool, particularly in resource-limited settings where AAP-recommended predischarge bilirubin measurements are impractical.[5] Unlike end-tidal carbon monoxide or serial bilirubin tests, which require specialized equipment or repeated sampling, ALP testing at birth offers a practical alternative with high negative predictive value.[27,28] However, the single-center design and short follow-up limit generalizability and may miss late-onset jaundice.

Unmeasured confounders, such as maternal nutrition or genetic factors, could also influence results.[10] Future multicenter studies with larger samples and extended follow-up are needed to validate ALP thresholds and explore its mechanistic role in NNHB. In conclusion, elevated cord blood ALP and lower hemoglobin levels are strongly associated with neonatal jaundice, supporting their use for early risk stratification. The significant consanguinity association highlights the need for genetic screening in high-risk populations. These findings advocate for integrating ALP testing into neonatal care protocols to enhance early intervention and reduce bilirubin-related morbidity in resource-constrained settings.

Conclusion

This study demonstrated a significant association between elevated cord blood alkaline phosphatase (ALP) levels and neonatal jaundice, highlighting ALP as a promising non-invasive biomarker for early risk stratification of neonatal hyperbilirubinemia (NNHB) in resource-limited settings. The findings also identified lower hemoglobin levels and parental consanguinity as key factors linked to jaundice, underscoring the role of hemolysis and genetic predisposition. Integrating ALP testing into routine neonatal care could facilitate timely interventions, reducing the risk of bilirubin-related neurological damage. The practical and cost-effective nature of cord blood ALP analysis makes it particularly valuable in settings with limited access to advanced diagnostic tools. Future research should focus on multicenter studies with larger, diverse cohorts to validate ALP thresholds and establish standardized cut-off values for clinical use. Additionally, exploring the mechanistic pathways of ALP in hemolysis and investigating genetic factors associated with consanguinity could enhance the understanding and management of NNHB.

References

1. Ambalavanan N, Carlo WA. Jaundice and hyperbilirubinemia in the Newborn. In: Kliegman RM, Behrman RE, Stanton BF, Schor NF, St Geme III JW, eds. Nelson Textbook of Pediatrics. 20th ed. Philadelphia: Elsevier; 2015:871-872.
2. Watchko JF, Tiribelli C. Bilirubin-induced neurologic damage-mechanisms and management approaches. N Engl J Med. 2013;369(21):2021-2030. DOI: https://doi.org/10.1056/NEJMra1308124 PMid:24256380
3. Hamza A. Kernicterus. Autops Case Rep. 2019;9(1):e2018057. DOI: https://doi.org/10.4322/acr.2018.057. PMid:30863731 PMCid:PMC6394357
4. American Academy of Pediatrics. Practice parameter: management of hyperbilirubinemia in the healthy term newborn. Pediatrics. 1994;94:558-565. DOI: https://doi.org/10.1542/peds.94.4.558
5. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114(1):297-316. DOI: https://doi.org/10.1542/peds.114.1.297 PMid:15231951

6. Gale R, Seidman DS, Stevenson DK. Hyperbilirubinemia and early discharge. J Perinatol. 2001;21(1):40-43. DOI: https://doi.org/10.1038/sj.jp.7200487 PMid:11268867
7. Tinnion RJ, Embleton ND. How to use alkaline phosphatase in neonatology. Arch Dis Child Educ Pract Ed. 2012;97:157-163. DOI: https://doi.org/10.1136/archdischild-2012-301633 PMid:22761487
8. Nalbantoglu A, Ovalı F, Nalbantoglu B. Alkaline phosphatase as an early marker of hemolysis in newborns. Pediatr Int. 2011;53:936-938. DOI: https://doi.org/10.1111/j.1442-200X.2011.03491.x PMid:22010794
9. Ahmadpour-Kacho M, Zahed Pasha Y, Haghshenas M, et al. Cord blood alkaline phosphatase as an indicator of neonatal jaundice. Iran J Pediatr. 2015;25(5):e718. DOI: https://doi.org/10.5812/ijp.718
10. Mitra S, Rennie J. Neonatal jaundice: aetiology, diagnosis and treatment. Br J Hosp Med (Lond). 2017;78(12):699-704. DOI: https://doi.org/10.12968/hmed.2017.78.12.699 PMid:29240507
11. Bhutani VK, Wong R. Bilirubin-induced neurologic dysfunction (BIND). Semin Fetal Neonatal Med. 2015;20(1):1. DOI: https://doi.org/10.1016/j.siny.2014.12.010 PMid:25577656
12. Ballard JL, Khoury JC, Wedig K, et al. New Ballard Score, expanded to include extremely premature infants. J Pediatr. 1991;119(3):417-423. DOI: https://doi.org/10.1016/S0022-3476(05)82056-6 PMid:1880657
13. Maisels MJ, Watchko JF, Bhutani VK, Stevenson DK. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. J Perinatol. 2012;32(9):660-664. DOI: https://doi.org/10.1038/jp.2012.71 PMid:22678141
14. Cloherty JP, Eichenwald EC, Hansen AR, Stark AR. Manual of Neonatal Care. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2012:304-309.
15. Flaherman VJ, Maisels MJ. ABM Clinical Protocol #22: Guidelines for management of jaundice in the breastfeeding infant 35 weeks or more of gestation-revised 2017. Breastfeed Med. 2017;12(5):250-257. DOI: https://doi.org/10.1089/bfm.2017.29042.vjf PMid:29624434
16. Riskin A, Tamir A, Kugelman A, Hemo M, Bader D. Is visual assessment of jaundice reliable as a screening tool to detect significant neonatal hyperbilirubinemia? J Pediatr. 2008;152(6):782-787. DOI: https://doi.org/10.1016/j.jpeds.2007.11.003 PMid:18492516
17. Khurshid F, Rao SP, Sauve C, Gupta S. Universal screening for hyperbilirubinemia in term healthy newborns at discharge: A systematic review and meta-analysis. J Glob Health. 2022;12:12007. DOI: https://doi.org/10.7189/jogh.12.12007 PMid:36579719 PMCid:PMC9798347
18. Rosner B. Fundamentals of Biostatistics. 8th ed. Boston: Cengage Learning; 2016.
19. World Medical Association. Declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-2194. DOI: https://doi.org/10.1001/jama.2013.281053 PMid:24141714
20. Nakagawa M, Ishida Y, Nagaoki Y, et al. Correlation between umbilical cord hemoglobin and rate of jaundice requiring phototherapy in healthy newborns. Pediatr Int. 2015;57(4):626-628. DOI: https://doi.org/10.1111/ped.12583 PMid:25533043
21. Gartner LM. Breastfeeding and jaundice. J Perinatol. 2001;21:S25-S29. DOI: https://doi.org/10.1038/sj.jp.7210629 PMid:11803412
22. Al Assal HM, Hablas HR, Ellatief Afia AA, Alhameed Khedr MA, Abd Elaal El kzaz HM. Utility of Cord Blood Alkaline Phosphatase Enzyme as a Predictor of Significant Neonatal Jaundice in Well Term Infants. New York Sci J. 2017;10(4):70-74.
23. Elgebaly S, Abdo M, et al. Cord blood alkaline phosphatase as a predictor of neonatal jaundice in full-term neonates. Zagazig Univ Med J. 2023;3016:29-306.
24. El-Amin DM, Ahmed YA, et al. Evaluation of cord blood alkaline phosphatase levels as an indicator of neonatal jaundice. Al-Amin Assiut Med J. 2020;18(2):112-117. DOI: https://doi.org/10.4103/AZMJ.AZMJ_92_19
25. Watchko JF. Hyperbilirubinemia and bilirubin toxicity in the late preterm infant. Clin Perinatol. 2006;33:839-852. DOI: https://doi.org/10.1016/j.clp.2006.09.002 PMid:17148008
26. Sally R, Eida M, et al. Evaluation of cord blood alkaline phosphatase as a predictor of hyperbilirubinemia in Egyptian neonates. J Arab Soc Med Res. 2020;15:11-17. DOI: https://doi.org/10.4103/jasmr.jasmr_30_19
27. Knupfer M, Pulzer F, et al. Predictive value of umbilical cord blood bilirubin for postnatal hyperbilirubinaemia. Acta Paediatr. 2005;94(5):581-587. DOI: https://doi.org/10.1111/j.1651-2227.2005.tb01943.x PMid:16188747
28. Okuyama H, et al. End-tidal carbon monoxide is predictive for neonatal non-hemolytic hyperbilirubinemia. Pediatr Int. 2001;43(6):329-333. DOI: https://doi.org/10.1046/j.1442-200X.2001.01412.x PMid:11472573