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Hepatic Dysfunction in Asphyxiated Neonates: Prospective Case-Controlled Study

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ABSTRACT

OBJECTIVE: This study was performed to determine the occurrence of hypoxic hepatitis in full-term neonates after perinatal asphyxia and to correlate between the rise in enzymes and severity of asphyxia with Apgar score and hypoxic ischemic encephalopathy (HIE) grading of the neonates.

METHOD AND MATERIAL: This prospective case-controlled study was conducted in a tertiary-level hospital in India for a period of 12 months. The study group A comprised 70 newborns suffering from birth asphyxia, while 30 healthy neonates were included in group B (control). All biochemical parameters of liver function, ie, serum alanine transferase (ALT), aspartate transferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total protein, serum albumin, bilirubin (total and direct), and international normalized ratio (INR), were measured on postnatal days 1, 3, and 10 in both study and control groups.

RESULTS: In group A, 22.8% newborns had severe (Apgar score 0–3), 47.1% had moderate (Apgar score 4–5), and 30% had mild (Apgar score 6–7) birth asphyxia at five minutes. In all, 14.28% babies were in HIE stage I, 25.73% babies were in HIE stage II, and 11.42% babies were in HIE stage III. The rest of the newborns, 48.57%, were normal. The prevalence of liver function impairment was seen in 42.85% of asphyxiated neonates. On day 1, ALT, AST, ALP, LDH, PT, and INR were significantly higher, and total protein and serum albumin were significantly lower in group A than in group B. However, ALT and AST correlated well with increasing severity of HIE score. On day 3, there was a rising trend observed in the concentration of mean LDH as HIE staging of neonates progressed from stage 0 to stage III, and among various HIE stages, the difference in LDH was statistically significant.

CONCLUSION: We concluded that AST, ALT at 24 hours, and LDH at 72 hours of animation can be a utilitarian diagnostic tool to differentiate asphyxiated neonates from non-asphyxiated neonates and to discover the severity of perinatal asphyxia because of easy accessibility and feasibility of tests. The outcomes of this survey would be useful for physicians who receive neonates for whom birth details are not easily documented as most of the time the referred newborn infants lack asphyxia history either because the attendants do not know clearly the whole birth history or it was an unattended delivery, or the referring health-care professional has not been observant because of legal threats. The neurological assessment also becomes difficult and inconclusive as ventilator treatment, sedative drugs, and anticonvulsant therapy would produce an evaluation of severity of hypoxic ischemic brain disease and neurological insult difficult.

KEYWORDS: birth asphyxia, hypoxic ischemic encephalopathy, hepatic dysfunction

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Introduction

Birth asphyxia is an eventuality having far-reaching effects in the neonatal period. The asphyxia attack leading to hypoxic ischemic encephalopathy (HIE) could start either at the antenatal or perinatal period.[1] The overall incidence of perinatal asphyxia is reported to be varying from 1.0 to 1.5% at several centers, and is linked to gestational age and birth weight.[2]

Perinatal hypoxia is considered when a neonate demonstrates all of the following: (a) profound metabolic or mixed acidemia (pH < 7.00) on an umbilical arterial blood sample, if obtained; (b) an Apgar score of 0–3 for longer than five minutes; (c) neurologic manifestation, example, seizure, coma, or hypotonia; and (d) evidence of multiorgan dysfunction.[3] The other criteria that can define asphyxia and HIE included (a) prolonged (>1 hour) antenatal acidosis, (b) fetal heart rate less than 60 bpm, (c) Apgar score ≤3 at ≥10 minutes, (d) need for positive pressure ventilation for >1 minute or first cry delayed for >5 minutes, (e) seizures within 12–24 hours of birth, and (f) burst suppression or suppressed background pattern on electroencephalography (EEG) or amplitude integrated electroencephalography (aEEG).[4]

Hypoxia can cause damage to almost every tissue and organ. In response to hypoxic-ischemic insult to the fetus, a series of protective reflexes, called diving sea reflexes, get initiated to prevent damage to more vital organs (brain, heart, and adrenals) at the expense of lesser vital organs (kidney, lungs, gastrointestinal tract, liver, and spleen) by an attempt to redistribute available blood flow.[5] Hepatic involvement is often found in the subjects as it highly involved in so many metabolic processes. Liver cell injury commonly occurs after perinatal asphyxia, and is similar to shock liver syndrome.[6] It is represented as an early, abrupt, and transient (within 24–72 hours after) insult increase in aminotransferases [aspartate transferase (AST) and alanine transferase (ALT)], alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) plasma activity. Later on, the peak aminotransferase level returns to near normal within 10 days. The prognosis of hypoxic hepatitis itself is safe, and it rarely progresses into complete hepatic failure. With improved survival of sick asphyxiated neonates because of improvements in medical care, the clinical entity of liver involvement is being increasingly recognized, and so this work was planned to recognize the prevalence of liver involvement in birth asphyxia and to study the severity and type of hepatic dysfunction in relation to Apgar score and HIE grading of asphyxiated newborns.

Methods and Material

This subject was a prospective case-controlled study, which was carried out in the Neonatal intensive care unit (NICU) of Umaid Hospital, tertiary care hospital in Jodhpur, India, for a period of 12 months. The study was approved by the Ethical Committee of the Dr SN Medical College, and conducted in accordance with the principles of the Declaration of Helsinki. Parents gave their written, informed consent for the enrollment of their children in the study. A total of 100 full-term neonates born in Umaid Hospital were enrolled. They were split into two groups: study group A (case) comprising 70 newborns, suffering from birth asphyxia, ie, an Apgar score of 7 or less at five minutes and study group B (control) comprising 30 healthy newborns with Apgar score >7 at five minutes. Neonates were further sorted according to Apgar score at five minutes as moderate (4 and 5) or severe (3 or less) and graded into HIE stages by the Sarnath and Sarnath staging system. In HIE stage I, no seizures are experienced and the EEG pattern is normal. The infant is conscious, but irritable and jittery. The jitteriness is seen together with increased heart rate and dilated pupils as signs of increased sympathetic activity. Reflexes are normal or increased, but the sucking can be miserable. In HIE stage II, seizures are usually seen within 12 hours after birth and the EEG is abnormal. The infant responds slowly to stimuli and spontaneous movement is scarce. Lower heart rate, increased secretions from mucus membranes, and constricted pupils are examined, and the infant is hypotonic and lethargic. In HIE stage III as for moderate HIE, seizures are frequently seen but are more often prolonged and difficult to treat with anticonvulsive drugs. Seizures occur in 70% of cases having moderate-to-severe HIE, and multiple types are seen, including non-convulsive types that can only be observed with EEG. The EEG is abnormal with decreased background activity and voltage suppression, or in its severest form isoelectric with short burst of high action. The infant is in stupor with neither reflexes nor spontaneous movements. He/she is likewise unable to breathe spontaneously.[7] Neonates having a congenital malformation and a primary disease of liver or bacterial sepsis, or receiving potentially hepatotoxic drug therapy were left out from the survey. Full medical history, including perinatal history and especially the history of anesthesia during Caesarean section and drug intake by mother or infant with clinical examination laying stress on abdominal examination except in newborns with liver disease or neonatal sepsis, was noted. All biochemical parameters of liver function, ie, the serum ALT (normal value 6–50 U/L), AST (normal value 35–140 U/L), ALP (normal value 150–400 U/L), LDH (normal value 160–450 U/L), total protein (normal value 4.5–8.4 g/dL), serum albumin (normal value 2.5–3.6 g/dL), bilirubin (total and direct) (normal value <2 mg/dL), prothrombin time (normal value 10–16.2 seconds), and international normalized ratio (INR) (normal value 1.1–1.2), were measured postnatal days 1, 3, and 10 in both study and control groups. Liver was observed for congenital malformation or abnormality of biliary tract within 24 hours of birth by an ultrasound. Newborn infants who developed liver dysfunction were managed conservatively as per the standard hospital protocol. The criteria for liver impairment were ALP >50 U/L, AST >140 U/L, ALP >420 U/L, LDH >580 U/L, total protein <4.5 g/dL, serum albumin <2.5 g/dL, prothrombin time >20 seconds, and/or INR >1.2. These measures were applied on day 1 of life, and any one of the criteria when fulfilled was considered as an indication of liver damage. Asphyxiated babies with impaired liver functions were grouped as A2 and the remaining children from group A with normal liver functions were grouped as A1. Statistical analysis was executed utilizing the student's *t*-test and chi-square test. *P* value less than 0.05 was considered statistically significant.

Result

Overall, 64% males were enrolled in the study. The mean birth weight of newborns in group A was 3.02 ± 0.36 kg as compared

to 2.90 ± 0.30 kg in group B. The birth weights of newborns were matched in both the groups, and the difference was statistically insignificant ($P > 0.1$). The mean gestational age in group A was 38.04 ± 0.8 weeks and in the control group was 38.64 ± 0.6 weeks ($P > 0.1$). In group A, 16 (23%) newborns had severe (Apgar score 0–3) and 33 (47%) had moderate (Apgar score 4–5) birth asphyxia at five minutes. Of the asphyxiated babies ($N = 70$), 36 cases (52%) had HIE with 14% in stage I and 26% in stage II, while 12% babies had HIE stage III with 34 babies having no evidence of HIE. The mean cord pH of the newborn in group A was 6.96 ± 0.02. The mean serum creatinine in group A was 1.4 ± 0.2 mg/dL (normal range 0.75 ± 0.2 mg/dL).

On day 1, ALT was 48.25 ± 30.62 U/L in group A as compared to 28.40 ± 15.45 U/L in group B, which was significant ($P < 0.001$). AST was 97.21 ± 49.45 U/L in group A and 68.16 ± 38.11 U/L in group B, the difference being statistically significant ($P < 0.001$). There was a rising trend in concentration of mean ALT and AST as HIE staging of neonates progressed from HIE stage 0 (mean ALT 39.0 ± 22.99 U/L and AST 70.02 ± 35.81 U/L) to HIE stage III (mean ALT 74.75 ± 31.44 U/L and AST 157.25 ± 0.25 U/L). Similar correlation was observed when ALT and AST levels were categorized according to Apgar score at five minutes, ie, higher values of ALT and AST were seen with lower Apgar scores (Table 1).

On day 1, LDH was 455.27 ± 305.83 U/L in group A (383.4 ± 216.35 U/L in group A1; 551.1 ± 373.85 U/L in group A2) as compared to 329.40 ± 154.89 U/L in group B, which was significant ($P < 0.001$). Serum ALP was 341.01 ± 98.65 U/L in group A (286.67 ± 68.70 U/L in group A1; 413.43 ± 85.06 U/L in group A2) and 254.8 ± 96.77 U/L in group B, the difference being statistically significant ($P < 0.001$). LDH and ALP levels were statistically insignificant when compared to various HIE stages and forms of asphyxia on day 1.

On day 3, LDH was 1205.42 ± 655.55 U/L in group A as compared to 322.33 ± 122.02 U/L in group B, which was significant ($P < 0.001$). There was a rising trend observed in the concentration of mean LDH as HIE staging of neonates progressed from HIE stage 0 to HIE stage III on day 3. Among various HIE stages, the difference in LDH was statistically significant between HIE 0–II ($P < 0.001$), HIE 0–III ($P < 0.001$), HIE I–II ($P < 0.001$), and HIE I–III ($P < 0.001$), while it was statistically insignificant when

Table 1. ALT and AST levels showing correlation with HIE staging.

HIE	n	ALT (U/L) (MEAN ± SD)	*P* VALUE	AST (U/L) (MEAN ± SD)	*P* VALUE
0	34	39.0 ± 22.99	<**0.05**	70.02 ± 35.81	<**0.01**
I	10	53.0 ± 31.80	<**0.001**	88.8 ± 43.67	<**0.01**
II	18	54.33 ± 32.18	<**0.01**	98.44 ± 49.70	<**0.05**
III	08	74.75 ± 31.44	<**0.001**	157.25 ± 0.25	<**0.001**
Total	70	48.25 ± 30.62	<**0.001**	97.20 ± 49.45	<**0.001**
Control (B)	30	28.40 ± 15.45		68.16 ± 38.11	

Table 2. Table showing liver function test on day 1 lo life.

	ALT (U/L)	AST (U/L)	LDH (U/L)	ALP (U/L)	TP (g/dl)	ALBUMIN (g/dl)	TSB (mg/dl)	DSB (mg/dl)	PT (sec)	INR
Group A1 (n = 40)	32.97 ± 8.17	81.32 ± 18.65	383.4 ± 216.35	286.67 ± 68.70	5.60 ± 0.38	3.13 ± 0.50	4.16 ± 1.68	1.15 ± 0.68	14.85 ± 1.59	1.10 ± 0.07
Group A2 (n = 30)	76.63 ± 26.27	136.93 ± 32.49	551.1 ± 373.85	413.43 ± 85.06	4.89 ± 0.43	2.64 ± 0.39	4.89 ± 1.64	1.25 ± 0.65	16.61 ± 1.44	1.20 ± 0.12
Group A (n = 70)	48.25 ± 30.62	97.21 ± 49.45	455.27 ± 305.83	341.01 ± 98.65	5.30 ± 05.4	3.04 ± 0.57	4.47 ± 1.70	1.19 ± 0.67	15.69 ± 1.76	1.49 ± 0.12
Group B (n = 30)	28.40 ± 15.45	68.16 ± 38.11	329.4 ± 154.89	254.8 ± 96.77	5.70 ± 0.38	3.24 ± 0.39	3.45 ± 1.91	1.10 ± 0.47	14.37 ± 1.70	1.13 ± 0.07
P value	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.05$	$P < 0.01$	$P = 0.3$	$P < 0.001$	$P < 0.001$

Notes: A1: Asphyxiated babies with no hepatic dysfunction. A2: Asphyxiated babies with hepatic dysfunction.
Comparison of groups:
A1 vs B: Significant no difference.
A2 vs B: All parameters except TSB and DSB showed significant difference.
A1 vs A2:

Table 3. On day 3, the correlation of LDH levels with HIE staging and the difference among various HIE stages.

HIE	n	LDH (U/L) (MEAN ± SD)	*P* VALUE
0	34	823.79 ± 301.82	<**0.01**
I	10	1010.0 ± 254.30	<**0.001**
II	18	1846.72 ± 377.62	<**0.001**
III	08	2303.75 ± 914.5	<**0.001**
Total	70	1205.42 ± 655.55	<**0.001**
Control (B)	30	322.33 ± 122.02	

Notes: The difference was significant statistically between HIE 0–II, HIE 0–III, HIE I–II, and HIE I–III ($P < 0.001$), while it was statistically insignificant between HIE 0–I and HIE II–III ($P > 0.1$).

compared between HIE 0–I and HIE II–III ($P > 0.1$) and according to the Apgar score (Table 3).

Total protein was 5.30 ± 05.4 g/dL in group A (5.60 ± 0.38 g/dL in group A1; 4.89 ± 0.43 g/dL in group A2) as compared to 5.70 ± 0.38 g/dL in group B, which was significant ($P < 0.001$). Serum albumin was 3.04 ± 0.57 g/dL in group A (3.13 ± 0.50 g/dL in group A1; 2.64 ± 0.39 g/dL in group A2) and 3.24 ± 0.39 g/dL in group B, the difference being statistically significant ($P < 0.05$). Yet in group A, total protein and serum albumin levels were comparable to that of controls in all the HIE stages and forms of asphyxia. Total serum bilirubin (TSB) was 4.47 ± 1.70 mg/dL in group A (4.16 ± 1.68 mg/dL in group A1; 4.89 ± 1.64 mg/dL in group A2) as compared to 3.45 ± 1.91 mg/dL in group B, which was significant ($P < 0.01$). Direct serum bilirubin (DSB) was 1.19 ± 0.67 mg/dL in group A (1.15 ± 0.68 mg/dL in group A1; 1.25 ± 0.65 mg/dL in group A2) and 1.06 ± 0.49 mg/dL in group B, the difference being statistically insignificant ($P = 0.3$). TSB and DSB levels were comparable to the controls and in between the HIE stages. Prothrombin time was 15.69 ± 1.76 seconds in group A as compared to 14.37 ± 1.7 seconds in group B, which was highly significant ($P < 0.001$). The INR was 1.49 ± 0.12 in group A and 1.13 ± 0.07 in group B, the difference being statistically significant ($P < 0.001$). In group A, prothrombin time and INR values were somewhat higher in asphyxiated neonates than those of controls, but these values were insignificant statistically in between HIE stages (Table 2).

Out of 70 asphyxiated newborns in study group A, 40 had normal liver function (group A1) and 30 had impaired liver function (group A2). In group A1, ALT, AST, LDH, ALP, PT, and INR values were significantly higher in newborns in all the HIE stages than those of controls, but the findings were not statistically significant. In group A2, the abovementioned parameters were significantly higher than those of controls in newborns in HIE stages I, II, and III, which was statistically highly significant. However, observed ALT, AST, and LDH levels were statistically significant in HIE III when compared with those of HIE 0 and HIE I. Only LDH was significantly higher in newborns with HIE on day 3, and the deviation observed between HIE 0 and III ($P < 0.05$), and HIE I and III ($P < 0.02$) was statistically significant, while the difference between other HIE was statistically insignificant.

Away of the 30 neonates, 4 (14%) expired and 2 (7%) still had abnormal liver function on day 10, but this too normalized on follow-up. Hepatic sonography performed in asphyxiated babies showed abnormalities in five (7%) cases in the form of altered echo texture and hypoechoic irregularities. Of the four babies who died, three were having HIE grade III and one had HIE grade II.

Discussion

The prognostic value of the Apgar score for detection of hypoxic ischemic brain disease is insufficient during the first hour of animation because it can be decreased during depression from maternal drugs, anomalous babies, trauma, or metabolic or infectious insults. A biochemical parameter that correlates with HIE is of interest since ventilator treatment, sedative drugs, and anticonvulsant therapy could bring on an evaluation of severity of HIE difficult.[8]

Multiple organ dysfunction in birth asphyxia is a possible issue of adaptive mechanism. Thus, if the contrary effects of hypoxia on the newborns are considered, there is a demand to identify infants who will be at high risk of hypoxic ischemic brain disease and early neonatal death as a result of perinatal hypoxia. Different kinds of markers have been studied to identify perinatal hypoxia, including electronic fetal heart monitoring, cord pH, electroencephalograms, and Doppler flow studies. Supplementary methods for diagnosis and prediction of antenatal and non-acidotic prolonged asphyxia are lacking. Injured cells leak intracellular enzymes such as LDH, alanine transaminase, and aspartate transaminase. These enzymes may be utilized as possible predictors of timing and grade of hypoxic ischemic injury in both perinatal period and in infants with antepartum asphyxia. To know whether hepatic dysfunction can be employed as a prognostic tool for assessment of the level of hypoxia ischemic brain disease during the beginning hours of life, the study was undertaken. We observed hepatic dysfunction in 42.85% of the asphyxiated babies. Similarly, Karlsson et al.[8] and Tarcan et al.[9] reported liver involvement in 46.15 and 39% of asphyxiated newborns, respectively, while Saili et al.[10] found liver involvement in 64.5% babies.

AST and ALT. ALT and AST levels increase as a result of hypoxia organ damage and mainly liver parenchyma, which calls for an equal quantity of oxygen, glucose, and nutrients for its use. Increased activities of ALT and AST are sensitive markers of impaired liver membrane, generally in situations with decreased intake of energetic substrates into the cell. A statistically significant depression in ALT and AST values of asphyxiated neonates was found on the third day of life because of stabilization of the babies and normalization of their liver functions on day 10. This study and also other

authors' study[8,11–14] noted that rise in ALT and AST levels on day 1 correlates well with the severity of HIE, and the poor degree of correlation was noticed with the severity of asphyxia according to the Apgar score.

Alkaline phosphatases. They are a family of zinc metalloenzymes. The mechanism by which ALP reaches the circulation is uncertain; leakage from the bile canaliculi into hepatic sinusoids may result from leaky tight junctions. Consequently, the estimation of alkaline phosphate levels can suggest any kind of liver abuse. The present work demonstrated that serum ALP increased more than the command group, and the differences were statistically significant, but significant correlation with stages of HIE was not established. Islam et al.[11] reported mean ALP similar to our study in asphyxiated neonates, but showed significant correlation with stages of HIE.

LDH. A serial rise in levels of LDH or failure to come down in the beginning few days of life indicates hepatic impairment. LDH levels increased in response to asphyxia insult. The level of price growth in levels of LDH depends on hepatic dysfunction. We observed significantly higher LDH in asphyxiated babies, and similarly, Karlsson et al.[8], Sánchez-Nava et al.[13], Lackmann and Töllner,[15] and Dutta et al.[16] reported higher mean LDH in asphyxiated neonates. In the current work, peak LDH levels were on day 3, and among various HIE stages, the difference in LDH was statistically significant and then declined to normal values.

Total protein and serum albumin. Albumin's numerous functions include maintenance of colloid osmotic pressure (accounting for 80%), buffering, and transport of bilirubin, uremic toxins, fatty acids, metals, cortisol, thyroxine, endotoxins, medications, and endogenous nitric oxide. Furthermore, it is supposed to be an important antioxidant and as such could play a role in neuronal survival during development. These functions are of vital importance to the critically ill newborn baby. Albumin can be measured cheaply and well. Thus, estimation of total protein and serum albumin can indicate hepatic insult. In the present work, we observed significantly lower values of total protein and serum albumin in asphyxiated neonates and that they correlate poorly with the severity of birth asphyxia as assessed by HIE stage and Apgar score. Islam et al.[11] reported mean total protein and serum albumin similar to our study in asphyxiated neonates. The prevalence of hypoproteinemia noted by Godambe and coworkers[16] was 34% in asphyxiated newborns. The present study showed 20% prevalence of hypoproteinemia. Tarcan et al.[9] showed that hypoproteinemia is an imprecise index of the severity of liver damage in birth asphyxia because of the long life of serum proteins, and caution was used in interpreting hypoalbuminemia as this can result from capillary leakage. Our results of low protein and albumin may not be applicable to preterm neonates as they normally have low protein and albumin because of hepatic immaturity.

TSB and DSB. Bilirubin is a breakdown product of hemoglobin. The liver is responsible for clearing of bilirubin. In this study, the rise of TSB in asphyxiated newborns was statistically significant when compared with group B, although it was found to be within normal limit in asphyxiated babies. Similarly, TSB levels were reported in asphyxiated babies by Islam et al.[11] (5.5 ± 2.01 mg/dL in asphyxia group versus 4.5 ± 1.2 mg/dL in normal neonates, $P < 0.001$).

Prothrombin time and INR. Clotting is the end effect of a complex series of enzymatic reactions that require at least 13 genes. The liver is the major site of synthesis of 11 blood coagulation proteins. Most of them are only present in excess, and abnormalities of coagulation results when there is substantial impairment in the ability of the liver to synthesize these factors; thus, it is a measure of liver dysfunction. Prothrombin time and INR were significantly higher in asphyxiated neonates; other authors also noted similar results.

Hypoproteinemia, and prolonged prothrombin time and INR were noted to be the ominous signs predicting mortality in our study. The limitation of our discipline is our inability to detect subtle injury to the liver by using sophisticated tests such as immunoflurometric assay for glutathione S-transferase A (GSTA) and histopathological alteration by taking a liver biopsy as availability, feasibility, and cost factor restrict their daily use.

Conclusion

We concluded that AST, ALT at 24 hours, and LDH at 72 hours of life can be useful as a diagnostic tool to differentiate asphyxiated neonates from non-asphyxiated neonates and to detect the severity of perinatal asphyxia because of easy availability and feasibility of tests. The outcomes of this survey will be useful for physicians who receive neonates for whom birth records are not easily kept. Birth asphyxia is a substantial case of liver dysfunction in newborns. Hypoproteinemia with prolonged prothrombin time and INR carries a bad forecast.

Abbreviations

HIE: hypoxic ischemic encephalopathy
INR: international normalized ratio
AST: aspartate transferase
ALT: alanine transferase
ALP: alkaline phosphatase
LDH: lactate dehydrogenase

Author Contributions

Conceived and designed the experiments: MC, DS. Analyzed the data: DD, DS. Wrote the first draft of the manuscript: MC, DS. Contributed to the writing of the manuscript: ML, SS, AP. Agree with manuscript results and conclusions: MC, DS, DD, ML, AP, SS. Jointly developed the structure and arguments for the paper: SS, AP. Made critical revisions and approved final version: MC, DS, DD, ML, AP, SS. All authors reviewed and approved of the final manuscript.

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