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Multiorgan impact of neonatal encephalopathy: higher burden in preterm infants

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Neonatal hypoxic-ischemic encephalopathy (HIE) is the leading cause of neonatal encephalopathy (NE) and is associated with multi-organ dysfunction (MOD) and long-term complications.[1] The impact of oxygen deprivation and redistribution of cardiac output to vital organs is likely higher in preterm neonates (born before 35 weeks of gestation) with the added burden of hypoxia and immaturity.[2] Studies typically focus on term infants, due to limitation of the neurological assessment in preterm examination and lack of therapeutic options in vulnerable preterm group.[3]

We aim in this brief communication to compare the incidence of and severity of MOD term versus preterm infants. We leverage a prospective neuronicu registry started in 2009 with strict protocols in all infants with suspected HIE to measure laboratory end organ measures for hepatic (AST and ALT), cardiac (troponin and echocardiography), and renal (creatinine and oliguria, based on KDIGO score) injury at birth and prior to discharge.[4]

Using American Academy of Pediatrics (AAP) established criteria to define HIE,[5] we examined all charts with HIE diagnosis between January 2009 and 2023. Laboratory definitions of MOD included: hepatic injury (AST or ALT > 100 U/L), cardiac injury (troponin T > 0.1 ng/mL and/or abnormal echocardiography), and renal dysfunction (KDIGO-based classification for creatinine and oliguria[4]). Statistical comparisons between term and preterm infants (<36 weeks gestation) were performed using non-parametric testing (Wilcoxon rank-sum test), with $p < 0.05$ considered significant. All analyses were completed in R (v4.4.0) under institutional IRB approval, following STROBE guidelines.

Of 135,708 live births during the study period, 506 infants were diagnosed with HIE—452 term and 54 preterm (Fig. 1). Preterm infants under 36 weeks gestation accounted for 10% of all birth in this cohort, characteristics summarized in Table 1. The incidence of HIE diagnosis was similar in both groups at 3/1000. Our results reveal contrasting outcomes based on gestational age including higher risk for seizures. Mortality was significantly higher among preterm infants (18% vs. 9%). Multiorgan dysfunction (MOD) was also more prevalent in preterm (80% vs. 57%). Hepatic injury emerged as the most frequent abnormality in both groups (67% in preterm vs. 57% in terms), followed by cardiac (55% vs. 55%) and renal (37% vs. 44%) injuries. Notably, organ involvement was not only more frequent but also more severe in preterm infants. Median AST values on day one were more than twice as high in preterm (277 vs. 130 U/L), and troponin T levels similarly reflected greater myocardial stress (0.3 vs. 0.23 ng/mL). The resolution of organ injury biomarkers was slower in the preterm group.

Furthermore, the involvement and burden of multiple organs were significantly greater in preterm (39% vs. 13%). This also included Brain MRI which demonstrated 83% abnormal findings in preterm vs 60% in term infants. The watershed and basal ganglia lesions pathognomonic of HIE injury were similar in term and preterm (17% vs 18%), while preterm infants demonstrated added lesions as intraventricular hemorrhage, cerebellar hemorrhages and isolated white matter injury predominant white matter and cortical injury.[6] These results suggest a differential vulnerability of the developing brain and other organ systems to hypoxic insult based on gestational age.

Collectively, our findings indicate that MOD in HIE disproportionately affects preterm infants. The increased systemic burden may reflect a combination of factors: immature organ development, reduced autoregulatory capacity, and heightened vulnerability to inflammation and infection.[7] Preterm neonates also lack robust collateral circulatory mechanisms and are less capable of redistributing cardiac output in response to hypoxia, which may exacerbate systemic injury.

We confirm the cerebral vulnerabilities with preterm infants demonstrating a more diffuse pattern with bleeding, possibly due to altered cerebrovascular autoregulation and developmental susceptibilities.[8] While most infants demonstrated resolution of overt organ dysfunction by discharge, persistent elevations in troponin and creatinine were observed among preterm survivors, suggesting possible ongoing subclinical cardiac and renal stress. These likely contribute to the developmental origins of adult disease (DOHAD) observations postulating early repetitive insult during critical periods of brain development to contribute to later developmental, cardiovascular, and metabolic outcomes through the life span. These data underscore the need for longitudinal organ-specific monitoring, particularly in preterm infants. They also highlight the limitations of an exclusively neurocentral framework for evaluating and managing HIE.

This emerging evidence challenges the prevailing therapeutic paradigm in HIE, which remains largely focused on term infants. The concept of "encephalopathy of prematurity" must expand to include the systemic multiorgan involvement.

Our findings suggest that preterm neonates although less than 10% of births have equal incidence and higher burden from HIE, in fact, represent a subgroup in greater need of systemic protective strategies.[9] A more inclusive research approach is warranted in preterm newborns to investigate therapies that mitigate MOD alongside neurologic injury.[8]

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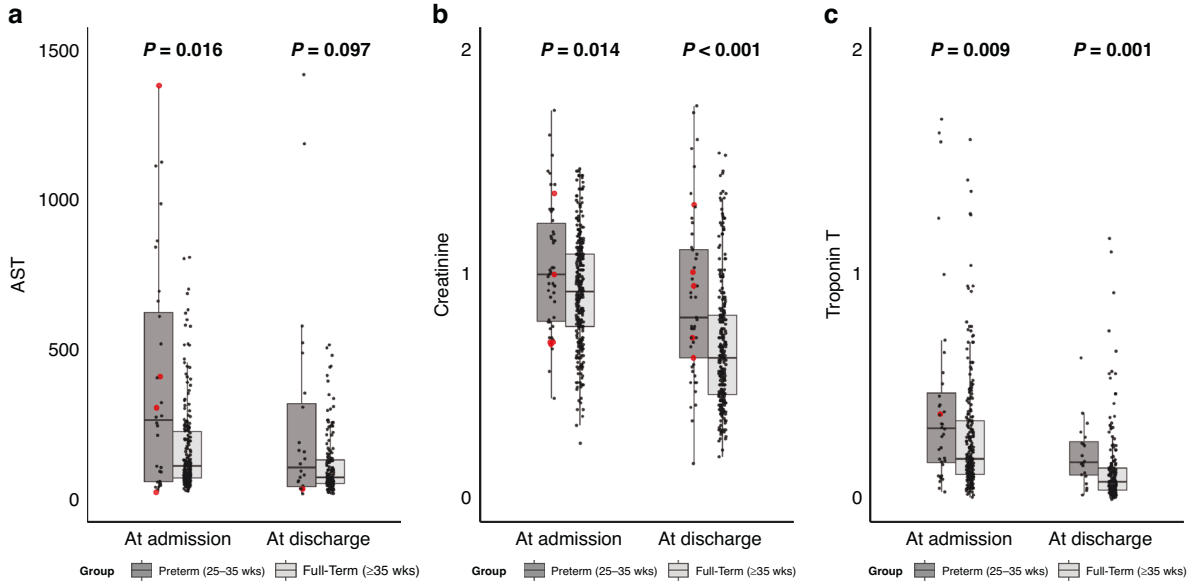

Fig. 1 Biomarkers of organ dysfunction in encephalopathy. Biomarkers: **a** liver (AST), **b** kidney (creatinine), **c** heart (troponin). Data are shown for two time points on x axis (admission and discharge). Term babies are depicted in light gray; preterm babies are depicted in dark gray color.

Table 1. Maternal and neonatal characteristics in HIE cohort.

Characteristics	Preterm (*N* = 54)	Full-term (*N* = 452)	*P*-Value
Maternal			
Maternal age (years)	30 [26 34]	27 [22 33]	0.090
Gravidity	4 [2, 4]	2 [1, 4]	<0.001
Parity	2 [1, 2]	1 [0, 2]	<0.001
Route of Delivery, N. (%)			0.002
Vaginal	5 (9)	135 (30)	
C-section	49 (91)	315 (70)	
Prenatal care, N. (%)	51 (94)	430 (96)	0.447
Clinical Chorioamnionitis, N. (%)	5 (9)	108 (26)	<0.001
Neonatal			
Race, N. (%)			0.322
White	36 (67)	334 (75)	
Black	17 (31)	96 (22)	
Asian	1 (2)	13 (3)	
Ethnicity, N. (%)			0.303
Non-Hispanic	20 (37)	134 (30)	
Hispanic	34 (63)	310 (69)	
Sex, N. (%)			0.748
Male	29 (54)	252 (56)	
Female	25 (46)	198 (44)	
Gestational age (weeks)	32 [30, 33]	39 [38, 40]	-
Birth weight (grams)	1747 ± 521	3262 ± 620	-
Apgar 1 min	1 [0, 2]	2 [1, 4]	<0.001
Apgar 5 min	4 [2, 6]	6 [3, 7]	<0.001
Apgar 10 min	5 [3, 7]	6 [4, 8]	0.001
Blood gas pH at birth	7.1 [6.8 7.3]	7.0 [6.9 7.1]	0.073
Blood gas Base Deficit at birth	13 [6, 25]	17 [13, 22]	0.048
Seizures during hospital stay, N.(%)	19 (35)	72 (16)	<0.001
Total hospital days	35 [23, 65]	12 [7, 22]	<0.001
Death, N. (%)	10 (18)	30 (7)	0.006

Continuous variables were compared using Student's *t*-test or the Wilcoxon rank-sum test, and categorical variables using the chi-square (χ^2) test or Fisher's exact test; when normality was violated, data were summarized as median (IQR) and analyzed with the Wilcoxon rank-sum test.

Future research must validate our findings across diverse populations, include long-term follow-up of systemic and neurodevelopmental outcomes, and evaluate targeted interventions that may modulate MOD. It is also imperative that future classification systems for HIE incorporate multiorgan data—potentially redefining severity not solely based on clinical encephalopathy, but also on systemic indicators of physiologic stress.

In conclusion, our data reveal a disproportionate burden of MOD in preterm infants with HIE. Gestational age appears to be a crucial determinant of both vulnerability and recovery, with significant implications for diagnosis, prognostication, and therapeutic development. A paradigm shift toward integrated, gestational age–specific, multiorgan care strategies is essential for optimizing outcomes in this vulnerable population.[10]

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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