Cord blood biomarkers in infants with hypoxic-ischemic encephalopathy: A systematic review and meta-analysis

Rallis D[1], Smolkova M[2], Walsh B[3,4], Murray D[3,4], Christou H[5], El-Dib M[5]

1.Aristotle University of Thessaloniki, Papageorgiou Hospital, Thessaloniki, Greece
2.School of Clinical Medicine, University of Cambridge, Cambridge, UK
3.INFANT Research Centre, University College Cork, Cork, Ireland
4.Department of Paediatrics and Child Health, College of Medicine and Health, University College Cork, Cork Ireland
5.Division of Newborn Medicine, Mass General Brigham for Children, Harvard Medical School, Boston, USA

Background and Purpose

Biomarkers in hypoxic-ischemic encephalopathy offer important diagnostic and prognostic insights and may help identify neonates most likely to benefit from targeted interventions.

Our aim was to evaluate whether cord blood biomarkers could improve the diagnosis of neonatal HIE.

Methods

A systematic review and meta-analysis was conducted. PubMed, Scopus, OVID MEDLINE, Embase, and Cochrane were searched through July 2024.

- Populations neonates with a gestational age of ≥36 weeks.
- Intervention was NE of any stage.
- Comparisons were between neonates with and without NE and between neonates with NE compared to neonates with perinatal asphyxia (PA).
- Outcome was the levels of any biomarkers examined. Additional outcomes were related to the distinct degrees of severity of NE (mild, moderate, severe).

Eligible studies were prospective, retrospective, longitudinal, or cross-sectional in English. Reviews, case series, case-control, and opinion articles were excluded.

Standardized mean differences were calculated with random-effects models; heterogeneity was assessed with I² and bias with Egger's test.

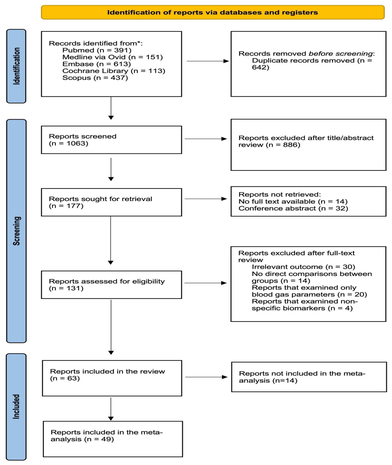
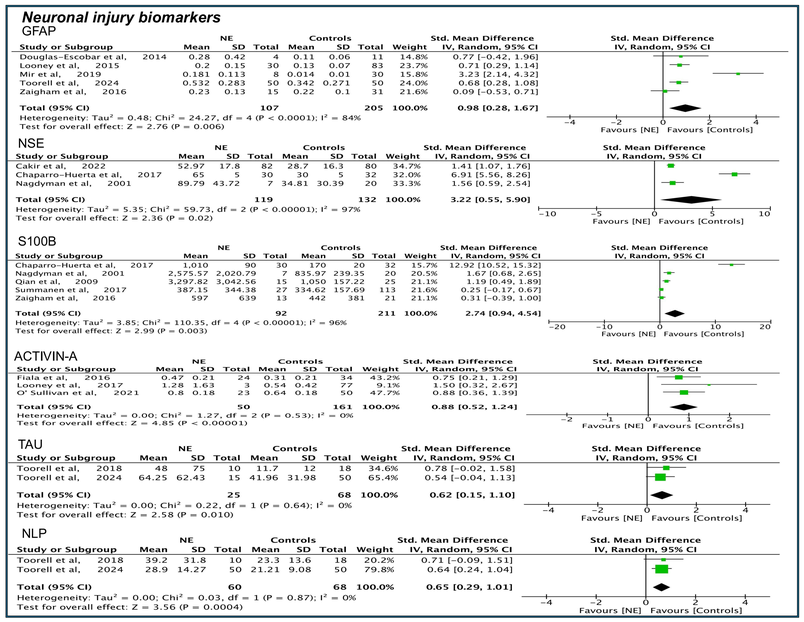


Table. Biomarkers in neonates with and without HIE

Biomarker	Mean Difference	95% CI	p-value	Overall effect Z	Heterogeneity
Glial fibrillary acidic protein, ng/ml	0.98	0.28–1.67	0.006	2.76	84%
Neuron-specific enolase, ng/ml	3.22	0.55–5.90	0.020	2.36	97%
S100 calcium-binding protein B, pg/ml	2.74	0.94–4.54	0.003	2.99	96%
Activin-A, ng/ml	0.88	0.52–1.24	<0.00001	4.85	0%
Neuronal protein tau, pg/ml	0.62	0.15–1.10	0.010	2.58	0%
Neurofilament light protein, pg/ml	0.65	0.29–1.01	0.0004	3.56	0%
Prooxidant-antioxidant balance, HK	0.80	0.59–1.00	<0.00001	7.55	0%
Interleukin-6, pg/ml	1.38	0.67–2.09	0.0001	3.83	93%
Interleukin-16, pg/ml	0.45	0.18–0.73	0.001	3.28	3%
Interleukin-1, pg/ml	2.84	1.14–4.53	0.001	3.28	97%
Tumor necrosis factor-alpha, pg/ml	3.34	2.52–4.15	<0.00001	8.05	62%
Nucleated red blood cells, /100 WBC	1.81	1.14–2.49	<0.00001	5.28	96%
Troponin, ng/l	6.13	3.33–8.93	<0.00001	4.29	99%
Creatine kinase-MB, ng/ml	2.63	0.96–4.31	0.002	3.08	98%
Creatine kinase-BB, ng/l	1.80	0.97–2.62	<0.00001	4.28	47%
Neutrophil gelatinase-associated lipocalin, ng/ml	2.31	1.11–3.51	0.0002	3.77	86%
Malondialdehyde, µmol/l	2.57	1.17–3.97	0.0003	3.6	91%
Hypoxanthine, µmop/l	0.60	0.12–1.09	0.010	2.44	54%

NE, neonatal encephalopathy; CI, confidence intervals



Results

We screened 1705 studies and selected 63 for review. Of these, 49 studies were included in the meta-analysis and they described 51 distinct cord blood biomarkers plus metabolomic and micro/mRNA expression profiles.

Several biomarkers were significantly elevated in neonates with HIE compared to neonates without HIE. The most useful biomarkers, based on magnitude, statistical strength, consistency, and biological specificity, were:

- Neurofilament light protein (mean difference 0.65 pg/ml; 95%CI 0.29–1.01)
- Glial fibrillary acidic protein (0.98 ng/ml; 95%CI 1.28–1.67)
- Neuron-specific enolase (3.22 ng/ml; 95%CI 0.55–5.90)
- Interleukin-6 (1.38 pg/ml; 95%CI 0.67–2.09)

Other elevated markers included S100 calcium-binding protein B, Activin-A, tau, prooxidant-antioxidant balance, interleukin-16, interleukin-1, tumor necrosis factor-alpha, NRBC, troponin, CK-MB, CK-BB, NGAL, malondialdehyde, and hypoxanthine.

S100 calcium-binding protein B and interleukin-6 were higher in moderate-to-severe than mild HIE.

Metabolomic changes involved amino acids, acylcarnitines, lipids, and oxidative stress markers, while altered miRNA expression was also reported.

Conclusion

- The most clinically useful cord blood biomarkers were neurofilament light protein, GFAP, and to a lesser extent NSE, as they combine biologic specificity for brain injury with relatively stronger and more reproducible evidence compared to highly significant but nonspecific systemic markers.
- Further prospective studies are needed to validate biomarker panels for clinical use.

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