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

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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 I^2 and bias with Egger's test.

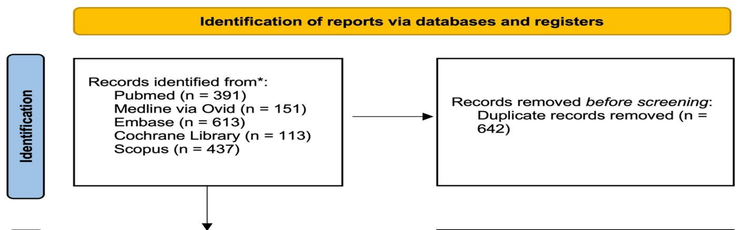
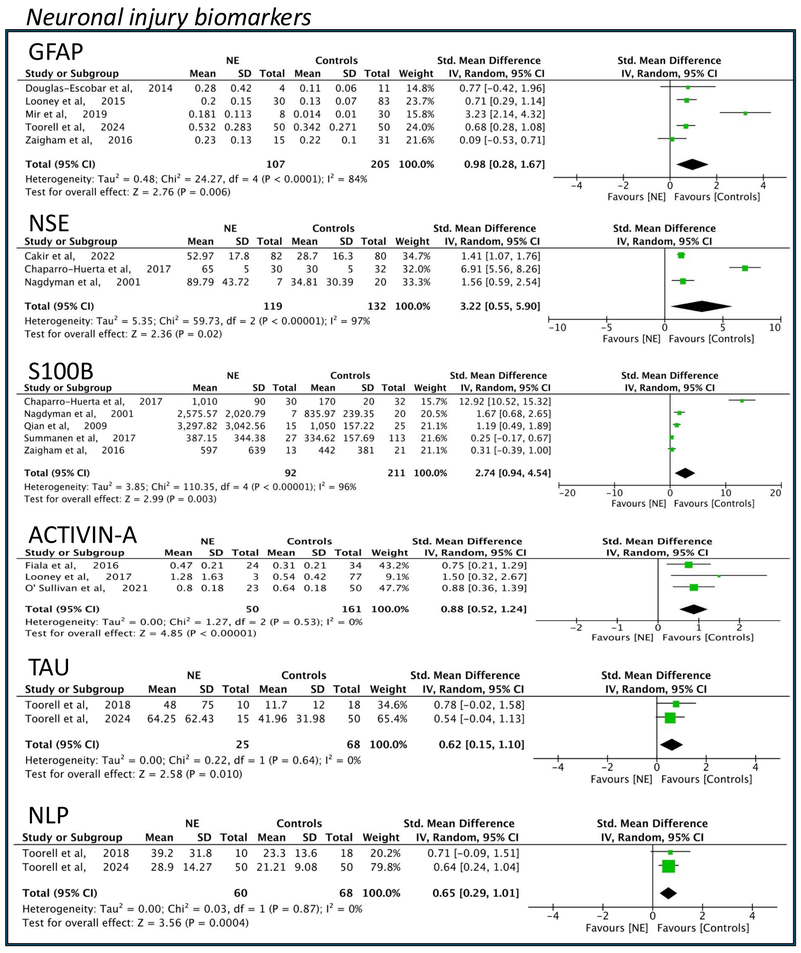


Table 1. Biomarkers in neonates with and without HIE (Ranked by Significance)

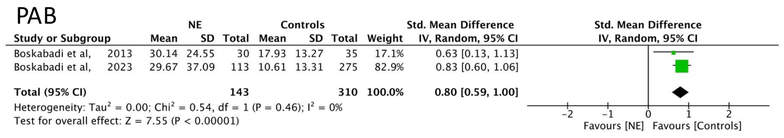
Biomarker	Mean Difference	95% CI	p-value	Overall effect Z	Heterogeneity
Tumor necrosis factor-alpha, pg/ml	3.34	2.52–4.15	<0.00001	8.05	62%
Prooxidant-antioxidant balance, HK	0.80	0.59–1.00	<0.00001	7.55	0%
Nucleated red blood cells, /100 WBC	1.81	1.14–2.49	<0.00001	5.28	96%
Activin-A, ng/ml	0.88	0.52–1.24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

HIE, hypoxic-ischemic encephalopathy; CI, confidence intervals

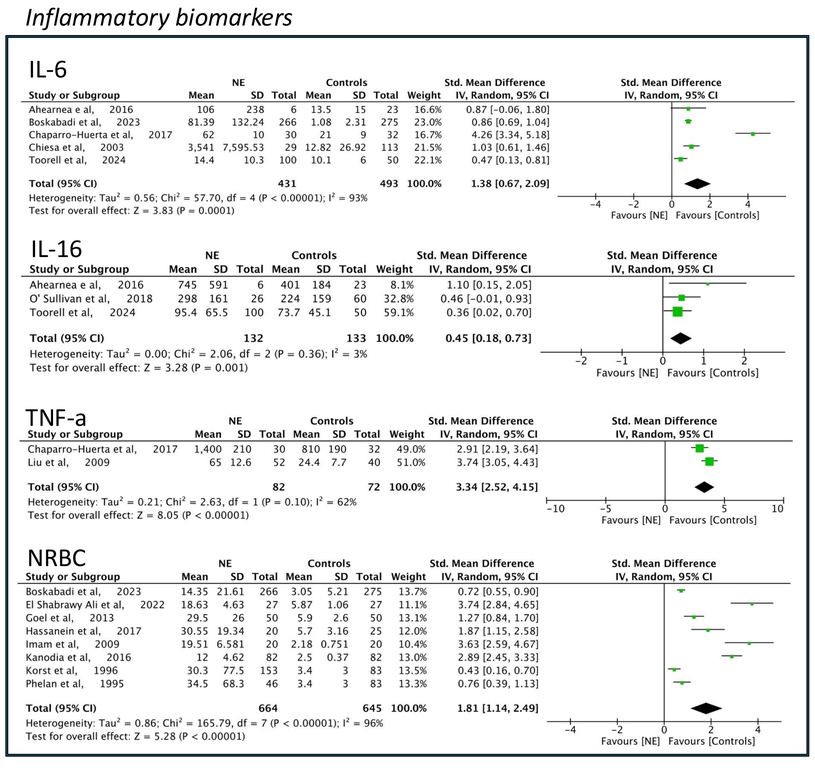
Neuronal injury biomarkers



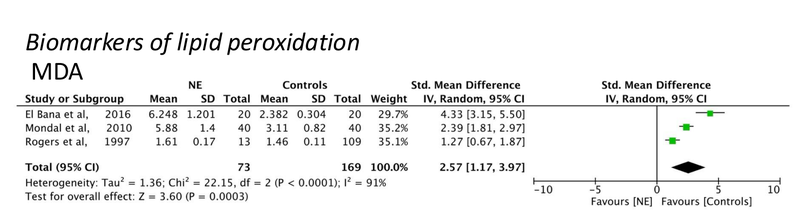
Biomarkers of oxidative stress



Inflammatory biomarkers



Biomarkers of lipid peroxidation



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 strongest associations were seen with

- Tumor necrosis factor-alpha (mean difference 3.34 pg/ml; 95%CI 2.52–4.15)
- Prooxidant-antioxidant balance (0.80; 95%CI 0.59–1.00)
- Activin-A (0.88 ng/ml; 95%CI 0.52–1.24)
- troponin (6.13 ng/l; 95%CI 3.33–8.93)
- S100 calcium-binding protein B (2.74 pg/ml; 95%CI 0.94–4.54)

Other elevated markers included glial fibrillary acidic protein, neuron-specific enolase, tau, neurofilament light protein, interleukin-6, interleukin-1, malondialdehyde, hypoxanthine, and nucleated red blood cells.
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

- Cord blood biomarkers—particularly S100 calcium-binding protein B, interleukin-6, tumor necrosis factor, prooxidant-antioxidant balance, and activin-A—show promise for early HIE diagnosis and severity assessment.
- Further prospective studies are needed to validate biomarker panels for clinical use.

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