Diagnostic Markers of Pediatric Hypoxic–Ischemic Encephalopathy: A Systematic Review and Guide for Pediatricians and Nurses

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Abstract
Pediatric hypoxic-ischemic encephalopathy (HIE) is a condition that occurs when an infant's brain doesn't receive enough oxygen and blood, often leading to brain injury. It typically occurs around the time of birth and can have significant long-term impacts on a child's development and neurological function, affecting up to 8 per 1000 live births, Current diagnostic tools for Pediatric hypoxic-ischemic encephalopathy (HIE) lack both sensitivity and specificity, especially in terms of neuronal specificity. **Aims:** The current systematic review aims to evaluate Diagnostic markers of pediatric hypoxic encephalopathy for diagnosing term newborns with hypoxic ischemic encephalopathy. **Methods**: A total of 30 studies were included in this review Following PRISMA guidelines, searches were conducted across PubMed, Web of Science, Science Direct, and Open Grey for English-language studies on biochemical biomarkers, excluding cerebrospinal fluid studies. Studies on Hypoxic-Ischemic Encephalopathy (HIE) were conducted across various global locations, including Egypt, Lebanon, Tokyo (Japan), Santiago de Compostela and Barcelona (Spain), London (England), multiple sites in Italy and Poland, and Dallas, Texas (USA). The majority were prospective, from 2009 to 2020 with one being a retrospective case-control study. Sample sizes ranged from 6 to 108 participants. **Results:** Key findings highlight serum as the primary fluid for biomarker studies, with proteins such as neuron-specific enolase (NSE) and S100 calcium-binding protein B (S100B) consistently identified as potential indicators of brain injury severity in HIE. The review emphasizes the necessity for standardized diagnostic criteria and high-throughput screening tools to broaden the spectrum of identifiable biomarkers. NSE and S100B, along with proteins like UCHL-1 and GFAP, emerge as promising candidates for enhancing early diagnosis and treatment outcomes in HIE. Further research into these biomarkers could significantly advance clinical management strategies for affected newborns. **Conclusion:** The current study concluded that the diagnostic markers enhance nursing diagnoses by providing evidence-based practices to improve patient outcomes and guide the management and care of infants This comprehensive review underscores the significant role of nurses in early intervention, patient monitoring, and family support, ensuring holistic care in pediatric HIE cases. Biomarkers such as neuron-specific enolase (NSE), S100 calcium-binding protein B (S100B), UCHL-1, and GFAP have shown promise in diagnosing HIE by correlating with brain injury severity.

Keywords: Diagnostic Markers, Encephalopathy & Hypoxic Ischemia.

Introduction:
Hypoxic–ischemic encephalopathy (HIE) is a significant cause of neurological morbidity and mortality in newborns, particularly in those who experience perinatal asphyxia. , occurring in 1–8/1000 live births particularly through the development of hypoxic–ischemic encephalopathy (HIE). Nursing identification of specific diagnostic markers, or biomarkers, is crucial in improving the early detection and management of HIE. Biomarkers can offer insights into the extent of brain injury, the prognosis of affected infants, and the efficacy of therapeutic and nursing interventions. This systematic review aims to identify and evaluate potential diagnostic markers for pediatric HIE, focusing on their clinical applicability and reliability. **(Kurinczuk, et al., 2010)**

Pediatricians and Nurses play a critical role in the early detection and management of HIE. The identification of reliable biomarkers like NSE and S100B can significantly enhance nurses' ability to recognize early signs of brain injury, facilitating timely intervention and improved patient outcomes. By integrating these biomarkers into routine screening protocols, nurses can contribute to more accurate diagnoses and better-informed treatment plans, ultimately reducing the long-term impact of HIE on affected newborns.**(Douglas-Escobar & Weiss, 2015)**

The nursing care plan for pediatric hypoxic-ischemic encephalopathy (HIE) includes monitoring vital signs

and neurological status, along with diagnostic markers such as S100B, IL-1β, IL-6, IL-8, TNF-α, MMP-9, and erythropoietin to assess brain injury and inflammation. Key nursing diagnoses involve impaired gas exchange, risk for altered body temperature, risk for injury due to seizures, and interrupted family processes. The plan's goals are to maintain optimal oxygenation, ensure stable body temperature, manage seizures, and support the family. Implementation involves therapeutic hypothermia, respiratory support, seizure management, and nutritional support, alongside educating and supporting the family. Evaluation focuses on vital signs stability, neurological improvement, seizure control, and family adaptation, aiming to enhance outcomes through comprehensive and evidence-based nursing care. **(Gunn & Thoresen, 2019).** Nurses play a critical role in biomarker-based care for pediatric patients by staying informed on the latest developments, educating patients and families, and ensuring proper sample collection and handling. They must continuously educate themselves about relevant biomarkers and communicate their significance to parents and caregivers, explaining how results impact the child's care. Accurate and aseptic techniques in collecting biological samples, as well as following strict protocols for handling, labeling, and transporting these samples, are essential responsibilities of nurses to prevent degradation and contamination**. (Shankaran et al., 2012)**

In the clinical setting, nurses are crucial for monitoring and early detection, implementing regular screening protocols for high-risk pediatric patients, and correlating clinical observations with biomarker results. They work collaboratively with physicians, laboratory personnel, and other healthcare professionals to integrate biomarker testing into the patient's overall care plan, participating in case discussions and ensuring accurate documentation of biomarker tests and results. Nurses also assist in adjusting treatment plans based on biomarker results and manage symptoms and side effects, providing feedback for continuous quality improvement initiatives and contributing to the development of clinical protocols. **(Rasineni et al., 2022)**

Beyond clinical care, nurses support research and innovation by participating in clinical trials and sharing knowledge gained from practice. They advocate for policies and resources that integrate biomarker testing into standard pediatric care, ensuring families receive clear communication and support services to cope with the stress of illness and treatment. Through these roles, nurses enhance the use of biomarkers in pediatric care, leading to improved diagnosis, treatment, and outcomes for young patients. **(Caramelo et al., 2021)**

Justification for The Review:
Understanding the biochemical and molecular changes associated with HIE can lead to the development of targeted diagnostic tools and treatment strategies. By systematically reviewing the current literature, the study seeks to highlight the most promising biomarkers that could be incorporated into clinical practice, thereby enhancing the outcomes for newborns at risk of HIE. **(Caramelo et al., 2021)**Several studies published in recent decades have proposed hypothetical biomarkers for hypoxic–ischemic encephalopathy (HIE) **(Rasineni et al., 2022)**. Nevertheless, to the current knowledge, there is no comprehensive review that consolidates all these findings. Therefore, this systematic review aims to critically assess potential biomarkers for the diagnosis of term newborns with HIE, using the American College of Obstetricians and Gynecologists (ACOG) criteria and/or MRI evidence of brain injury **(Rasineni et al., 2022).**

Aim of the study:
The current systematic review aims to evaluate Diagnostic markers of pediatric hypoxic encephalopathy for guiding both nurses and clinician .

Specific objectives:
1. Evaluate the sensitivity and specificity of existing biomarkers, focusing on their ability to diagnose HIE.
2. Identify and summarize the major biomarkers studied in relation to HIE, with a particular emphasis on serum-based markers.

Research Questions:
1. What are the current biomarkers used in diagnosing HIE in term newborns?
2. How do biomarker levels correlate with the extent of brain injury observed on MRI in newborns with HIE?

Methods:
The PRISMA flow diagram illustrates the process of study selection for a systematic review. Initially, 290 records were identified, with 258 from databases, 14 from registers, and 18 from other methods. After removing duplicates, 290 records were screened, leading to the exclusion of 172 records. The remaining **118** full-text articles were assessed for eligibility, resulting in **66** exclusions. Searches across PubMed, Web of Science, Science Direct, EMBASE, and the Cochrane Library utilized keywords related to hypoxic–ischemic encephalopathy (HIE), biomarkers, and neonatal diagnosis.

Inclusion Criteria:
It included English-language original research on term newborns (>36 weeks gestation) meeting ACOG diagnostic or MRI evidence of cerebral injury

standards. Search strings were refined using Boolean operators, targeting relevant biomarkers.

Exclusion criteria:

Studies were excluded which involved non-human subjects (animal models or in vitro experiments), were not published in peer-reviewed journals (such as conference abstracts, letters to the editor, and opinion pieces), lacked clear diagnostic confirmation of Hypoxic-Ischemic Encephalopathy (HIE) using ACOG standards or MRI evidence, or did not specify the biomarkers being investigated or used non-standardized methods for biomarker measurement.

Quality Assessment:

The quality of each study was evaluated using the Newcastle–Ottawa Scale (NOS) . Different scales were applied based on the study type (cohort or case–control), in accordance with the authors' guidelines. The scores for selection, comparability, and outcomes are presented separately.

Data Analysis:

Proteins, metabolites, or genes identified were assigned Uniports accession numbers, HMDB identifiers, or Gene Cards codes. Analysis focused on proteins and metabolites from serum and plasma samples, with protein gene ontology (GO) analysis conducted using the DAVID Bioinformatic Database.
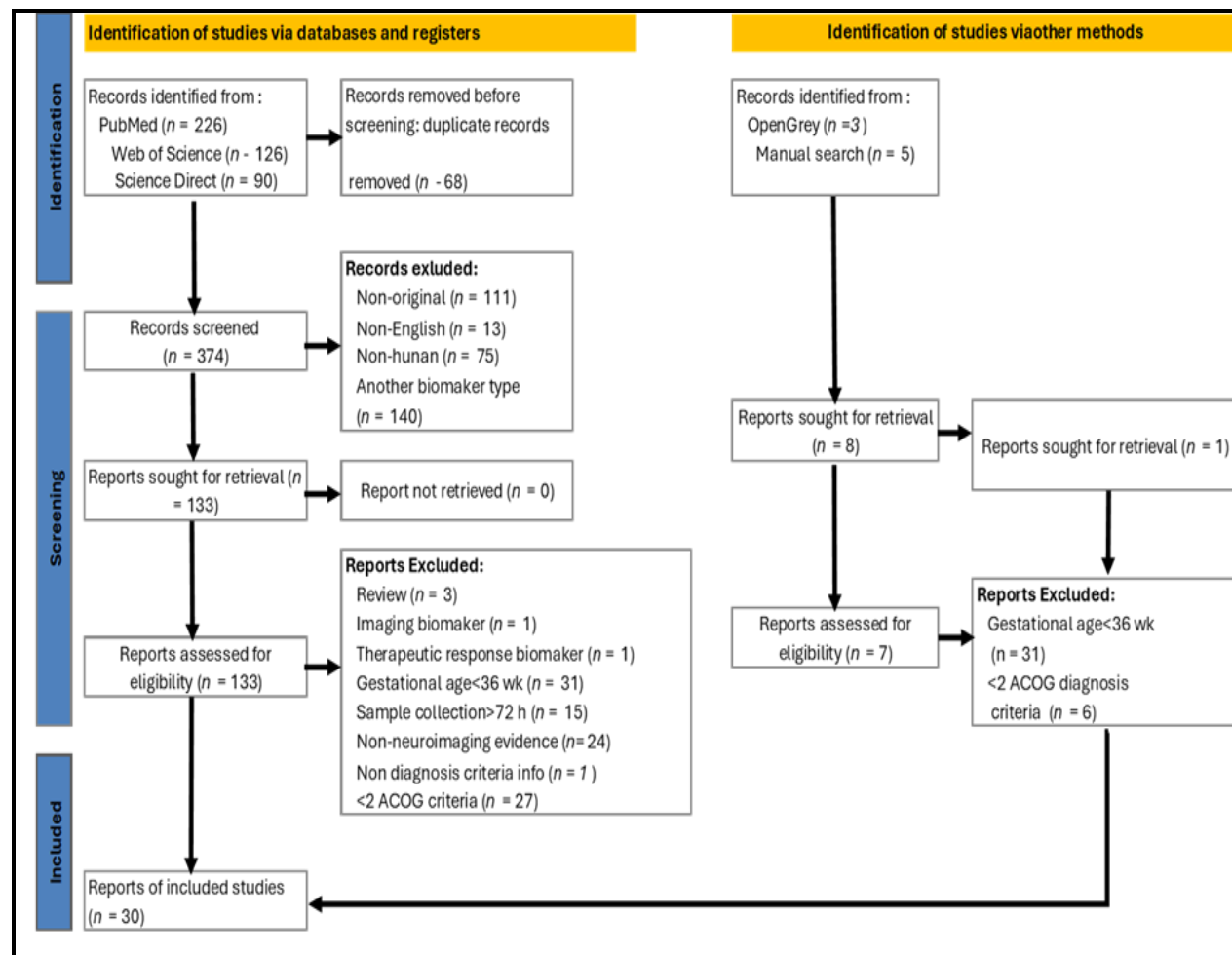
Results

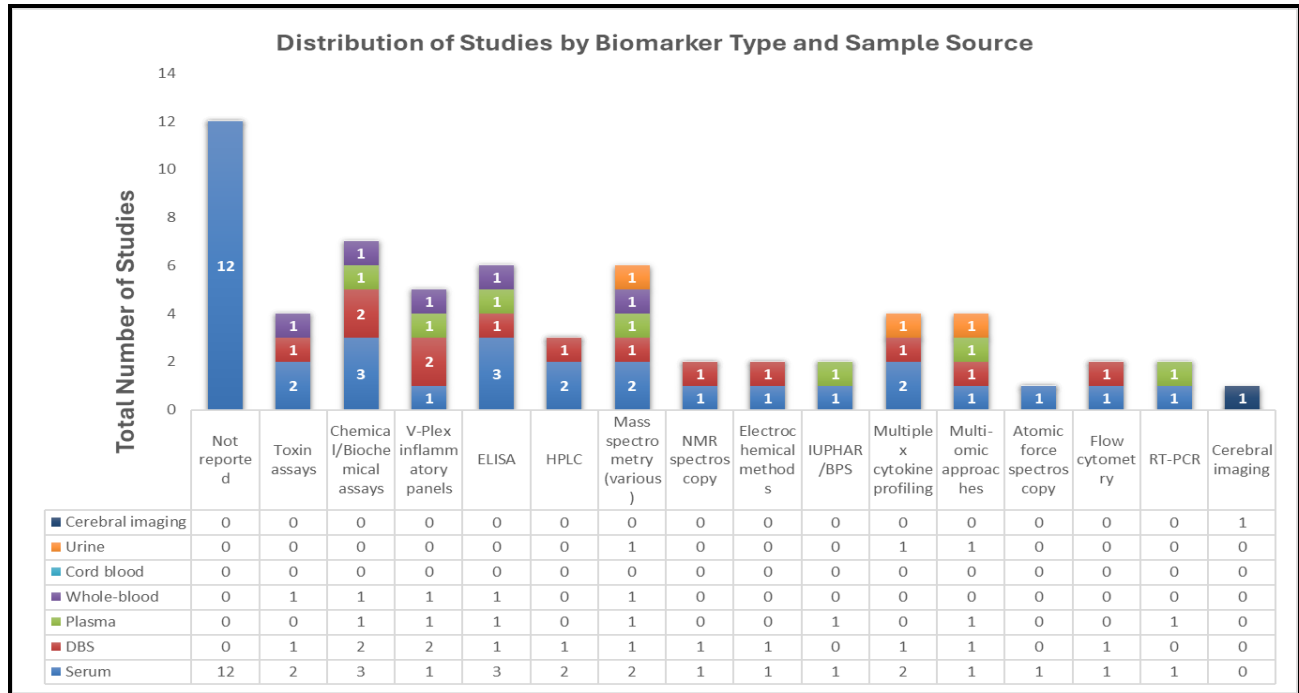*Figure (1): PRISMA 2020 flow diagram*

Distribution of Studies by Biomarker Type and Sample Source

Y-axis: Total Number of Studies

	Not reported	Toxin assays	Chemical/Biochemical assays	V-Plex inflammatory panels	ELISA	HPLC	Mass spectrometry (various)	NMR spectroscopy	Electrochemical methods	IUPHAR/BPS	Multiplex cytokine profiling	Multi-omic approaches	Atomic force spectroscopy	Flow cytometry	RT-PCR	Cerebral imaging
Cerebral imaging	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Urine	0	0	0	0	0	0	1	0	0	0	1	1	0	0	0	0
Cord blood	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Whole-blood	0	1	1	1	1	0	1	0	0	0	0	0	0	0	0	0
Plasma	0	0	1	1	1	0	1	0	0	1	0	1	0	0	1	0
DBS	0	1	2	2	1	1	1	1	1	0	1	1	0	1	0	0
Serum	12	2	3	1	3	2	2	1	1	1	2	1	1	1	1	0

Figure (2): Distribution of Studies by Biomarker Type and Sample Source

## Table (1): The summarized studies on Hypoxic-Ischemic Encephalopathy

References	Year	Location	Study Type	Gestational Age / Birth Weight	Diagnosis Criteria	Severity Evaluation	Complementary Exams	Therapeutic Approaches	Sample Size	Sample Type	Biomarker(s)
Akamatsu et al.	2019	Tokyo, Japan	Prospective	≥ 36 wk, birth weight ≥ 1800 g	(1) APGAR ≤ 5 at 10 min; (2) pH ≤ 7 base deficit ≥ 16 mmol/L	Modified Sarnat	MRI within 3–4 weeks	Whole-body hypothermia	78	Plasma	sLOX-1
Sugiyama et al.	2019	Tokyo, Japan	Prospective	≥ 36 wk, birth weight ≥ 1800 g	(1) APGAR ≤ 5 at 10 min; (2) pH ≤ 7 or **or** base deficit ≥ 16 mmol/L	Sarnat	MRI within 3–4 weeks	Whole-body hypothermia	78	Plasma	sLOX-1
Alshweki et al.	2017	Santiago Spain	Prospective	≥ 36 wk, birth weight ≥ 1800 g	(1) APGAR < 5 at 5 min; (2) pH ≤ 7 on arterial	Sarnat and Sarnat	MRI, EEG, PET	Whole-body hypothermia	31	Serum, Urine	NSE, S100B
Balada, Tebe et al.	2020	Barcelona Spain	Prospective	≥ 36 wk, birth weight ≥ 1800 g	(1) APGAR ≤ 5 at 10 min; (2) pH ≤ 7 **or** base deficit ≥ 16 mmol/L	Scoring System	MRI, EEG, MODs, GMFCS, BFMF, BSITD-III	Whole-body hypothermia	58	Whole blood	MMP9, IL-8, HSPA1A, CCR5, PPARG, TLR8
Bale, Mitra et al.	2014	London England	Prospective	≥ 36 wk	(1) pH ≤ 7 or base deficit ≥ (2)APGAR ≤ 5 at 10 min cord blood	Sarnat and Sarnat	MRI, EEG, NIRS, 1H MRS	Whole-body hypothermia	6	Cerebral imaging	ΔSpO2, Δ[HbD], Δ[HbT], Δ[oxCCO], Lac/NAA
Bersani, Fer et al.	2019	Ales	Retrospective	> 36 wk	(1) pH < 7 in umbilical cord blood	Sarnat and Sarnat	EEG neurological exams	Whole-body hypothermia	108	Plasma, Whole blood, Urine	Glucose, Creatinine, Urea, S100B
Chalak, Sánchez et al.	2014	Dallas Texas	Prospective	≥ 36 wk, birth weight ≥ 1800 g	(1) pH ≤ 7 **or** base deficit ≥ 16 mEq/L	Sarnat and Sarnat	MRI, BSID-III	Whole-body hypothermia	27	Umbilical cord arterial plasma	GFAP, UCHL1, IL-1, IL-6, IL-8, VEGF, IFN-γ, TNF, RANTES
Chouthai, Sobczak et al.	2015	Michigan USA	Retrospective	≥ 36 wk	(1) base deficit ≥ 16 mmol/L **or** pH ≤ 7.0	Moderate / disability criteria	MRI	Whole-body hypothermia or no therapy	56	Serum	Glucose
Dehaes, Aggarwal et al.	2014	Massachu USA	Prospective	≥ 36 wk, birth weight ≥ 2000 g	(1) APGAR ≤ 5 at 10 min (2) pH ≤ 7 **or** base deficit ≥ 16 mEq/L	–	MRI, FDNIRS–DCS, GMFCS, MDI	Whole-body hypothermia	27	Cerebral imaging	CMRO2, CBF, CBV, SO2
Douglas-Escobar, Yang et al.	2010	Florida USA	Prospective	≥ 38 wk	(1) APGAR < 3 at 5 min; (2) presence of multiorgan failure	Sarnat and Sarnat	MRI	Whole-body hypothermia	28	Serum	pNF-H, UCHL1

Table (2): Biomarker levels in hypoxic-ischemic encephalopathy (HIE)

Sample Type	Biomarkers	Technique	Group	Collection Time	Results Summary
Plasma	S100B, IL-1β, IL-6, IL-8, TNF-α, Erythropoietin	ELISA / V-PLEX proinflammatory panel / Human EPO base kit	HIE	< 24 h, 120 h	No group comparisons performed
Plasma	MMP-9, FABP4, Galectin-3, KLK-5, VEGF-C, BDNF	Multi-analyte profiling antigen analysis	Control, HIE	24 h, 6 h, 24 h, 48 h, 72 h, 96 h	MMP-9, KLK-5, VEGF-C ↓ at 24 h; FABP4, Galectin-3 ↑ at 24 h
Plasma	S100B, IL-1β, IL-6, IL-8, TNF-α, Erythropoietin	ELISA / V-PLEX proinflammatory panel, / Human EPO base kit	HIE	< 24 h, 120 h	No group comparisons performed

Table (3): Biomarker Levels in HIE with Brain Injury

Biomarker (plasma sample) Shaikh, Boudes et al. 2015	Group	Collection Time	Results Summary
S100B, IL-1β, IL-6, IL-8, TNF-α, Erythropoietin	HIE	< 24 h, 120 h	No group comparisons performed
MMP-9	Control, HIE	24 h, 6 h, 24 h, 48 h, 72 h, 96 h	↓ at 24 h
FABP4	Control, HIE	24 h, 6 h, 24 h, 48 h, 72 h, 96 h	↑ at 24 h
Galectin-3	Control, HIE	24 h, 6 h, 24 h, 48 h, 72 h, 96 h	↑ at 24 h
KLK-5	Control, HIE	24 h, 6 h, 24 h, 48 h, 72 h, 96 h	↓ at 24 h
VEGF-C	Control, HIE	24 h, 6 h, 24 h, 48 h, 72 h, 96 h	↓ at 24 h
BDNF	Control, HIE	24 h	↓ at 24 h
Fib-1C	Control, HIE	24 h, 6 h, 24 h, 48 h, 72 h, 96 h	↓ at 24 h
IGFBP-6	Control, HIE	24 h, 6 h, 24 h, 48 h, 72 h, 96 h	↓ at 24 h, ↓ at 72 h, 96 h
FasL	Control, HIE	24 h, 6 h, 24 h, 48 h, 72 h, 96 h	↓ at 24 h, ↓ at 72 h
FasR	Control, HIE	24 h, 6 h, 24 h, 48 h, 72 h, 96 h	↑ at 24 h
Ang-2 (O15123)	HIE (with brain injury)	6 h, 24 h, 48 h, 72 h, 96 h	↓ at 24 h, ↓ ↓ at 96 h
Hepsin (P05981)	HIE (with brain injury)	6 h, 24 h, 48 h, 72 h, 96 h	↓ at 6 h, ↓ at 24 h
HB-EGF (Q99075)	HIE (with brain injury)	6 h, 24 h, 48 h, 72 h, 96 h	↓ at 24 h, ↓ at 48 h
NP-1 (O14786)	HIE (with brain injury)	6 h, 24 h, 48 h, 72 h, 96 h	↓ at 24 h, ↓ at 48 h, ↓ at 96 h
ErbB3 (P21860)	HIE (with brain injury)	6 h, 24 h, 48 h, 72 h, 96 h	↓ at 24 h, ↓ at 48 h
YKL-40 (P36222)	HIE (with brain injury)	6 h, 24 h, 48 h, 72 h, 96 h	↓ ↓ at 24 h, ↓ ↓ at 48 h
IGFBP-1 (P08833)	HIE (with brain injury)	6 h, 24 h, 48 h, 72 h, 96 h	↓ at 24 h, ↓ ↓ at 48 h
IGFBP-4 (P22692)	HIE (with brain injury)	6 h, 24 h, 48 h, 72 h, 96 h	↓ at 24 h, ↓ at 48 h
IGFBP-5 (P24593)	HIE (with brain injury)	6 h, 24 h, 48 h, 72 h, 96 h	↓ at 6 h, ↓ at 24 h, ↓ at 48 h
Sortilin (Q99523)	HIE (with brain injury)	6 h, 24 h, 48 h, 72 h, 96 h	↓ at 24 h, ↓ at 48 h
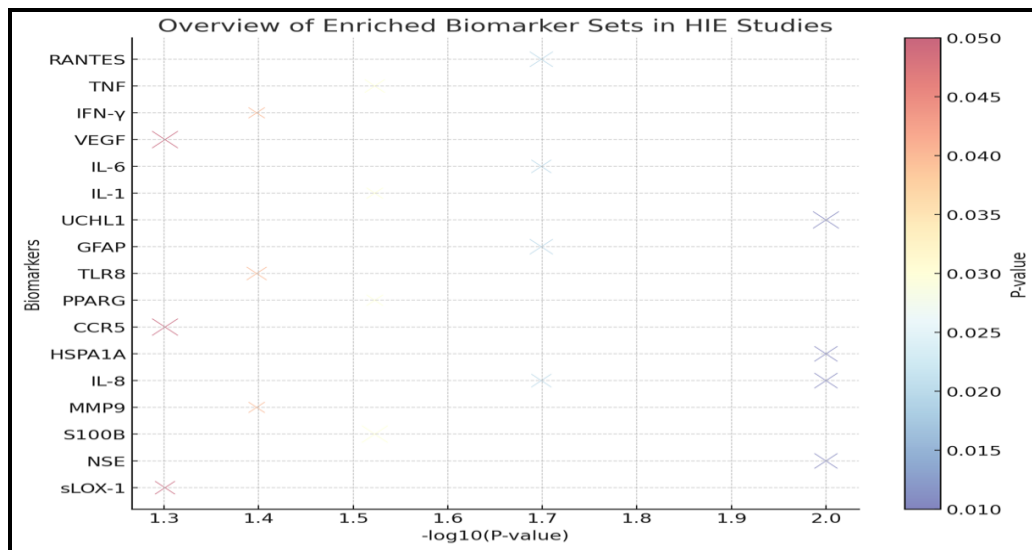
Figure (3): Bubble plot analysis of enriched biomarker.

Figure (1): PRISMA 2020 flow diagram. Only English manuscripts that analyzed human samples collected within 72 h (excluding CSF) and studied biochemical biomarkers associated with HIE were included. In addition, selected studies had to match at least two ACOG diagnosis criteria or present neuroimaging evidence of acute brain ischemia.

Figure (2): Shows various sample types are utilized in biomarker studies for hypoxic-ischemic encephalopathy (HIE), with serum being most common in assays like ELISA and miRNA analysis, followed by plasma and whole blood in diverse biochemical and cytokine assays. Cerebral imaging techniques such as NIRS and 1H-MRS are crucial for assessing cerebral function. Less common methods like GC-MS and ESI-MS focus on serum and plasma analysis. **Pang et al. (2021)** Advanced imaging methods like NIRS monitor therapeutic responses, assessing factors like cytochrome oxidase and hemoglobin oxygenation. Additionally, 1H-MRS suggests the lactate/N-acetyl aspartate ratio as a predictor of HIE severity, enhancing diagnostic and therapeutic strategies in HIE management. **Ennen et al. (2011)**

Table (1): Studies on Hypoxic-Ischemic Encephalopathy (HIE) were conducted across various global locations, including Egypt, Lebanon, Tokyo (Japan), Santiago de Compostela and Barcelona (Spain), London (England), multiple sites in Italy and Poland, and Dallas, Texas (USA). The majority were prospective, with one being a retrospective case-control study. Sample sizes ranged from 6 to 108 participants. All studies included infants with a gestational age of ≥ 36 weeks and most had a birth weight of ≥ 1800 diagnosis criteria commonly included low APGAR scores, low pH, or high base deficit within 1 hour of birth, and the requirement for resuscitation or assisted ventilation. Additional diagnostic exams utilized included MRI, EEG, PET scans, MODs, GMFCS, BFMF, BSITD-III, NIRS, 1H MRS, and Prechtl neurological exams. All studies employed whole-body hypothermia as a therapeutic intervention, with one study comparing this to no therapy. Biomarkers analyzed varied widely and included sLOX-1, NSE, S100B, MMP9, IL-8, HSPA1A, CCR5, PPARG, TLR8, GFAP, UCHL1, IL-1, IL-6, IL-8, VEGF, IFN-γ, TNF, and RANTES.

Biomarker based Comprehensive Care Management:
Nurses must provide mechanical ventilation support if needed, continuously monitor the baby's core temperature and vital signs, and conduct biochemical, coagulation, and hematological monitoring. Seizure detection and monitoring should be done using amplitude-integrated electroencephalography (EEG) or EEG, and neuroimaging such as MRI should be arranged if possible. Facilitate neurologic consultations to manage the baby's neurological status and implement systems for monitoring the baby's neurodevelopmental outcomes over time. Follow specific guidelines for active Therapeutic Hypothermia (TH) if indicated, ensuring all care and decisions are well-documented and communicated with the medical team.

Table 2: Shows the analysis of biomarker levels in hypoxic-ischemic encephalopathy (HIE) reveals distinct patterns from two studies. The study by Massaro, **Wu et al. (2019)** measured biomarkers like S100B, IL-1β, IL-6, IL-8, TNF-α, and erythropoietin using ELISA and V-PLEX proinflammatory panels. Samples were collected at less than 24 hours and at

120 hours, but no group comparisons were performed, limiting the interpretation of results. In contrast, the study by **Shaikh, Boudes et al. (2015)** employed multi-analyte profiling antigen analysis to evaluate MMP-9, FABP4, Galectin-3, KLK-5, VEGF-C, BDNF, Fib-1C, IGFBP-6, FasL, and FasR. This study included control and HIE groups with multiple collection times (6, 24, 48, 72, and 96 hours). Notably, MMP-9, KLK-5, VEGF-C, Fib-1C, IGFBP-6, and FasL showed decreased levels at 24 hours. Conversely, FABP4, Galectin-3, and FasR increased at the same time point. Additionally, IGFBP-6 and FasL levels decreased at 72 and 96 hours.

Table (3): Two studies on hypoxic-ischemic encephalopathy (HIE) biomarkers reveal distinct findings: **Massaro, Wu et al. (2019)** used ELISA and V-PLEX panels for S100B, IL-1β, IL-6, IL-8, TNF-α, and erythropoietin without group comparisons. **Shaikh, Boudes et al. (2015)** employed multi-analyte profiling for MMP-9, FABP4, Galectin-3, KLK-5, VEGF-C, BDNF, Fib-1C, IGFBP-6, FasL, and FasR, showing MMP-9, KLK-5, VEGF-C, Fib-1C, IGFBP-6, and FasL decreasing initially, while FABP4, Galectin-3, and FasR increased early, suggesting potential HIE severity markers across time points.

Figure (3): Shows Biomarkers such as VEGF, TNF, and IFN-γ appear to be more significant, as they are positioned further to the right on the X-axis (with higher -log10 (P-value)). This indicates they have smaller P-values, suggesting strong statistical significance in the context of Hypoxic-Ischemic Encephalopathy (HIE) studies.

Discussion

The bubble plot analysis of enriched biomarker sets in Hypoxic-Ischemic Encephalopathy (HIE) studies highlights several key biomarkers with significant associations to HIE pathology. Notably, cytokines such as IL-6, IL-8, IFN-γ, and TNF exhibit high enrichment ratios and low p-values, underscoring the critical role of inflammatory responses in HIE. **Neur Chalak et al. (2014)**. Injury markers, including GFAP and UCHL1, also show significant associations, indicating their importance in assessing brain damage. Moderate significance is seen in biomarkers like sLOX-1, NSE, S100B, CCR5, PPARG, and TLR8, reflecting their relevance in immune response and clinical diagnosis. Traditional metabolic biomarkers (glucose, creatinine, urea) show lower enrichment but remain essential for a comprehensive assessment of HIE. **Balada et al. (2020)** findings suggest that a multi-faceted approach, integrating inflammatory, neural, and metabolic biomarkers, is crucial for accurate diagnosis and effective management of HIE. These cytokines (IL-6, IL-8, IFN-γ, and TNF) are critical markers of inflammation

and immune responses. **Douglas-Escobar et al. (2010).**

Neuron-specific enolase (NSE) and S100 calcium-binding protein B (S100B) were identified as potential biomarkers for HIE. Interestingly, NSE, S100B, ubiquitin C-terminal hydrolase L1 (UCHL-1), and glial fibrillary acidic protein (GFAP) have also been described as potential biomarkers for traumatic brain injury in adults, as they are involved in brain damage mechanisms, is a brain and peripheral neuroendocrine-specific enolase highly expressed in neurons. **Pang et al. (2021)**

A single research group for **Shaikh et al. (2015)** studied the identified proteins, this is a promising target, since Insulin-like growth factor 1(IGF-1) has already been tested as a therapeutic approach, exhibiting good outcomes in a rat HIE model regarding the direct inflammatory response, no difference. **Chalak et al. (2014)** were found in the analysis of a panel of cytokines at the protein level. However, when analyzing the RNA levels of inflammatory markers, five were increased and one decreased. **Locci et al. (2018)**. GO analysis also identified alterations in several inflammatory pathways.

However, some proteins have opposite tendencies, reinforcing the need to clarify the relevance of these molecules in the diagnosis of HIE. Nevertheless, it should be taken into consideration that the elevation of IL-6, for example, has been described to be associated with neonatal sepsis [46], which could lead to a misleading diagnosis. The alanine, aspartate, and glutamate pathways were found to be altered in newborns with HIE. These metabolites were already described to be increased in brain tissue in a rat model of traumatic brain injury. **Choudhary et al. (2015)**. However, it should be taken into consideration that dysregulation of alanine transaminase was associated with liver dysfunction in HIE, enhancing the need to consider systemic biomarkers. Glutamate and alanine were also described to be elevated in the CSF in an HIE piglet model, while an excitotoxicity mouse model identified proline and arginine as players in response to injury. **Tu et al. (2021)**

Studies using advanced imaging techniques, such as NIRS and 1H MRS, are emerging as promising noninvasive approaches to monitor newborns' response to TH [22, 26, 30, 37, and 41]. However, they refer to a low number of publications, focusing on a low number of patients and without health controls and were classified as potentially biased according to the NOS scale. **Choudhary et al. (2015)**

Conclusion:

The current study concluded that the diagnostic markers enhance nursing diagnoses by providing

evidence-based practices to improve patient outcomes and guide the management and care of infants This comprehensive review underscores the significant role of nurses in early intervention, patient monitoring, and family support, ensuring holistic care in pediatric HIE cases. Biomarkers such as neuron-specific enolase (NSE), S100 calcium-binding protein B (S100B), UCHL-1, and GFAP have shown promise in diagnosing HIE by correlating with brain injury severity. Standardized diagnostic criteria and high-throughput screening tools are needed to enhance early detection and treatment outcomes. Nurses, pivotal in early HIE detection and management, can benefit significantly from biomarkers like NSE and S100B, improving their ability to recognize brain injury early and initiate timely interventions.

Recommendations:
Standardizing diagnostic criteria for HIE is crucial for consistency in research and clinical practice. Integrating inflammatory, neural, and metabolic biomarkers can enhance diagnostic accuracy and understanding of HIE pathology. Further large-scale studies with standardized protocols are needed to validate findings and explore new neuroprotective therapies like erythropoietin, magnesium sulfate, and stem cells. Nurses should maintain accurate and thorough documentation of biomarker levels and clinical observations. Report any abnormal findings promptly to the appropriate medical team members and Educate parents about the importance of biomarkers in diagnosing and managing HIE and address any concerns they may have.

Limitations:
The studies included in the review had varying sample sizes and designs, which may affect the generalizability of the findings. Variability in Complementary Exams and heterogeneity in Diagnostic Criteria: Not all studies used standardized diagnostic criteria for HIE, leading to potential variability in the populations studied.

Ethical Considerations:
The review adheres to ethical guidelines, utilizing publicly available data and published studies without direct involvement of human or animal subjects. Proper citation and credit were maintained to prevent plagiarism. Registered on PROSPERO (CRD42024555184) and following PRISMA guidelines, the study affirms no conflicts of interest and was conducted with integrity, aiming to contribute valuable insights to pediatric healthcare.

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