International Journal of Nursing and Health Care Research

OPEN ACCESS

Munteanu AI, et al. Int J Nurs Health Care Res 5: 1330.

www.doi.org/10.29011/2688-9501.101330

www.gavinpublishers.com

GAVIN PUBLISHERS

Research Article

Interdisciplinary Approach and the Value of a Scoring System for Hypoxic Ischemic Encephalopathy in Predicting Newborn Neurodevelopmental Outcome

Andrei Ioan Munteanu[1,4], Otilia Marginean[2,4*], Marioara Boia[3,4]

[1]Department XI Paediatrics, Discipline I Paediatrics, University of Medicine and Pharmacy „Victor Babes" from Timişoara, Romania, Eftimie Murgu square, no. 2, 300041, Timisoara, RO

[2]Department XI Paediatrics, Discipline I Paediatrics, Disturbances of Growth and development on children – BELIVE, headquarters Iosif Nemoianu, street no. 2-3, 300011, Timisoara, RO

[3]Department XII Obstetrics - Gynecology, Discipline of Neonatology and Childcare, University of Medicine and Pharmacy „Victor Babes" from Timisoara, Romania, Eftimie Murgu square, no. 2, 300041, Timisoara, RO

[4]Emergency Hospital for Children „Louis Țurcanu", Street Iosif Nemoianu, no. 2, 300011, Timisoara, Romania

[*]**Corresponding author:** Otilia Marginean, Department XI Paediatrics, Discipline I Paediatrics, Disturbances of growth and development on children-BELIVE, headquarters Iosif Nemoianu street, no. 2-3, 300011, Timișoara, Romania

Citation: Munteanu AI, Marginean O, Marioara B (2022) Interdisciplinary approach and the value of a scoring system for hypoxic ischemic encephalopathy in predicting newborn neurodevelopmental outcome. Int J Nurs Health Care Res 5: 1330. DOI: 10.29011/2688-9501.101330

Received Date: 04 August, 2022; **Accepted Date**: 19 August, 2022; **Published Date**: 25 August, 2022

Abstract

Awareness of the neurological complications of critical illness and their impact on the developing brain is important in neonatology units. That is why adequate and prompt management is very important. Neonatal encephalopathy and its complications are the most common conditions treated in a neonatal intensive care unit. A prompt intensive care approach can mitigate adverse effects among neonates with HIE by preventing secondary brain injury, prompt recognition and treatment of neurologic complications, correct management using guidelines and protocols, and use of appropriate equipment. Aim. The development of an easy and quick method for evaluating the severity of NE based on the biological investigations, carried out to help neonatologists to interpret in a clinical context the biological investigations performed in the first hours of life. Results. An „EVOLUTIVE SCORE" was elaborated, in which each investigation carried out, both at time t1 and at time t2, was marked with an indicator from 1 to 5, thus tracking the biological evolution and the degree of modification of the biological parameters during the 96 follow-up hours. Conclusion. „EVOLUTIVE SCORE" indicates that a higher score obtained by the newborn at time t1 correlates with a favorable evolution and reduced mortality.

Keywords: Evolutive Score; Hypoxic-ischemic encephalopathy; Neonatal encephalopathy; Nursing; Newborn; Premature

Abbreviations: CRP: C-Reactive Protein; CBC: Complete Blood Count; HB: Hemoglobin; HIE, Hypoxic Ischemic Encephalopathy; LDH: Lactate Dehydrogenase; LE: Leukocyte; LY: Lymphocyte; Ne: Neutrophil; NE: Neonatal Encephalopathy; NICU: Neonatal Intensive Care Unit; PCT: Procalcitonin; TH: Therapeutic Hypothermia; t1: Time-Point 1 in the first 24 hours; t2: Time-Point 2 between 36 and 96 hours

Introduction

The prevalence of perinatal asphyxia in developed countries is 2 per 1,000 births, whereas it is 10 times higher in developing countries. The prevalence of neonatal encephalopathy is 3 per 1,000 births, whereas that of hypoxic-ischemic encephalopathy (HIE) is 1.5 per 1,000 births. It is well known that infants with moderate to severe HIE are at risk for adverse events, such as cerebral palsy, neurodevelopmental disorders, or death [1].

Using the term NE vs. HIE is controversial. It was proposed that the term NE should be used for small term and premature infants without identifiable causes. It is difficult to demonstrate the presence of hypoxic-ischemia injury outside of animal models and particularly in cases of neonatal stroke. Some authors state that HIE is the cause of NE in 50-80% of cases based on clinical, EEG and MRI criteria [2].

There is increasing evidence from experimental animal and human clinical studies to suggest that the developing brain is unique in its response to injury, and that recovery is mediated by different mechanisms from those observed in adults. First, excitation predominates in the developing cerebral cortex and limbic structures, leading to a lower threshold for seizures and excitotoxic hypoxic/ischemic injury. Second, the neonatal brain is selectively vulnerable to oxidative stress due to relatively high levels of free iron. Third, inflammation plays a different role. Since the neonatal blood-brain barrier appears more resistant than its adult counterpart, microglia may be supportive rather than harmful, and cytokines may be different in their mediating effects. Fourth, the perinatal period is unique in terms of neurogenesis, gliogenesis, and circuit formation, all of which can be impacted by disease. Indeed, these differences appear to result in the selective vulnerability of different cell populations through development [3].

Newborns who developed severe perinatal asphyxia and suffer fetal acidemia, require intensive resuscitation, and showed an abnormal EEG are at the highest risk for HIE complications. Several biomarkers were done for proper assessment of the severity of brain damage. An ideal biomarker for the diagnosis of HIE should be specific, early, rapid, and easily done. The results of these biomarkers should be interpreted in conjunction with the clinical history and physical examination [4]. Neonatal neurocritical care has emerged over the last decade as a subspecialty that involves a culture change toward a 'brain-focused' approach with all bedside providers (physicians, nurses, respiratory technologists, and trainees) maintaining constant awareness of the potential neurological complications of critical illnesses, as well as the impact of management on the developing or injured brain. Several important advances have prompted this culture change, including increased survival from critical illness, as well as the advent of digital monitoring and safe, high-resolution magnetic resonance imaging (MRI). Conditions cared for in a neurocritical care unit include neonatal encephalopathy (and hypoxic-ischemic encephalopathy, HIE), seizures, intracranial hemorrhage, ischemic stroke and intracranial infection, among others [5].

The role of the neonatologist. The neonatologist has an early active role from the moment of the initial presentation of neurological signs or symptoms in hospitalized newborns. It usually acts as the first physician to care for and identify newborns who are at risk of developing hypoxic-ischemic brain injury. In patients with HIE, neonatologists will perform the initial resuscitation and manage the patient with special attention to physiologic homeostasis, with emphasis on cardiopulmonary support, maintenance of normal electrolyte and glucose levels, and temperature control to minimize secondary brain injury [5]. Recognizing the etiology of HIE can guide investigations, such as metabolic and sepsis analyses, to ensure optimal management. Understanding the etiology of HIE may allow the development of targeted adjuvant therapies related to the underlying mechanism.

Neonatologists will initiate specialized treatment and will monitor both the performance of the treatment by the medical assistant and the results obtained under the prescribed treatment. The clinical management for NE is primarily supportive care, with additional neuroprotective therapy [6]. The intensive care neonatology doctor will continue monitoring patients in a highly specialized department [7]. He will initiate specific therapies, monitor and adjust the ventilatory parameters, monitor the response to these therapies. Follow up and treat any complications that arise promptly. He will follow the evolution of anthropometric and neurological parameters. The nursing of a critical patient being a medical act of great importance performed by a mixed medical team. From the moment of birth until the discharge of the patient, the neonatal neurocritical care team serves to prevent secondary injuries, implement neuroprotective strategies, including therapeutic hypothermia which in case of mild NE should not be considered as the standard of care [8], manage neurological complications, optimizing developmental care and establishing outpatient developmental services and follow-up for the high-risk patient.

It is desired and sustained efforts are being made to develop specific protocols to help the neonatology doctor in hospital units that don't have specialized training in neonatal intensive care. With the help of these protocols/strategies, it is possible to identify early and specifically the newborns who need senior medical assistance. The transfer of patients to intensive care units should be done early and within safety limits, thus avoiding complications that are difficult to treat and with a potential for unfavorable evolution. We emphasize what was said before, that the neonatologist is the first doctor who investigates, treats and evaluates a case, being also well informed and prepared to be able to anticipate and decide the optimal, early moment for the transfer of a patient. Instead, it was proposed that in order to avoid some unnecessary transfers, telemedicine consultations can be performed for patients suspected of NE [9]. In newborns with perinatal asphyxia, the first 6 h of life constitute a crucial window in which care involves different stages from birth to the moment TH is initiated: (1) resuscitation and stabilization of the patient, (2) control of comorbidities, (3) accurate assessment of HIE severity, and (4) urgent transport to referral hospitals offering integral care for these newborns,

including TH [10].

As the inpatient care of neurologically ill patients has become increasingly more complex, neurologist specializing in intensive therapy have more commonly been involved as physicians with specific inpatient expertise who focus not only on direct patient care but also on issues related to quality and safety [11].

The role of the neurologist. The neurologist serves to document a detailed neurological examination, as well as to guide and implement strategies for the management of neurological complications that arise (eg: seizures) and follow up on the dynamics of neurological development. Neonates with encephalopathy due to perinatal asphyxia should receive neurophysiological monitoring using continuous video EEG and/or a simplified bedside aEEG monitoring setup. Continuous neurophysiological monitoring is important to assess the dynamic change of background brain activity and the degree of encephalopathy as well as seizures. The neurologist interprets the EEG and cranial imaging in collaboration with the medical radiologist [5]. Together with the neonatologist, the neurologist manages the patient and communicates with the family during the period of critical illness. Finally, the neurologist's perspective is especially important when discussing prognosis and neurologic follow-up with the family, and the neurologist helps plan outpatient services such as physical and occupational therapy or rehabilitation programs, especially if it is expected that the child to have long-term disabling neurological disorders.

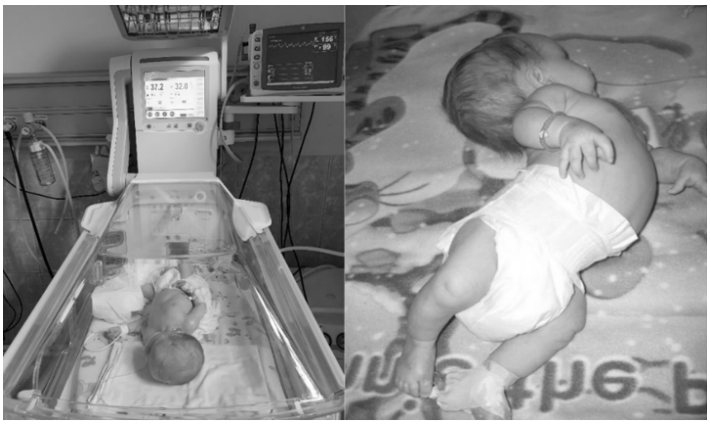

Figure 1: Newborn in critical condition in neonatal intensive care unit.

The role of the hematologist. Newborns with HIE have multiple changes in terms of the hematological parameters caused both by the determining factors of HIE and as a consequence of the neurological damage. Thus, anemia, thrombocytopenia, changes in the leukocyte formula, and coagulation disorders can be discovered in a newborn with hypoxia at birth, therefore the intervention of a hematologist is very important to suggest specialized investigations, to guide the monitoring of the dynamics of the hematological parameters and in the implementation of specific therapeutic strategies such as anticoagulant treatments or with biological products to stimulate granulocyte colonies or to monitor transfusions of blood products that are so used in a neonatal intensive care unit. Coagulopathy is common in NE at up to 40% and blood product transfusion requirement is common [12].

The role of the nurse. The medical assistant has a vital role in the neonatal intensive care unit. These assistants have highly specialized training, are prepared to respond promptly in case of emergency, perform invasive and non-invasive procedures of a high degree of difficulty and, perform specific therapies. It monitors vital functions, physiological parameters, anthropometric indices.

This assessment includes:

1. Anthropometric indices for a newborn include weight, length, and head, and chest circumference

2. Vital signs: Temperature, Pulse, Respiration, Blood Pressure

3. Physiological function: Cardiovascular System, Respiratory System

4. Gastrointestinal System, Urinary System, Neuromuscular SystemThe Senses [13].

Learn to use medical equipment, monitors, ventilators, and incubators in case of crisis situations. The assistant knows how to use phototherapy or hypothermia devices when indicated by the doctor, monitors the patient and reports any changes. He also knows how to administer treatments and take care of central venous approaches, ensuring the asepsis of the venous catheters, their integrity and functioning within normal parameters. The nurse learns to recognize neurologic signs and symptoms so that the physician can be alerted at the first sign of clinical or electrographic seizure or worsening encephalopathy. The bedside nurse can help optimize care by quickly setting up the cooling blanket and EEG/aEEG machine, allowing for faster treatment. In addition, nurses learn to follow management guidelines and anticipate next steps in care, safely transport critically ill neonates, and communicate effectively with families. Nurses play a significant role in the care of the newborn, as part of the therapeutic team, adapting to the individual needs of the patient. The primary task of a neonatal nurse is to make a quick and accurate diagnosis of patient care problems. Choosing the right elements of the care plan can make a significant contribution to shortening the length of hospital stay, reducing the number and severity of adverse events and preventing further complications [14].

- Risk of unstable glycemia related to altered mental status, compromised physical health status.
- Impaired tissue integrity related to damage to the ocular surface

- Care plan for the diagnosis of excess fluid volume
- Care plan for the diagnosis of bleeding risk related to essential coagulopathies
- Care plan for the diagnosis of aspiration risk
- Care plan for the diagnosis of impairment of physical mobility
- Care plan for the diagnosis of risk of developmental delay
- Care plan for the diagnosis of deterioration of skin integrity
- Care plan for the diagnosis of acute pain related to harmful agents [15].

Care planning should take into account both the newborn's needs during this transition period and the mother's need for adequate rest. Although the woman needs to learn as much as possible about caring for the newborn, she also needs to go home from the hospital environment with enough energy to practice what she has learned. Nurses can help mothers, teach and encouraging them not only to start breastfeeding but also to continue it during the first 6 months of life.

Our ability as clinicians to accurately identify neonates with certain poor or devastating prognosis is limited by the types of tools that are currently available and by the amount of subjective interpretation that is required. Bias also limits the ability to interpret the results of most cohort studies that discuss the ability of these tools to predict death in the neonatal period, as most deaths result after redirection of care to comfort measures only, creating the concern for a self-fulfilling prophecy. In addition, studies of predictors of death or poor outcome may be influenced by the culture in which the study occurs. In some cultures, withdrawal of care is not presented as an option to families; in others, it is only offered to families of those neonates who are neurologically devastated; and in others, withdrawal of care is offered for a range of possible outcomes along the moderate-severe spectrum [16].

Over time, multiple methods for easy diagnosis of HIE have been developed, one of which is the „Siben Score". The use of this clinical score can improve the objectivity of the assessment and monitoring of newborns and the early start of treatment. The use of the Siben Neurological Score proved to be easy to implement and provided a more objective and early diagnosis of HIE. It may be of greater value in poor and/or developing countries, or in neonatal units without access to high-cost diagnostic examinations (imaging, laboratory, and others) [17]. A score was also made at Groote Schuur Hospital's Neonatal Intensive Care Unit. It is based on that of Sarnat and Sarnat but is much simpler and wanted to satisfy the need in the developing world for an unsophisticated, yet predictive assessment of infants with HIE [18]. Some countries have developed neurological scores that can be used as an early tool by clinicians to counsel parents/caretakers on the neurodevelopmental outcome of their infants [19]. We wanted the same thing from the „EVOLUTIVE SCORE" compiled in our clinic. Many scores are based on clinical signs, discovered and interpreted in the first minutes of life, we developed a score based on routine biological investigations.

Material and Method

This is a retrospective, cross-sectional cohort study. This study was carried out in the Department of Neonatology at the Emergency Hospital for Children „Louis Turcanu" Timişoara. This study was conducted over a 3-year period from January 1, 2016 to December 31, 2018. The study included 78 newborns weighing between 1 kg and 3.8 kg at birth.

Enrollment of patients was carried out after applying the inclusion criteria and the availability of data in the hospital's information system. Biological blood samples were collected from the patients and analyzed, the investigations being carried out in the specialized laboratory of the Emergency Hospital for Children „Louis Turcanu" „ Timisoara.

A database was compiled by computerized search of medical records in the medical unit's online database, which were analyzed using the statistical package (SPSS), version 23.0 (IBM, Corp.). A p value <0.05 was considered to indicate a statistically significant difference.

Results and Discussion

Post-ischemic neuroinflammation is an important pathophysiological factor in the development of HIE-related lesions. Several studies have shown that neonatal HIE triggers extensive inflammatory responses in the brain, which includes activation of the innate immune system. Experimental studies in neonatal animals have demonstrated that inhibition of proinflammatory biomediators is neuroprotective. The early neuroinflammatory response is associated with the production of more active immune cytokines/chemokines, activation of microglia, and infiltration of peripheral immune cells. The identification of early biomarkers is a vital issue, especially in the first days of life, because it could provide valuable, beneficial and advanced diagnostic evidence when clinical and radiological signs are still unexpressed [20]. Therefore, this study aimed to identify potential biomarkers for the mechanisms underlying hypoxic-ischemic injury and the early neuroinflammatory response by focusing on blood levels of inflammatory mediators and comparing their levels.

A number of 78 newborns who met the inclusion criteria were enrolled in the study. Of these, 52.6% (n = 41) were female and 47.4% (n =37) were male. Regarding the place of origin, 65% come from urban areas and 35% from the village. 60.2% were premature and 39.8% were term neonates. The average birth weight was 2,311 grams.

Classification of patients was done according to prognosis. The prognosis was based on the following criteria: birth weight, biological markers obtained, the evolution of the patient during hospitalization and also the days of hospitalization in which they needed therapy. Depending on these 4 criteria, patients were considered to have a good or poor prognosis; thus 82% (n=64) had a favorable prognosis and 18% (n=14) an unfavorable prognosis.The tables below (Table 1) show the average values of the results of the biological investigations collected on the two studied groups, and it can be observed that, in the case of patients with unfavorable evolution, the hematological parameters were lower, and the values of the average inflammatory samples were higher than those recorded in patients with a favorable evolution.

		Mean /µl	Std. Deviation	Std. Error of Mean	P-value
Media Zile spitalizare- prog fav	N=64	26.88	15.869	1.984	P<0.001
Media Zile spitalizare- prog nefav	N=14	9.79	10.349	2.766	
Gr. Med- prog fav	N=64	2338.125	728.9199	91.1150	
Gr. Med- prog nefav	N=14	2192.143	905.9562	242.1270	
Hb t1- good prog	N=64	17.098	2.3933	.2992	P<0.004
Hb t1- bad prog	N=14	14.907	3.0771	.8224	
Hb t2- good prog	N=63	15.91	2.605	.328	P<0.001
Hb t2- bad prog	N=12	12.93	3.822	1.103	
Le t1- good prog	N=64	18955.000	11583.1448	1447.8931	
Le t2- bad prog	N=14	15947.857	6433.7179	1719.4834	
Le t2 -good prog	N=63	12276.49	6776.461	853.754	P<0.012
Le t2- bad prog	N=12	17876.67	7762.101	2240.725	
Ne t1- good prog	N=64	10046.17	4734.125	690.543	
Ne t1- bad prog	N=11	10823.64	4585.600	1382.610	
Ne t2 -good prog	N=56	6093.21	3810.299	509.173	p<0.002
Ne t2- bad prog	N=10	10743.00	5772.775	1825.512	
Li t1- good prog	N=64	4565.10	1981.803	283.115	
Li t1- bad prog	N=14	4208.33	1761.373	508.464	
Li t2 -good prog	N=58	3345.00	1781.545	233.928	
Li t2- bad prog	N=10	4358.00	2366.407	748.324	
CRP t1- good prog	N=64	2.71	7.235	.912	
CRP t1- bad prog	N=14	8.10	17.293	4.622	
CRP t2 -good prog	N=39	1.51	2.336	.374	P<0.001
CRP t2- bad prog	N=8	19.82	32.854	11.616	
PCT t1- good prog	N=64	5.3480	13.34173	1.96713	
PCT t1- bad prog	N=14	9.1646	13.89117	3.85272	
PCT t2 -good prog	N=20	6.83	12.987	2.904	

PCT t2- bad prog	N=5	10.74	9.457	4.229	
LDH- good prog.	N=64	754.438	304.4003	38.0500	P<0.001
LDH- bad prog.	N=14	1235.429	955.3341	255.3238	
ALT t1- good prog	N=64	15.313	29.8222	3.7278	
ALT t1- bad prog	N=14	27.357	52.4296	14.0124	
AST t1 -good prog	N=64	61.672	24.5771	3.0721	P<0.01
AST t1- bad prog	N=14	102.000	72.2038	19.2973	

Tabel 1: Average values of biological markers evaluated at time t1 and t2.

Statistically significant differences were observed between the mean values of Hb both at birth and in the first 96 hours between the two studied groups; patients with unfavorable prognosis having on average lower Hb values or a more pronounced decrease in the first days of life ($P < 0.01$). The average variation in the evolution of leukocytes shows that, in the case of patients with a favorable prognosis, the LE values decreased on average by 6,688 µl, and in the case of patients with an unfavorable prognosis, the LE values increased on average by 2,139 µl, a fact that also correlates with the reports in the literature . In the evolution of LE2 ($p <0.012$), it was observed that, in patients with unfavorable prognosis, LE values increased compared to the values at birth [21].

Regarding the evolution of Ne values (t2), we can state that patients with a favorable prognosis had a decrease in Ne compared to the value determined in the first hours of life (t1), unlike patients with an unfavorable prognosis, whose value was approximately equal ($p <0.002$).

The mean values of Li in the two groups of patients were approximately equal in the first 24 hours, and in the evolution of the 96 hours there was a slight decrease in the values in patients with a favorable evolution and a stagnation of the values in the case of patients with an unfavorable evolution . The explanation for this is that an influx of lymphocytes actually occurs approximately one week after the cerebral ischemic incident and thus we can understand the mechanism of maintaining the number of Li higher in the case of patients with unfavorable evolution [21].

In addition to the hematological investigations performed in the two progressive times, the values of inflammatory markers such as C-reactive Protein (CRP) and Procalcitonin (PCT) were analyzed. In the evolution of CRP-type inflammatory parameters (t2), variations with statistically significant values ($P <0.001$) were observed between the two studied groups; therefore, patients with a favorable prognosis had average CRP values of 1.5 mg/dl, and those with an unfavorable prognosis - an average value of 19.82 mg/dl. Performing an analysis by risk groups, we observed 84.6% of newborns with unfavorable prognosis had PCT values above normal values. In the group with an unfavorable prognosis, 92.8% of the newborns with HIE had high LDH values, the average value being 1,235.42 U/l, which is in accordance with the literature reports that show an early increase of LDH activity (> 1050 U / L) compared to infants with signs of fetal distress who do not develop HIE. Ischemic liver injury occurs in approximately 40-60% of infants diagnosed with HIE. ALT and AST levels increase as a result of hypoxic organ damage and are sensitive markers of damaged liver membrane. AST and ALT values were observed to differ according to the degree of HIE, both biomarkers reflecting hepatocellular integrity. With a statistically significant value ($p<0.01$) within the two studied groups, increased average values of AST above the normal limit were obtained in patients with an unfavorable prognosis [21]. The findings of these studies indicated that these biomolecules, particularly LDH, display a significant increase in the initial perinatal period. The origin of these enzymes is various organs. ALT, followed by AST, is the most specific enzyme for the liver and is found, for example, in the erythrocytes, muscles, and myocardium, whereas LDH can be found in the majority of the tissues in the body. After the organ damage and asphyxia that occur immediately after birth, a significant increase regarding the levels of LDH, ALT, and AST is most probably due to this damage that follows asphyxia. This significant increase as well as their various disappearance rates from plasma (5-36 hours), leads these enzymes to be possible predictors of the hypoxic-ischemic insult's severity regarding the perinatal period [22].

Currently, the hypoxic-ischemic pathology of the newborn is correctly diagnosed, but it is not always classified in the correct degrees of severity, due to the expensive biological and imaging investigations. This classification in degrees of severity based on clinical and biological correlations could help to develop a medium and long-term prognosis. Identification of early predictors for mortality and neurological prognosis in infants with HIE is particularly important in predicting relevant clinical outcomes and rapid decision making. Ideal predictors for infants with HIE should be sensitive, specific, early, and easy to perform. The need to interpret the data obtained from the study in a clinical context

led to the development of an easy and quick method for evaluating the severity of the condition based on the biological investigations performed. Thus, depending on the severity of the changes in the biological samples, each patient received an indicator - noted from 1 to 5, where:

- 1= significant changes in biological investigations
- 5= normal values for the age of the biological samples.

The procedure entitled "EVOLUTION SCORE" included scoring with an indicator from 1 to 5 for each investigation carried out, both at time t1 and at time t2, following the biological evolution and the degree of modification of the biological parameters during the 96 hours of tracking. Also, an indicator was given to the patients depending on the number of days of hospitalization in which they required intensive therapy.

Hb t1 scores		**Hb t2 scores**	
>16,5g/dl	5 points	18,1 - 20g/dl	5 points
14,1 – 16,5 g/dl	4 points	16,1 – 18 g/dl	4 points
12,1 – 14 g/dl	3 points	14,1 – 16 g/dl	3 points
10,1 – 12 g/dl	2 points	12,1 – 14 g/dl	2 points
8 -10 g/dl	1 points	8 -12 g/dl	1 points
LE t1 scores		**LE t2 scores**	
20001-30000 mm^3	5 points	18001-21000 mm^3	5 points
15001-20000 mm^3	4 points	15001-18000 mm^3	4 points
10001-15000 mm^3	3 points	10001-15000 mm^3	3 points
5000-10000 mm^3	2 points	5000-10000 mm^3	2 points
<5000mm^3 sau >30001 mm^3	1 punct	<5000mm^3 sau >21001 mm^3	1 punct
Ne t1 scores		**Ne t2 scores**	
20001-25000 mm^3	5 points	10001-15000 mm^3	5 points
15001-20000 mm^3	4 points	6001-10000 mm^3	4 points
10001-15000 mm^3	3 points	3001-6000 mm^3	3 points
6000-10000 mm^3	2 points	1000-3000 mm^3	2 points
<6000mm^3 sau >25001 mm^3	1 points	<1000mm^3 sau >15001 mm^3	1 points
Li t1 scores		**Li t2 scores**	
>10001 mm^3	5 points	10001-15000 mm^3	5 points
5001-10000 mm^3	4 points	5001-10000 mm^3	4 points
2001-5000 mm^3	3 points	2001-5000 mm^3	3 points
1000-2000 mm^3	2 points	1000-2000 mm^3	2 points
<1000mm^3 sau >11001 mm^3	1 points	<1000mm^3 sau >15001 mm^3	1 points
LDH t1 scores		**CRP t1 and t2 scores**	
>1000 U/L	1 points	<3 mg/dl	5 points
701-1000 U/L	2 points	3,1 - 5 mg/dl	4 points

401-700 U/L	3 points	5,1 – 10 mg/dl	3 points
201-400 U/L	4 points	10,1 – 15 mg/dl	2 points
<200 U/L	5 points	>15,1 mg/dl	1 points
ALT t1 scores		**Hospitalization day score**	
>101 U/L	1 points	1 – 10 days	5 points
71-100 U/L	2 points	11 – 20 days	4 points
46-70 U/L	3 points	21 – 30 days	3 points
21-45 U/L	4 points	31 – 40 days	2 points
10 -20 U/L	5 punct	> 41 days	1points

Table 2: Biological evolution.

We wanted to observe whether these serial investigations at time t1 and t2 are necessary to be done for each patient every time or they do not influence the evolution and thus the costs related to the biological investigations carried out in the first 96 hours can be reduced.

All patients benefited from the entire investigation panel, but:

- In 29.4% of the patients, the interpretation of an investigation (CRP t2) was not included in the calculation because no substantially changed values were observed at time t2 compared to time t1.
- In 15.3% of the patients, two investigations (CRP-t2 and PCT) was not included in the calculation.
- In 7.6% of the patients three investigations (CRP-t2 and Ne-t2, Li-t2) were not included.
- In 6.4% of patients, four investigations were not included (CRP-t2, PCT and Ne-t2, Li-t2).
- In 6.4% of patients, five investigations were not included (CRP-t2, PCT and LE-t2, Ne-t2, Li-t2).
- In 1.2% of patients, six investigations were not included (CRP-t2, PCT and Hb-t2, LE-t2, Ne-t2, Li-t2).

In the first category in which all the analyzes were interpreted, it can be observed that, if the score was higher, then the average number of hospitalization days was low and the death rate low. In the case of patients with a score of around 30 points, the average number of hospitalization days is low because all patients died early due to the underlying pathology (Figure 1).

The same can be said in the case of study groups where one or more analyzes were not interpreted; If the score is higher, the average hospitalization days are shorter and the mortality is lower. In the case of those with a low score and a short hospitalization, it can be observed that the mortality is 100%.

In conclusion, we can say that performing this scoring is of real help to us and we have realized that if at time t1 a complete set of analyzes is collected and a score >40 is obtained accompanied by a good clinical evolution, then at time t2 we can give up performing some biological investigations because they don't influence the evolution, clinical and therapeutic management of the patient.

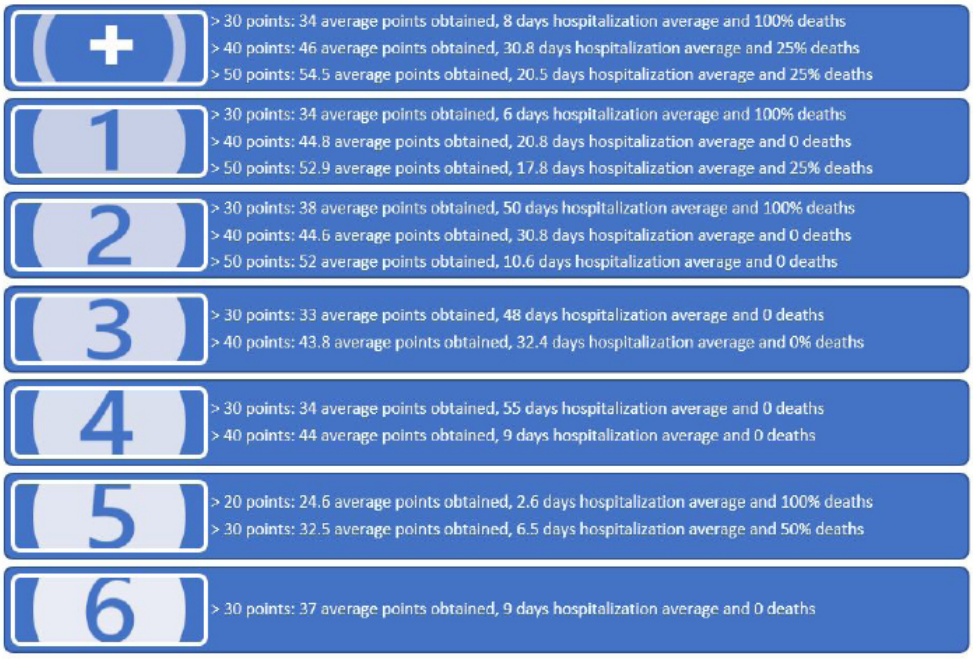

Figure 1: Evolution Score.

Conclusions

Practically, the purpose of this biological differentiation scale was to observe if, in patients hospitalized in the Neonatal Intensive Care Unit with asphyxia and neonatal hypoxic ischemic encephalopathy, the clinical evolution and average days of hospitalization correlate with the score given according to the biological investigations obtained (t1) and their evolution within 96 hours (t2). It was analyzed whether the non-interpretation/ non-performance of one or more investigations at time t2 can predictably negatively influence the evolution of these patients. If the score is higher, the average number of days of hospitalization and the mortality rate is lower. For patients with a score around 30 points, the average number of hospital days is lower because all patients died early from the underlying pathology.

„Evolution score" indicates that a higher value obtained at time t1 correlates with a reduced average of hospitalization days and mortality.

Considering these conclusions and by introducing this evaluation method in lower-ranking maternity hospitals (rank 1 and 2), over time an improvement in the evolution of patients and a decrease in mortality can be observed through a better interpretation of the optimal transfer time of the patient.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

AIM and MB conceived and designed the study; AIM collected the data. AIM and OM analyzed the data, edited the figures. AIM, MB and OM drafted the manuscript. MB revised the manuscript critically for important intellectual content. All authors contributed to the data interpretation and approved the submitted version.

Ethics Approval and Consent to Participate

Approval of the local ethics committee (Ethics Committee for Scientific Research of the Emergency Hospital for Children 'Louis Turcanu'/approval no. 76/2020) was obtained prior to starting the study. Parental or caregiver consent was obtained where applicable. This publication and the database does not contain personal data, does not compromise anonymity or confidentiality or breach local data protection laws.

References

1. Basiri B, Sabzehei M, Sabahi M (2021) Predictive factors of death in neonates with hypoxic-ischemic encephalopathy receiving selective head cooling. Clin Exp Pediatr 64: 180-187.

2. Aslam S, Strickland T, Molloy EJ (2019) Neonatal encephalopathy: Need for recognition of multiple etiologies for optimal management. Front Pediatr 7: 142.

3. Glass HC, Bonifacio SL, Peloquin S, Shimotake T, Sehring S, et al. (2010) Neurocritical Care for Neonates. Neurocrit Care 12: 421-429.

4. Alkholy UM, Abdalmonem N, Zaki A, Ali YF, Mohamed SA, et al. (2017) Early predictors of brain damage in full-term newborns with hypoxic ischemic encephalopathy. Neuropsychiatr Dis Treat 13: 2133-2139.

5. Glass HC, Rowitch DH (2016) The Role of the Neurointensive Care Nursery for Neonatal Encephalopathy. Clin Perinatol 43: 547-557.

6. Lin L, Liu W, Mu J, Zhan E, Wei H, et al. (2021) Effect of neonatal neuronal intensive care unit on neonatal encephalopathy. PLoS One 16: e0261837.

7. Glass HC, Rogers EE, Peloquin S, Bonifacio SL (2014) Interdisciplinary approach to neurocritical care in the intensive care nursery. Semin Pediatr Neurol 21: 241-247.

8. Kariholu U, Montaldo P, Markati T, Lally PJ, Pryce R, et al. (2020) Therapeutic hypothermia for mild neonatal encephalopathy: A systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed 105: 225-228.

9. Craig AK, McAllister LM, Evans S, Melendi ME (2021) Telemedicine consults to assess neonatal encephalopathy are feasible in the neonatal intensive care unit. J Perinatol 41: 1519-21.

10. Arnaez J, Garcia-Alix A, Calvo S, Lubián-López S, Diez-Delgado J, et al. (2018) Care of the newborn with perinatal asphyxia candidate for therapeutic hypothermia during the first six hours of life in Spain. An Pediatr 89: 211-21.

11. Josephson SA, Douglas VC, Lawton MT, English JD, Smith WS, et al. (2010) Improvement in intensive care unit outcomes in patients with subarachnoid hemorrhage after initiation of neurointensivist co-management: Clinical article. J Neurosurg 112: 626-30.

12. O'Dea M, Sweetman D, Bonifacio SL, El-Dib M, Austin T, et al. (2020) Management of Multi Organ Dysfunction in Neonatal Encephalopathy. Front Pediatr 8: 239.

13. Rhodes Alden K (2012) Nursing care of the newborn and family. Matern Women's Heal Care. 553-605.

14. Szydłowska-Pawlak P, Barszczewska O, Sołtysiak I, Librowska B, Kozlowski R, et al. (2022) Nursing Care Plan for a Newborn with the Defect of Congenital Gastroschisis in the Postoperative Period Using ICNP™ and the Dedicated Software. Int J Environ Res Public Health 19: 3498.

15. Sanchez Couto D, Rodriguez Flores AJ, De Oliveira PR, Castro Pereira QL (2019) Cuidados Integrales De Enfermería En Un Lactante Con Encefalopatía Isquémica Hipóxica Relacionada Con La Asfixia Perinatal. Enfermería Cuid Humaniz 8: 1-16.

16. Bonifacio SL, deVries LS, Groenendaal F (2015) Impact of hypothermia on predictors of poor outcome: How do we decide to redirect care? Semin Fetal Neonatal Med 20: 122-7.

17. Perez JMR, Golombek SG, Sola A (2017) Clinical hypoxic-ischemic encephalopathy score of the Iberoamerican Society of Neonatology (Siben): A new proposal for diagnosis and management. Rev Assoc Med Bras 63: 64-69.

18. Thompson CM, Puterman AS, Linley LL, Hann FM, Van Der Elst CW, et al. (1997) The value of a scoring system for hypoxic ischaemic encephalopathy in predicting neurodevelopmental outcome. Acta Paediatr Int J Paediatr 86: 757-761.

19. Mwakyusa SD, Manji KP, Massawe AW (2009) The hypoxic ischaemic encephalopathy score in predicting neurodevelopmental outcomes among infants with birth asphyxia at the Muhimbili National Hospital, Dar-es-Salaam, Tanzania. J Trop Pediatr 55: 8-14.

20. Borjini N, Sivilia S, Giuliani A, Fernandez M, Giardino L, et al. (2019) Potential biomarkers for neuroinflammation and neurodegeneration at short and long term after neonatal hypoxic-ischemic insult in rat. J Neuroinflammation 16: 1-18.

21. Munteanu AI, Manea AM, Jinca CM, Boia M (2021) Basic biochemical and hematological parameters in perinatal asphyxia and their correlation with hypoxic ischemic encephalopathy. Exp Ther Med 21: 259.

22. Elmoursi H, Abdalla M, Mesbah BE, Khashana A (2021) Salivary Lactate Dehydrogenase in Relationship to the Severity of Hypoxic-Ischemic Encephalopathy among Newborn Infants. Scientifica (Cairo) 2021: 9316277.