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Original Article

Analysis of the correlation between the severity of neonatal hypoxic ischemic encephalopathy and multiple organ dysfunction

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Abstract: Objective: To evaluate the hypoxic ischemic encephalopathy (HIE) and multiple organ dysfunction (MOD) in neonates and analyze the correlation between the two disorders. Methods: From January 2018 to January 2020, infants with HIE who were born in our hospital at or above 37 weeks of gestation, and those with ischemic hypoxic encephalopathy at or above 2000 grams were selected as study subjects. HIE and MOD monitoring were performed for three days. HIE severity was graded according to reported scores including amplitude integrated EEG. Multiple organ dysfunction was also assessed. The correlation between neonatal hypoxic ischemic encephalopathy and multiple organ dysfunction was analyzed. Results: Children with HIE were divided into three grades: mild, moderate and severe. There were statistically significant differences among the three groups in emergency caesarean section, Apgar 5 minutes, systemic hypothermia and neonatal mortality. Differences in MOD scores were found in three HIE stages per day from Day 1 to Day 3. Among children with mild HIE grading, the most common mildly affected organ systems are pH, electrolyte imbalance and liver system, and the least affected organs are kidney and blood systems. Among children with HIE grade of mild and severe, there was no significant difference in moderate-severe organ involvement, and the number of severely affected children was small. Conclusion: With the increase of HIE severity, multi-organ involvement is aggravated. The organ involvement of HIE children with different degrees of severity is different.

Keywords: Neonatal hypoxic ischemic encephalopathy, multiple organ dysfunction

Introduction

Hypoxic-ischemic encephalopathy (HIE) is an obvious clinical syndrome caused by fetal asphyxia in full-term newborns. In developed and developing countries, there are 1-8 and 25 HIE cases out of every 1000 newborns respectively each year [1-4]. The most common causes are placental exfoliation, umbilical cord prolapse and uterine rupture, which lead to systemic hypoxia-ischemia caused by fetal cerebral perfusion failure. Other causes of neonatal encephalopathy include ischemic stroke and intracranial hemorrhage, infection, developmental abnormalities and congenital metabolic defects [5, 6]. Prior to the application of hypothermia treatment, reports on the prognosis of children with acute perinatal asphyxia and/or neonatal encephalopathy had noted that the disability rate was between 6-21% in children with moderate encephalopathy and 42-100% in children with severe encephalopathy [7-10].

Multiple organ dysfunction (MOD) is one of the most common syndromes of critical illness and the leading cause of mortality among critically ill patients. MOD is the clinical consequence of a dysregulated inflammatory response, triggered by clinically diverse factors with the main pillar of management being invasive organ support. Given the lack of effective treatment for MOD, its early recognition, the early intensive care unit admission, and the initiation of invasive organ support remain the most effective strategies of preventing its progression and improving outcomes [11]. In a small single-center study, multiple organ dysfunction (MOD) involving the lung, central nervous system, kidney, heart, metabolic and blood systems was recorded in 28 non-birth full-term infants born

between 1980 and 1982 with severe perinatal asphyxia and moderate or severe encephalopathy [12]. Some studies have shown that MOD exists in all children with HIE after severe asphyxia [13]. Despite the application of hypothermia treatment, multiple organ dysfunction is still common in neonatal hypoxic-ischemic encephalopathy. There is a high correlation between the severity of hypoxic-ischemic encephalopathy and multiple organ dysfunction at 3 days after birth. Infants diagnosed with severe hypoxic-ischemic encephalopathy need to be highly suspected of associated multiple organ dysfunction. There is a wide range of variability in the severity of multiple organ dysfunction in patients with moderate hypoxic-ischemic encephalopathy [14].

In this study, we used the asymmetric grading scale to evaluate the MOD of a large number of patients with the severity of HIE, and then analyzed the correlation between HIE and MOD.

Materials and methods

General data

In this prospective study, infants born at or above 37 weeks of gestational weeks in our hospital from January 2018 to January 2020 with hypoxic-ischemic encephalopathy greater than or equal to 2000 grams were selected as subjects. This research was approved the Ethics Committee of the Affiliated Hospital of Yan'an University (No. 2018079) and performed in compliance with the *Declaration of Helsinki*. All the family members of the patients knew and agreed to the study and signed the informed consent form.

Inclusion and exclusion criteria

Inclusion criteria: (1) Meet the diagnostic criteria for HIE: Neonatal encephalopathy, as a syndrome of neurological dysfunction, is characterized by lower-than-normal consciousness or excessive tension in the palm (tremor, overactive muscle reflex, hypersensitivity to stimulation, or shock response) within 6 hours after birth; At least one of the following clinical manifestations of hypoxic brain injury: fetal heart rate pattern change, sentinel event, dystocia, Apgares equal to or more than 5 minutes, birth acidosis (arterial umbilical cord pH≤7.0). (2) Meet the diagnostic criteria for MOD: MODS is defined as the concurrent dysfunction of two or more organs or systems including respiratory, cardiovascular, hematological, neurological, gastrointestinal, hepatic and renal, as suggested in 2005 by Goldstein [15].

Exclusion criteria: (1) Congenital abnormality; (2) Other identifiable causes of neurological disorders; (3) Parents refused to sign informed consent form.

HIE severity assessment

The severity of HIE was graded according to reported scores, including amplitude integrated electroencephalogram (aEEG) [16]. The 81 children who were finally included were divided into mild group (25 cases), moderate group (25 cases), and severe group (31 cases) according to the severity of the disease. Newborns with moderate or severe HIE were treated with whole body hypothermia. All patients were evaluated and treated according to the strict clinical plan for the comprehensive management of HIE. Contraindications for hypothermia include near-death status, intractable severe pulmonary hypertension and intractable bleeding.

Assessment of multiple organ dysfunction

The MOD severity scale is shown in **Table 1**. A total of 23 parameters in 6 organ systems were studied. For each organ system, three severity levels were established (1-8, 10-19). Laboratory tests were performed at admission and 12, 24, 48 and 72 hours after birth. Laboratory examination of 6 objective biochemical indicators of organ systems, including cardiovascular system, kidney, respiratory system, blood system, liver, pH and electrolyte imbalance was conducted, and each system score was divided into five levels 0-4 (0 point means basically normal function, mortality rate <5%. A score of 4 means that the function is significantly impaired, and the mortality rate is ≥50%). The total MOD score was the sum of 6 system scores, and the scores were positively correlated with patient mortality. For each variable, the most abnormal value measured each day was selected as the score for the day [17]. If a value of a variable is not available, it is estimated by the average of the previous value and the next value [18].

Statistical processing

SPSS22.0 was used to analyze the data. Numeric variables were expressed as average

Table 1. Multiple organ dysfunction score scale

Organ variable	Score			
	0	1	10	20
Cardiovascular System				
Troponin T (μg/L)	<0.1	0.1-0.239	≥0.245	≥2 drugs
Need vasoactive drugs	No	1 drug <24 hr	1 drug ≥24 hr	
Kidney				
Serum creatinine (mg/mL)	<1 and	1-1.30 or	1.25-2.0 or	>1.6 or ↑≥0.3 in 24 hr
Polyuria (mL/kg/hr)	≥1 and	0.97-0.50	≤0.55	or
Need alternative therapy	No			Yes
Respiratory System				
Need respiratory support	No	High-speed nasal intubation	MV≥24 hr	NO
Blood System				
White blood cell count (mm)				
Lower limit	≥5.0 and	<4.0 or		
Upper limit	≤30 and	>30 or		
Platelet count (mm)	≥150 and	149-51 or	50-21	≤20
Activated partial thromboplastin time (s)	≤45 and	>45 or	0r	or
Quantity of fresh frozen plasma concentrate (unit)	0	≤2 in 24 hr	>2 in 24 hr	≥4 in 24 hr
Liver				
Glutamate oxalyl acetate transaminase (Ul/L)	<100 and	≥100 or	≥500 and	≥1,000 and
Prothrombin activity (%)	>60	≤60	<40	≤20
pH and electrolyte imbalance				
pH				
Upper limit	≤7.5 and	7.5-7.6 or	7.5-7.6 or	≥7.5 or
Lower limit	≥7.3 and	7.3-7.2 or	7.2-7.1 or	≤7.0
Na^+ (mmol/L)				
Upper limit	≤140 and	141-154 or	≥155 or	
Lower limit	≥130 and	129-116 or	≤115 or	
K^+ (mmol/L)				
Upper limit	≤5.5 and	5.6-6.4 or	≥6.5 or	
Lower limit	≥3.5 and	3.4-2.6 o	≤2.5 or	
Ca^+ (mmol/L)				
Upper limit	≤1.2 and	1.21-1.39 or	≥1.4 or	
Lower limit	≥1	1.0-0.7	≤0.7	

and standard deviation or median and quartile ranges, and classification variables were expressed as frequencies and percentages. HIE staging was compared by single factor analysis of variance (ANOVA) and post hoc. test was adopted for the comparison between two groups. The differences between qualitative variables were analyzed by chi-square test or Fisher exact test. HIE stages were compared by univariate analysis. Distribution of quantitative variables was compared with the Kruskal-Wallis test. Dichotomous variables were created for each organ-system: (1) no involvement/mild involvement versus moderate-to-severe involvement, and (2) no involvement versus mild-to-severe involvement. Positive predictive value (PPV) and negative predictive value (NPV) for significant HIE (moderate or severe) versus mild HIE were estimated.

Results

Perinatal data according to stages of hypoxic-ischemic encephalopathy

A total of 88 patients were included in this study, and 7 patients were further excluded (1 stroke, 2 cerebrovascular malformations, and 4 sepsis-meningitis confirmed by culture). As shown in **Table 2**, children were divided into mild, moderate and severe groups according to the severity of HIE. There were significant differences among the three groups in emergency caesarean section, Apgar 5 minutes, systemic hypothermia and neonatal mortality (*P<0.001*).

Correlation between HIE score and MOD score

As shown in **Figure 1**, the difference of MOD score was found in 3 HIE stages every day from

Table 2. Comparison of perinatal data of children with different severity of HIE

Perinatal data	Total number	Mild HIE	Moderate HIE	Severe HIE	*P*
	81	25 (31)	25 (31)	31 (38)	
Gestational age, mean ± SD, week	38.6 (1.6)	39.1 (1.8)	38.4 (1.8)	37.7 (2.4)	0.53
Weight, mean ± SD, g	3070 (560)	3182 (501)	2877 (398)	2894 (551)	0.12
Male, n (%)	54 (67)	14 (56)	17 (68)	23 (74)	0.83
Treatment time, mean ± SD, h	3.7 (3.1)	1.6 (2.2)	3.6 (2.3)	4.8 (3.4)	0.005
Growth retardation, n (%)	11 (14)	3 (13)	6 (24)	2 (6)	0.52
Outpost incident, n (%)	26 (33)	8 (35)	12 (48)	6 (19)	0.46
Dystocia, n (%)	71 (88)	17 (68)	23 (92)	31 (100)	0.03
Emergency caesarean section, n (%)	60 (74)	16 (64)	18 (72)	26 (84)	<0.001
Heart rate pattern change, n (%)	55 (68)	13 (52)	18 (72)	24 (77)	0.006
Apgar 1 min, Median (IQR)	2 (1-4)	3 (2-4)	2 (1-3)	2 (0-3)	0.04
Apgar 5 min, Median (IQR)	5 (3-7)	6 (5-7.8)	6 (3.6-7)	4 (1-5)	<0.001
Apgar 10 min, Median (IQR)	7 (6-8)	7 (7-8)	7 (6-8)	5 (3.8-7)	0.002
Artery at birth pH, mean ± SD	6.92 (0.19)	7.05 (0.16)	6.85 (0.17)	6.93 (0.19)	0.002
Advanced recovery, n (%)	52 (64)	12 (48)	16 (64)	24 (77)	0.12
Systemic hypothermia, (72 hr) n (%)	57 (72)	1 (4)	25 (100)	31 (100)	<0.001
Hospitalization treatment, mean ± SD, day	12 (10.5)	8.7 (9.4)	12.1 (5.3)	10.8 (13.6)	<0.001
Neonatal death, n (%)	21 (27)	0 (0)	1 (4)	20 (65)	<0.001

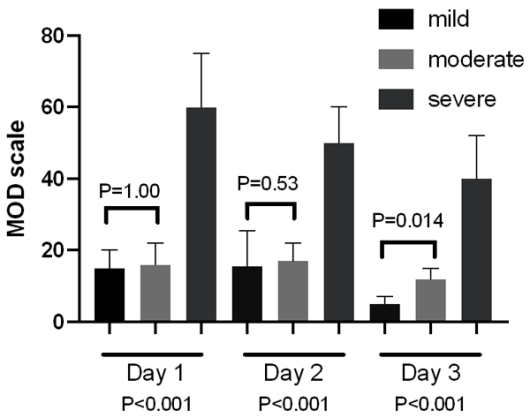

Figure 1. Multiple organ dysfunction scale scores according to hypoxic-ischemic encephalopathy stage. Note: Open circle exceeds >1.5 times interquartile range (IQR); asterisk exceeds >3 times IQR. HIE = hypoxic-ischemic encephalopathy.

Day 1 to Day 3 (*P<0.001*). Post-mortem analysis showed that there was a significant difference between severe HIE and other HIE stages (*P<0.05*). There was no difference in the scores of moderate and mild HIE on the first day and the second day (*P>0.05*), but there was significant difference on the third day (*P<0.001*).

The ability of MOD scale to distinguish between moderate to severe HIE patients and mild HIE patients was evaluated by ROC analysis, the area under the curve was more than 0.76, and the results had high authenticity (**Figure 2**).

Comparison of mild organ involvement in children with different HIE grades

The most common mildly involved organ systems in children with mild HIE grades were pH and electrolyte imbalance, as well as the liver system. The kidneys and blood systems were the least affected. However, in moderate to severe HIE, the most common mildly affected organ systems were the respiratory system, pH and electrolyte imbalance on the first day, and cardiovascular system on the second day. As shown in **Figure 3**.

Comparison of moderate and severe organ involvement in children with different HIE grades

Through the monitoring of children with HIE for 3 days, it was found that there was no significant difference in moderate and severe organ involvement between mild and severe HIE grades, and the number of children with severe organ involvement was less. However, in the children with severe HIE classification, the severe organ involvement was more serious, and the number of children with severe cardiovascular system, respiratory system, pH and electrolyte imbalance was more on the first day.

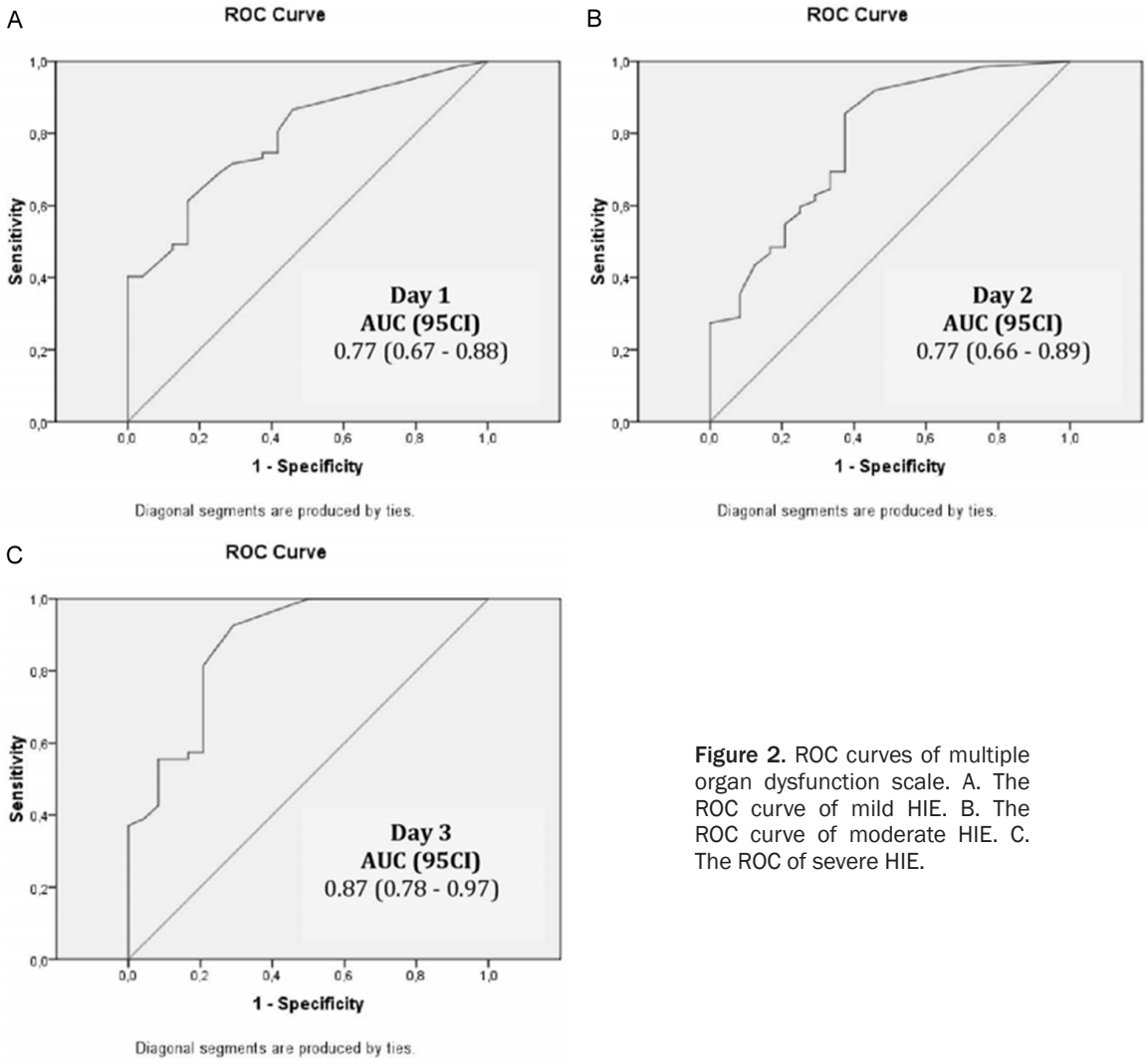

Figure 2. ROC curves of multiple organ dysfunction scale. A. The ROC curve of mild HIE. B. The ROC curve of moderate HIE. C. The ROC of severe HIE.

The imbalance of kidney, liver, pH and electrolyte decreased on the second and third day, but the number of people involved in respiratory system remained high, and the cardiovascular system showed an upward trend. As shown in **Figure 4**.

Discussion

For HIE infants who need to be hospitalized in the neonatal ward, damage to other tissues outside the brain is almost common [19-21]. In our study, all children were involved in at least one extra-brain organ system on the first day of birth, and almost 90% of patients involved three to six organ systems [22-24].

This study showed that the severity of MOD was related to the severity of HIE. We found that the number of affected organ systems was positively correlated with the severity of HIE. In contrast, a previous retrospective study did not find a correlation between the number of affected organ systems and poor prognosis (death or neurological retardation) [13]. However, the proportion of patients with data loss in its study was high (57%), and caution was recommended in interpreting these results. In addition, our study found that when only mild organ damage was considered, there was a stronger correlation between the severity of MOD and HIE: 13% and 75% of moderate and severe HIE patients, respectively, showed moderate to severe dysfunction of more than two organ systems, which did not occur in any mild HIE case. Using our MOD scale, we can compare the organ dysfunction in different stages of HIE. Therefore, the severe MOD (moderate or severe) group coincided well with the severe HIE group.

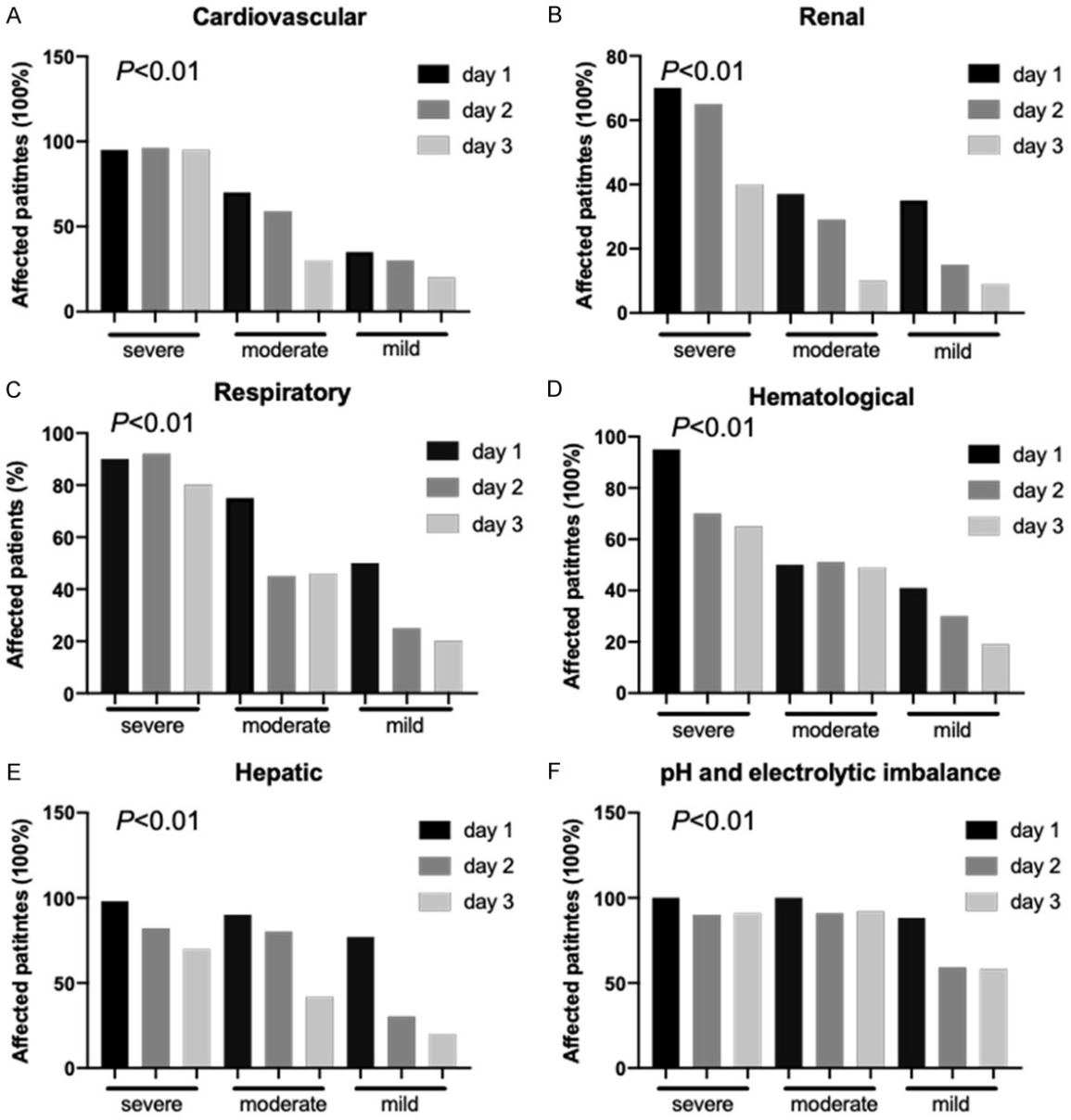

Figure 3. Mild organ involvement in children with different HIE grades. A. Cardiovascular involvement in children with different HIE grades. B. Renal involvement in children with different HIE grades. C. Respiratory involvement in children with different HIE grades. D. Hematological involvement in children with different HIE grades. E. Hepatic involvement in children with different HIE grades. F. PH and electrolytic imbalance involvement in children with different HIE grades.

In the past few decades, some studies have produced new data on the safety of hypothermia therapy and the behavior of biomarkers of organ damage during perinatal asphyxia [25-30]. This study provides a complete map of organ system dysfunction, based on which we can establish the MOD spectrum in the era of hypothermia. Future studies on hypothermia should include the categories of newborns excluded from published clinical trials, namely, infants less than 37 weeks of pregnancy, PNC or stroke, or hospitalized outside the identified 6-hour window, and newborns with encephalopathy that cannot be classified as HIE. The new admission criteria will enable a considerable number of newborns to benefit from this treatment [31]. The study found that the benefits of hypothermia on survival and neurodevelopment outweigh the short-term negative effects. If full-term and late pre-

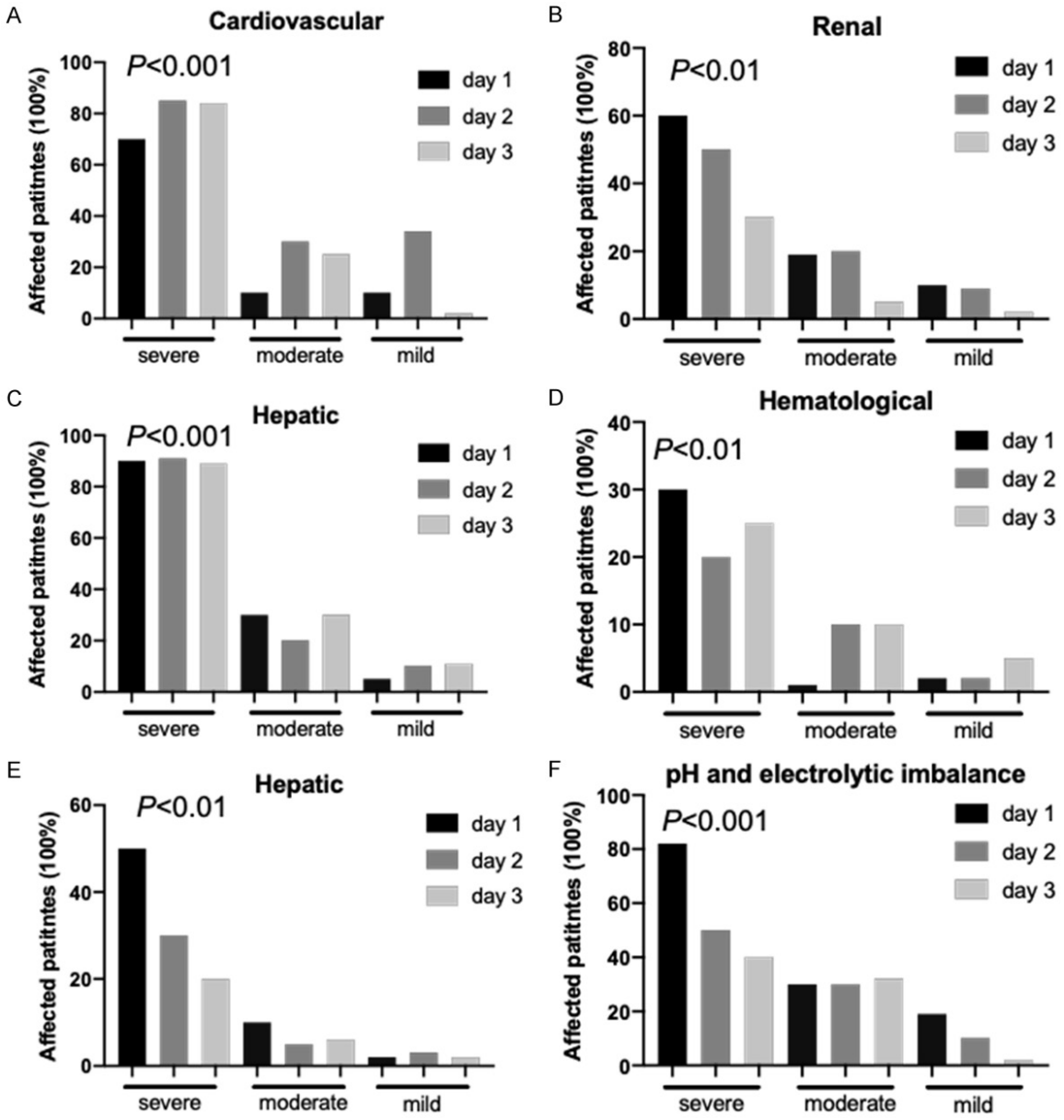

Figure 4. Moderate to severe organ involvement in children with different HIE grades. A. Cardiovascular involvement in children with different HIE grades. B. Renal involvement in children with different HIE grades. C. Hepatic involvement in children with different HIE grades. D. Hematological involvement in children with different HIE grades. E. Hepatic involvement in children with different HIE grades. F. PH and electrolytic imbalance involvement in children with different HIE grades.

mature infants with moderate to severe hypoxic-ischemic encephalopathy were found 6 hours ago, they should begin to lower their body temperature. Further trials to determine appropriate cooling techniques, including refinement of patient selection, cooling time, and methods of providing hypothermia treatment, will improve our understanding of this intervention [32].

Our study has several limitations: (1) Our scale was based on the study of MOD in perinatal asphyxia, the safety study of hypothermia, and the study of special biomarkers of organ damage in asphyxiated newborns, but it has not been confirmed. However, the purpose of this study was not to determine the prognostic value of the scale, but to use it as a means of analyzing data. (2) We chose the compensator

of organ damage which is universally recognized by each organ system. Although other more specific biomarkers have been reported (for example, ejection fraction is used to evaluate cardiovascular function [28]), we used the biomarkers that are easily available in most hospitals in order to maximize the applicability of our results to the clinical environment. (3) Our study was conducted in a single center and used the same encephalopathy rating scale for homogeneous training of hypoxic-ischemic infants. Although this is an advantage of the study, it needs to be taken into account when popularizing the results of the study.

In summary, with the increase of HIE severity, multi-organ involvement is aggravated. The organ involvement of HIE children with different degrees of severity is different.

Disclosure of conflict of interest

None.

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