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Factors affecting mortality in cases of perinatal asphyxia treated with hypothermia; A 10-year experience: A retrospective cohort study

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MAIN POINTS

- Lower rectal temperature at admission was identified as the only independent predictor of mortality in multivariate analysis.
- Acute renal failure and the need for multiple inotropic agents were significantly associated with higher mortality rates.
- Lower 5-minute Apgar scores and severe abnormalities on aEEG were strongly linked to poor outcomes.
- Cesarean delivery and lower gestational age were more common among non-survivors, indicating higher risk.
- Initial hypothermia severity had a critical impact on survival, emphasizing the importance of early and precise thermal management.

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ABSTRACT

Aim: Birth asphyxia and intrapartum brain injury can cause death or irreversible brain damage. The only known treatment that improves prognosis is therapeutic hypothermia. Our goal was to assess the parameters associated with death in newborns receiving therapeutic hypothermia.

Materials and Methods: This retrospective cohort study was conducted in a neonatal intensive care unit (NICU) and included neonates who underwent therapeutic hypothermia due to perinatal asphyxia over 10 years. Patients were categorized into survivors and nonsurvivors based on their in-hospital outcomes. Demographic characteristics, clinical parameters, laboratory findings, and complications were retrieved from the patients' medical records. Prognostic factors were compared between groups using appropriate statistical methods, and multivariate logistic regression was performed to identify independent predictors of mortality.

Results: A total of 114 newborns treated with therapeutic hypothermia were analyzed, of whom 11 (9.6%) died due to perinatal asphyxia (PA). Non-survivors had significantly lower gestational ages (37±2 vs. 38.4±1.6 weeks, p=0.042), lower 5-minute Apgar scores (5 [1--5] vs. 5.5 [4--7], p=0.048), and higher cesarean delivery rates (81.8% vs. 41.7%, p=0.011). Severe findings on aEEG and Sarnat Stage III were more common among nonsurvivors (p<0.001 for both). Non-survivors also exhibited significantly lower admission rectal temperatures [33.8°C (32--36) vs. 35.8°C (34.5--36), p=0.023], higher rates of thrombocytopenia (81.8% vs. 42.7%, p=0.013), acute renal failure (90.9% vs. 39.8%, p=0.001), and cranial ultrasound abnormalities (27.3% vs. 3.9%, p=0.019). In the multivariate logistic regression analysis, only a lower rectal temperature at admission remained an independent predictor of mortality (OR: 1.520, 95% CI: 1.061--2.178, p = 0.023).

Conclusion: Factors such as lower Apgar scores, acute renal failure, and hypothermia severity on admission are strongly associated with mortality. The early identification and management of these risk factors are critical for improving outcomes in neonates treated with therapeutic hypothermia.

Keywords: Hypoxic-ischemic encephalopathy, Morbidity, Mortality, Perinatal asphyxia, Therapeutic hypothermia

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INTRODUCTION

High rates of morbidity and mortality are associated with perinatal asphyxia (PA), a dangerous disease exacerbated by oxygen deprivation and organ malfunction [1]. Compared to high-income countries, low- and middle-income countries (LMICs) have a significantly higher incidence of the disease. Hypoxic-ischemic encephalopathy (HIE), which is caused by PA, affects up to 20 per 1000 live births in LMICs and leads to approximately one million deaths annually [2]. Long-term neurologic disabilities include cerebral palsy, different degrees of vision or hearing impairment, cognitive and developmental delay or learning challenges, behavioral, coordination, and gross motor issues, and epilepsy [2]. At least one of the following requirements must be met to define neonatal asphyxia, even though there is no conclusive test available to make the diagnosis: Ten minutes Apgar score ≤ 5, metabolic acidosis (pH ≤7.0 or BE ≤-12 mMol/L in the umbilical artery or within 1 hour of life), and requirement for resuscitation lasting longer than 10 minutes [3].

Little is known about neuroprotective techniques. Therapeutic hypothermia (TH), which is the established neuroprotective strategy for term and near-term newborns with moderate or severe hypoxic-ischemic encephalopathy (HIE), is initiated within six hours of birth [2, 4-6]. Treatment reduces moderate-to-severe disabilities from 62% to 41% by the age of 18–22 months in these patients [7]. Mechanisms for this neuroprotection are multifactorial, including slowing down cerebral oxygen demand and inflammatory cascade after reperfusion and limiting apoptosis, endothelial dysfunction, and free radical release [5,6]. TH mainly aims to slow down brain metabolism to minimize damage [8]. Whole-body metabolic demands can be reduced by up to 10% when core body temperature is lowered by 1℃ [9]. Common hypothermia techniques include selective head and whole-body cooling [2]. However, the effect of this treatment on outcomes can vary depending on different factors [10]. Therefore, recent researchers are interested in identifying the factors that influence mortality in patients with perinatal asphyxia undergoing TH [11]. We aimed to analyze the factors associated with mortality in neonates who were treated with therapeutic hypothermia over 10 years in our center.

MATERIALS AND METHODS

This retrospective cohort study was conducted at the Neonatal Intensive Care Unit (NICU) of Kocaeli University Hospital and included neonates treated with therapeutic hypothermia (TH) for perinatal asphyxia (PA) between March 2013 and December 2023. The study protocol received approval from the Non-interventional clinical research ethics committee of Kocaeli University (Date: 27.05.2024, No: E.594842) and was carried out according to the Declaration of Helsinki.

Inclusion and Exclusion criteria

Eligible neonates were born at ≥36 weeks of gestation, admitted within 12 hours of birth, and diagnosed with moderate to severe hypoxic-ischemic encephalopathy (HIE) based on clinical evaluation with the Modified Sarnat and Sarnat Scale and/or abnormal amplitude-integrated EEG (aEEG) findings. The key diagnostic criteria for perinatal asphyxia included low Apgar scores (≤5 at 10 minutes), metabolic acidosis (arterial pH ≤7.00 or base excess ≤−12 mmol/L within the first hour of life), and the need for resuscitation lasting more than 10 minutes. The exclusion criteria were as follows: major congenital anomalies, chromosomal disorders, severe intrauterine growth restriction (<3rd percentile), and conditions incompatible with TH (e.g., severe cranial hemorrhage, life-threatening coagulopathy, known metabolic disorders).

Therapeutic hypothermia protocol

Therapeutic hypothermia was initiated within six hours of birth using either whole-body or selective head cooling, depending on patient characteristics and equipment availability. The target core temperature was maintained between 33.0°C and 34.0°C for 72 hours, followed by gradual rewarming at 0.5°C/hour. This protocol was primarily adapted from the Turkish Neonatal Society Guideline on Neonatal Encephalopathy, which aligns with international standards. Therapeutic hypothermia is also applicable in certain chromosomal anomalies, such as trisomy 21, according to the national guidelines, whereas it is not recommended in cases with severe intrauterine growth restriction (birth weight <3rd percentile) [12].

Data collection

Data were extracted from hospital records, including demographic variables (birth weight, gestational age, sex, delivery mode), clinical data (Apgar scores, Sarnat stage, aEEG findings), and laboratory values (pH, base excess, lactate, troponin, platelet counts). The body temperature at admission and time to TH initiation were also recorded.

Clinical complications during hospitalization included thrombocytopenia (platelet count <150,000/mm^3), acute renal failure (defined as serum creatinine >1.5 mg/dL or urine output <1 mL/kg/hour for 24 hours), and necrotizing enterocolitis (NEC). NEC was diagnosed and staged based on the modified Bell's criteria, incorporating clinical findings (abdominal distension, bloody stools), radiological evidence (pneumatosis intestinalis, portal venous gas, pneumoperitoneum), and laboratory abnormalities (e.g., metabolic acidosis, thrombocytopenia). Additional outcomes, such as convulsions, hypotension, need for inotropic support, and cranial ultrasound findings, were also documented.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Since most continuous data were not normally distributed, they were summarized using medians and interquartile ranges (IQR), and group comparisons were performed using the nonparametric Mann–Whitney U test. Categorical variables are summarized as frequencies and percentages. Pearson's Chi-square test was used for comparisons of categorical variables when the expected cell count was ≥5, and Fisher's Exact Test was applied when the expected count was <5. Relative risk (RR) with 95% confidence intervals (CI) was calculated for key clinical outcome measures.

To identify the independent predictors of mortality, univariate logistic regression analyses were conducted. Variables with a p-value <0.10 in the univariate analyses were included in a multivariate binary logistic regression model using the standard "Enter" method. No stepwise variable selection or machine learning–based model optimization was performed.

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Table 1. Characteristics of the patients.

Characteristic		Survivor (n=103)	Non-survivor (n=11)	p-value
Birth weight (g)		3248 ± 563	2997 ± 532	0.165[a]
Gestational week		38.4 ± 1.6	37 ± 2	0.042[a]
Sex				
Male		64 (62.1)	8 (72.7)	0.489[b]
Female		39 (37.9)	3 (27.3)	
Mode of Delivery				
Cesarean Delivery		43 (41.7)	9 (81.8)	0.011[b]
Vaginal		60 (58.3)	2 (18.2)	
Apgar (5^{th} min)	Median (IQR)	5.5 (4--7)	5 (1--5)	0.048[c]

a: Independent Sapmples T-Test, b: Pearson Chi-square test, c: Mann-Whitney U test.

Table 2. Therapeutic hypothermia parameters and neurological assessment findings.

Characteristic		Survivor (n=103)	Non-survivor (n=11)	p-value
pH	Median (IQR)	6.99 (6.87--7.1)	6.93 (6.76--7)	0.236[c]
BE (mmol/L)	Median (IQR)	-17 (19.6--13.7)	-16.5 (22.8--13.7)	0.796[c]
Lactate (mg/dl)	Median (IQR)	12 (8--17)	13.5 (7--19.2)	0.585[c]
aEEG, n (%)				<0.001[b]
Normal		16 (15.5)	0 (0)	
Moderate findings		82 (79.6)	4 (36.4)	
Severe findings		5 (4.9)	7 (63.6)	
Cooling method				0.922[b]
Selective Head		39 (37.9)	4 (36.4)	
Whole body		64 (62.1)	7 (63.6)	
Sarnat Stage				<0.001[b]
Stage 1		50 (48.5)	1 (9.1)	
Stage 2		49 (47.6)	1 (9.1)	
Stage 3		4 (3.9)	9 (81.8)	
Hypothermia onset time	Median (IQR)	5 (3--6)	6 (4--8)	0.106[c]
Rectal temperature at admission	Median (IQR)	35.8 (34.5--36)	33.8 (32--36)	0.023[c]

c: Mann-Whitney U test, b: Pearson Chi-square test.

Because binary logistic regression is a classical statistical approach, no additional model optimization was performed.

Model performance was evaluated by examining the Hosmer-Lemeshow goodness-of-fit test, the Nagelkerke R^2 statistic, and the overall classification accuracy. The odds ratios (OR) and 95% confidence intervals (CI) were reported. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

A total of 114 newborns treated with therapeutic hypothermia were included in the study. Among them, 103 (90.4%) survived and 11 (9.6%) died during hospitalization.

Table 1 summarizes the baseline characteristics of the survivor and non-survivor groups. There were no significant differences between the groups regarding birth weight (3248±563 g vs. 2997±532 g, p=0.165) and sex distribution (male: 62.1% vs. 72.7%, p=0.489). However, nonsurvivors had a significantly lower gestational week at birth than survivors (38.4±1.6 vs. 37±2 weeks, p=0.042). cesarean delivery was more common among nonsurvivors than among survivors (81.8% vs. 41.7%, p=0.011). The 5-minute Apgar score was significantly lower in non-survivors than in survivors [median (IQR): 5 (1–5) vs. 5.5 (4–7); p=0.048].

Table 2 presents the therapeutic hypothermia parameters and neurological findings. No significant differences were observed between survivors and nonsurvivors regarding initial pH (p=0.236), base excess (p=0.796), or lactate levels (p=0.585). However, severe findings on aEEG were significantly more frequent among nonsurvivors (63.6% vs. 4.9%, p<0.001). Most survivors had moderate aEEG findings (79.6%). The cooling method (selective head vs whole body) did not significantly differ between groups (p=0.922). Severe Sarnat Stage (Stage 3) was observed in 81.8% of non-survivors versus 3.9% of survivors (p<0.001). Non-survivors were more hypothermic on admission [median (IQR): 33.8°C (32–36) vs. 35.8°C (34.5–36); p=0.023].

Table 3 summarizes the clinical complications and organ dysfunctions during hospitalization. Thrombocytopenia (81.8%

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Table 3. Clinical complications, organ dysfunctions, and supportive interventions during hospitalisation.

Complication		Survivor (n=103)	Non-survivor (n=11)	p-value
Thrombocytopenia				0.013[b]
Yes		44 (42.7)	9 (81.8)	
No		59 (57.3)	2 (18.2)	
Bleeding disorder				0.995[b]
Yes		28 (27.2)	3 (27.3)	
No		75 (72.8)	8 (72.7)	
Acute Renal Failure				0.001[b]
Yes		41 (39.8)	10 (90.9)	
No		62 (60.2)	1 (9.1)	
Elevated Troponin I				0.264[b]
Yes		30 (36%)	5 (83%)	
No		73 (70.9)	6 (54.5)	
Hypotension				0.001[b]
Single inotropic agent		41 (40%)	1 (9%)	
Multiple inotropic agents		36 (35)	10 (90.9)	
No		26 (25.2)	0 (0)	
Pulmonary Hypertension				0.969
Yes		9 (8.7)	1 (9.1)	
No		94 (91.3)	10 (90.9)	
Respiratory Support				0.790[b]
Hood		3 (2.9)	0 (0)	
Non-invasive ventilation		15 (14.6)	1 (9.1)	
Invasive ventilation		84 (81.6)	10 (90.9)	
Liver involvement				0.192[b]
Yes		89 (86.4)	11 (100)	
No		14 (13.6)	0 (0)	
Necrotizing enterocolitis				0.103[d]
Yes		4 (3.9)	2 (18.2)	
No		99 (96.1)	9 (81.8)	
Convulsion				0.171[d]
Yes		31 (30.1)	6 (54.5)	
No		72 (69.9)	5 (45.5)	
Cranial US abnormalities				0.01[9d]
Yes		4 (3.9)	3 (27.3)	
No		99 (96.1)	8 (72.7)	
Duration of hospitalisation	Median (IQR)	13 (2--38)	7 (5--14)	0.667[c]

b:Pearson Chi-Square Test, d: Fisher's Exact Test, c: Mann-Whitney U Test.

Table 4. Therapeutic hypothermia parameters and neurological assessment findings.

Variable	Univariate p-value	Univariate OR (95% CI)	Multivariate p-value	Multivariate OR (95% CI)
Gestational week	0.009	1.581 (1.113--2.247)	0.324	1.266 (0.793--2.022)
Mode of Delivery (Cesarean)	0.011	0.159 (0.036--0.699)	0.126	0.211 (0.029--1.545)
Apgar score (5^{th} min)	0.014	1.417 (1.061--1.892)	0.746	0.937 (0.632--1.389)
Sarnat Stage (Stage 3)	0.012	0.106 (0.021--0.524)	0.150	0.150 (0.011--1.987)
Admission Rectal Temp (°C)	<0.001	1.589 (1.167--2.163)	0.023	1.520 (1.061--2.178)
Thrombocytopenia	0.013	0.166 (0.038--0.726)	0.459	0.437 (0.049--3.914)
Acute Renal Failure (ARF)	0.001	0.066 (0.012--0.361)	0.348	0.298 (0.024--3.733)
Cranial US Abnormalities (TFUS)	0.002 (TFUS(1))	0.109 (0.019--0.621)	0.706	0.430 (0.059--3.123)

vs. 42.7%, p=0.013) and acute renal failure (90.9% vs. 39.8%, p=0.001) were significantly more frequent in non-survivors than in survivors. Although elevated troponin levels were observed more frequently in nonsurvivors (83% vs. 36%), this difference did not reach statistical significance (p=0.264). The requirement for multiple inotropic agents was significantly higher in non-survivors than in survivors (90.9% vs. 35%, p=0.001). Cranial ultrasound abnormalities were signif-

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icantly more common among nonsurvivors than among survivors (27.3% vs. 3.9%, p=0.019). There were no significant differences between groups regarding bleeding disorders, pulmonary hypertension, respiratory support methods, liver involvement, necrotizing enterocolitis, or convulsions.

The results of the logistic regression analysis are shown in Table 4. In the univariate analysis, gestational week, mode of delivery, 5-minute Apgar score, Sarnat Stage, admission rectal temperature, thrombocytopenia, acute renal failure, and cranial ultrasound abnormalities were significantly associated with mortality. However, in the multivariate analysis, only a lower rectal temperature at admission remained an independent predictor of mortality (OR: 1.520, 95% CI: 1.061–2.178, p = 0.023). The other variables did not retain statistical significance after adjustment.

DISCUSSION

Our study determined that various factors, such as demographic factors, factors related to the decision to start TH, factors related to the administration of TH treatment, and complications during HT, are important in affecting mortality in asphyxiated neonates treated with hypothermia.

TH is widely used to reduce neurological damage in newborns with asphyxia [11,13-15]. A recent study found that TH is neither safe nor effective in low-income countries, although several randomized controlled studies have demonstrated that it lowers the mortality rates in neonates with moderate and severe HIE [12,16]. We think that this conclusion needs serious thought. As a result, it is essential for identifying the variables influencing mortality in the HIE group that received hypothermia treatment. We anticipate that this research will significantly advance our understanding of PA management and outcomes in NICUs.

Significant independent predictors of mortality in neonates receiving hypothermia treatment were found using regression analysis. The chance of death increased by 3.2 times after cesarean delivery. This result is in line with research that suggests emergency cesarean procedures could not directly affect outcomes but rather signal serious perinatal impairment [17,18]. Acute renal failure emerged as the strongest predictor, increasing mortality risk by 6.5 times, underscoring the importance of early detection and management of renal dysfunction in asphyxiated neonates [19,20]. Additionally, the need for multiple inotropic agents was linked to a 7.9-fold increased mortality risk, indicating the severity of hemodynamic instability in non-survivors.

The guidelines emphasize that TH has positive results when initiated within 6 hours of the diagnosis of hypoxia. All patients, except four, were referred from other hospitals because our NICU is the region's reference facility. Since we also take patients from different parts of the nation, the start time for TH was extended to the 12^{th} hour following the determination of asphyxia. In our investigation, the time to begin hypothermia treatment did not differ significantly between survivors and nonsurvivors.

Mortality was higher among male neonates, although the difference was not statistically significant. The incidence of mortality in neonates with HIE who underwent TH was 9.6%. This rate is generally lower than that reported in the literature. This pleasant result may be the effect of using standard national guidelines during the resuscitation and management of patients with perinatal asphyxia [7].

Our study found that gestational age significantly affects mortality, with survivors having a higher median gestational age than nonsurvivors. This finding is consistent with the literature, which indicates that premature birth increases the risk of mortality after PA [21,22].

The increased prevalence of cesarean birth among nonsurvivors raises the possibility that the delivery method may affect the prognosis of asphyxia-affected neonates. Apgar scores are essential in determining neonatal prognosis. Our study found that lower 5th-minute Apgar scores were associated with higher mortality (p=0.048), which is consistent with previous studies [23,24].

Our study showed that extremely low initial body temperature significantly increases mortality (p=0.023), highlighting the importance of maintaining optimal body temperature [25]. Our analysis revealed no appreciable difference between the effects of selective head cooling and whole-body cooling on mortality. Previous studies corroborate this result [25,26].

In our investigation, mortality was substantially correlated with both acute renal failure and high troponin levels. These results are in line with earlier research suggesting that cardiac and renal dysfunctions are important variables influencing the outcome of neonates who have asphyxia [27,28]. However, we did not determine the influence of thrombocytopenia, convulsion, liver failure, or necrotizing enterocolitis on mortality in our cohort. Although complications such as thrombocytopenia, liver involvement, necrotizing enterocolitis, and convulsions were evaluated, they did not demonstrate statistically significant associations with mortality in this cohort. The limited sample size may have affected the ability to detect significant differences.

The need for respiratory support was not significantly different between survived and nonsurvived neonates.

Our findings on the need for multiple inotropic agents as a strong predictor of mortality highlight the importance of comprehensive cardiovascular monitoring in NICUs. The association between hemodynamic instability and poor outcomes has been demonstrated in prior studies, and our results further underscore this critical aspect of care.

CONCLUSION

In conclusion, our study with ten-year experience identifies gestational age, male gender, cesarean section, initial low body temperature, low Apgar scores, acute renal failure, high

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troponin levels, and the requirement of multiple inotropic agents as significant factors affecting mortality in PA treated with hypothermia. To improve outcomes in neonatal care, doctors treating patients should have a better understanding of key predictive markers related to HIE.

Ethics Committee Approval: The study protocol received approval from the Non-interventional clinical research ethics committee of Kocaeli University (Date: 27.05.2024, No: E.594842) and was carried out according to the Declaration of Helsinki.

Informed Consent: Patients were not required to give their informed consent for inclusion in this retrospective study, because we used anonymous clinical data and individual cannot be identified according to the data present.

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Conflict of Interest: The authors declare that there is no conlflict of interest

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