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The prognostic role of clinical, electroencephalographic and neuro-radiological parameters in predicting outcome in pediatric non-traumatic coma

Pediatrik non-travmatik koma prognozunu öngörmede klinik, elektroensefalografik ve nöroradyolojik parametrelerin rolü

Ayşe Anık, Hasan Tekgül, Sanem Yılmaz, Bülent Karapınar, Ömer Kitiş, Gül Aktan, Sarenur Gökben

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Abstract

Purpose: To investigate the early outcome of non-traumatic coma (NTC) in pediatric critical care in relation to the prognostic role of clinical, electroencephalographic, and neuro-radiological factors.

Materials and methods: A total of 77 children (means of age: 70.5±68.7 months, 55.8% were boys) with acute encephalopathy, and NTC were included in this retrospective cross-sectional study. Data on patient demographics (age, gender, etiology of NTC) and prognostic factors [Glasgow coma scores (GCS), pupillary light reflex (PLR), electroencephalography (EEG) and cranial magnetic resonance imaging (MRI) findings] and neurological outcome (intensive care unit period and first 3 months after discharge) were recorded in each patient.

Results: Hypoxic-ischemic encephalopathy (35.1%) and central nervous system infection (22.1%) were the most common etiologies in this study. The favorable and unfavorable neurological outcome was noted in 57% and 43% of patients, respectively. Lack of PLR (OR 3.09, 95% CI: 2.17 to 4.40, p<0.001), GCS ≤5 (OR 7.85, 95% CI: 2.77 to 22.37, p<0.001), poor prognostic pattern in EEG (OR 13.76, 95% CI: 1.62 to 116.54, p=0.004) and presence of MRI lesions (OR 4.04, 95% CI: 1.15 to 14.19, p=0.029) were significant determinants of unfavorable neurological outcome.

Conclusion: We conclude that combined use of clinical, EEG, and MRI findings might provide a more accurate estimation of neurological outcome in pediatric NTC.

Key words: Non-traumatic coma, neuroimaging, prognostic factors.

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Özet

Amaç: Pediatrik non-travmatik komada (NTK) erken dönem prognozun; klinik, elektroensefalografi (EEG) ve nöroradyolojik faktörlerle ilişkisini araştırmak amaçlandı.

Gereç ve yöntem: Bu retrospektif kesitsel çalışmaya, akut ensefalopati ve NTK tanılı 77 çocuk hasta (ortalama yaş 70,5±68,7 ay, %55,8 erkek) alınmıştır. Hastaların demografik özellikleri (yaş, cinsiyet, komanın sebebi), prognozlarını belirleyen faktörler [Glasgow koma skoru (GKS), pupil ışık refleksi, EEG ve kraniyal manyetik rezonans görüntüleme (MRG) sonuçları] ve erken nörolojik sonuçları (yoğun bakım dönemi ve taburculuk sonrası ilk 3 ay) kaydedildi.

Bulgular: Hipoksik iskemik ensefalopati (%35,1) ve santral sinir sistemi enfeksiyonu (%22,1) bu çalışmadaki en sık etiyolojik nedenlerdi. İyi ve kötü nörolojik sonuçlar sırasıyla %57 ve %43 olarak bulundu. Işık refleksinin olmaması (OR 3,09, %95 CI: 2,17-4,40, p<0,001), GKS ≤5 (OR 7,85, %95 CI: 2,77 to 22,37, p<0,001), EEG'de

Ayşe Anık, MD, Ege University Faculty of Medicine, Department of Pediatrics, Izmir, Turkey, e-mail: drayseank@yahoo.com (orcid.org/0000-0002-0673-3403)

Hasan Tekgül, MD, Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Neurology, Izmir, Turkey, e-mail: hasan.tekgul@ege.edu.tr (orcid.org/0000-0002-9972-0651) (Corresponding Author)

Sanem Yılmaz, MD, Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Neurology, Izmir, Turkey, e-mail: sanem.yilmaz@ege.edu.tr (orcid.org/0000-0002-8719-0665)

Bülent Karapınar, MD, Ege University Faculty of Medicine, Division of Pediatric Intensive Care, Izmir, Turkey, e-mail: bulent.karapinar@ege.edu.tr (orcid.org/0000-0002-6034-189X)

Ömer Kitiş, MD, Ege University Faculty of Medicine, Department of Radiology, Izmir, Turkey, e-mail: omer.kitis@ege.edu.tr (orcid.org/0000-0003-4201-5449)

Gül Aktan, MD, Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Neurology, Izmir, Turkey, e-mail: gul.aktan@ege.edu.tr (orcid.org/0000-0002-5367-2236)

Sarenur Gökben, MD, Ege University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Neurology, Izmir, Turkey, e-mail: sarenur.gokben@ege.edu.tr (orcid.org/0000-0001-7896-5716)

kötü prognostik patern izlenmesi (OR 13,76, %95 CI: 1,62-116,54, *p*=0,004) ve kraniyal MRG'de lezyon varlığı (OR 4,04, %95 CI: 1,15-14,19, *p*=0,029) kötü prognostik bulgu olarak değerlendirildi.
Sonuç: Pediatrik NTK'da klinik, EEG ve kraniyal MRG bulgularının kombine değerlendirilmesinin, hastanın nörolojik prognozunu değerlendirmede daha doğru sonuçlar verebileceğini düşünüyoruz.

Anahtar kelimeler: Non-travmatik koma, nörogörüntüleme, prognostik faktörler.

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Introduction

Non-traumatic coma (NTC) is a common cause of pediatric critical care admission, while the clinical outcome varies from a full neurological recovery to significant morbidity and mortality depending on the etiology of coma and clinical status at the time of presentation [1-7].

However, despite the importance of the early prediction of the neurologic outcome in the pediatric critical care, prediction of the clinical outcome early in the course of the disease is considered challenging alongside the limited and rather inconclusive data available in the literature on potential prognostication parameters in the acute phase of NTC among children [2, 4, 6-12].

In order to improve outcomes in these patients, it is imperative that the problem is studied in a more. This requires studying the common etiologies of NTC in specific regions as well as studying clinical features and laboratory parameters that may be identified early in the course of disease in order to assist in the prediction of poor outcome [8].

While potential prognostic role of several anamnestic, clinical, biologic, and electrophysiological factors have been investigated in NTC, a more comprehensive investigation with the use of multimodal combined analysis of potential prognostic criteria is considered more useful in estimating the outcome of NTC [11, 13, 14].

This retrospective study was therefore designed to investigate the potential prognostic role of clinical, electroencephalographic, and neuro-radiological parameters in predicting outcome in pediatric NTC.

Material and methods

Study population

A total of 77 pediatric patients (means of age: 70.5 (68.7) months, 55.8% were boys) with acute encephalopathy, and NTC who had electroencephalography during their hospitalization in pediatric intensive care unit were included in this retrospective study conducted at Ege University Children's Hospital.

The study was conducted in full accordance with local GCP guidelines and current legislation, while the permission was obtained from our institutional ethics committee for the use of patient data for publication purposes.

Assessments

Data on patient demographics (age, gender), etiology of NTC, pediatric risk of mortality (PRISM) scores, neurological examination [Glasgow coma scores (GCS), pupillary light reflex (PLR)], electroencephalography (EEG) and cranial magnetic resonance imaging (MRI) findings and neurological outcome during intensive care unit (ICU) hospitalization and in the post-discharge 3rd month were recorded in each patient. Neurological outcome (favorable vs. unfavorable) was evaluated with respect to study parameters and poor prognostic risk factors for neurological outcome were analyzed using Odd's ratios (OR).

PRISM scores

PRISM scores at ICU admission were calculated based on hemodynamic (systolic and diastolic blood pressure, pulse), respiratory (respiration per minute, PCO_2, PaO_2/FiO_2), neurological (GCS, PLR), metabolic (blood glucose, bilirubin, calcium, and bicarbonate levels) and coagulation parameters.

Prognostic outcome

The overall prognostic outcome was based on neurological examination during ICU hospitalization and at the 3rd month of hospital discharge with consideration of a favorable prognostic outcome in survivors with normal status and mild neurologic disabilities, while consideration of unfavorable outcome in those with moderate or severe neurologic disabilities and death.

Qualitative EEG analysis

Bedside-EEG recordings followed a standard protocol as outlined by the international 10-20 system, with the same device (Nihon-Kohden Neurofax EEG-1200), and by the same experienced EEG technician. EEG recordings were performed during normothermia (core temperature > 36°C) and off sedation, 24-36 hours after coma.

EEG records were re-analyzed by the same pediatric neurologist (H.T.) who was unaware of the clinical data. Using the simple five-grade system described by Amodio et al. [15] in 1999, EEG findings were classified into 5 grades: 0- normal; 1- focal (focal suppression, ictal discharges, inter-ictal discharges (focal, bilateral or generalized periodic discharges, tri-phasic waves); 2- beta coma, spindle coma, low voltage background activity); 3-alpha coma, burst suppression pattern, mixed coma pattern), 4- electro-cerebral inactivity.

Overall, EEG patterns were further categorized into two groups including good prognostic patterns (focal suppression, ictal discharges, inter-ictal discharges, beta coma, and spindle coma) and poor prognostic patterns (alpha coma, burst suppression, electro-cerebral inactivity] [16].

MRI findings

MRI records were re-analyzed by the same pediatric neuroradiology specialist (O.K.) who was unaware of the clinical data using two different classification systems based on evaluation of cortical plus extra-cortical lesions (Grade 0: no lesion, Grade 1: unilateral cortical involvement; Grade 2: bilateral cortical involvement; Grade 3: cortical + subcortical involvement; Grade 4: extra-axial involvement). Overall, cranial MRI findings were also categorized based on the absence and presence of any lesion.

Statistical analysis

Statistical analysis was made using computer software (SPSS version 13.0, IBM, New York, USA). In the univariate analyses, the relations between multiple categorical variables were analyzed using Fisher's exact test, while the Mann-Whitney U test was used for the analysis of numerical variables. ROC curve was plotted to determine performance of prognostic markers in discrimination of unfavorable outcome with the calculation of AUC values. Step-wise logistic regression was performed to determine factors predicting unfavorable neurologic outcome. Data were expressed as "mean (standard deviation; SD)", percent (%) and median (25-75%) where appropriate. $P<0.05$ was considered statistically significant. Data were expressed as "mean (standard deviation; SD)", percent (%), median (min-max), and OR with 95% confidence interval (CI, min to max) where appropriate.

Results

Baseline characteristics

Hypoxic-ischemic encephalopathy (HIE, 35.1%) and central nervous system (CNS) infection (22.1%) were the most common etiologies underlying the coma. During ICU hospitalization, the neurological outcome was normal or with mild neurological disability in 28 (36.4%) patients, whereas moderate to severe neurological disability was noted in 23 (29.8%) patients. In-hospital mortality occurred in 26 (33.8%) of 77 patients, including 66.7% of patients with coma due to toxic-metabolic causes, 61.5% of patients with coma due to structural causes and 33.3% of patients with hypoxic-ischemic encephalopathy, whereas only 5.9% of patients with CNS infection and none of the patients with status epilepticus died during ICU hospitalization (Table 1).

We re-tested EEG recordings on 9 patients with status epilepticus 2 days after withdrawal of sedative agents.

At the 3rd month of hospital discharge in survivors (n=51), favorable and unfavorable neurological outcome was noted in 46 (90%) and 5 (10%) of patients, respectively (Table 1).

Overall, during ICU hospitalization and after discharge, favorable neurological outcome (categories I-II) and unfavorable neurological outcome (categories III-IV-V) were noted in 57.0% and 43.0% of patients, respectively (Table 1).

Table 1. Baseline characteristics, etiology and outcome of children with NTC

Age (month), mean (SD, min-max)		70.5 (68.7, 2.0-216.0)
Gender, n (%)		
Female		34 (44.2)
Male		43 (55.8)
PRISM score, mean (SD, min-max)		15.93 (11.81, 0.00-43.0)
Etiology of non-traumatic coma		
Hypoxic-ischemic encephalopathy		27 (35.1)
CNS infection		17 (22.1)
Structural causes		13 (16.9)
Toxic metabolic causes		12 (15.6)
Status epilepticus		8 (10.4)
In-hospital (ICU) outcome (n=77)		**n (%)**
I. Normal		17 (22.1)
II. Mild Neurologic Disability		11 (14.3)
III. Moderate Neurologic Disability		18 (23.3)
IV. Severe Neurologic Disability		5 (6.5)
V. Death	Total	26 (33.8)
	Toxic metabolic causes (n=12)	8 (66.7)
	Structural causes (n=13)	8 (61.5)
	Hypoxic-ischemic encephalopathy (n=27)	9 (33.3)
	CNS infection (n=17)	1 (5.9)
	Status epilepticus (n=8)	0 (0.0)
Post-discharge 3rd month outcome (n=51)		
Favorable (I-II)		46 (90)
Unfavorable (III-IV-V)		5 (10)
Overall outcome (ICU + post-discharge 3rd month) (n=77)		
Favorable (I-II)		44 (57.0)
Unfavorable (III-IV-V)		33 (43.0)

SD: Standart deviation; PRISM: Pediatric risk of mortality;
CNS: Central nervous system; ICU: Intensive care unit

Neurological examination, EEG and cranial MRI findings with respect to overall neurological outcome

Overall, unfavorable vs. favorable neurological outcome was associated with significantly higher likelihood of lack of PLR (100.0% vs. 0.0, p<0.001), GCS of ≤8 (61.4% vs. 38.6, p<0.001) or ≤5 (72.4% vs. 27.6%, p<0.001), grade 2 (55.9% vs. 44.1% p<0.001), grade 3 (80.0% vs. 20.0%, p<0.001), and grade 4 (100.0% vs. 0.0%, p<0.001) EEG patterns, poor prognostic EEG patterns (88.9% vs. 11.1%, p=0.04), grade 3 (62.5% vs. 37.5%, p<0.05) and grade 4 (66.7% vs. 33.3%, p=0.037) MRI findings, as well as lesser likelihood of lack of MRI lesions (18.2% vs. 81.8%, p=0.029) (Table 2).

Table 2. Study parameters with respect to overall neurological outcome

		Total	Overall neurological outcome		*p* value
			Favorable (n=44)	Unfavorable (n=33)	
Lack of pupillary light reflex, n (%)		12 (15.6)	0 (0.0)	12 (100.0)	**<0.001**
GCS, %	>8	27.0	81.8	18.2	**<0.001**
	≤8	17.0	38.6	61.4	
	>5	36.0	75.0	25.0	**<0.001**
	≤5	8.0	27.6	72.4	
EEG-grading system, n (%)					
Grade 0		11 (14.3)	10 (90.9)	1 (9.1)	**<0.001**
Grade 1		23 (29.9)	18 (78.3)	5 (21.7)	
Grade 2		34 (44.2)	15 (44.1)	19 (55.9)	
Grade 3		5 (6.5)	1 (20.0)	4 (80.0)	
Grade 4		4 (5.2)	0 (0.0)	4 (100.0)	
EEG-overall, n (%)					
Good prognostic patterns		68 (88.3)	43 (63.2)	25 (36.8)	**0.04**
Poor prognostic patterns		9 (11.7)	1 (11.1)	8 (88.9)	
MRI findings, n (%)					
Grade 0		23 (38.3)	19 (82.6)	4 (17.4)	
Grade 1		11 (18.3)	8 (72.7)	3 (27.3)	**0.037**
Grade 2		7 (11.7)	5 (71.4)	2 (28.6)	
Grade 3		16 (26.7)	6 (37.5)	10 (62.5)	
Grade 4		3 (5)	1 (33.3)	2 (66.7)	
Total		60 (100)	39 (65)	21 (35)	
Cranial MRI- overall, n (%)					
Lack of lesion		22 (36.7)	18 (81.8)	4 (18.2)	
Presence of lesion		38 (63.3)	21 (55.3)	17 (44.7)	**0.029**
Total		60 (100)	39 (65)	21 (35)	

GCS: Glasgow coma score; EEG: Electroencephalogarphy; MRI: Magnetic resonance imaging

Logistic regression analysis for risk factors for unfavorable neurological outcome in NTC

Lack of PLR (OR 3.09, 95% CI: 2.17 to 4.40, $p<0.001$), GCS ≤5 (OR 7.85, 95% CI: 2.77 to 22.37, $p<0.001$), poor prognostic pattern in EEG (OR 13.76, 95% CI: 1.62 to 116.54, $p=0.004$) and presence of MRI lesions (OR: 4.04, 95% CI: 1.15 to 14.19, $p=0.029$) were determined to predict unfavorable neurological outcome in NTC patients (Table 3).

ROC analysis for performance of prognostic factors in the identification of unfavorable neurological outcome

Lack of PLR (sensitivity of 63%, a specificity of 100%, the positive predictive value of 100% and negative predictive value of 29%), GSC of ≤5 (sensitivity of 65%, a specificity of 81%, the positive predictive value of 72% and negative predictive value of 25%), poor prognostic pattern in EEG (sensitivity of 25%, a specificity of 97%, the positive predictive value of 88% and negative predictive value of 63.2%) and presence of MRI lesion (sensitivity of 81%, a specificity of 48% positive predictive value of 46% and negative predictive value of 82.6%) were determined to identify the overall unfavorable neurological outcome.

Discussion

Our findings in a retrospective cohort of pediatric patients with NTC revealed an in-hospital mortality rate of 33.8% in ICU and overall unfavorable neurological outcome in 43.0% of patients at 3rd month of hospital

Table 3. Poor prognostic factors for early outcome in non-traumatic coma

	Odd's ratio	95% confidence interval		*p* value
		Lower bound	Upper bound	
Risk factors				
Lack of pupillary light reflex	3.09	2.17	4.40	**<0.001**
Glasgow coma score ≤5	7.85	2.77	22.37	**<0.001**
Poor prognostic pattern in EEG	13.76	1.62	116.54	**0.004**
Presence of MRI lesions	4.04	1.15	14.19	**0.029**

EEG: Electroencephalogarphy; MRI: Magnetic resonance imaging

discharge. Although HIE and CNS infections were the most common etiologies, toxic-metabolic and structural causes were associated with the highest rate of mortality. Lack of PLR (OR 3.09, 95% CI: 2.17 to 4.40, $p<0.001$), GCS ≤5 (OR 7.85, 95% CI: 2.77 to 22.37, $p<0.001$), poor prognostic pattern in EEG (OR 13.76, 95% CI: 1.62 to 116.54, $p=0.004$) and presence of MRI lesions (OR 4.04, 95% CI: 1.15 to 14.19, $p=0.029$) were determined to predict unfavorable neurological outcome in NTC patients. Lack of PLR, GCS ≤5, and poor prognostic patterns in EEG showed a performance with high specificity (100.0%, 81.0%, and 97.0%, respectively), whereas the presence of an MRI lesion was associated with high sensitivity (81.0%) in discriminating unfavorable neurological outcome.

Mortality rate (33.8%) in our cohort seems consistent with the country-specific mortality rates reported in past studies among pediatric NTC patients that ranged from 16.6 to 50.0% [4, 5, 8, 9, 12, 17-19]. Infective pathologies are considered to be the most common cause of NTC in children in developing countries, while toxic-metabolic causes and HIE show higher prevalence in Western countries [3-5, 19, 20]. In addition, infectious etiology was also reported to be associated with higher mortality rates compared to other NCT etiology groups [3, 4, 6, 8, 9, 20, 21]. Our findings are in line with the high prevalence of infectious etiology in pediatric NTC cases, whereas do not support the associated high risk of mortality given the mortality rate of 5.9% in our patients NTC due to infectious etiology. Similarly, in a prospective study among 82 children with acute NTC, CNS infections were reported to be the most common etiology and the overall mortality rate was 30%, while survival was reported to be significantly better in those with infectious etiology than with toxic-metabolic etiology [22]. In an analysis of 100 pediatric NTC cases, metabolic causes (33%) and CNS infections (28%) were reported to be the most common etiologies along with overall mortality rate of as high as 50.0% [19]. Association of toxic-metabolic causes with the highest mortality rates (66.7%) in our cohort of NTC patients seems notable in this regard. Notably, in an analysis of 100 consecutive cases of NTC, infections (60%) and toxic-metabolic conditions (19%) were reported as the most common etiologies, while the overall mortality rate was 35% and higher in those with toxic-metabolic causes (73%) than those with infection (36%) [4]. In addition, consistent with lower mortality rates in our cohort for the etiologies including status epilepticus and infections, in a past study among 155 NTC patients, infectious (32.7%) etiology and status epilepticus (29.4%) were reported as the two most common etiology, along with overall mortality rate of 16.6% [9].

Indeed, non-convulsive status epilepticus has been considered as a robust predictor of a poor outcome in pediatric patients with a critical illness, irrespective of the cause [23-26], while the risk of poor neurodevelopmental outcome was shown to be higher in those presented with idiopathic or febrile etiology than those with acute encephalopathy (infectious, metabolic, vascular, and toxic) etiologies [27]. In addition, electrographic seizures have been noted in up to 65% of comatose children along with association status epilepticus with a greater risk of poor outcome than other types of seizures [28]. However, continuous EEG is not easily applicable neurophysiological modality in intensive care units. Hence, the absence of mortality among NTC cases with status epilepticus etiology in our cohort seems to support the consideration of morbidity

rather than the mortality to be more prevalent in pediatric status epilepticus [23, 27]. This also emphasizes the challenges considered in an association of status epilepticus with the outcome due to potential confounding factors such as the underlying etiology of status epilepticus and heterogeneity of studies in terms of study design, study populations, and outcome measures [23, 27]. Nonetheless, it should be noted that there is a considerable geographic difference in prevalent etiologies of NTC across the world and being familiar with the common causes of NTC coma in the specific geographical region is considered to be important for physicians to implement accurate diagnostic and therapeutic measures [21].

In-hospital rates for none-mild disability (36.4%) and moderate to severe disability (29.8%) in our cohort seems consistent with rates for none-mild disability (25%) and moderate to severe disability (35%) reported in NTC patients [4]. In addition, rates for favorable (90%) and unfavorable (10%) neurological outcome among survivors in our cohort support the data from a study in 100 children with NTC indicated that 58% of survivors showed no disability and 41% showed neurological or motor disability [8].

Inconsistent data exist on the predictive value of GCS score in pediatric NTC with consideration of GCS to be predictive for neurological outcome among survivors but not mortality in some studies [17, 29-31]. Nonetheless, our findings support the studies that reported poor GCS (GSC <5) and non-reactive pupils at admission to be independent significant predictors of poor prognosis in NTC [4, 5, 8, 11, 19, 32-35].

The significant role of poor prognostic EEG patterns in predicting unfavorable neurological outcome in our cohort supports the data from a past study among 100 children with NTC which revealed that abnormal EEG was a predictor of mortality and associated with increased risk of disability among survivors [36]. Likewise, in a prospective cohort of 57 children who were mechanically ventilated for HIE throughout a 3-year period; the presence of spikes or epileptiform discharges was associated with an unfavorable outcome [11].

Diagnostic and prognostic significance of EEGs in neonatal HIE is well-established with consideration of abnormal EEG background activity and persistent abnormality in serial EEG to be a potential marker of or prognosis in terms of neurologic sequela [37-39]. EEG has also been suggested to be a potential predictor of developmental outcome in severe but not in mild-to-moderate HIE cases [40, 41]. Background abnormalities on the initial EEG including burst suppression, slow activity, low voltage, and an isoelectric pattern were also shown to be associated with a markedly increased risk of mortality or unfavorable neurodevelopmental outcome in HIE patients [42].

In a retrospective analysis of 39 children with NTC, a significant correlation was reported between EEG findings and neurologic outcome after a mean follow-up period of 30 months, along with an increase in the prognostic power of assessment with a combination of MRI and electrophysiology findings [10].

MRI is the neuroimaging of choice in acute NTC [43], while considered to be a robust predictor of a poor neurodevelopmental outcome neonatal encephalopathy [44] alongside the well-established diagnostic and prognostic significance in neonatal HIE [41]. In an analysis of the prognostic value of MRI in children with NTC, a significant correlation was reported between the first MRI and neurologic outcome (sensitivity 96%) [45]. Likewise, our findings revealed that the presence of MRI lesions was a significant determinant of (OR 4.04, 95% CI: 1.15 to 14.19, p=0.029) poor prognosis, as associated with high sensitivity (81.0%) in discriminating unfavorable neurological outcome in pediatric NTC patients.

Consistent with our findings on the high sensitivity of MRI and high specificity of EEG in the detection of the prognostic outcome, neuroimaging was reported to be highly sensitive but less specific, while electrophysiological tests were considered highly specific but less sensitive in identification of prognostic outcome in pediatric NTC cases [10]. Moreover, in a study on the relationship between MRI lesions and EEG findings full-term neonates with acute encephalopathy, abnormal MRI findings including severe basal ganglia lesions were shown to be accompanied with an abnormal

EEG background rhythm [46]. In addition, in a study on 26 neonates with perinatal asphyxia presence of MRI lesions involving basal ganglia was reported to be a poor prognostic factor independent of EEG and clinical findings [47].

There is also evidence on the association of nonreactive electroencephalographic patterns with unfavorable outcome in terms of morbidity and mortality among comatose children [11, 48]. Therefore, EEG assessment in NTC has been suggested to focus not only the EEG prognostic patterns (burst-suppression, alpha-like activity, low amplitude, and suppression) but also the electroencephalographic reactive patterns (a change in the frequency or voltage of the background activity) for better understanding of the clinical outcome [48]. The authors also noted the likelihood of electroencephalographic reactive pattern to be an independent prognostic predictor, irrespective of the etiology, coma score, and electroencephalographic pattern [48].

Our findings confirm the role of clinical variables (PLR, GCS score) as the most readily available tools for prognostic assessment of NTC, and emphasize the predictive role of EEG patterns and presence of MRI lesion to identify those who are most likely to develop unfavorable neurological outcome in children with NTC. Hence, our findings emphasize the importance of early neuroimaging and electrophysiological investigation in providing an estimate of the likelihood of poor outcome with reasonable accuracy in children with NTC [10].

There are some limitations in our study. Firstly, this is a retrospective study. Secondly, serial EEG monitoring was not performed in patients other than status epilepticus. Thus, a large prospective trial is warranted to confirm the prognostic role of serial EEG monitoring in pediatric patients with non-traumatic coma.

In conclusion, our findings in a retrospective cohort of pediatric patients with NTC revealed in-hospital mortality in one-third of patients and overall unfavorable neurological outcome in almost half of the patients. Although HIE and CNS infections were the most common etiologies, toxic-metabolic and structural causes were associated with a higher rate of mortality. Lack of PLR, GCS ≤5, and poor prognostic patterns in EEG were the prognostic factors with high specificity, whereas the presence of MRI lesion was the prognostic factor with high sensitivity in predicting and discriminating unfavorable neurological outcome in children with NTC. Hence, our findings emphasize that combined use of clinical, EEG, and MRI findings might provide a more accurate estimation of neurological outcome in pediatric NTC.

Conflict of interest: No conflict of interest was declared by the authors.

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Contributions of authors

H.T. conceptualized and designed the article, A.A. coordinated and collected the clinical data, reviewed the literature, wrote and drafted the initial manuscript. S.Y. analyzed the EEG records, critically reviewed and revised the manuscript. B.K. made the initial analysis, collected the data, chosed the figures, reviewed the literature. Ö.K. collected the data and analyzed MRI records. G.A. made the initial analysis, collected the data, analyzed the EEG records. S.G. made the initial analysis and interpretation, coordinated and supervised the data collection, H.T. and S.G. critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.