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Original Article

Predicting the outcomes of targeted temperature management for children with seizures and/or impaired consciousness accompanied by fever without known etiology

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Abstract

BACKGROUND: Seizures and/or impaired consciousness accompanied by fever without known etiology (SICF) is common in the pediatric emergency setting. No optimal strategy for the management of SICF in childhood currently exists. We previously demonstrated the effectiveness of targeted temperature management (TTM) against SICF with a high risk of morbidity; however, some patients with SICF develop neurological sequelae despite TTM, which necessitate additional neuroprotective treatment. The clinical characteristics of these severe cases have not been studied. Accordingly, the aim of this study was to identify the clinical characteristics of children with SICF who exhibit poor outcomes after TTM.

METHODS: The medical records of children admitted to Kobe Children's Hospital (Kobe, Japan) between October 2002 and September 2016 were retrospectively reviewed. Patients with SICF treated using TTM were included and divided into the satisfactory and poor outcome groups. Univariate and multivariate logistic regression analyses were used to compare clinical characteristics and laboratory findings between the two groups.

RESULTS: Of the 73 included children, 10 exhibited poor outcomes. Univariate logistic regression analysis revealed that acute circulatory failure before TTM initiation,

the use of four or more types of anticonvulsants, methylprednisolone pulse therapy, and an aspartate aminotransferase (AST) level ≥73 IU/L were associated with poor outcomes. Multivariate logistic regression analysis identified an elevated AST level as a significant independent predictor of a poor outcome.

CONCLUSIONS: An elevated AST level within 12 h of onset in children with SICF is an independent predictor of a poor outcome after TTM initiated within 24 h of onset.

Key words: acute encephalopathy; children; predictor; poor outcome; targeted temperature management

Introduction

Seizures and/or impaired consciousness accompanied by fever without known etiology (SICF) is common in the pediatric emergency setting. Most of the children with SICF exhibit benign clinical courses and are finally diagnosed with febrile seizures (FS) [1]. However, in some patients with SICF, sequelae persist, with a final diagnosis of acute encephalopathy (AE) [1].

Research has shown that AE, a rare and serious complication of common childhood infections, is the most prevalent in East Asia [2]. Clinical guidelines for AE treatment in Japan describe strategies such as methylprednisolone pulse therapy, intravenous immunoglobulin, and targeted temperature management (TTM) [3]. Nevertheless, there is no optimal strategy for managing AE in childhood. However, TTM exerts neuroprotective effects in cases of encephalopathy related to perinatal asphyxia [4-6] and adult cardiac arrest [7,8]. Moreover, TTM has been attempted for several neurological emergencies because it has been considered theoretically effective against various brain injuries [9,10]. With regard to SICF including AE, we previously demonstrated the effectiveness of TTM against SICF with a high risk of neurological sequelae [11]. In addition, another study showed that the early initiation of TTM against SICF has the potential to improve the neurological outcomes of AE [12]. However,

some patients with severe cases of SICF develop neurological sequelae despite the timely administration of TTM [12], and thus necessitate additional neuroprotective treatment. The clinical characteristics of such cases have not yet been characterized. Accordingly, the aim of this study was to identify the clinical characteristics of children with SICF who exhibited a poor outcome after TTM.

Methods

Subjects

The study protocol was approved by the Ethics Committees of Hyogo Prefectural Kobe Children's Hospital and Kobe University Hospital in Kobe, Japan. Given the retrospective design of the study and the use of anonymized patient data, the requirement for informed consent was waived. The medical records of children aged 1 month to 15 years who were admitted with SICF at the pediatric intensive care unit in Kobe Children's Hospital, a tertiary referral hospital, between October 2002 and September 2016 were retrospectively reviewed. As in our previous report [1], SICF was defined as the presence of seizures and/or impaired consciousness accompanied by fever without known etiology such as epilepsy, metabolic disorders, structural anomalies in the central nervous system, or central nervous system infection with

pleocytosis (cerebrospinal fluid cells: > 8 cells/μL).

The inclusion criteria were children who exhibited SICF and were treated with TTM. The exclusion criteria were as follows: a history of neurological problems (chromosomal abnormality or mental retardation), initiation of TTM at >24 h after onset, and the use of a hypothermic TTM (target temperature: 34.5 ± 0.5°C) regimen that was different from the regimen described in the next section.

The following information was collected from patient records: age, sex, history of FS, body temperature at admission, duration of convulsive seizure(s), prodromal infection, acute circulatory failure before TTM initiation, presence of electrical seizures detected by electroencephalography (EEG) before TTM initiation, laboratory examination results within 12 h of onset, total number of anticonvulsants used, types of anesthetic drugs used continuously, and methylprednisolone pulse therapy applied within 24 h of onset. Convulsive seizure was defined as a persistent convulsion or sequence of intermittent convulsions without full recovery of consciousness between convulsions. Blood tests included the following measurements: white blood cell count; platelet count; and aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), creatine kinase (CK), creatinine (Cre), lactate, blood sugar, and C-reactive protein levels. When multiple values were available for blood data, the

maximum value was selected for analysis. Cerebrospinal fluid samples were obtained before the initiation of TTM.

TTM Regimen

The body temperature of patients was monitored using a bladder-temperature probe. The body temperature was decreased to a targeted temperature of 36.0 ± 0.5°C for at least 48 h using a cooling blanket. After TTM, the skin temperature (measured at the axilla) was maintained below 38.5°C using acetaminophen. All patients were intubated and intravenously anesthetized, following which they received continuous anticonvulsant medication during the cooling phase. Inotropic agents and other supportive drugs were administered at the discretion of pediatric intensivists.

The depth of anesthesia was considered uniform because the type and amount of anesthetic drug(s) used during TTM were predetermined by the TTM protocol in this study. Based on the protocol, we administered repeated intravenous bolus injections of 1–2 mg/kg of thiamylal until we confirmed the burst-suppression pattern on EEG. Subsequently, thiamylal was continuously administered at 5 mg/(kg·h) on the first day of TTM and tapered off over the next day. When hemodynamic instability after the administration of thiamylal was noted, the anesthetic drug was changed to midazolam

and the appropriate dose for maintaining stable circulation and suppressing seizures on EEG was continuously administered.

To monitor electrical seizures during TTM, we used a digital EEG device (EEG-9100; Nihon Kohden, Tokyo, Japan) and recorded EEG activity using 4 channels placed on the bilateral frontal (Fp1-A1 and Fp2-A2) and occipital regions (O1-A1 and O2-A2), as reported by Yamaguchi et al. [13], according to the International 10-20 system. The definition of an electrical seizure was in accordance with that reported by Claassen et al. [14]. Briefly, persistent rhythmic waves, spikes, spikes and waves, or persistent, high-amplitude slow waves with an evolution lasting at least 10 s were judged as electrical seizures.

Prespecified Criteria for TTM Initiation

We previously reported three clinical criteria for predicting poor outcomes in children with SICF [15,16]. The criteria were as follows: refractory status epilepticus, elevated AST levels within 6 h of onset, and impaired consciousness lasting longer than 6 h [15,16].

In this study protocol, the physicians referred the patients to pediatric neurologists, who examined the necessity of TTM when the patients met one or more of

the three prespecified criteria mentioned above. When the neurologists judged that TTM was necessary, they provided the parents or guardians with a sufficient explanation, and initiated TTM after obtaining written informed consent.

Outcome and Final Diagnosis

Neurological outcomes were assessed by a trained pediatric neurologist using the Pediatric Cerebral Performance Category scale (PCPC) [17] with the following scores: 1, normal performance; 2, mild disability; 3, moderate disability; 4, severe disability; 5, a persistent vegetative state; and 6, death. The neurological outcome was assessed 1 month after onset; accordingly, the patients were divided into the satisfactory (PCPC score, 1) and poor (PCPC score, 2–6) outcome groups. The clinical characteristics and laboratory findings were compared between the two groups.

The final diagnoses of AE syndrome were based on the clinical guidelines of AE [3]. The diagnosis of acute disseminated encephalomyelitis was performed according to the criteria proposed and revised by the International Pediatric Multiple Sclerosis Study Group [18].

Statistical Analysis

In the logistic regression analyses, we divided the parameters of age, body temperature at admission, and duration of convulsive seizure(s) into three categories. The parameter of age was categorized as follows: <1 year (toddler), 1–5 years (preschooler), and 6–15 years (school-age children). Body temperature was categorized as follows: <38.0°C, 38–39.9°C, and ≥40°C. The duration of convulsive seizure(s) was categorized as <60 min, 60–119 min, and ≥120 min. Subsequently, we examined the association between these parameters and poor outcomes, using the first category as a reference.

Differences between the satisfactory and poor outcome groups were compared using logistic regression analyses in EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (version 3.0.2; The R Foundation for Statistical Computing, Vienna, Austria) [19]. More precisely, EZR is a modified version of R commander (version 2.0-3), featuring statistical functions that are frequently used in biostatistics. Mann-Whitney U tests were used to analyze numerical variables, while univariate logistic regression analyses were used for categorical variables. Variables with a p-value < 0.05 were further tested in multivariate logistic regression analyses with backward stepwise procedures. The level of statistical significance was set at $p < 0.05$.

Results

During the study period, 659 children with SICF, aged 1 month to 15 years, were admitted. Of these, 276 children met the prespecified criteria for TTM initiation. Explanations were provided to the parents or guardians of these children regarding the risks and benefits of TTM, and 176 of the children did not receive TTM because the parents or guardians did not provide consent and/or because of the attending neurologists' decision; thus, the medical records of the 100 children who underwent TTM were reviewed. Among these patients with SICF treated using TTM, 8 children with histories of developmental delay and/or chromosomal abnormalities were excluded. In addition, 10 children who underwent delayed TTM (initiated >24 h after onset) and 9 who were treated with hypothermic TTM (target temperature: 34.5 ± 0.5°C) were excluded. Consequently, 73 children with SICF treated using normothermic TTM initiated within 24 h of onset were included in our analysis (Figure 1).

The patient characteristics are summarized in Table 1. There were 37 boys and 36 girls. The median age was 24.2 months (range, 2.9–174.9 months), the mean body temperature at admission was 38.8 ± 1.3°C, and the median duration of convulsive seizure(s) was 135 min (range, 3–728 min). Twenty patients had a history of FS. The

causative pathogen for the prodromal infection was identified in 21 patients, with the confirmation of influenza A infection in 11. Three patients developed acute circulatory failure before the initiation of TTM. Continuous EEG was recorded before the initiation of TTM in 72 patients, and electrical seizures were detected in 19. The median number of anticonvulsants used was three (range, 1–5). Methylprednisolone pulse therapy was additionally used for 13 patients. Intravenous immunoglobulin was not used for any patient. Mechanical ventilation was required for all patients. All patients met at least one of the three prespecified criteria for TTM initiation and received TTM.

Sixty-three patients exhibited satisfactory outcomes, 54 of whom were finally diagnosed with FS. Ten patients exhibited poor outcomes, with a final confirmed diagnosis of AE; these included 8 patients exhibiting acute encephalopathy with biphasic seizures and late reduced diffusion (AESD), one with Reye-like syndrome, and one with unclassified encephalopathy.

Table 2 presents a comparison of blood parameters between the poor and satisfactory outcome groups. The maximum AST, ALT, LDH, CK, and Cre levels within 12 h after onset were significantly higher in the poor outcome group than in the satisfactory outcome group. For the multivariate logistic regression analysis, it was necessary to remove the strongly correlated parameters. Since AST is reportedly a

predictor of poor outcome in patients with AE and status epilepticus [15,20-22], we selected the AST level as a reference parameter for blood tests and examined the correlations between the AST level and the other significant parameters. The serum ALT, LDH, CK, and Cre levels were positively associated with the AST level (i.e., the correlation coefficient between the AST and ALT levels was 0.839, $p < 0.001$; Supplemental Figure 1). Therefore, only the AST level was included in the logistic regression analysis. The values obtained were converted to categorical values using a cutoff of 73 IU/L, which was determined based on a receiver operating characteristics curve analysis (Figure 2). Univariate logistic regression analysis revealed that acute circulatory failure before the initiation of TTM, the use of four or more types of anticonvulsants, methylprednisolone pulse therapy, and an AST level ≥73 IU/L were significantly associated with a poor outcome (Table 3). Multivariate logistic regression analysis confirmed that an elevated AST level was a significant independent predictor of a poor outcome (Table 3). Of the 10 children with poor outcomes, 8 exhibited a serum AST level ≥73 IU/L, one exhibited an AST level of 33 IU/L, and one exhibited an AST level of 49 IU/L (Table 4). Eight of these 10 children were eventually diagnosed with AESD, which is a syndrome of encephalopathy caused by excitotoxic neuronal injury (Table 4) [23].

Discussion

In the present study, we identified an elevated serum AST level to be an independent predictor of a poor outcome, including neurological sequelae, in patients with SICF treated using TTM. To the best of our knowledge, this is the first study to examine the characteristics of patients with SICF who develop neurological sequelae despite the timely administration of TTM.

The majority of patients with poor outcomes in this study had AESD and elevated serum AST levels. Mizuguchi et al. [2] classified AE into the following three types according to the pathology: cytokine storm, metabolic error, and excitotoxic types. In our previous studies, AST elevation in the acute phase was found to be more characteristic of the cytokine storm and/or metabolic error types than the excitotoxic type [15,16].

There are a few reasons for our observation of an association between a poor prognosis and AESD with AST elevation. First, AST elevation is observed in AESD as well as cytokine storm- and metabolic error-type encephalopathy [24]. In our previous study investigating the effectiveness of TTM against SICF without AST elevation, we did not observe neurological sequelae in the children treated with TTM, and most of the

patients with neurological sequelae who did not receive TTM were finally diagnosed with AESD [11]. It is possible that TTM alone is insufficient to prevent neuronal injury in severe cases with elevated AST levels, leading to the clinical presentation of AESD.

Second, it is possible that TTM ameliorated neuronal injury related to AE with AST elevation via the suppression of increased free radical formation, excess glutamate release, ion pump dysfunction, and cellular metabolism [25,26]. Through this mechanism, TTM may partially change the clinical course of cytokine storm- and metabolic error-type encephalopathy. When excitotoxicity was also partially involved in the pathology, there is a possibility that patients who would have been diagnosed with the cytokine storm- or metabolic error-types of AE if left untreated, exhibited another clinical course due to treatment using TTM, and were finally diagnosed with the excitotoxic type of AE.

Third, the indications for TTM were subject to selection bias in this study. Since TTM suppresses cardiorespiratory function(s) [26], it cannot be applied to patients with unstable vital signs. In our TTM regimen, we used thiamylal as an anesthetic drug, which was repeatedly administered intravenously until we confirmed the presence of the burst-suppression pattern on EEG, and it was continuously administered for 2 days. Therefore, the total dose of anesthetic drugs used was high. In

general, high-dose anesthetic drugs tend to suppress the circulation. As such, our TTM regimen is difficult to use in patients whose circulation dynamics are not stable. In addition, unstable circulation dynamics are common in cytokine storm-type encephalopathies such as hemorrhagic shock and encephalopathy syndrome, acute necrotizing encephalopathy, and Reye-like syndrome. Hence, it is often challenging to apply TTM for patients with cytokine storm-type encephalopathies. Indeed, during the study period, we identified 13 patients with cytokine-storm type encephalopathies who met the prespecified criteria for TTM initiation (data not shown). Although the introduction of TTM was considered in all patients with cytokine-storm type encephalopathies, only two patients were actually treated with TTM. The other 11 patients did not receive TTM owing to hemodynamic instability. Therefore, this study design, which focused on patients who received TTM treatment, may have been biased towards selection of patients who exhibited stable circulation dynamics. This is probably why we observed only two patients with encephalopathy caused by a cytokine storm (one exhibited a satisfactory outcome and the other exhibited a poor outcome).

Our findings suggest a need to revise the treatment approach for SICF with early AST elevation in childhood. In this study, ALT, LDH, CK, and Cre levels were positively correlated with the AST level (Supplemental Figure 1). These increases might

indicate the progression of tissue damage, including brain damage. Thus, earlier and additional treatments are required to improve the outcomes in such cases.

Although Kawano et al. [27] reported that TTM initiated within 12 h of AE onset was associated with improved outcomes, the effective therapeutic time window for pediatric cases has not been established. In the present study, the median time from onset to TTM initiation was within 12 h for all patients, regardless of the outcome (Supplemental Figure 2). Previous studies involving animal models of ischemia [28-30] and traumatic brain injury [31], as well as a human clinical study investigating neonatal asphyxia [32], have suggested that the therapeutic window for TTM is less than several hours and that earlier TTM initiation may improve the neurological outcome.

Limitations

The present study has several limitations. First, although we identified the indications for TTM in previous studies [15,16] and used the prespecified clinical criteria for TTM initiation in order to minimize the heterogeneity of patients' severity, final decisions were made by the attending neurologists; therefore, the cohort may have been subject to selection bias. Second, because the effective therapeutic time window for TTM against AE in childhood is unclear, the timing of TTM initiation varied among

patients, resulting in some treatment heterogeneity. Third, the sample size did not provide an adequate power for multivariate logistic regression analysis. Consequently, future large-scale studies are required to confirm whether high AST levels are an independent predictor of a poor outcome in children with SICF treated using TTM.

Conclusion

The present study demonstrates that an elevated AST level within 12 h of onset in children with SICF is an independent predictor of a poor outcome after TTM initiated within 24 h of onset. Further studies are needed to confirm and extend these findings.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Author Contribution

T.T., H.N., and A.M. contributed to the conception and design of this study; T.T., H.N., H.Y., Y.I., K.T., M.N., D.T., A.M., and K.F. collected the data; T.T. performed the statistical analysis and drafted the manuscript; H.N., M.N., K.N., N.N., H.K., R.T., and K.I. critically reviewed the manuscript. All authors read and approved the final manuscript.

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Figure legends

Figure 1. Study enrollment procedure. PICU, pediatric intensive care unit; SICF, seizures and/or impaired consciousness accompanied by fever without known etiology; TTM, targeted temperature management.

Figure 2. Receiver operating characteristic (ROC) curve for the aspartate aminotransferase (AST) level, predicting a poor outcome after targeted temperature management for children with seizures and/or impaired consciousness accompanied by fever without known etiology. The cutoff level is 73 IU/L (where the apex of the ROC curve is the closest to the upper left corner). AUC, area under the curve; CI, confidence interval.

Supplemental Figure 1. Correlations among serum alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatinine kinase (CK), creatinine (Cre), and aspartate aminotransferase (AST) levels in children with seizures and/or impaired consciousness accompanied by fever without known etiology. Each value is logarithmically transformed and plotted. Spearman's correlation analysis shows that ALT, LDH, CK, and Cre levels are correlated with the AST level.

Supplemental Figure 2. Time from onset to targeted temperature management (TTM) initiation in children with seizures and/or impaired consciousness accompanied by fever without known etiology exhibiting satisfactory or poor outcomes. Fifty-nine patients from the satisfactory outcome group and nine from the poor outcome group were analyzed because the actual time of TTM initiation could not be determined for some patients. There is no statistically significant difference between the two groups. Data are presented as the median (range).

Table 1. Demographic characteristics of pediatric patients with seizures and/or impaired consciousness accompanied by fever without known etiology who underwent targeted temperature management (n = 73)

Characteristic	Value
Age, months	24.2 (2.9–174.9)
Male sex	37 (50.7)
History of FS	20 (27.4)
Temperature at admission, °C	38.8 ± 1.3
Duration of convulsive seizure(s), min	135 (3–728)
Prodromal infection	
Influenza A	11 (15.1)
Influenza B	4 (5.5)
HHV6	3 (4.1)
Rota virus	3 (4.1)
Pertussis	1 (1.4)
Unknown	51 (69.9)
Acute circulatory failure before the initiation of TTM	3 (4.1)
Electrical seizures detected before the initiation of TTM	19 (26.0)
Management	
Number of anticonvulsants used in the acute setting	3 (1–5)
Electroencephalogram monitoring	72 (98.6)
Mechanical ventilation	73 (100)
Methylprednisolone pulse therapy	13 (17.8)
Intravenous immunoglobulin	0 (0)
TTM	73 (100)
Clinical criteria met at TTM initiation	
Met ≥ one of the three prespecified criteria for TTM	73 (100)
Refractory status epilepticus	46 (63.0)
Impaired consciousness lasting >6 h	45 (61.6)
AST elevation within 6 h of onset	11 (15.1)
Baseline neurological status	
PCPC score, 1	73 (100)
PCPC score, 2–6	0 (0)
Neurological outcome at 1 month after onset	
PCPC score, 1	63 (86.3)
PCPC score, 2	2 (2.7)

PCPC score, 3	5	(6.8)
PCPC score, 4	2	(2.7)
PCPC score, 5	0	(0)
PCPC score, 6	1	(1.4)
Poor outcome (PCPC score, 2–6)	10	(13.7)
Final diagnosis for patients with a satisfactory outcome		
AESD	3	(4.1)
HSES	1	(1.4)
Unclassified encephalopathy	4	(5.5)
ADEM	1	(1.4)
FS	54	(73.9)
Final diagnosis for patients with a poor outcome		
AESD	8	(10.9)
Unclassified encephalopathy	1	(1.4)
Reye-like syndrome	1	(1.4)

Data are presented as the median (range), mean ± standard deviation, or number (%).
ADEM, acute disseminated encephalomyelitis; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; AST, aspartate aminotransferase; FS, febrile seizures; HHV6, human herpes virus 6; HSES, hemorrhagic shock and encephalopathy syndrome; PCPC, Pediatric Cerebral Performance Category scale; TTM, targeted temperature management

Table 2. Comparison of laboratory data between pediatric patients with seizures and/or impaired consciousness accompanied by fever without known etiology stratified into the satisfactory and poor outcome groups after targeted temperature management

Parameter		Outcome				p
		Satisfactory (n = 63)		Poor (n = 10)		
WBC	(cells/μL)	12300	(2250–39900)	16450	(8100–72300)	0.08
PLT	(10^4/μL)	24.7	(8.2–65.9)	23.5	(10.8–50.7)	0.61
AST	(IU/L)	42	(17–152)	197	(33–623)	<0.001
ALT	(IU/L)	17	(7–126)	41	(12–166)	<0.001
LDH	(IU/L)	320	(195–1088)	898.5	(306–2199)	<0.001
CK	(IU/L)	134	(49–12340)	215	(82–51230)	<0.05
Cre	(mg/dL)	0.31	(0.18–0.81)	0.425	(0.21–1.03)	<0.05
Lac	(mmol/L)	2.1	(0.5–9.0)	4.9	(1.1–14.7)	0.06
BS	(mg/dL)	167	(80–364)	195	(105–290)	0.26
CRP	(mg/dL)	0.62	(0–4.69)	0.465	(0–3.12)	0.83

Data are presented as the median (range) unless otherwise indicated.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BS, blood sugar; CK, creatinine kinase; Cre, creatinine; CRP, C-reactive protein; Lac, lactate; LDH, lactate dehydrogenase; PLT, platelet; WBC, white blood cell

Table 3. Findings of the logistic regression analysis performed to determine predictors of a poor outcome in pediatric patients with seizures and/or impaired consciousness accompanied by fever without known etiology treated using targeted temperature management

		Outcome			
		Satisfactory	Poor		
	n = 73	(n = 63)	(n = 10)	OR (95% CI)	p
Univariate logistic regression analysis					
Age at onset, years					
<1	11	7 (63.6)	4 (36.4)	Reference	
1–5	50	45 (90.0)	5 (10.0)	0.40 (0.10–1.55)	0.19
6–15	12	11 (91.7)	1 (8.3)	0.53 (0.06–4.58)	0.56
Male sex	36	31 (86.1)	5 (13.9)	1.03 (0.27–3.92)	0.96
Body temperature at admission, °C					
<38.0	13	11 (84.6)	2 (15.4)	Reference	
38–39.9	48	41 (85.4)	7 (14.6)	1.25 (0.29–5.33)	0.76
≥40	12	11 (91.7)	1 (8.3)	0.53 (0.06–4.58)	0.56
History of febrile seizures	20	15 (75)	5 (25)	3.20 (0.81–12.60)	0.10
Duration of convulsive seizure(s), min					
<60	9	9 (100)	0 (0)	Reference	
60–119	21	18 (85.7)	3 (14.3)	1.11 (0.25–4.95)	0.89
≥120	37	31 (83.8)	6 (16.2)	1.74 (0.40–7.64)	0.46

Influenza A infection	11	10	(90.9)	1	(9.1)	0.59	(0.07–5.17)	0.63
Acute circulatory failure before the initiation of TTM	3	1	(33.3)	2	(66.7)	15.50	(1.26–191.00)	<0.05
Electrical seizures detected before the initiation of TTM	19	14	(73.7)	5	(26.3)	3.43	(0.87–13.60)	0.07
Use of ≥4 types of anticonvulsants in the acute setting	29	22	(75.9)	7	(24.1)	4.35	(1.02–18.50)	<0.05
Anesthetic drugs used continuously during TTM						1.64	(0.16–16.40)	0.67
Thiamylal	68	59		9				
Midazolam	5	4		1				
Methylprednisolone pulse therapy	13	6	(46.2)	7	(53.8)	22.20	(4.51–109.00)	<0.001
AST elevation (≥73 IU/L)	16	8	(50.0)	8	(50.0)	26.50	(4.75–148.00)	<0.001
Multivariate logistic regression analysis								
AST elevation (≥73 IU/L)						26.50	(4.75–148.00)	<0.001

Data are presented as the number (%) unless otherwise indicated.

AST, aspartate aminotransferase; CI, confidence interval; OR, odds ratio; TTM, targeted temperature management

Table 4. Characteristics of pediatric patients with a poor outcome after targeted temperature management for seizures and/or impaired consciousness accompanied by fever without known etiology

Patient	Sex	Age (months)	Acute circulatory failure	Electrical seizures	Total number of anticonvulsants used	mPSL	Maximum AST level within 12 h of onset (IU/L)	Baseline PCPC score	PCPC score at 1 month after onset	Final diagnosis
1	Female	29	–	–	3	+	201	1	2	AESD
2	Male	8	–	+	4	–	49	1	2	AESD
3	Male	9	–	–	4	+	193	1	3	AESD
4	Female	20	–	+	5	–	73	1	3	AESD
5	Female	20	–	+	4	+	159	1	3	AESD
6	Male	3	+	–	3	+	247	1	3	Unclassified encephalopathy
7	Male	49	–	–	4	–	33	1	3	AESD
8	Male	137	–	–	4	+	623	1	4	AESD
9	Female	27	–	+	3	+	278	1	4	AESD
10	Female	7	+	+	4	+	504	1	6	Reye-like syndrome

AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; AST, aspartate aminotransferase; mPSL, methylprednisolone pulse therapy; PCPC, Pediatric Cerebral Performance Category scale; TTM, targeted temperature management

Figure 1

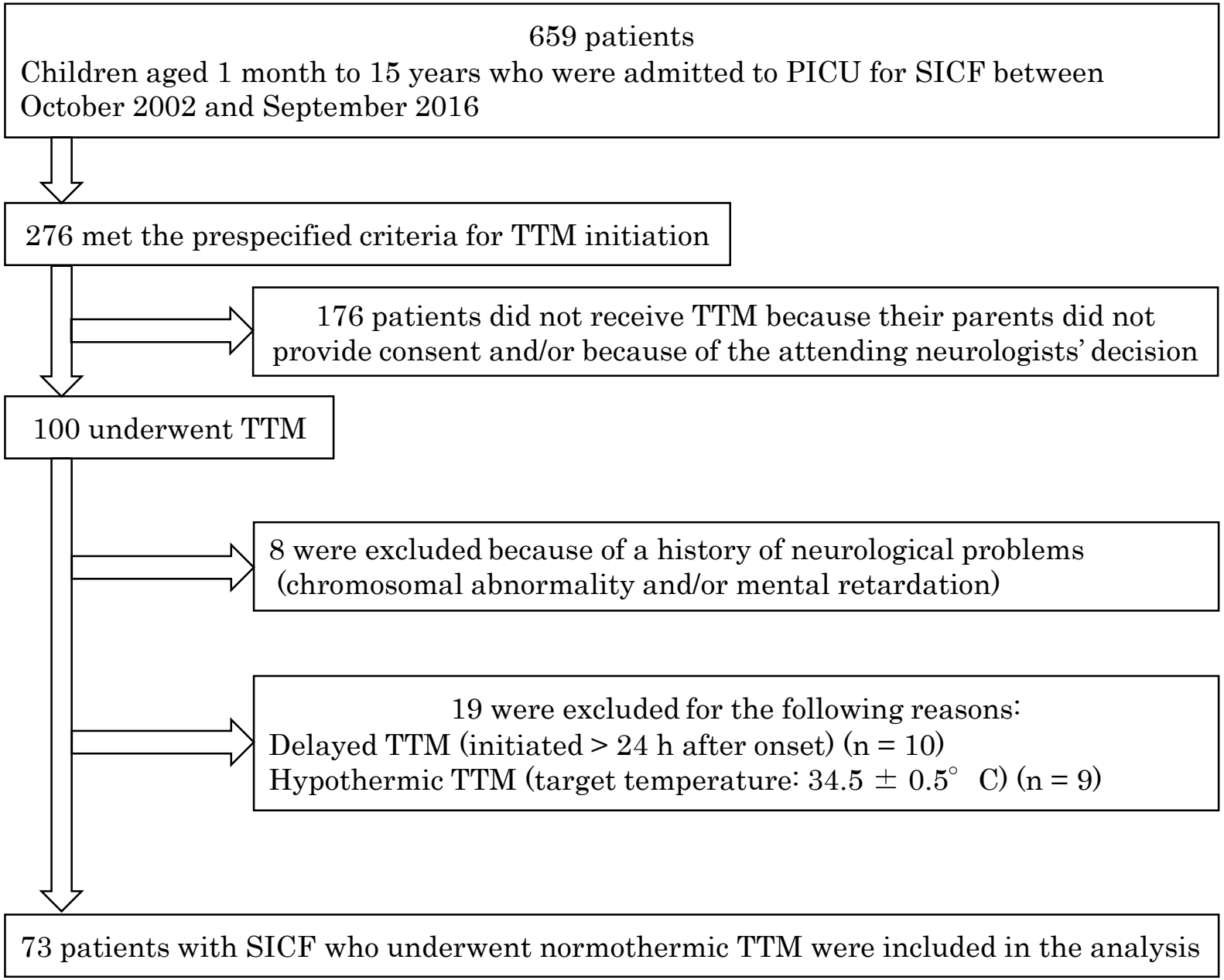
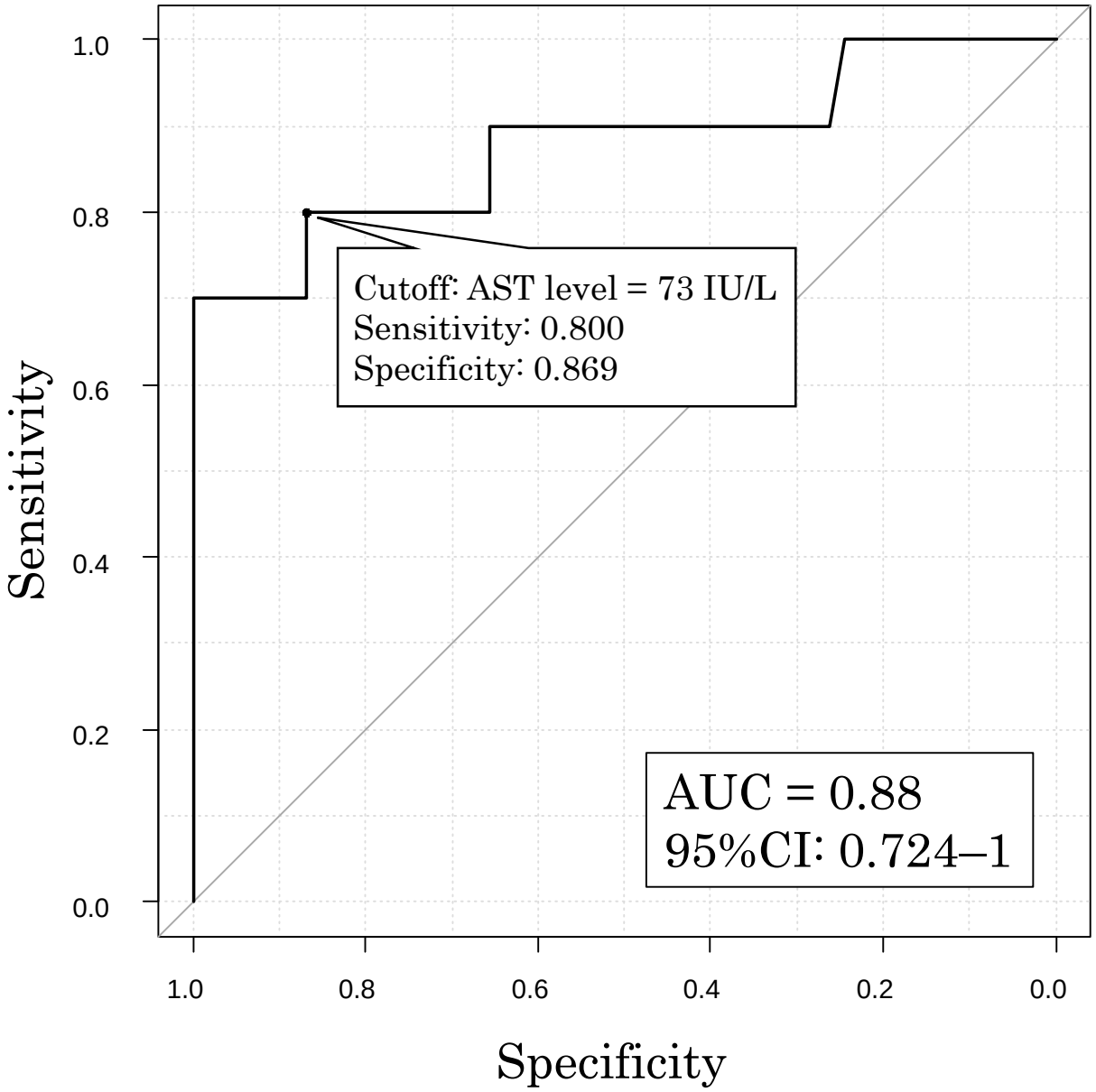
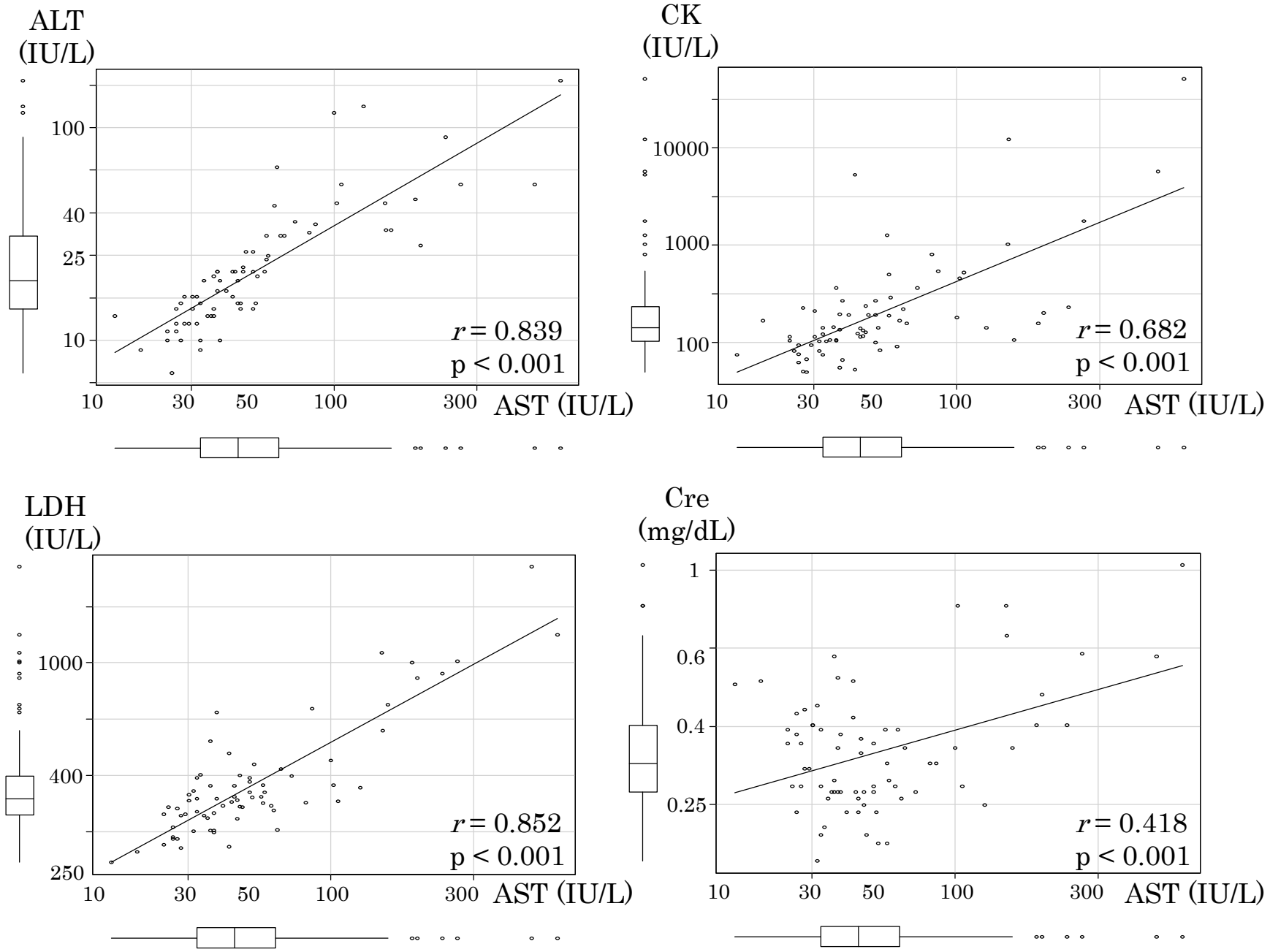

659 patients
Children aged 1 month to 15 years who were admitted to PICU for SICF between October 2002 and September 2016
276 met the prespecified criteria for TTM initiation
176 patients did not receive TTM because their parents did not provide consent and/or because of the attending neurologists' decision
100 underwent TTM
8 were excluded because of a history of neurological problems (chromosomal abnormality and/or mental retardation)
19 were excluded for the following reasons:
Delayed TTM (initiated > 24 h after onset) (n = 10)
Hypothermic TTM (target temperature: 34.5 ± 0.5° C) (n = 9)
73 patients with SICF who underwent normothermic TTM were included in the analysis

Figure 2


Sensitivity
1.0
0.8
0.6
0.4
0.2
0.0
Cutoff: AST level = 73 IU/L
Sensitivity: 0.800
Specificity: 0.869
AUC = 0.88
95%CI: 0.724–1
1.0
0.8
0.6
0.4
0.2
0.0
Specificity

Supplemental Figure 1



Supplemental Figure 2