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**Early risk factors for mortality in children with seizure and/or impaired consciousness  
accompanied by fever without known etiology**

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## **ABSTRACT**

**BACKGROUND:** Children who present with seizure and/or impaired consciousness accompanied by fever without known etiology (SICF) may be diagnosed with either acute encephalopathy (AE) or febrile seizure (FS). Although approximately 5% of AE cases are fatal, it is difficult to identify fatal cases among children with SICF, which are often critical by the time of diagnosis. Thus, early prediction of outcomes for children with SICF, prior to diagnosis, may help to reduce mortality associated with AE. The aim of the present study was to identify clinical and laboratory risk factors for mortality acquired within 6 h of onset among children with SICF.

**METHODS:** We retrospectively reviewed the medical records of children who had been admitted to Kobe Children's Hospital (Kobe, Japan) with SICF between October 2002 and September 2015. We compared clinical and laboratory characteristics acquired within 6 h of onset and outcomes between survivors and non-survivors using univariate and multivariate analyses.

**RESULTS:** The survivor and non-survivor groups included 659 and nine patients, respectively. All patients in the non-survivor group received a final diagnosis of AE. Univariate analysis revealed significant differences between the groups with regard to seizure duration and the following laboratory parameters: aspartate transaminase (AST), alanine aminotransferase, lactate dehydrogenase, sodium, and lactate. The multivariate analysis identified AST as a significant

independent factor associated with mortality.

**CONCLUSIONS:** Elevation of AST within 6 h of onset is independently correlated with mortality in children with SICF. Our result may elucidate earlier intervention for patients with high risk of mortality.

**Keywords:**

acute encephalopathy, febrile seizure, mortality, risk factors

## INTRODUCTION

Children with either febrile seizure (FS) or acute encephalopathy (AE) exhibit seizures and/or impaired consciousness accompanied by fever without known etiology (SICF). Whereas FS is a transient condition in which children do not experience sequelae [1], AE is defined as impaired consciousness lasting longer than 24 h and is often associated with neurological sequelae. Previous studies have indicated that the mortality rate among patients with AE is 5.6% [2]. Although FS and AE differ greatly in severity and outcome, it is often difficult to distinguish AE from FS in the early stages of the disease. Furthermore, children with a certain subtype of AE—hemorrhagic shock and encephalopathy syndrome (HSES) [3]—are almost always in critical condition and exhibit multiple organ failure (MOF) by the time of diagnosis [4]. Thus, early prediction of outcomes for children with SICF, prior to diagnosis, may help to reduce mortality associated with AE.

Although some previous studies have investigated risk factors associated with the morbidity or specific syndromic diagnosis of AE [5-8], to the best of our knowledge, no studies have aimed to identify acute-phase risk factors associated with mortality in children with SICF. In previous studies, we revealed that risk factors for morbidity could be obtained within 6 h of onset in patients with SICF [5,8]. Therefore, the aim of the present study was to identify risk factors for mortality acquired within 6 h of onset among children with SICF.

## **PATIENTS AND METHODS**

The present retrospective study was conducted following approval from the Ethics Committee of Hyogo Prefectural Kobe Children's Hospital (KCH) (Kobe, Japan), who waived the requirement for informed consent due to the retrospective nature of the study. We retrospectively reviewed the medical records of consecutive patients (age range: 1 month to 15 years) admitted to the pediatric intensive care unit (PICU) in KCH with SICF between October 2002 and September 2015. KCH provides tertiary pediatric services for the Hyogo prefecture (population: 5.6 million), with a PICU that can provide treatment for patients who require advanced respiratory and/or circulatory support, and for those exhibiting impaired consciousness. We defined SICF as the presence of seizures and/or impaired consciousness accompanied by fever without known etiology such as epilepsy, known metabolic disorders, structural anomalies in the central nervous system (CNS), or CNS infection with pleocytosis (cerebrospinal fluid cells >8 cells/ $\mu$ l). Onset time was defined as the time at which seizure or altered mental state was first observed in conjunction with a temperature >38°C.

### **Methods**

We retrospectively reviewed the medical records, patient characteristics, and the

following clinical data obtained within 6 h of onset: clinical presentation, laboratory data, existence of abnormalities on brain computed tomography (CT) images and therapeutic data. The laboratory data evaluated included white blood cells (WBC), hemoglobin (Hb), platelets (PLT), prothrombin time (PT), aspartate transaminase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), creatine kinase (CK), sodium ( $\text{Na}^+$ ), calcium ( $\text{Ca}^{2+}$ ), glucose (Glu), C-reactive protein (CRP), and lactate (Lac). Although magnetic resonance imaging (MRI) may provide more informative findings [9], only a few patients had undergone MRI. Furthermore, it is impossible to obtain MRI data for critically ill patients. Therefore, MRI findings were not included in our analyses of clinical data. We also evaluated the frequency of intubation, steroid treatment, targeted temperature management (TTM), and the number of anti-epileptic drugs (AEDs) administered within the first 24 hours of disease onset.

Onset was defined as the time at which the patient's neurological symptoms were first observed. Neurological outcomes were defined based on Pediatric Cerebral Performance Category (PCPC) [10] scale scores at the time of discharge. We divided the patients into survivor (PCPC score = 1-5) and non-survivor (PCPC score = 6) groups, following which we compared the data between the two groups. When multiple laboratory values were available due to repeated testing, we chose the first value obtained. Patients who had been diagnosed with AE were further classified

based on the specific syndrome, such as acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) [11]; acute necrotizing encephalopathy (ANE) [12]; acute encephalitis with refractory, repetitive partial seizures (AERRPS) [13]; HSES [3]; and Reye-like syndrome [14].

## **Statistical analysis**

All statistical analyses were performed using EZR (Saitama Medical Center, Jichii Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R Commander designed to add statistical functions frequently used in biostatistics [15]. Univariate analysis was performed in the survivor and non-survivor groups using Fisher's exact tests and Mann-Whitney U-tests. Variables for which significant differences were observed in univariate analyses were subjected to multiple regression analysis, followed by an analysis of Pearson's correlation coefficients. For all statistical analyses, the level of statistical significance was set at  $p < 0.05$ .

## **RESULTS**

### **Patient Characteristics (Table 1)**

A total of 793 children with SICF were admitted to our hospital during the study period. We excluded 112 children with epilepsy, 10 with CNS infection such as meningitis or encephalitis, and three with known metabolic disorders. Consequently, 668 children were enrolled in the present study. Ages ranged from 1 month to 15 years, and the median age was 32 months. The median baseline PCPC score prior to SICF onset was 1. The most common final diagnosis was FS (597 patients, 87.9%), followed by AE (67 patients, 10.0%), acute demyelinating encephalomyelitis (ADEM), and acute cerebellar ataxia. Among the 67 patients with AE, disease subtypes included AESD (n=22), HSES (n=8), AERRPS (n=5), Reye-like syndrome (n=4), and ANE (n=2). In 26 patients, AE could not be classified into a specific syndrome.

### **Summary of non-survivors (Table 2)**

The non-survivor group included nine patients (1.3%; four boys, five girls). Baseline PCPC scores were 1 in five patients, 2 in one patient, 3 in one patient, and 4 in two patients. All patients were diagnosed with AE. Among these patients, disease subtypes included HSES (n=6), Reye-like syndrome (n=2), and ANE (n=1). MOF, shock, and disseminated intravascular coagulation (DIC) were observed in all but two cases (Patients 1 and 2), while brain edema was observed in four patients (Patients 1, 2, 6, and 7). However, it was difficult to identify the exact

causes of death because symptoms appeared suddenly and simultaneously in many cases.

### **Univariate analysis (Table 3)**

There were nine and 659 patients in the non-survivor and survivor groups, respectively. A significant difference in seizure duration was observed between the two groups. However, there was no difference in sex, median age, history of FS, baseline PCPC score, body temperature (BT) on admission, or the presence of convulsion at onset. Head CT was performed in 512 patients of the survivor group and eight patients of the non-survivor group, although we observed no significant differences in the ratio of abnormalities on brain imaging between the two groups. Analyses of laboratory data revealed significant differences between survivors and non-survivors with regard to AST, ALT, LDH, Na<sup>+</sup>, and Lac levels. However, there were no significant differences in WBC, Hb, PLT, PT, CK, Ca<sup>2+</sup>, Glu, or CRP values between the two groups. Analyses of therapeutic interventions revealed significant differences in intubation and steroid use. However, there were no significant differences in the use of TTM or the number of AEDs.

### **Multivariate analysis (Table 4)**

Among the variables in which significant differences were observed in univariate analysis, AST, ALT, and LDH levels were strongly correlated with one another, in accordance with the findings of previous studies [6, 7] (Suppl. Fig. 1, 2). Because AST has often been reported to exhibit a correlation with morbidity [5, 8, 15], we chose to retain AST, although we excluded ALT and LDH. Because intubation and steroid use were used in all severe cases, we excluded these variables as well. So we took AST, Na<sup>+</sup>, Lac, and seizure duration for covariates for the multivariate logistic regression analysis. Thresholds for multivariate analyses were determined as follows: AST > 90 IU/l, Na  $\geq$  136 mEq/l, Lac  $\geq$  2 mmol/l, and duration of convulsion  $\geq$  60 min. Thresholds for AST and seizure duration were determined based on the findings of our previous reports [5, 8]. Thresholds for Na<sup>+</sup> and Lac were determined based on the definition of hyponatremia and the upper limit of the normal range for lactate levels. The multivariate analysis identified AST as a significant independent factor associated with mortality.

## **DISCUSSION**

The present study is the first to identify risk factors for mortality acquired within 6 h of disease onset in children admitted to the hospital with SICF. Although most patients were finally diagnosed with FS or AE, these diagnoses were not made on admission because both FS and AE are

diagnosed based on clinical course and exclusion. Because approximately 5% of AE cases are fatal, and such cases often exhibit a fulminant clinical course, patients must be treated and evaluated prior to diagnosis. Thus, our findings should aid clinicians in making treatment decisions in emergency settings.

Final diagnoses in the non-survivor group included the following AE subtypes: HSES, Reye-like syndrome, and ANE. These findings were consistent with those of previous studies regarding the outcome of each AE subtype [2, 17]. These syndromes are considered systemic disorders in which inflammatory cytokines play a major role. In severe cases, patients may exhibit signs of systemic inflammatory response syndrome, including shock, MOF, and DIC [17]. Inflammatory cytokines cause mitochondrial dysfunction, ultimately leading to organ failure, metabolic dysfunction, and mortality [18]. In various diseases, mitochondrial damage leads to the storage of Lac [18], as well as elevation of liver enzymes due to multiple organ failure [4]. Univariate analyses revealed that elevated levels of AST, Lac, and other enzymes were associated with mortality in the non-survivor group. Multivariate analyses further supported our findings, identifying elevated AST levels as an independent risk factor for mortality. Taken together, these results suggest that MOF occurred due to mitochondrial dysfunction caused by inflammatory cytokines. In addition, regarding screening performance of AST value, the sensitivity and

specificity for the mortality was 56% and 95% respectively. However the purpose of this study is to clarify the risk factors instead of predictors for the mortality of SICF, we found that AST value is not suitable as a predictor because of low sensitivity. Although DIC may be caused by systemic inflammation, we observed no significant difference in PT between the two groups, suggesting that coagulation dysfunction may be undetectable at 6 h from SICF onset.

Univariate analysis revealed that seizure duration was significantly longer in the non-survivor group than in the survivor group, consistent with the findings of previous reports regarding the association between the duration of status epilepticus and morbidity or mortality [20, 21]. However, our multivariate analysis did not identify seizure duration as an independent risk factor for mortality. While this independence may have been lost due to the correlation between seizure duration and Lac levels [22], other research groups have reported that seizure duration is not associated with mortality [23]. Thus, it remains controversial whether the duration of convulsive status epilepticus affects mortality in children [24]. Further studies involving larger samples of patients in the non-survivor group are required.

Univariate analysis revealed that serum Na<sup>+</sup> concentration was higher in non-survivors than in survivors, although multivariate analysis did not identify the absence of hyponatremia (Na<sup>+</sup>  $\geq$ 136 mEq/l) as an independent risk factor for mortality. Six of the nine patients in the non-survivor

group were diagnosed with HSES, which is often accompanied by vomiting and/or diarrhea. Among children with HSES, it is possible that water loss caused by vomiting or diarrhea resulted in higher serum Na<sup>+</sup> concentration in non-survivors than in survivors. In contrast, the median level of Na<sup>+</sup> in survivors was 136 mEq/l, which reflects the lower limit of the normal range [25]. Children with acute illness such as bacterial or viral infection exhibit higher levels of arginine vasopressin (AVP) as well as hyponatremia [26, 27]. In animals, induction of pyrexia increases AVP production and causes hyponatremia [28], and previous studies have indicated that AVP may play a role as an endogenous antipyretic [29]. Because all patients presented with fever in our study, it is possible that insufficient reactive AVP production due to pituitary dysfunction resulted in a higher serum Na<sup>+</sup> concentration in the non-survivor group than the survivor group. Further investigation of AVP levels in patients with AE and/or FS may help to elucidate the mechanisms underlying differences in serum Na<sup>+</sup> concentration between the two groups.

The present study had several limitations. First, patients with FS represented a large portion of the survivor group. These patients do not usually exhibit abnormal laboratory findings in the acute stage, and typically experience favorable outcomes. However, physicians usually manage patients with SICF without distinguishing AE from FS in the early stages of disease, as AE cannot be diagnosed within 6 hours of onset. For this reason, we included patients with FS in the SICF

survivor group in order to investigate early risk factors for mortality among those with SICF. However, the positive and negative predictive values obtained in the present study must be interpreted with caution, as these results may have been influenced by the large number of patients with FS in the survivor group. Nonetheless, the odds ratios, sensitivity, and specificity values were unlikely to be affected by the number of patients with FS, supporting the validity of our study. Second, our investigation was a retrospective study conducted using data from a single institution, and the number of patients was small, especially in the non-survivor group. Because of these limitations, we were only able to investigate the characteristics of the non-survivor group, and we were unable to develop a clinical prediction rule. Further multi-center studies involving larger samples of patients are required to develop such a rule.

In conclusion, our findings demonstrated that elevated AST within 6 h of disease onset was associated with mortality in children with SICF. These findings suggest that fatal cases are associated with systemic inflammatory response syndrome (e.g., shock, MOF, and DIC) caused by mitochondrial dysfunction, which likely occurs due to increases in levels of inflammatory cytokines.

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**Supplemental figure legends**

Supplemental Figure 1. Correlation between ALT and AST using Spearman's rank correlation coefficients. ALT was correlated with AST (correlation coefficient: 0.671;  $p < 0.01$ ). ALT: alanine aminotransferase; AST: aspartate transaminase.

Supplemental Figure 2. Correlation between AST and LDH using Spearman's rank correlation coefficients. LDH was correlated with AST (correlation coefficient: 0.557,  $p < 0.01$ ). ALT: alanine aminotransferase; AST: aspartate transaminase; LDH: lactate dehydrogenase.

## Tables

**Table 1.** Patient characteristics

	n=668
Sex, male	372 (55.7)
Age, months	12 (1-187)
Baseline functional status	
PCPC 1	535 (80.1)
PCPC 2	46 (6.9)
PCPC 3	47 (7.0)
PCPC 4	38 (5.7)
PCPC 5	2 (1.3)
Non-survivors	9 (1.3)
Final diagnosis	
Febrile seizure	597 (87.4)
ADEM	3 (0.4)
Acute cerebellar ataxia	1 (0.1)
Acute encephalopathy/encephalitis	67 (10.0)
AESD	22
HSES	8
AERRPS	5
Reye-like syndrome	4
ANE	2
unclassified	26

PCPC, Pediatric Cerebral Performance Category; ADEM, acute demyelinating encephalomyelitis; AESD, acute encephalopathy with biphasic seizure and late reduced diffusion; HSES, hemorrhagic shock and encephalopathy syndrome; AERRPS, acute encephalitis with refractory, repetitive partial seizures; ANE, acute necrotizing encephalopathy.

Data are shown as the number of children (%).

**Table 2.** Diagnoses in the non-survivor group

Case	Sex	Age (year)	Baseline PCPC	Diagnosis
1	Female	0	1	Reye like syndrome
2	Male	1	1	HSES
3	Male	1	3	HSES
4	Female	4	2	Reye-like syndrome
5	Male	5	4	HSES
6	Female	8	1	HSES
7	Female	8	1	ANE
8	Male	14	1	HSES
9	Female	15	4	HSES

PCPC, Pediatric Cerebral Performance Category; HSES, hemorrhagic shock and encephalopathy syndrome; ANE, acute necrotizing encephalopathy.

Data are shown as the number of children (%) or median (range).

**Table 3.** Univariate analysis

	Survivors (n=659)	Non-survivors (n=9)	<i>p</i> value
Patient characteristics			
Sex, male (n)	368 (56%)	4 (44%)	0.52
Age, months	32 (1-174)	61 (6-180)	0.17
History of FS (n)	243 (37%)	3 (33%)	1.00
PCPC before onset			0.10
PCPC 1	528	5	
PCPC 2	45	1	
PCPC 3	46	1	
PCPC 4	36	2	
PCPC 5	2	0	
BT on admission (°C)	38.7 (35.8-42.0)	39.6 (37.4-41.0)	0.09
Seizure at onset (n)	572 (87%)	6 (67%)	0.08
Seizure duration (min)	40 (1-1240)	184 (65-218)	<0.01
Abnormality on brain imaging (n)	79/512 (15%)	3/8 (38%)	0.12
Laboratory data			
WBC (/μl)	11300 (1700-48400)	14400 (7800-44690)	0.14
Hb (g/dl)	12.2 (8.3-16.7)	12.9 (9.5-14.9)	0.48
PLT (10 <sup>4</sup> /μl)	27.6 (3.9-79.3)	31.1 (3.9-71.1)	0.34
PT (%)	77 (37-139)	47 (30-102)	0.11
AST (IU/l)	34 (13-3186)	125 (44-7230)	<0.01
ALT (IU/l)	15 (5-2191)	83 (22-3410)	<0.01
LDH (IU/l)	288 (80-2294)	463 (232-7650)	<0.01
CK (IU/l)	117 (25-19746)	135 (72-9100)	0.32
Na <sup>+</sup> (mEq/l)	135 (113-146)	142 (136-148)	<0.01
Ca <sup>2+</sup> (mg/dl)	9.3 (7.75-10.9)	10.1 (8.7-10.6)	0.17
Glu (mg/dl)	130 (9-526)	105 (10-382)	0.61
CRP (mg/dl)	0.4 (0.0-13.9)	0.3 (0.0-1.1)	0.72
Lac* (mg/dl)	2.2 (0.6-9.7)	11.5 (6.0-13.8)	<0.01
Therapeutic data			
Intubation (n)	129 (20%)	9 (100%)	<0.01

Steroid use (n)	28 (4%)	6 (67%)	<0.01
TTM (n)	89 (14%)	2 (22%)	0.35
Number of AEDs $\geq$ 3 (n)	120 (18%)	3 (33%)	0.22

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\*Values were analyzed for 485 patients, including five non-survivors.

FS, febrile seizure; PCPC, Pediatric Cerebral Performance Category; BT, body temperature; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; PT, prothrombin time; AST, aspartate transaminase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; Na<sup>+</sup>, sodium; Ca<sup>2+</sup>, calcium; Glu, glucose; CRP, C-reactive protein; Lac, lactate; TTM, targeted temperature management; AED, anti-epileptic drug.

Data are shown as the number (%) or median (range).

**Table 4.** Multivariate logistic regression analysis

Risk factor	OR (95% CI)	<i>p</i> value
AST >90 IU/l	2.03e+01 (2.09-198)	<0.01
Na $\geq$ 136 mEq/l	1.13e+08 (0.00-Inf)	1.00
Lac $\geq$ 2 mmol/l	9.50e+07 (0.00-Inf)	1.00
Seizure duration $\geq$ 60 min	2.78e+08 (0.00-Inf)	1.00

AST, aspartate transaminase; Na, sodium; Lac, lactate; OR, odds ratio; CI, confidence interval.