Prediction of AESD and neurological sequelae in febrile status epilepticus

Nishiyama, Masahiro ; Ishida, Yusuke ; Yamaguchi, Hiroshi ; Tokumoto, Shoichi ; Tomioka, Kazumi ; Hongo, Hiroto ; Toyoshima, Daisaku ;…

(Citation)
Brain and Development,43(5):616-625

(Issue Date)
2021-05

(Resource Type)
journal article

(Version)
Accepted Manuscript

Prediction of AESD and neurological sequelae in febrile status epilepticus

Masahiro Nishiyama[a,*], Yusuke Ishida[b], Hiroshi Yamaguchi[a], Shoichi Tokumoto[a,b], Kazumi Tomioka[a], Hiroto Hongo[b], Daisaku Toyoshima[b], Azusa Maruyama[b], Hiroshi Kurosawa[c], Ryojiro Tanaka[d], Kandai Nozu[a], Kazumoto Iijima[a], Hiroaki Nagase[a]

[a] Department of Pediatrics, Kobe University Graduate School of Medicine, Hyogo, Japan
[b] Department of Neurology, Hyogo Prefectural Kobe Children's Hospital, Hyogo, Japan
[c] Department of Pediatric Critical Care Medicine, Hyogo Prefectural Kobe Children's Hospital, Hyogo, Japan
[d] Department of Emergency and General Pediatrics, Hyogo Prefectural Kobe Children's Hospital, Hyogo, Japan

20 text pages and 2 figures

***Corresponding author:**
Masahiro Nishiyama, M.D., PhD
Department of Pediatrics, Kobe University Graduate School of Medicine, Hyogo, Japan
7-5-2 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan
Tel: +81-78-382-6090, Fax: +81-78-382-6099
E-mail: nishiya@med.kobe-u.ac.jp

Abstract

Objective: The clinical prediction rule (CPR) for acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) was developed with an area under the receiver operating characteristic curve (AUC) of 0.95 – 0.96. Our objective was to verify the AESD CPR in a new cohort and compare the utilities of three CPRs of acute encephalopathy: the Tada, Yokochi, and Nagase criteria.

Methods: We reviewed the clinical data and medical charts of 580 consecutive patients (aged < 18 years) with febrile convulsive status epilepticus lasting for ≥ 30 min in 2002 – 2017 and measured the performance of the CPRs in predicting AESD and sequelae.

Results: The CPRs predicted AESD with an AUC of 0.84 – 0.88. The Tada criteria predicted AESD with a positive predictive value (PPV) of 0.25 and a negative predictive value (NPV) of 0.99. The Yokochi criteria predicted AESD with a PPV and NPV of 0.20 and 0.95, respectively, after 12 hours. The Nagase criteria predicted AESD with a PPV and NPV of 0.14 and 1.00, respectively, after 6 hours. The PPVs of the Tada, Yokochi, and Nagase criteria for sequelae were 0.28, 0.28, and 0.17, respectively; the corresponding NPVs were 0.97, 0.95, and 0.98, respectively.

Conclusions: The effectiveness of the AESD CPR in a new cohort was lower than that in the derivation study. CPRs are not sufficient as diagnostic tests, but they are useful as screening tests. The Nagase criteria are the most effective for screening among the three CPRs due to their high NPV and swiftness.

Keywords: acute encephalopathy with biphasic seizures and late reduced diffusion; children; clinical prediction rule; convulsion; pediatrics; prognosis; seizure

1. Introduction

Acute encephalopathy is a brain dysfunction usually caused by viral infections in childhood [1, 2]. National surveillance has shown that among several acute encephalopathy syndromes, acute encephalopathy with biphasic seizures and late reduced diffusion (AESD) is the most common syndrome (34 % of the total cases) in Japan [3, 4]. Acute encephalopathy causes neurological sequelae and death in 35 % and 5 % of cases, respectively [3]. In particular, 61 % of AESD cases involved neurological sequelae [3]. Initial neurological symptoms in AESD are usually febrile status epilepticus lasting more than 30 min [4, 5]. In contrast, most febrile status epilepticus cases do not develop AESD or neurological sequelae.

Based on the above, a clinical prediction rule (CPR), which is a mathematical tool with combinations of multiple clinical findings or tests to predict the probability of a diagnosis or prognosis [6, 7], was developed for AESD or neurological sequelae [8-10]. The Tada criteria is a CPR that predicts AESD with 89 % sensitivity and 90 % specificity [9]. The Yokochi criteria is another CPR that predicts AESD with 93 % sensitivity and 91 % specificity [10]. Lastly, the Nagase criteria is a CPR that predicts neurological sequelae for acute encephalopathy with 94 % sensitivity and 67 % specificity [8]. Several biomarkers or prognostic factors have also been reported to predict AESD or neurological sequelae in acute encephalopathy [11-17]. However, the accuracy of these CPRs or biomarkers is yet to be verified in other populations. Moreover, the predictive accuracy or usefulness of these CPRs is yet to be compared.

Therefore, the primary objective of this study was to verify AESD CPR in a new patient population. Moreover, we also completed secondary analyses to compare the predictive accuracy and utility of the Tada, Yokochi, and Nagase criteria to predict AESD or neurological sequelae.

2. Materials and Methods

2.1. Study design and patients

This study was conducted under the approval of the Ethics Committee of Kobe University Graduate School of Medicine and Kobe Children's Hospital, with a waiver for informed consent owing to the design of the observational study.

We retrospectively analyzed data collected from consecutive patients (aged < 18 years) who were admitted to the Kobe Children's Hospital with febrile convulsive status epilepticus lasting for ≥ 30 min between October 2002 and December 2017. Patients with neurological histories (epilepsy, intellectual disability, developmental delay, or chromosomal

abnormality), meningoencephalitis (cerebrospinal fluid cells > 8 cells/μl), sepsis, or symptomatic hyponatremia were excluded from this study (Figure 1). Most data were obtained from our database, which consisted of prospectively collected data on demographics, clinical presentation, treatments, laboratory findings, and prognosis. We also reviewed the medical charts and collected data on clinical presentation and laboratory findings for this study.

2.2. Definitions

The diagnosis of acute encephalopathy and AESD was based on the clinical consensus and guidelines for acute encephalopathy in children [2, 3]. Briefly, acute encephalopathy was diagnosed according to the following criteria: 1) acute onset of impaired consciousness following a preceding infection, and 2) exclusion of well-defined intracerebral inflammation. AESD was diagnosed based on the following criteria: 1) the disease develops during the fever stage of the infection; 2) convulsions develop on the same day or the day post fever onset; 3) convulsions recur, or consciousness deteriorates 3 – 7 days following disease onset; 4) high signal intensity in the subcortical white matter or cortex is seen on diffusion-weighted imaging 3 – 14 days following disease onset; 5) residual lesions or atrophy are confirmed using computed tomography (CT), magnetic resonance imaging (MRI), or decreased blood flow on a single-photon emission CT (SPECT) 2 weeks following disease onset. AESD was diagnosed if criteria 3) and/or 4) and/or 5) were met in addition to criteria 1) and 2). Neurological performance was assessed using the Pediatric Cerebral Performance Category (PCPC) scale, with a score of 1 representing normal performance; 2, mild disability; 3, moderate disability; 4, severe disability; 5, persistent vegetative state; 6, death [18]. Patients with a PCPC score ≥ 2 at baseline were categorized as having a neurological history and were excluded from the study. Therefore, the PCPC score at baseline was 1 in all eligible patients. Neurological sequelae were defined as a PCPC score ≥ 2 at 1 month post onset. Seizure onset was defined as the beginning of any neurological symptoms, including convulsion [19]. Convulsive seizure was defined as a persistent convulsion or a sequence of intermittent convulsions without full recovery of consciousness between the convulsions [20]. A convulsion was preceded by a non-convulsive seizure in some patients, although all individuals had a convulsive seizure lasting for 30 min. Initial blood examinations were performed following seizure onset. If the patient was referred from another hospital, data from the previous hospital were analyzed.

2.3. CPRs and scoring modifications

Three CPRs (Tada, Yokochi, and Nagase criteria) were used as previously reported [8-10]. In brief, the Tada criteria consisted of 7 variables [consciousness level 12–24 hours after seizures,

score 0, 2, or 3; age, score 0 or 1; duration of convulsions, score 0 or 1; mechanical ventilation, score 0 or 1; serum aspartate aminotransferase (AST) on admission, score 0 or 1; serum glucose on admission, score 0 or 1; serum creatinine on admission, score 0 or 1; total score 0 – 9]. Yokochi criteria consisted of 6 variables [consciousness level 11 hours post seizures, score 0 or 2; serum pH, score 0 or 1; serum alanine aminotransferase (ALT), score 0 or 2; serum glucose, score 0 or 2; serum creatinine, score 0 or 1; serum ammonia, score 0 or 2; total score 0 – 10]. Nagase criteria consisted of 3 variables (refractory status epilepticus, score 0 or 1; consciousness level 6 hours from onset, score 0 or 1; serum AST within 6 hours of onset, score 0 or 1; Total score 0 – 3).

Originally, patients with a Glasgow Coma Scale (GCS) of 15 or Japan Coma Scale (JCS) of 0 at 12 – 24 hours post seizures received a Tada score of 0. Patients with a GCS 14 – 9 or JCS 1 – 30 at 12 – 24 hours post seizures received a Tada score of 2. Patients with a GCS of 8 – 3 or JCS of 100 – 300 at 12 – 24 hours post seizures received a Tada score of 3. However, since we could not identify the GCS or JCS between 12 and 24 hours post seizures, we modified the Tada criteria as follows: First, consciousness level was categorized as alert (GCS 15) or impaired consciousness (GCS 3 – 14) 12 hours post seizures; second, alert consciousness was scored as 0, and impaired consciousness was scored as 2; as a result, the total score was set as 0 – 8. Originally, Yokochi criteria led to scores of 0 or 2 in patients with alert (GCS 15) or impaired consciousness (GCS 3 – 14) 11 hours post seizures. However, because we could not identify consciousness levels 11 hours post seizures, we modified the Yokochi criteria as follows: Consciousness level was categorized as alert (GCS 15) or impaired consciousness (GCS 3 – 14) 12 hours post seizures. Finally, to be more comprehensible and clinically useful, serum variables were evaluated and scored only at the initial blood examinations after seizures. If serum variables were not included in the initial blood examinations, the variables were treated as a deficit.

2.4. Primary analyses

To verify the AESD CPRs in a new patient population, we applied the Tada criteria and Yokochi criteria to cohort A. To match the derivation studies with our study, we excluded patients with acute encephalopathy except AESD. Therefore, cohort A consisted of 322 patients who were admitted to the hospital between October 2002 and December 2017 and who were diagnosed with AESD (n = 27) or febrile seizure (n = 295) at discharge from the hospital (Figure 1).

We tried to score the Tada and Yokochi criteria in all patients; however, the scores were not identified in several patients, especially when applying the Yokochi criteria to our cohort. We excluded patients without complete scoring from the analysis.

We plotted an empirical receiver operating characteristic (ROC) curve and calculated its area under the curve (AUC) to predict AESD. The threshold was determined from the ROC curve. We calculated AESD CPR performance (sensitivity and specificity) using the threshold determined above. We also calculated AESD CPR performance using the original threshold (Tada criteria 4 points; Yokochi criteria 4 points).

2.5. Secondary analyses

We compared the predictive accuracy and utility of the Tada, Yokochi, and Nagase criteria to predict AESD or neurological sequelae. The Nagase criteria were originally developed by analyzing patients between October 2002 and December 2008. Therefore, we applied each CPR to cohort B for the prediction of AESD or neurological sequelae. Cohort B consisted of 254 patients who were admitted to the hospital between January 2009 and December 2017 (Figure 1).

We tried to obtain a score for each CPR in all patients; however, scores were not identified in several patients, especially when applying the Yokochi criteria. We excluded patients without complete scoring from the analysis. Therefore, 220, 146, and 245 patients were finally analyzed with respect to the Tada, Yokochi, and Nagase criteria, respectively. We compared the characteristics of eligible patients who met the Tada (n = 220), Yokochi (n = 146), and Nagase criteria (n = 245). We calculated the AESD prediction performance (sensitivity, specificity, predictive values, and likelihood ratios) and neurological sequelae prediction performance (sensitivity, specificity, predictive values, and likelihood ratios) using the original threshold (Tada criteria 4 points; Yokochi criteria 4 points; Nagase criteria 1 point).

2.5. Statistical Analysis

All analyses were performed using JMP® 11 (SAS Institute Inc., Cary, NC, USA). Results are expressed as numbers (%), medians [interquartile range (IQR) (1st quartile – 3rd quartile)] or means [standard deviation (SD) (± SD)]. The numerical data were compared using a Mann-Whitney U test or Kruskal-Wallis test. Categorical data were compared using a Fisher's exact test or Pearson's chi-square test. P-value < 0.05 was considered statistically significant.

3. Results

3.1. Primary analyses

3.1.1 Eligible patients

Of 322 patients in cohort A who were admitted to the hospital between October 2002 and December 2017, 276 and 171 patients, respectively, met the Tada and Yokochi criteria. As ammonia (n = 121), pH (n = 52), and creatinine (n = 31) were not evaluated in the initial blood examination, a few patients were missing for complete scoring. The characteristics of the eligible patients are presented in Table 1.

Table 1. The characteristics of eligible patients applied to the Tada and Yokochi criteria for each clinical parameter in cohort A.

	Tada criteria (n = 276)	Yokochi criteria (n = 171)
Age, months	23.9 (16.2–43.0)	22.7 (15.8–43.8)
Sex		
Male	139 (50.4)	86 (50.3)
Female	137 (49.6)	85 (49.7)
Convulsive seizure duration, minute	63 (45–118)	60 (44–99)
Level of consciousness		
Full recovery within 6 hours	165 (59.8)	109 (63.7)
Full recovery within 12 hours	39 (14.1)	23 (13.5)
Absence of full recovery at 12 hours	72 (26.1)	39 (22.8)
Initial blood examination		
AST (IU/l)	37 (31–47)	38 (30–48)
ALT (IU/l)	15 (13–20)*	15 (13–20)
Cre (mg/dl)	0.29 (0.25–0.35)	0.29 (0.24–0.34)
Glu (mg/dl)	154 (115–196)	143 (114–190)
Ammonia (μg/dl)	58 (44–72)**	57 (44–71)
pH	7.31 (7.18–7.38)***	7.33 (7.24–7.38)
Mechanical ventilation	66 (23.9)	34 (19.9)
Final diagnosis		
AESD	23 (8.3)	12 (7.0)
Febrile seizure	253 (91.7)	159 (93.0)
Neurological sequelae	20 (7.2)	10 (5.8)

Data are presented as numbers (%) or medians (interquartile range).

AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cre, creatinine; Glu, glucose

*n = 275, **n = 187, ***n = 249

3.1.2 Validation of Tada criteria

Among the 276 patients in whom the Tada score was applied, 8.3 % developed AESD. The median age of patients was 23.9 months (IQR, 16.2 – 43.0). The mean age of patients with AESD and febrile seizure was 32.2 months (SD, ± 37.6) and 36.1 months (SD, ± 31.0), respectively. The number of males was 139 (50.4 %). The median duration of convulsive seizure was 63 min (IQR, 45 – 118). Neurological sequelae were identified in 20 patients

(7.2 %). The ROC curve for predicting AESD using the Tada criteria is presented in Figure 2a. The AUC was 0.882. The cut-off value determined from the ROC curve was 4, similar to that in the derivation study. The sensitivity and specificity were 91.3 % and 75.5 %, respectively. The mean scores of Tada criteria in AESD and febrile seizure were 5.4 (SD, ± 1.5) and 2.5 (SD, ± 1.8), respectively.

3.1.3 Validation of Yokochi criteria

Among the 171 patients in whom the Yokochi score was applied, 7.0 % developed AESD. The median age of patients was 22.7 months (IQR, 15.8 – 43.8). The median age of patients with AESD and febrile seizure was 20.0 months (IQR, 18.0 – 39.4) and 22.8 months (IQR, 15.8 – 46.4), respectively. The number of males was 86 (50.3 %). The median duration of convulsive seizure was 60 min (IQR, 44 – 99). Neurological sequelae were identified in 10 patients (5.8 %). The ROC curve for predicting AESD using the Yokochi criteria is presented in Figure 2b. The AUC was 0.840. The cut-off value determined from the ROC curve was 2. The sensitivity and specificity were 91.7 % and 65.0 %, respectively. The sensitivity was 50.0% and the specificity was 86.2 % using the threshold that was applied in the derivation study (4 points). The mean scores of Yokochi criteria in AESD and febrile seizure were 4.0 (SD, ± 2.0) and 1.5 (SD, ± 1.9), respectively.

3.2. Secondary analyses

3.2.1 Comparison of characteristics in eligible patients

Of 254 patients in cohort B who were admitted to the hospital between January 2009 and December 2017, the Tada, Yokochi, and Nagase criteria were applied to was 220, 146, and 245 patients, respectively. The characteristics of the eligible patients are presented in Table 2. The characteristics of eligible patients were not significantly different among the three groups. The proportion of patients with AESD was 8.6 % in the Tada criteria group, 7.5 % in the Yokochi criteria group, and 7.8 % in the Nagase criteria group. The proportion of neurological sequelae was 10.5 % in the Tada criteria group, 8.9 % in the Yokochi criteria group, and 10.2 % in the Nagase criteria group.

Table 2. Comparison of the characteristics of eligible patients the Tada, Yokochi, and Nagase criteria as applied to each clinical parameter in cohort B.

	Tada criteria (n = 220)	Yokochi criteria (n = 146)	Nagase criteria (n = 245)	P-Value
Age, months	23.5 (16.4–46.0)	23.0 (15.9–48.2)	23.0 (16.3–43.8)	0.755
Sex				0.862
Male	108 (49.1)	72 (49.3)	115 (46.9)	
Female	112 (50.9)	74 (50.7)	130 (53.1)	
Convulsive seizure duration, minute	63 (45–110)	58 (44–92)	65 (46–117)	0.200
Level of consciousness				0.846
Full recovery within 6 hours	137 (62.3)	96 (65.8)	149 (60.8)	
Full recovery within 12 hours	24 (10.9)	17 (11.6)	28 (11.4)	
Absence of full recovery at 12 hours	59 (26.8)	33 (22.6)	68 (27.8)	
Initial blood examination				
AST (IU/l)	38 (31–48)	38 (30–48)	38 (31–48)[#]	0.843
ALT (IU/l)	15 (13–20)[*]	15 (13–20)	15 (13–20)[##]	0.996
Cre (mg/dl)	0.28 (0.25–0.35)	0.28 (0.24–0.34)	0.28 (0.25–0.35)[###]	0.939
Glu (mg/dl)	146 (114–198)	144 (114–190)	146 (114–198)[####]	0.867
Ammonia (μg/dl)	59 (46–74)[**]	59 (46–75)	59 (46–76)[#####]	0.982
pH	7.30 (7.13–7.38)[***]	7.32 (7.19–7.38)	7.30 (7.10–7.38)[######]	0.356
Mechanical ventilation	59 (26.8)	29 (19.9)	70 (28.6)	0.151
Final diagnosis				0.912
AESD	19 (8.6)	11 (7.5)	19 (7.8)	
Febrile seizure	189 (85.9)	127 (87.0)	212 (86.5)	
Acute encephalopathy except AESD	12 (5.5)	8 (5.5)	14 (5.7)	
Neurological sequelae	23 (10.5)	13 (8.9)	25 (10.2)	0.880

Data are presented as numbers (%) or medians (interquartile range).

AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cre, creatinine; Glu, glucose

[*]n = 219, [**]n = 153, [***]n = 205, [#]n = 227, [##]n = 226, [###]n = 223, [####]n = 222, [#####]n = 154, [######]n = 210

3.2.2 Comparison of predictive accuracy for AESD

Table 3 presents the predictive accuracy of AESD. The AUC to predict AESD by Tada, Yokochi, Nagase criteria was 0.864, 0.830, and 0.786, respectively (Supplementary Figure). The ROC curve identified that the optimal threshold was 2 points in the Yokochi criteria (Supplementary Figure). However, we calculated the AESD prediction performance

(sensitivity, specificity, predictive values, and likelihood ratios) using the original threshold (Tada criteria 4 points; Yokochi criteria 4 points; Nagase criteria 1 point).

Among the 220 patients who met the Tada criteria, 69 (31 %) met ≥ 4 points. Sensitivity and specificity were 89 % and 74 %, respectively. The positive predictive value (PPV) and negative predictive value (NPV) were 25% and 99%, respectively. The positive likelihood ratio (LR+) and negative likelihood ratio (LR-) were 3.46 and 0.14, respectively. Among the 146 patients who met the Yokochi criteria, 25 (17%) met ≥ 4 points. Sensitivity and specificity were 46 % and 85 %, respectively. PPV and NPV were 20 % and 95 %, respectively. LR+ and LR- were 3.07 and 0.64, respectively. Among the 245 patients who met the Nagase criteria, 132 (54%) met ≥ 1 point. Sensitivity and specificity were 100 % and 50 %, respectively. PPV and NPV were 14 % and 100 %, respectively. LR+ and LR- were 2.00 and 0.00, respectively.

Table 3. Comparison of the predictive accuracy for AESD among the Tada, Yokochi, and Nagase criteria in cohort B.

	Tada criteria (n = 220)		Yokochi criteria (n = 146)		Nagase criteria (n = 245)	
	AESD	Non-AESD	AESD	Non-AESD	AESD	Non-AESD
Criteria positive	17	52	5	20	19	113
Criteria negative	2	149	6	115	0	113
	Value	95 % CI	Value	95 % CI	Value	95 % CI
Sensitivity	0.89	0.70–0.97	0.46	0.22–0.71	1.00	0.84–1.00
Specificity	0.74	0.72–0.75	0.85	0.83–0.87	0.50	0.49–0.50
PPV	0.25	0.19–0.27	0.20	0.10–0.31	0.14	0.12–0.14
NPV	0.99	0.96–1.00	0.95	0.93–0.97	1.00	0.97–1.00
LR+	3.46	2.52–3.86	3.07	1.32–5.53	2.00	1.63–2.00
LR-	0.14	0.04–0.42	0.64	0.34–0.94	0.00	0.00–0.33

AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value

3.2.3 Comparison of predictive accuracy for neurological sequelae

Table 4 presents the predictive accuracy for neurological sequelae. The AUC to predict neurological sequelae by Tada, Yokochi, and Nagase criteria was 0.817, 0.850, and 0.799, respectively (Supplementary Figure). The ROC curve identified that the optimal threshold was 2 points in the Yokochi criteria (Supplementary Figure). However, we calculated the

neurological sequelae prediction performance (sensitivity, specificity, predictive values, and LRs) in the original threshold (Tada criteria 4 points; Yokochi criteria 4 points; Nagase criteria 1 point).

Among the 220 patients who met the Tada criteria, 69 (31 %) met ≥ 4 points. Sensitivity and specificity were 83 % and 75 %, respectively. PPV and NPV were 28 % and 97 %, respectively. LR+ and LR- were 3.26 and 0.23, respectively.

Among the 146 patients who met the Yokochi criteria, 25 (17%) met ≥ 4 points. Sensitivity and specificity were 54% and 87%, respectively. PPV and NPV were 28 % and 95 %, respectively. LR+ and LR- were 3.98 and 0.53, respectively.

Among the 245 patients who met the Nagase criteria, 132 (54%) met ≥ 1 point. Sensitivity and specificity were 92 % and 50 %, respectively. PPV and NPV were 17 % and 98 %, respectively. LR+ and LR- were 1.86 and 0.16, respectively.

Table 4. Comparison of the predictive accuracy for neurological sequelae among the Tada, Yokochi, and Nagase criteria in cohort B.

	Tada criteria (n = 220)		Yokochi criteria (n = 146)		Nagase criteria (n = 245)	
	Sequelae	Non-sequelae	Sequelae	Non-sequelae	Sequelae	Non-sequelae
Criteria positive	19	50	7	18	23	109
Criteria negative	4	147	6	115	2	111
	Value	95% CI	Value	95% CI	Value	95% CI
Sensitivity	0.83	0.64–0.93	0.54	0.31–0.75	0.92	0.76–0.98
Specificity	0.75	0.73–0.76	0.87	0.84–0.89	0.50	0.49–0.51
PPV	0.28	0.21–0.31	0.28	0.16–0.39	0.17	0.14–0.19
NPV	0.97	0.95–0.99	0.95	0.93–0.97	0.98	0.95–0.99
LR+	3.26	2.33–3.84	3.98	1.93–6.60	1.86	1.48–2.00
LR-	0.23	0.09–0.49	0.53	0.28–0.83	0.16	0.04–0.50

CI, confidence interval; LR+, positive likelihood ratio; LR-, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value

4. Discussion

4. 1. Validation of AESD CPRs

The performance of AESD CPRs has now been verified in a new patient population. The AUC of ROC curve for predicting AESD according to the Tada criteria was 0.88, and it was 0.84 in our cohort according to the Yokochi criteria. These results indicate that the accuracy levels of both AESD CPRs are relatively low compared to the findings in the derivation study (Tada, AUC 0.95; Yokochi, AUC 0.96) [9, 10]. Validation studies typically show a reduction in accuracy compared to that in the original study [6]. However, there might be additional reasons for the reduction in accuracy in our cohort.

The population in this study was equivalent to those in the CPR derivation studies to some extent. The characteristics of the derivation cohort have been reported previously [9, 10]. Briefly, in the derivation cohort for the Tada criteria, the proportion of males was 50 %; the mean ages of AESD patients and febrile seizure patients were 1.7 years and 2.5 years, respectively; and the median seizure durations in AESD and febrile seizure were 58 min and 35 min, respectively [9]. In the derivation cohort for the Yokochi criteria, the proportion of males was 57 %; the median ages of AESD patients and febrile seizure patients were 19 months and 23 months, respectively; and the median seizure durations in AESD and febrile seizures were 50 min and 40 min, respectively [10]. The characteristics of patients (age, sex, seizure duration, blood test findings, and mechanical ventilation) were similar between our study and the derivation studies. However, a few population components are different. First, our cohort consisted of consecutive patients with febrile convulsive status epilepticus without past neurological histories in a single institution. In contrast, the population in the Tada study consisted of AESD patients from more than 10 institutions and febrile seizure patients in one institution. These population differences might affect the accuracy of the CPRs. Nevertheless, our results can be directly applied to real-world clinical settings due to the consecutive characteristics in our cohort. Eligible patients in the Yokochi study were consecutive patients; however, 25 % of the population in the Yokochi study had past neurologic diseases, including epilepsy, intellectual disability, cerebral palsy, or hypoplasia of the corpus callosum. Therefore, these differences might have affected the results. We excluded patients with neurological histories in this study to make the characteristics uniform and to avoid the misevaluation of neurological performance and consciousness level.

It is also possible that the modifications we applied to the scoring might have affected the results. Given that we could not identify the GCS or JCS after 12–24 hours, we chose to modify the scoring of consciousness according to the Tada criteria. That is, we gave patients a score of 0 in cases where they were alert at 12 hours and a score of 2 in cases of impaired consciousness. Although the earlier scoring is useful for clinical management, it might reduce the accuracy of CPRs.

The mean scores of the Tada criteria in this study were similar to those in the original study (this study, 5.4 for AESD and 2.5 for febrile seizure; Tada study, 5.9 for AESD and 1.8 for febrile seizure). In contrast, the mean Yokochi scores in this study seem to be lower than

those in the original study (this study, 4.0 in AESD and 1.5 in febrile seizure; Yokochi study, exact data not shown, but the score ≥ 4 in 14 out of 15 AESD cases). The optimal cut-off value was also different (this study, 2 points; Yokochi study, 4 points). The major reason for the score differences might depend on blood sampling because five of the six variables in the Yokochi criteria were laboratory findings. The timing of blood sampling is also important because laboratory data, including AST, ALT, glucose, creatinine, ammonia, and pH, dynamically change within a few hours of acute encephalopathy [21, 22]. Importantly, it is mentioned in the Yokochi study that "*We selected a set of laboratory data that can be measured in any institution and has a short analysis time.*" [10]. Nevertheless, it is possible to select some laboratory findings from the second or third sampling after seizure onset.

4. 2. Comparison of CPRs with AESD and neurological sequelae

The predictive accuracy levels of the three CPRs for AESD or neurological sequelae are not perfect as diagnostic tests. Effective CPR for diagnostic tests needs reliability, high specificity, and high PPV [7]. However, the PPV of the Tada criteria for AESD and neurological sequelae were 25 % and 28 %, respectively. Furthermore, the PPV of the Yokochi and Nagase criteria was lower than that of the Tada criteria. In contrast, the Tada and Nagase criteria are effective for screening AESD and neurological sequelae. An effective screening test is simple and has high sensitivity and high NPV [7]. Therefore, the Nagase criteria are the most effective among the three CPRs for screening AESD and neurological sequelae. In contrast, the Yokochi criteria are less effective for screening tests because of their relatively low NPV. In addition, the limited number of applied samples to Yokochi criteria (n = 146) indicated relative complexity.

For CPRs to be useful to clinicians, clarity regarding which patients the CPRs can be applied to is also important. Secondary analyses were conducted on febrile convulsive status epilepticus lasting for ≥ 30 min, including acute encephalopathy and excluding AESD. Therefore, the findings in this study can be applied to almost all cases of febrile convulsive status epilepticus not involving a neurological history.

The Tada and Yokochi criteria were developed as AESD CPRs, whereas the Nagase criteria were developed as a neurological sequelae CPR. However, the predictive performance for AESD or neurological sequelae was the same across the three CPRs. These findings indicate the existence of an overlap between AESD and neurological sequelae in these conditions, and these three CPRs could be applied for both predictions.

For the clinical application of CPRs, the presence or absence of effective treatments is also important. The presence of effective treatments to improve prognosis or less invasive therapies supports the more aggressive application of CPRs as decision-making tools. Various therapies such as steroids, targeted temperature management, dextromethorphan, cyclosporine,

and mitochondrial cocktails have been employed in an attempt to improve the prognosis of acute encephalopathy including AESD [23-29]. However, currently there is no effective therapy with a high level of supporting evidence. The clinical acceptance of CPRs as decision-making tools depends on the number needed to treat (NNT) [30]. Effective treatments improve the NNT; therefore, the utility of those CPRs improve. For example, CPR within 6 hours after birth predicted death or disability with PPV of 52 % in neonatal hypoxic-ischemic encephalopathy [31]. PPV on CPR with neonatal hypoxic-ischemic encephalopathy is much higher than CPRs with acute encephalopathy, but not perfect. Nevertheless, therapeutic hypothermia reduces death or severe disability with an NNT of 9, and this treatment is widely used in neonatal hypoxic conditions based on CPR within 6 hours after birth [31]. In the condition of febrile status epilepticus, current CPRs with low PPV of 17% – 28 % are only acceptable to start treatments on the premise of treatments with high efficacy or those with rare significant adverse event. For neuroprotection, early initiation of therapies is also important. Therapeutic hypothermia for post-cardiac arrest and neonatal hypoxic-ischemic encephalopathy is effective when induced within 6 hours of onset [32]. Hypothermia in convulsive status epilepticus has also been attempted by induction within 8 hours of onset, although randomized controlled trials failed to show the effectiveness of this technique [33]. For earlier decision making, the Nagase criteria are superior to others because the scoring is performed 6 hours post onset.

4.3. Limitations

As mentioned previously, one of the major limitations of the study is the difference in population recruitment between the derivation studies and this study. Unlike the original studies, our population included consecutive patients without a past neurological history. However, in this population, we were able to calculate the PPV and NPV, which clinicians will easily be able to apply to the CPRs in their patients. Second, we modified the scoring of the Tada and Yokochi criteria, which might have affected the performance of the CPRs. However, this modification allows for an earlier scoring after seizure onset. Third, when we compared the characteristics in our cohort with those in the derivation studies, we were unable to perform statistical analyses because some of the data from the derivation studies were unavailable. Finally, this study was conducted in a single institution. Treatment strategies in our institution could affect the results. Therefore, the findings in this study will not be directly applicable to other populations. Multicenter validation studies are necessary in the future.

4.4. Conclusions

The performance of two AESD CPRs was further verified in a new patient population. However, the accuracy of the two AESD CPRs was found to be lower than that of the derivation studies, indicating that the effectiveness of these CPRs is smaller than those in the original study.

The PPV and NPV to predict AESD or neurological sequelae in children with febrile convulsive status epilepticus were also identified. A comparison among the three CPRs regarding acute encephalopathy suggests important findings. First, these three CPRs are not sufficient as diagnostic tests in the absence of effective treatment for AESD or other types of acute encephalopathies. Second, the Nagase criteria are the most effective for screening AESD and neurological sequelae among the three CPRs because of their high NPV, simplicity, and swiftness. Additional research is needed to optimize CPR use in clinical practice and to validate its effect on clinical outcomes.

Acknowledgments

We thank Dr. Yusuke Seino, Kazunori Aoki, Naoko Tanizawa, Satoshi Matsui, Shinsuke Kajihara, Mayumi Kusumoto, Takuro Hayashi, Yoshimichi Yamaguchi, Hiroki Takeda, and other doctors in the Department of Pediatric Critical Care Medicine and Department of Emergency and General Pediatrics of Hyogo Prefectural Kobe Children's Hospital for treating the patients. We also thank the Clinical and Translational Research Center of Kobe University for the statistical analysis of the data. We would like to thank Editage (www.editage.com) for English language editing.

This work was partly supported by a Grant-in-Aid for Young Scientists (B) (18K15711) of JSPS KAKENHI and a Grant-in-Aid for Research on Measures for Intractable Diseases (H30-Nanji-Ippan-007) from the Ministry of Health, Labour and Welfare.

Conflicts of interest

The authors declare no conflicts of interest.

References

[1] Mizuguchi M, Yamanouchi H, Ichiyama T, Shiomi M. Acute encephalopathy associated with influenza and other viral infections. Acta Neurol Scand 2007;115:45-56.

[2] Mizuguchi M, Ichiyama T, Imataka G, Okumura A, Goto T, Sakuma H, et al. Guidelines for the diagnosis and treatment of acute encephalopathy in childhood. Brain Dev. 2021;43:2-31.

[3] Kasai M, Shibata A, Hoshino A, Maegaki Y, Yamanouchi H, Takanashi JI, et al. Epidemiological changes of acute encephalopathy in Japan based on national surveillance for 2014–2017. Brain Dev 2020;42:508-14.

[4] Takanashi J, Oba H, Barkovich AJ, Tada H, Tanabe Y, Yamanouchi H, at al. Diffusion MRI abnormalities after prolonged febrile seizures with encephalopathy. Neurology 2006;66:1304-9.

[5] Yamaguchi H, Nishiyama M, Tokumoto S, Ishida Y, Tomioka K, Aoki K, et al. Detailed characteristics of acute encephalopathy with biphasic seizures and late reduced diffusion: 18-year data of a single-center consecutive cohort. J Neurol Sci 2020;411:116684.

[6] Adams ST, Leveson SH. Clinical prediction rules. BMJ 2012;344:d8312.

[7] Cowley LE, Farewell DM, Maguire S, Kemp AM. Methodological standards for the development and evaluation of clinical prediction rules: a review of the literature. Diagn Progn Res 2019;3:16.

[8] Nagase H, Nakagawa T, Aoki K, Fujita K, Saji Y, Maruyama A, et al. Therapeutic indicators of acute encephalopathy in patients with complex febrile seizures. Pediatr Int 2013;55:310-4.

[9] Tada H, Takanashi JI, Okuno H, Kubota M, Yamagata T, Kawano G, et al. Predictive score for early diagnosis of acute encephalopathy with biphasic seizures and late reduced diffusion (AESD). J Neurol Sci 2015;358:62-5.

[10] Yokochi T, Takeuchi T, Mukai J, Akita Y, Nagai K, Obu K, et al. Prediction of acute encephalopathy with biphasic seizures and late reduced diffusion in patients with febrile status epilepticus. Brain Dev 2016;38:217-24.

[11] Hosoya M, Kawasaki Y, Katayose M, Sakuma H, Watanabe M, Igarashi E, et al. Prognostic predictive values of serum cytochrome c, cytokines, and other laboratory measurements in acute encephalopathy with multiple organ failure. Arch Dis Child 2006;91:469-72.

[12] Hayashi N, Okumura A, Kubota T, Tsuji T, Kidokoro H, Fukasawa T, et al. Prognostic factors in acute encephalopathy with reduced subcortical diffusion. Brain Dev 2012;34:632-9.

[13] Tsukahara H, Fujii Y, Matsubara K, Yamada M, Nagaoka Y, Saito Y, et al. Prognostic value of brain injury biomarkers in acute encephalitis/encephalopathy. Pediatr Int 2013;55:461-4.

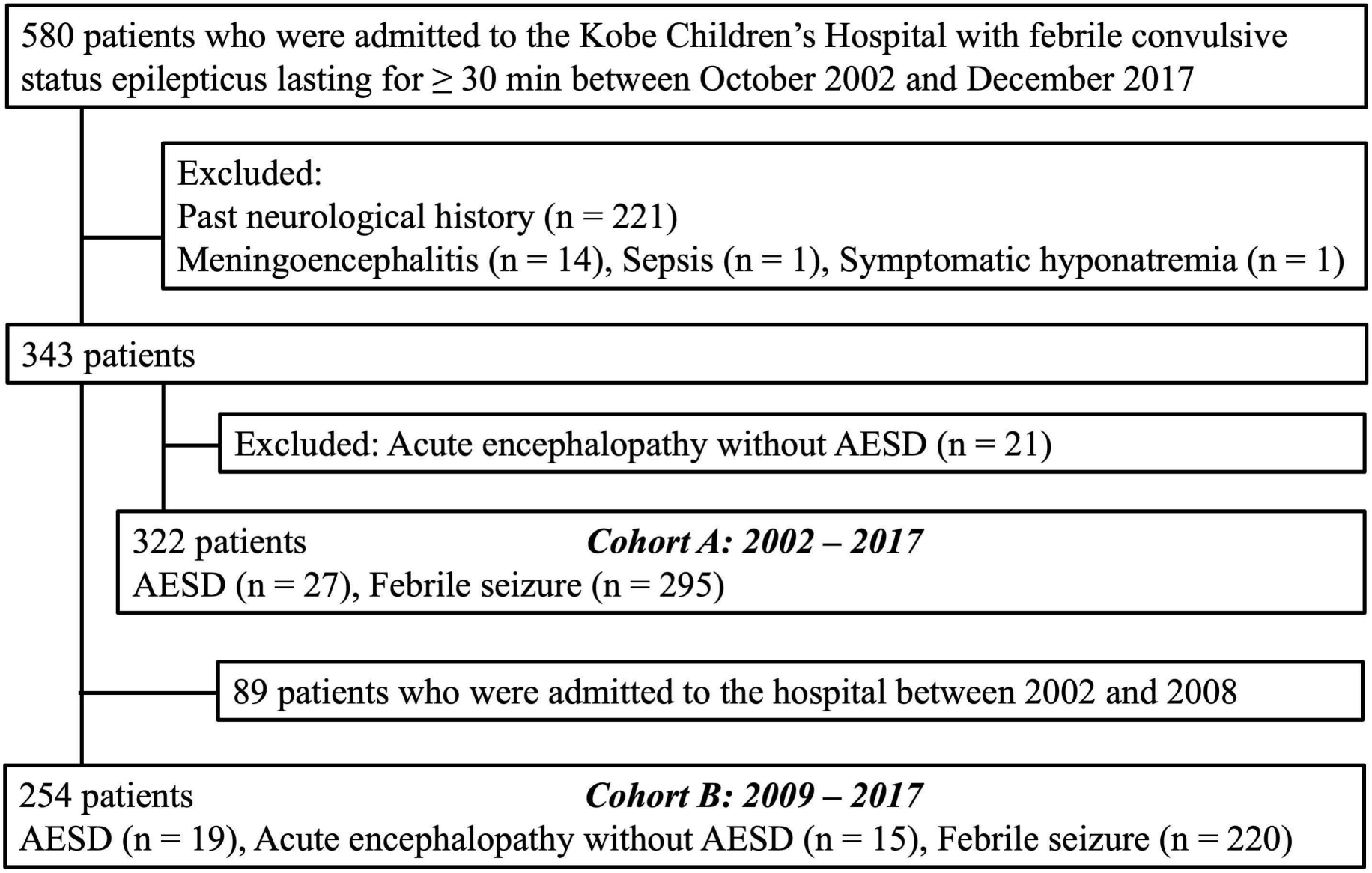
[14] Yamamoto H, Okumura A, Natsume J, Kojima S, Mizuguchi M. A severity score for acute necrotizing encephalopathy. Brain Dev 2015;37:322-7.
[15] Lee S, Sanefuji M, Torio M, Kaku N, Ichimiya Y, Mizuguchi S, et al. Involuntary movements and coma as the prognostic marker for acute encephalopathy with biphasic seizures and late reduced diffusion. J Neurol Sci 2016;370:39-43.
[16] Fujii Y, Yashiro M, Yamada M, Kikkawa T, Nosaka N, Saito Y, et al. Serum procalcitonin levels in acute encephalopathy with biphasic seizures and late reduced diffusion. Dis Markers 2018;2018:2380179.
[17] Yamanaka G, Morichi S, Takamatsu T, Takahashi R, Watanabe Y, Ishida Y, et al. Granzyme A participates in the pathogenesis of infection-associated acute encephalopathy. J Child Neurol 2020l;35;208-14.
[18] Fiser DH. Assessing the outcome of pediatric intensive care. J Pediatr 1992;121:68-74.
[19] Yamaguchi H, Nagase H, Nishiyama M, Tokumoto S, Ishida Y, Tomioka K, et al. Nonconvulsive seizure detection by reduced-lead electroencephalography in children with altered mental status in the Emergency Department. J Pediatr 2019;207:213-9.
[20] Ishida Y, Nishiyama M, Yamaguchi H, Tomioka K, Tanaka T, Takeda H, et al. Thiamylal anaesthetic therapy for febrile refractory status epilepticus in children. Seizure 2020;80:12-7.
[21] Fukuyama T, Yamauchi S, Amagasa S, Hattori Y, Sasaki T, Nakajima H, et al. Early prognostic factors for acute encephalopathy with reduced subcortical diffusion. Brain Dev 2018;40:707-13.
[22] Tomioka K, Nishiyama M, Nagase H, Ishida Y, Tanaka T, Tokumoto S, et al. Detailed clinical course of fatal acute encephalopathy in children. Brain Dev 2019;41:691-8.
[23] Okumura A, Mizuguchi M, Kidokoro H, Tanaka M, Abe S, Hosoya M, et al. Outcome of acute necrotizing encephalopathy in relation to treatment with corticosteroids and gammaglobulin. Brain Dev 2009;31:221-7.
[24] Matsuo M, Maeda T, Ono N, Sugihara S, Kobayashi I, Koga D, et al. Efficacy of dextromethorphan and cyclosporine a for acute encephalopathy. Pediatr Neurol 2013;48:200-5.
[25] Watanabe Y, Motoi H, Oyama Y, Ichikawa K, Takeshita S, Mori M, et al. Cyclosporine for acute encephalopathy with biphasic seizures and late reduced diffusion. Pediatr Int 2014;56:577-82.
[26] Murata S, Kashiwagi M, Tanabe T, Oba C, Shigehara S, Yamazaki S, et al. Targeted temperature management for acute encephalopathy in a Japanese secondary emergency medical care hospital. Brain Dev 2016;38:317-23.
[27] Nishiyama M, Tanaka T, Fujita K, Maruyama A, Nagase H. Targeted temperature management of acute encephalopathy without AST elevation. Brain Dev 2015;37:328-33.

[28] Omata T, Fujii K, Takanashi J, Murayama K, Takayanagi M, Muta K, et al. Drugs indicated for mitochondrial dysfunction as treatments for acute encephalopathy with onset of febrile convulsive status epileptics. J Neurol Sci 2016;360:57-60.
[29] Fukui KO, Kubota M, Terashima H, Ishiguro A, Kashii H. Early administration of vitamins B1 and B6 and l-carnitine prevents a second attack of acute encephalopathy with biphasic seizures and late reduced diffusion: A case control study. Brain Dev 2019;41:618-24.
[30] Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. N Engl J Med 1988;318:1728-33.
[31] Edwards AD, Brocklehurst P, Gunn AJ, Halliday H, Juszczak E, Levene M, et al. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data. BMJ 2010;340:c363.
[32] Andresen M, Gazmuri JT, Marín A, Regueira T, Rovegno M. Therapeutic hypothermia for acute brain injuries. Scand J Trauma Resusc Emerg Med 2015;23:42.
[33] Legriel S, Lemiale V, Schenck M, Chelly J, Laurent V, Daviaud F, et al. Hypothermia for neuroprotection in convulsive status epilepticus. N Engl J Med 2016;375:2457-67.

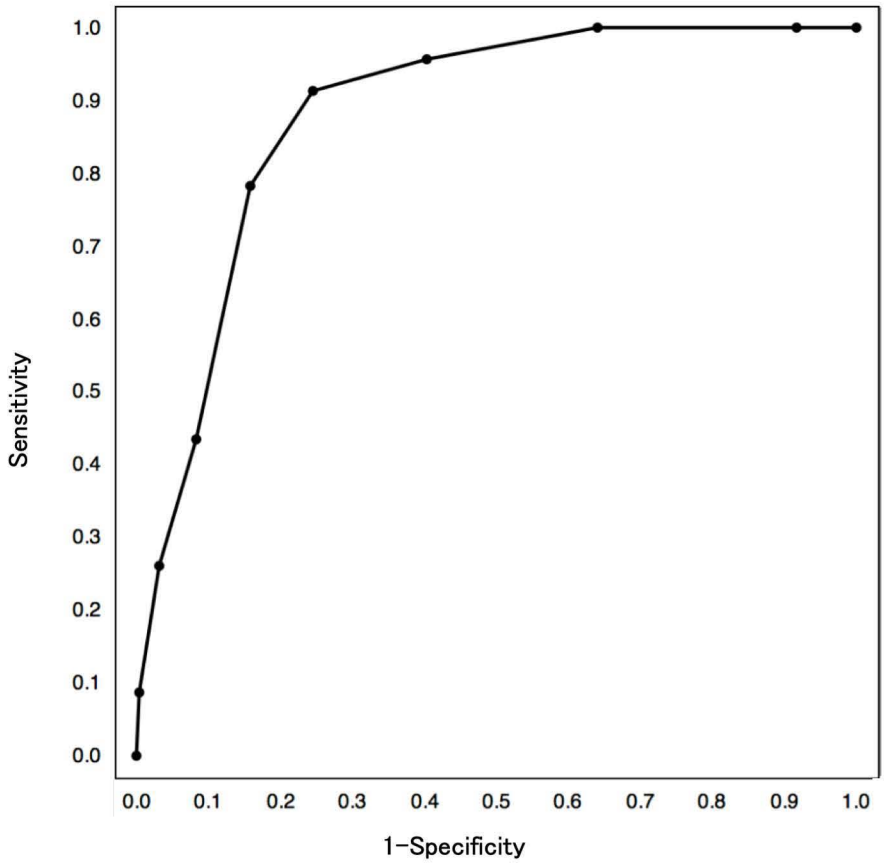
Figure Legends

Figure 1. Eligible patients.

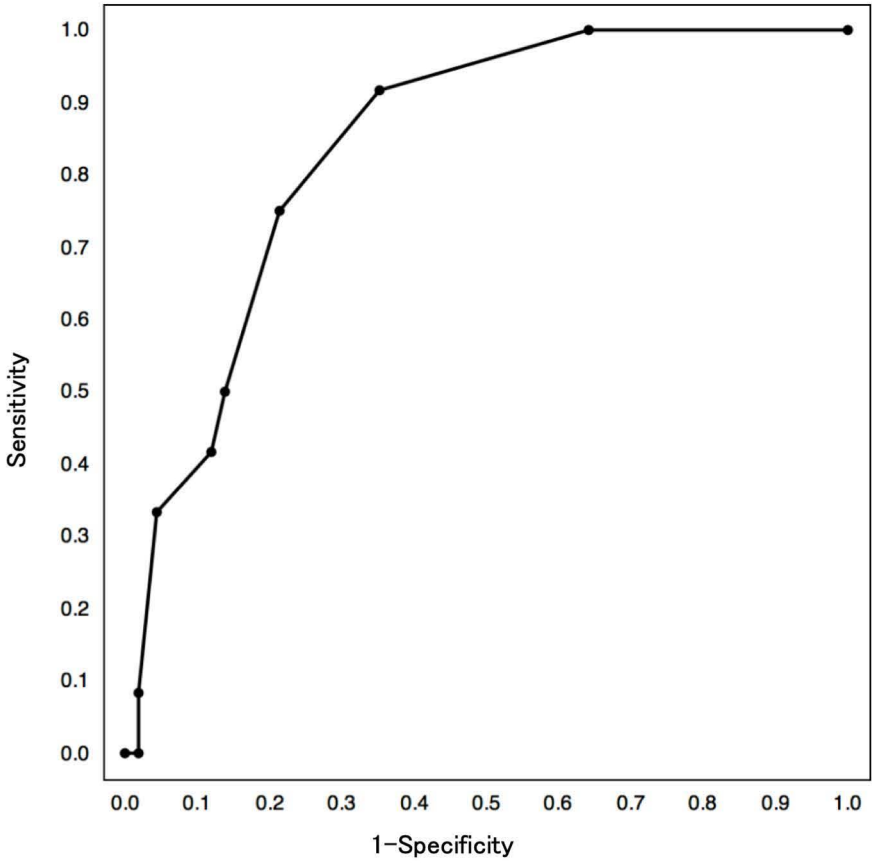
Figure 2. ROC curve for AESD CPR. a) Tada criteria. AUC was 0.882. The cut-off value determined from a ROC curve was 4. b) Yokochi criteria. AUC was 0.840. The cut-off value determined from a ROC curve was 2.

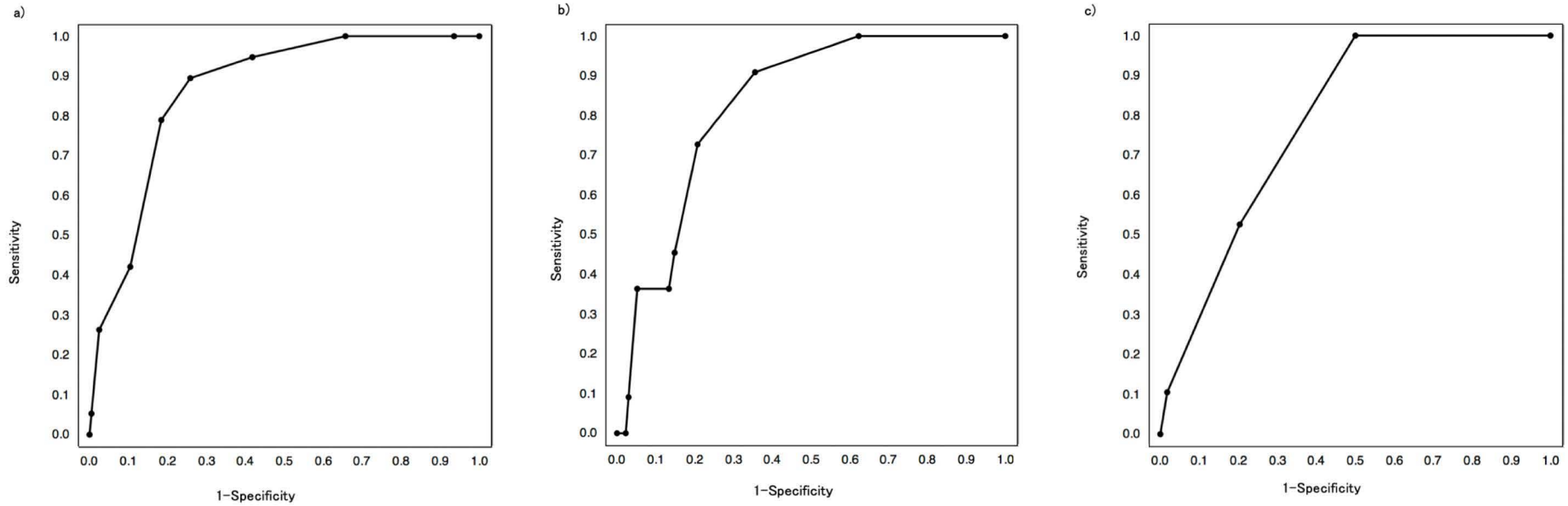

580 patients who were admitted to the Kobe Children's Hospital with febrile convulsive status epilepticus lasting for ≥ 30 min between October 2002 and December 2017
Excluded:
Past neurological history (n = 221)
Meningoencephalitis (n = 14), Sepsis (n = 1), Symptomatic hyponatremia (n = 1)
343 patients
Excluded: Acute encephalopathy without AESD (n = 21)
322 patients
Cohort A: 2002 – 2017
AESD (n = 27), Febrile seizure (n = 295)
89 patients who were admitted to the hospital between 2002 and 2008
254 patients
Cohort B: 2009 – 2017
AESD (n = 19), Acute encephalopathy without AESD (n = 15), Febrile seizure (n = 220)

a)

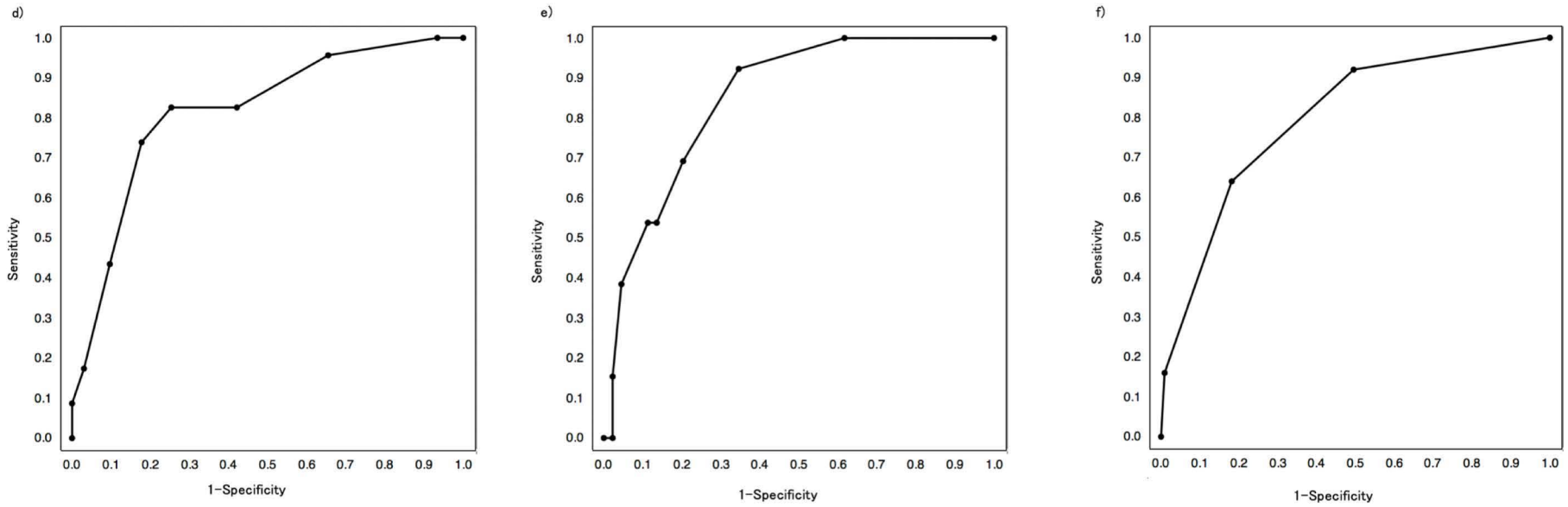

Sensitivity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
1−Specificity

b)


Sensitivity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
1−Specificity



Supplementary Figure 1 a–c. ROC curve for AESD.
a) Tada criteria. AUC was 0.864. The cut-off value determined from a ROC curve was 4. b) Yokochi criteria. AUC was 0.830. The cut-off value determined from a ROC curve was 2. c) Nagase criteria. AUC was 0.786. The cut-off value determined from a ROC curve was 1.



Supplementary Figure 1 d–f. ROC curve for neurological sequelae.
d) Tada criteria. AUC was 0.817. The cut-off value determined from a ROC curve was 4. e) Yokochi criteria. AUC was 0.850. The cut-off value determined from a ROC curve was 2. f) Nagase criteria. AUC was 0.799. The cut-off value determined from a ROC curve was 1.