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Uric acid is a useful marker to differentiate between responsive and refractory status epilepticus

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ABSTRACT

Objectives: Early recognition of refractory status epilepticus (RSE) is essential to select an appropriate treatment strategy and is closely associated with the outcome. Only few studies of RSE biomarkers exist; hence, we investigated the serum levels of uric acid (UA), albumin, and C-reactive protein (CRP) as potential serologic biomarkers for RSE.

Patients and Methods: Consecutive status epilepticus (SE) patients who had serial conventional blood tests in a referral hospital over a period of 10 years were retrospectively analyzed. Patients with anoxic encephalopathy, renal failure, acute stroke, and myocardial infarction were excluded. RSE was defined as seizure continuing after the first- and second-line treatments. We also assessed SE severity in all included patients using the Status Epilepticus Severity Score (STESS). General demographics and blood test findings were compared between responsive SE and RSE patients.

Results: A total of 141 patients (99 responsive and 42 refractory) were recruited from our SE registry. Compared to responsive patients, patients with RSE showed a higher STESS, lower initial albumin levels, lower initial UA levels, lower follow-up UA levels, and greater reduction of UA levels. The RSE group more frequently had acute symptomatic etiology, showed longer hospitalization, and had poorer functional outcomes compared to the responsive-SE group. All evaluated UA level parameters exhibited significant areas under the curve in receiver operating characteristic analyses, predictive of RSE. Initial UA levels, as well as changes therein, were significantly associated with RSE in multivariate logistic regression analysis.

Conclusion: UA levels at initial and follow-up evaluations, and changes therein differentiated responsive SE and RSE, demonstrating the feasibility of UA serum levels as a biomarker for RSE.

1. Introduction

Status epilepticus (SE) is a clinical condition with abnormally long electrographical and clinical seizures. SE is classified into responsive and refractory types based on the success of the first- and second-line therapies [1,2]. Refractory SE (RSE) is particularly devastating, with two-thirds of affected patients never recovering their baseline functional status and another quarter dying in the hospital [3]. Various treatment modalities have been used to treat RSE in intensive care settings, such as immunotherapy, hypothermia, and coma induced by continuous anesthetic infusion [4]. Therefore, early recognition of RSE is essential for the clinician to determine the most feasible treatment protocol. Although SE etiology and consciousness level have been reported as clinical markers for the initial recognition of RSE, few studies have examined RSE biomarkers systematically [5].

Continuing epileptic seizures trigger an inflammatory cascade [6] and an increase in pro-inflammatory cytokine levels, which in turn induces pronounced changes in the serum concentrations of acute-phase reactant proteins [7,8]. Albumin, C-reactive protein (CRP), and procalcitonin levels have been reported to predict the functional outcomes of SE and RSE, suggesting that neuroinflammation induced by continuing seizures reflects a pivotal pathologic mechanism of RSE [5,9,10].

Moreover, SE is associated with increased levels of reactive oxygen (ROS) and nitrite (RNS) species induced by glutamate neurotoxicity, disturbed free radical homeostasis, mitochondrial dysfunction, and energy depletion in neurons [11], which lead to progressive neuronal death in RSE [12–14]. Uric acid (UA) is the most abundant endogenous

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anti-oxidant and ROS/RNS scavenger [15,16]. Decrease of UA is known phenomenon in ischemic-reperfusion injury state after recanalization in acute ischemic stroke, recanalized stroke patients showed greater reduction of serum uric acid level than that of non-recanalized patients [17]. Recanalization of ischemic stroke could result in increasing ROS and RNS [18], presumably similar situation in RSE patients

We hypothesized that RSE was associated with lower UA levels or greater UA reduction as compared to responsive SE. In the present study, we tested this hypothesis to determine whether UA could be used as a serologic biomarker for RSE.

2. Patients and methods

We retrospectively analyzed patients entered in our prospective in-hospital SE registry from September 2007 to August 2017. We managed all admitted SE patients according to a standard management protocol (Supplementary Fig. 1). Patients who met the following criteria were selected for analysis: 1) diagnosis of SE at the age of 16 years or older; 2) initial and follow-up serologic tests of blood urea nitrogen (BUN), creatinine (Cr), albumin, CRP, and UA within 24 h after admission or prior to induced-coma therapy; 3) electroencephalogram (EEG) within 12 h of first-line treatment initiation; and 4) normal Cr level at initial evaluation and no history of medical conditions affecting serum UA levels, such as chronic renal failure, end-stage renal disease, acute stroke, and acute myocardial infarction. We excluded patients with SE caused by anoxic encephalopathy following cardiopulmonary arrest.

All selected patients were reclassified according to a recently proposed system [2], in which SE etiologies are categorized into the following 5 groups: 1) drug withdrawal; 2) acute symptomatic; 3) remote symptomatic; 4) progressive symptomatic; and 5) cryptogenic etiology. We also assessed SE severity in all included patients using the Status Epilepticus Severity Score (STESS) [19].

All EEG data were recorded according to the international 10–20 system using a Comet or Comet plus EEG apparatus (GrassTelefactor, Chicago, IL, USA) with 21 electrodes. Whenever possible, continuous EEG (cEEG) monitoring was performed for at least 24 h or until SE subsided; when not possible, repeated (at least twice per day) 30-minute routine EEGs were recorded until SE subsided.

Following interpretation of the EEG data (either routine or cEEG), the patients were divided into 4 groups: 1) unequivocal electrographical seizures; 2) continuous or abundant ($\geq$ 50%) duration of a periodic discharge (PD)/rhythmic delta activity (RDA)/spontaneous burst suppression (BS) pattern; 3) less than abundant ($<$ 50%) PD/RDA/BS; and 4) other findings (including interictal epileptiform discharge, and focal or generalized slowing). Electrographical seizures or non-convulsive SE were defined according to existing criteria [20–22], and PD/RDA/BS interpretation was based on the 2012 ACNS terminology [23]. We also classified EEG states as ictal (electrographical seizure present), ictal-interictal continuum (IIC; PD/RDA present), and post-/interictal (PIC; PD/RDA absent). One expert and one experienced adult epileptologist independently reviewed the EEG data, and any discrepancies in the interpretations were resolved through review and discussion.

We monitored the levels of albumin, CRP, and UA as potential serologic markers to predict RSE and also measured Na^+, BUN, and Cr concentrations as sample reference controls. All serologic markers were measured using a Cobas 8000 C702 system (Roche Diagnostic Systems, Basel, Switzerland). Colorimetric assays were used to measure albumin and UA levels. Immunoturbidimetric assays were used to measure CRP levels. T1 indicated the initial serum concentration of each marker, and T2 indicated the follow-up serum level. Changes in marker serum levels were expressed as Δ's and calculated as follows: Δ (change [%]) = ([T2 – T1]/T1) × 100.

Statistical analysis was conducted using SPSS 18.0. Differences between the responsive-SE and RSE groups were analyzed using the χ^2 test, Fisher's exact test, or Student's *t*-test, as appropriate, for both continuous and categorical variables. If continuous variables did not show a normal distribution in the Kolmogorov-Smirnov test, they were analyzed using non-parametric tests. Serologic marker comparison among EEG states was analyzed by ANOVA or the Kruskal-Wallis test. We also conducted a receiver operating characteristic (ROC) curve analysis for each serologic marker to show its ability to predict RSE, as well as for the STESS. Univariate and multivariate logistic regression analyses were performed to determine independent variables that were significantly associated with RSE. Potential clinical and serologic markers were analyzed using a univariate logistic regression model; markers that showed significance in the univariate analysis were included in a multivariate analysis. A stepwise backward conditional method was used in the multivariate regression model, and statistical significance was defined as $p < 0.05$.

3. Results

3.1. Participant selection

During the 10-year period from September 2007 to August 2017, 348 cases of SE were documented at our institution. Among these, 207 cases were excluded for the following reasons: 1) lack of a follow-up serologic test (n = 149) within 24 h after admission or prior to induced-coma therapy; 2) delayed EEG acquisition (n = 41); 3) SE caused by anoxic encephalopathy (n = 6); and 4) high initial serum Cr level, a history of renal failure, or acute stroke or myocardial infarction (n = 11). Among the 141 episodes included in the final analysis, 99 were responsive to first- or second-line anti-epileptic drug (AED) treatment; the remaining 42 patients exhibited RSE. Supplementary Fig. 2 shows the patient selection process.

3.2. Patient demographics

Table 1 compares clinical, electrographical, and serological variables between the responsive-SE and RSE groups. No significant differences in age or sex were found between the 2 groups. The RSE group had a higher total STESS than that of the responsive group (responsive 2 (1–3) vs. RSE 3 (2–4), p = 0.012). Among the STESS subcategories, the most severe seizure type and history of previous seizures differed between the 2 groups. The RSE group had fewer partial (simple or complex) and absence seizure cases, and more generalized tonic-clonic and non-convulsive SE cases than the responsive group (partial seizure, responsive 22.22% vs. RSE 7.14%, p = 0.004). The RSE group also contained fewer cases with a history of seizures than the responsive group (no seizure history, responsive 50.51% vs. RSE 76.19%, p = 0.005).

The etiology of SE also differed between the groups. The RSE group had fewer cases of drug withdrawal than the responsive group (responsive 16.17% vs. RSE 2.38%, $p = 0.001$), and more cases with acute symptomatic causes (responsive 33.33% vs. RSE 66.67%, $p = 0.001$). The EEG data also were significantly different between the 2 groups. More than 75% of the RSE patients experienced EEG seizures, and the remaining patients exhibited at least abundant PD (lateralized, bilateral independent, or generalized). By contrast, none of the responsive group patients experienced ongoing EEG seizures. Almost responsive SE patients, even those with less than abundant PD, exhibited regional or generalized slow activity, or interictal epileptiform discharges. The first- and second-line AED, diuretic, and antibiotic treatments were not different between the responsive and RSE groups. In addition, treatment initiation time after SE onset was not significantly different between the 2 groups.

Functional outcomes at discharge were worse in the RSE group than in the responsive group. In the responsive group, good functional outcomes at discharge (modified Rankin score [mRS] of 0–2) occurred in 81.82% of the cases, compared with 38.10% in the RSE group (p < 0.001). Furthermore, the RSE group patients were hospitalized

Table 1
Comparison between responsiveness and refractoriness in status epilepticus.

Variable		Responsive SE (n = 99)	Refractory SE (n = 42)	*p value*	Estimated OR for Refractory SE					
					Univariate			*Multivariate*		
General Demographics					OR	95% CI	*p*	OR	95% CI	*p*
Age	m ± SD	50.65 ± 18.97	51.14 ± 20.22	*0.889*	*1.01*	*0.98-1.02*	*0.888*			
Gender	Female, n (%)	41 (41.41)	18 (42.86)	*0.874*	*1.06*	*0.51-2.20*	*0.874*			
Clinical features										
STESS total	score, median (IQR)	2 (1, 3)	3 (2, 4)	*0.012*	1.39	1.05-1.86	*0.022*	–	–	–
STESS subfield										
Consciousness	Stupor/coma, n (%)	52 (52.53)	25 (59.52)		*1.33*	*0.64-2.76*	*0.446*			
Seizure type	Partial, n (%)	22 (22.22)	3 (7.14)	*0.004*	*Ref*					
	GTC, n (%)	77 (77.78)	35 (83.33)		*3.33*	*0.94-11.88*	*0.063*			
	NCSE in coma, n (%)	0	4 (9.53)							
Age	≥ 65, n (%)	27 (27.28)	11 (26.19)	*0.895*	*0.95*	*0.42-2.14*	*0.895*			
Prior Seizure history	No, n (%)	50 (50.51)	32 (76.19)	*0.005*	*3.14*	*1.39-7.06*	*0.006*			
Cause of SE	Drug withdrawal, n (%)	16 (16.17)	1 (2.38)	*0.001*	*Ref*			*Ref*		
	Acute symptomatic, n (%)	33 (33.33)	28 (66.67)		*13.58*	*1.69-108.89*	*0.014*	*9.49*	*0.91-98.96*	*0.060*
	Remote symptomatic, n (%)	38 (38.34)	6 (14.29)		*2.53*	*0.28-22.71*	*0.408*	*3.38*	*0.28-40.42*	*0.335*
	Progressive, n (%)	1 (1.01)	1 (2.38)		*16.00*	*0.52-493.99*	*0.113*	*11.38*	*0.08-1678.59*	*0.340*
	Cryptogenic, n (%)	11 (11.11)	6 (14.29)		*8.73*	*0.92-82.96*	*0.06*	*10.75*	*0.79-145.91*	*0.074*
Treatment time after SE onset	> 1 hour, n (%)	58 (58.6)	21 (50)	*0.360*	*0.71*	*0.34-1.46*	*0.35*			
1st line treatment	Midazolam, n (%)	61 (61.6)	24 (57.1)	*0.687*	*Ref*					
	Lorazepam, n (%)	37 (37.4)	18 (42.9)		*1.236*	*0.59-2.58*	*0.571*			
	Valproate, n (%)	1 (1.0)	0							
2nd line treatment [a]	(fos)phenytoin, n (%)	67 (75.3)	29 (69.0)	*0.745*	*Ref*					
	Valproate, n (%)	9 (10.1)	5 (11.9)		*1.28*	*0.39-4.16*	*0.678*			
	Levetiracetam, n (%)	13 (14.6)	8 (19)		*1.42*	*0.53-3.79*	*0.48*			
Diuretics use	Yes, n (%)	15 (15.2)	5 (11.9)	*0.793*	*0.76*	*0.25-2.24*	*0.614*			
Antibiotics use	Yes, n (%)	41 (41.4)	23 (54.8)	*0.195*	*1.71*	*0.83-3.54*	*0.147*			
EEG finding	Other (Slow, IED), n (%)	82 (82.83)	0	*< 0.001*						
	< Abundant PD, n (%)	5 (5.05)	0							
	≥ Abundant PD, n (%)	12 (12.12)	10 (23.81)							
	EEG seizure, n (%)	0	32 (76.19)							
Outcome										
Hospitalization	Days, m ± SD	14.01 ± 16.14	36.12 ± 38.07	*0.001*						
mRS at discharge	mRS 3˜6	18 (18.18)	26 (61.90)	*< 0.001*						
Serologic markers										
BUN	T1, mg/dl	13.32 ± 6.53	13.72 ± 6.25	*0.738*	1.01	0.96-1.07	*0.736*			
	T2, mg/dl	12.32 ± 6.50	12.99 ± 6.75	*0.577*	1.02	0.96-1.07	*0.575*			
	Δ, %	−6.94 ± 26.81	−2.62 ± 29.31	*0.397*	1.01	0.99-1.02	*0.396*			
Creatinine	T1, mg/dl	1.01 ± 0.29	0.92 ± 0.34	*0.121*	0.36	0.10-1.31	*0.122*			
	T2, mg/dl	0.88 ± 0.27	0.85 ± 0.60	*0.509*	0.64	0.17-2.42	*0.506*			
	Δ, %	−12.11 ± 14.98	−7.64 ± 15.69	*0.112*	1.02	0.99-1.05	*0.114*			
Na^+	T1, mMol/L	139.66 ± 3.88	138.26 ± 4.79	*0.072*	0.92	0.85-1.00	*0.075*			
	T2, mMol/L	139.63 ± 3.79	138.36 ± 4.85	*0.098*	0.93	0.85-1.01	*0.101*			
	Δ, %	−0.07 ± 1.67	0.07 ± 1.19	*0.747*	1.04	0.82-1.31	*0.776*			
Albumin	T1, g/dl	4.24 ± 0.53	3.96 ± 0.58	*0.005*	0.40	0.20-0.78	*0.007*	*0.21*	*0.07-0.66*	*0.007*
	T2, g/dl	3.69 ± 0.51	3.52 ± 0.68	*0.104*	0.60	0.32-1.12	*0.109*			
	Δ, %	−12.33 ± 10.82	−11.21 ± 11.20	*0.580*	1.01	0.98-1.05	*0.578*			
CRP	T1, mg/dl	1.74 ± 3.71	2.07 ± 3.87	*0.627*	1.02	0.93-1.12	*0.626*			
	T2, mg/dl	4.03 ± 6.00	4.06 ± 5.68	*0.979*	1.00	0.94-1.06	*0.979*			
	Δ, %	+1479.82 ± 4398.46	+2452.24 ± 7329.39	*0.427*	1	1	*0.812*			
Uric acid	T1, mg/dl	6.98 ± 4.06	4.87 ± 2.45	*< 0.001*	0.82	0.71-0.94	*0.004*	*0.81*	*0.68-0.97*	*0.023*
	T2, mg/dl	5.21 ± 3.22	2.20 ± 1.18	*< 0.001*	0.46	0.34-0.64	*< 0.001*	–	–	–
	Δ, %	−23.03 ± 26.04	−53.27 ± 15.45	*< 0.001*	0.92	0.89-0.95	*< 0.001*	*0.92*	*0.88-0.95*	*< 0.001*
Interval between T1 and T2	hours, m ± SD	18.76 ± 4.03	16.29 ± 5.06	*0.002*						

a: In responsive group, 2nd line treatment was applied for 89 patients.
STESS: Status Epilepticus Severity Score, SE: Status epilepticus, EEG: electroencephalogram, IED: Interictal epileptiform discharge, PD: Periodic discharge, mRS: modified Rankin score, BUN: Blood urea nitrogen, CRP: C-reactive protein, OR: Odds ratio.

for longer than the responsive patients (responsive 14.01 ± 16.14 days vs. RSE 36.12 ± 38.07 days, mean ± SD, $p = 0.001$).

3.3. Comparison of serologic markers

We compared the levels of the following serologic markers between the responsive-SE and RSE groups: Na^+, BUN, Cr, albumin, CRP, and UA. No differences were observed in the Na^+, BUN, and Cr levels

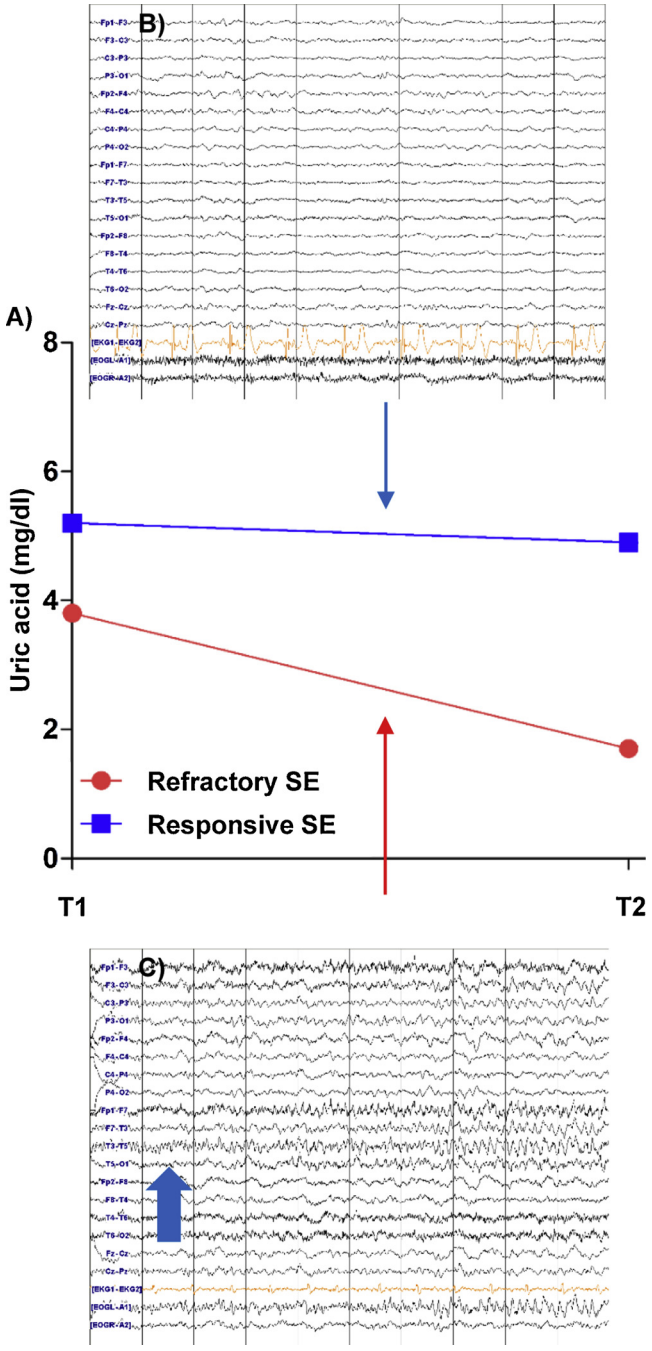

Fig. 1. Representative figure to show serial uric acid level and associated electroencephalography (EEG) findings. (A) shows serial uric acid level from T1 to T2. Note lower uric acid level at T1 and T2 period in refractoriness patients. (B) shows EEG finding in patient with responsiveness after intravenous fosphenytoin loading. Continuous generalized slowing was noted. (C) shows EEG finding in patient with refractoriness after intravenous valproate and levetiracetam loading. There were frequent runs of EEG seizures arising from left temporal area (C, arrow). After adding three additional anti-seizure drugs (topiramate, fosphenytoin and clobazam), EEG seizures were disappeared. SE; status epilepticus.

between the 2 groups. The T1 albumin levels were significantly lower in the RSE group than in the responsive group (responsive 4.24 ± 0.53 g/dL vs. RSE 3.96 ± 0.58 g/dL, p = 0.005); however, the T2 albumin levels, as well as the albumin Δ, did not differ significantly between the groups. Neither the CRP levels (T1 or T2) nor the CRP Δ differed significantly between the 2 groups. However, the UA levels at T1 and T2, and the UA Δ were significantly different between the responsive and RSE patients (T1 UA, responsive 6.98 ± 4.06 mg/dL vs. RSE 4.87 ± 2.45 mg/dL, p < 0.001; T2 UA, responsive 5.21 ± 3.22 mg/dL vs. RSE 2.20 ± 1.18 mg/dL, p < 0.001; UA Δ, responsive -23.03 ± 26.04% vs. RSE -53.27 ± 15.45%, p < 0.001). The interval between T1 and T2 was shorter in the RSE group than in the responsive group. Fig. 1 shows representative cases of serial UA levels at the T1/T2 time points and EEG findings between the UA level measurements in the RSE and responsive-SE groups.

Because RSE group had more acute symptomatic etiologies and lower UA level, UA levels were reanalyzed according to etiologies: non-acute symptomatic etiologies and acute symptomatic etiology. There were also significant differences of T1 UA, T2 UA and UA Δ between responsive and RSE patients with non-acute symptomatic etiologies (T1 UA, responsive 7.48 ± 4.30 mg/dL vs. RSE 5.07 ± 2.06 mg/dL, p = 0.003; T2 UA, responsive 5.57 ± 3.34 mg/dL vs. RSE 2.56 ± 1.09 mg/dL, p < 0.001; UA Δ -22.77 ± 27.29% vs. RSE -48.90 ± 15.57, p < 0.001). In patients with acute symptomatic etiology, T2 UA and UA Δ were significantly different between responsive and RSE patients but not in T1 UA (T1 UA, responsive 5.99 ± 3.38 mg/dL vs. RSE 4.77 ± 2.66 mg/dL, p = 0.12; T2 UA, responsive 4.50 ± 2.90 mg/dL vs. RSE 2.03 ± 1.21, p < 0.001; UA Δ responsive -23.54 ± 23.72% vs. -55.56 ± 15.19, p < 0.001).

We also analyzed the relationship between serologic marker levels and the EEG state (PIC, IIC, or ictal). All of the measured albumin and UA parameters showed significant differences among the EEG states (T1 albumin: p = 0.019, T2 albumin: p = 0.001, albumin Δ: p = 0.024; T1 UA: p = 0.033, T2 UA: p < 0.001, UA Δ: p < 0.001). Intriguingly, only UA serum levels showed a progressive decrease at both initial evaluation and follow-up, with the relative reduction between the 2 time points increasing with increasing EEG severity (T1 UA [mg/dL]: PIC, 7.05 ± 4.15 vs. IIC, 5.54 ± 3.39 vs. ictal, 5.26 ± 2.57, *p = 0.033*; T2 UA [mg/dL]: PIC, 5.38 ± 3.38 vs. IIC, 3.35 ± 2.27 vs. ictal, 2.39 ± 1.25, *p < 0.001*; Δ [%]: PIC, -21.15 ± 26.76 vs. IIC, -39.57 ± 21.98 vs. ictal, -53.57 ± 14.53, *p < 0.001*). Albumin levels did not show such a correlation (T1 albumin [g/dL]: PIC, 4.26 ± 0.52 vs. IIC, 4.00 ± 0.60 vs. ictal, 4.00 ± 0.56; T2 albumin [g/dL]: PIC, 3.76 ± 0.43 vs. IIC, 3.31 ± 0.73 vs. ictal, 3.61 ± 0.64; Δ [%]: PIC, -11.20 ± 9.20 vs. IIC, -16.99 ± 13.29 vs. ictal, -9.81 ± 11.77). Fig. 2 shows the serologic marker levels in each EEG state.

3.4. ROC curve analysis for RSE discrimination

Fig. 3 illustrates a ROC curve analysis of various factors for RSE prediction. The total STESS was able to predict RSE with statistical significance (area under the curve [AUC] = 0.63, p = 0.005). Among the examined serologic parameters, all UA parameters and the initial albumin level were predictive of RSE. The UA parameters exhibited larger AUCs than did the initial albumin level, with the change in UA levels showing the largest AUC (AUC for T1 albumin = 0.643, p = 0.005; AUC for T1 UA = 0.653, p = 0.001; AUC for T2 UA = 0.825, p < 0.001; AUC for UA Δ = 0.866, p < 0.001). Table 2 summarizes the ROC analysis results, including the sensitivity, specificity, and positive and negative predictive values.

3.5. Disrupted correlation between albumin and UA levels in RSE

Because the serum levels of albumin and UA had been shown to be closely correlated [24], we investigated the correlation between the concentrations of these markers at T1 and T2 in each patient group. Interestingly, the RSE group exhibited no significant correlation at T2 examination (r = -0.043, p = 0.78), whereas the responsive group showed a significant positive correlation (r = 0.199, p = 0.048). Both groups exhibited significant positive correlations between the T1 serum levels of albumin and UA (responsive, r = 0.280, p = 0.004; and RSE group, r = 0.329, p = 0.03).

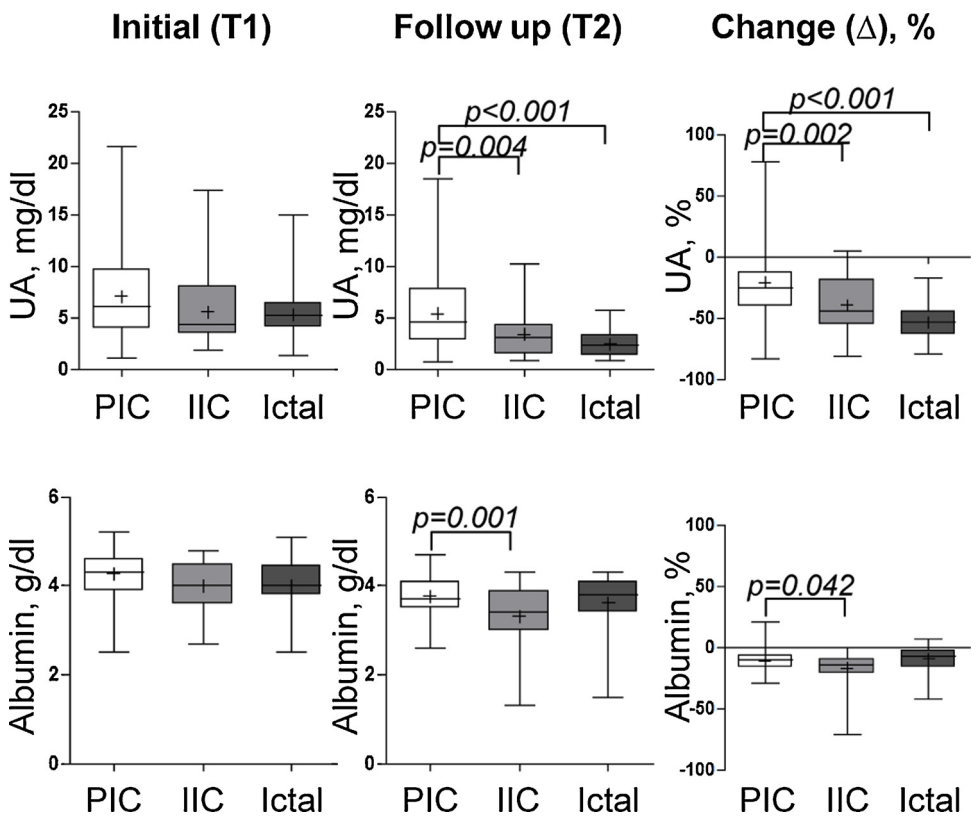

Fig. 2. Comparison of serologic markers among electroencephalographic states. Albumin and uric acid (UA) show significant differences among three EEG states. Only UA shows sequentially lower levels or greater reduction of serum levels according to EEG states but not albumin.

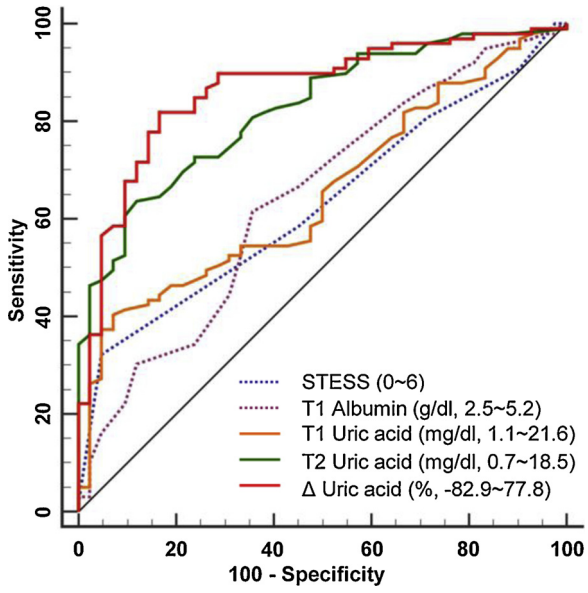

Fig. 3. Receive operating characteristic (ROC) analysis of predictive factors for refractory status epilepticus (RSE) Changes in uric acid (Δ UA) levels exhibited the largest area under the curve (0.866) of the serologic parameters that were investigated.

3.6. Logistic regression analysis

Finally, we sought to identify the factors associated with RSE the most strongly (Table 1). Univariate logistic regression showed that the STESS, a history of seizures, acute symptomatic etiology, T1 albumin level, T1 and T2 UA levels, and UA Δ were significantly associated with RSE. A multivariate stepwise logistic regression analysis showed that T1 albumin level (OR: 0.211, 95% CI: 0.068-0.658, $p = 0.007$), T1 UA level (OR: 0.810, 95% CI: 0.676-0.971, $p = 0.023$), and UA Δ (OR: 0.917, 95% CI: 0.887-0.648, $p < 0.001$) were significantly associated variables of RSE. Because albumin serum concentrations and SE severity (STESS) are known to be predictive of SE outcomes, we also investigated predictive markers of poor functional outcomes at discharge, defined as a mRS score above 2 (Supplementary Table 1). A multiple stepwise logistic regression analysis showed that the total STESS score (OR: 1.769, 95% CI: 1.217–2.572, $p = 0.003$), RSE (OR: 6.995, 95% CI: 2.745–17.822, $p < 0.001$) and T1 albumin level (OR: 0.383, 95% CI: 0.152-0.969, $p = 0.041$) were significantly associated variables of a poor functional outcome.

4. Discussion

Identification of RSE biomarkers is essential because early recognition helps develop a treatment strategy to improve the patient's outcome. In the present study, we found the serum levels of UA and changes therein to correlate with SE refractoriness more strongly than previously reported markers such as a clinical score (STESS) and serologic markers (albumin and CRP).

4.1. UA levels in RSE

In the present study, the UA levels were lower and showed greater decline in the RSE group than in the responsive-SE group. All 3 UA parameters examined had greater ROC AUCs than the other factors, and the UA Δ was the most significant factor in multivariable logistic regression for RSE. Also, UA concentrations were lower and showed greater decline than albumin with EEG states progressing from PIC to ictal. Taken together, our results suggest that UA levels may serve as a biomarker for RSE, reflecting persistent seizures in which ROS/RNS production is increased [25]. In addition, the disrupted correlation

Table 2
ROC curve analysis for refractory status epilepticus.

Variable		AUC	95% CI	*p value*	Cut off value	Sensitivity (%)	Specificity (%)	+PV (%)	-PV (%)
STESS total		0.63	0.545-0.710	*0.005*	> 1	95.24	32.32	37.4	94.1
BUN	T1	0.53	0.44-0.61	*0.627*	> 10.9	69.05	45.45	34.9	77.6
	T2	0.54	0.45-0.62	*0.443*	> 7.6	90.48	25.25	33.9	86.2
	Δ	0.54	0.45-0.62	*0.508*	> -14.71	71.43	43.43	34.9	78.2
Creatinine	T1	0.61	0.52-0.69	*0.035*	≤ 1.06	78.57	42.42	36.7	82.4
	T2	0.54	0.46-0.63	*0.398*	≤ 0.99	78.57	36.36	34.4	80.0
	Δ	0.59	0.51-0.67	*0.077*	> -9.09	57.14	64.65	40.7	78.0
Albumin	T1	0.64	0.56-0.72	*0.005*	≤ 4.1	64.29	61.62	41.5	80.3
	T2	0.55	0.47-0.64	*0.344*	≤ 3.2	28.57	83.84	42.9	73.5
	Δ	0.56	0.47-0.64	*0.333*	≤ -7.69	47.62	74.75	44.4	77.1
CRP	T1	0.51	0.42-0.59	*0.860*	> 7.1	11.9	96.97	6.25	72.2
	T2	0.52	0.43-0.60	*0.724*	> 1.78	59.52	54.55	35.7	76.1
	Δ	0.51	0.43-0.60	*0.847*	> 13.64	40.48	71.72	37.8	74.0
Uric acid	T1	0.65	0.57-0.73	*0.001*	≤ 7.4	92.86	40.40	39.8	93.0
	T2	0.83	0.75-0.88	*< 0.001*	≤ 3.4	88.10	63.64	50.7	92.6
	Δ	0.87	0.80-0.92	*< 0.001*	≤ -43.9	83.33	81.82	66.0	92.0

AUC: Area under the curve, CRP: C-reactive protein, +PV: positive predictive value, -PV: negative predictive value.

between the UA and albumin concentrations in the RSE group can be interpreted as a result of UA being consumed before, and at a greater rate than albumin, when RSE disrupts the blood-brain barrier and enables serum components to enter the brain parenchyma [6,26]. These results suggest increased ROS/RNS production, rather than neuroinflammation, may be the main pathophysiologic cause of RSE. Although UA levels differences according to etiologies can not be totally excluded, even if UA levels were compared according to different etiologies, UA levels differences is shown between responsive SE and RSE group. This result suggests that RSE may be bigger effect than etiologies to UA levels.

UA is the most abundant endogenous antioxidant, known to exhibit neuroprotective effects in neurological diseases such as Alzheimer's disease, multiple sclerosis, and Parkinson's disease through its antioxidant activity [27]. In addition, UA supplementation was shown to be effective in the treatment of ischemic cerebral infarction in a recent study [28]. Therefore, based on the results of the present and previous studies, it may be possible to develop a novel treatment strategy for RSE based on UA supplementation.

4.2. RSE and conventional biomarkers

Systemic inflammation results in changes in acute-phase reactant protein levels, e.g., increased CRP and decreased albumin concentrations. CRP is an exclusively acute-phase reactant protein, responding to increased levels of pro-inflammatory cytokines such as interleukin-6 [29]. Although seizures increase or potentiate systemic inflammation, the main inflammatory lesions in SE are localized within the brain parenchyma [30]. Consequently, CRP serum levels are not expected to be elevated shortly after intra-parenchymal brain inflammation. Thus, it is not surprising that CRP levels were not predictive of RSE in the present study. Albumin is both an endogenous antioxidant and an acute-phase reactant protein [31,32]. Albumin serum levels may be expected to be affected in RSE because of its antioxidant properties. Unlike CRP concentrations, serum albumin levels have previously been reported to be consistently predictive of RSE [5]. This finding may be explained by the different biological roles of the 2 proteins.

4.3. Biomarkers for SE functional outcomes

Despite the UA level being a predictor of RSE, it did not predict the functional outcomes of SE patients. By contrast, the initial albumin level showed a significant association with the functional outcome, and CRP levels at follow-up were potentially predictive of the functional outcome. These results are consistent with a previously reported association between acute-phase proteins and mortality in SE patients [9]. In the present study, the total STESS and SE refractoriness were strong predictors of functional outcomes. These findings externally validated the usefulness of the STESS and demonstrated the importance of RSE [33].

With continuous seizure activity, systemic or general conditions also affect the functional outcome. Albumin and CRP are acute phase proteins that react to systemic inflammatory and concurrent infectious conditions. Thus, decreased albumin and increased CRP levels may reflect ongoing systemic inflammatory processes or concurrent infections in SE patients. General conditions such as pneumonia have been reported to affect SE outcomes [34]. Therefore, because albumin and CRP are acute-phase reactant proteins, their elevated levels can predict poor functional outcomes, whereas the UA level is expected to be a more accurate predictor of RSE.

4.4. Limitations

The generalizability of this study may be limited because it involved retrospective analysis of data obtained at a single tertiary referral medical center. First, the blood sampling interval between T1 and T2 was not consistent. However, the RSE group did show multiple significant changes compared to the responsive-SE group, suggesting that the differences between the 2 groups might have been greater if the T1-T2 interval had been constant. Second, we cannot rule out the possibility of missing subtle EEG seizures in some patients because of the unavailability of cEEG. However, missing such seizures is unlikely to have affected our findings because a recent report showed that the results of cEEG and repeated routine EEG did not differ significantly in an intensive care setting [35]. Prospective multicenter studies using continuous EEG monitoring and consistent blood sampling timing are required to further investigate the predictive power of UA levels in RSE.

5. Conclusion

Low UA serum levels, and greater reductions in UA levels at follow-up, were the strongest serologic correlates of RSE, demonstrating the feasibility of using the UA serum concentration as a predictive RSE biomarker. The UA level was not predictive of functional outcomes in SE. Further investigation in prospective multicenter studies is required to validate our findings.

Disclosure

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2019.105454.

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