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ORIGINAL RESEARCH

Role of lactate measurement in predicting recurrence of seizure within 24 hours in simple febrile seizure patients

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Abstract

Pediatric febrile seizure (FS) is classified into two types, simple febrile seizures (SFSs) and complex febrile seizures (CFSs). The prognosis of CFS and SFS is distinct from each other. Even after diagnosis of SFS, patients with recurrence of seizure within 24 hours are defined as CFS. And it is crucial to predict the recurrence of seizure in SFS patients. The purpose of this study was to investigate the role of lactate levels in predicting recurrence of seizure within 24 hours in SFS patients. This retrospective study was conducted on patients who visited the emergency department with FS from January 2017 to February 2020 at a single tertiary university hospital. They were divided into the recurrence group and the SFS group according to the recurrence of seizures. Multivariable analysis was performed to confirm whether lactate levels could be an independent factor in predicting recurrence of seizure within 24 hours in SFS patients. Of the 177 patients, 38 patients were classified into the recurrence group. High lactate levels (odds ratio = 1.45; 95% confidence interval: 1.04–2.03, p = 0.031) were found to be a significant factor in predicting recurrence of seizure within 24 hours in SFS patients. The areas under the ROC curve for lactate was 0.733. In patients with FS, high lactate levels were shown to be a useful and independent factor in predicting recurrence of seizure within 24 hours in SFS patients.

Keywords

Lactate; Seizures; Febrile; Recurrence; Pediatric patient

1. Introduction

Febrile seizures (FSs) affect children between 6 and 60 months and occur in 2% to 5% of the childhood population [1]. Complex febrile seizures (CFS) are defined as focal seizure, that last longer than 15 minutes and/or multiple seizures that occur within 24 hours [2]. CFSs account for 25–30% of all FSs [1, 3].

Although most patients with FS have a benign clinical course, special attention is needed for differentiation of FS [4]. Regarding differentiation of simple febrile seizure (SFS) and CFS, focal seizures or seizure with prolonged duration (>15 minutes) are unargued features of CFS, but it is hard to discriminate first episode of multiple seizures within 24 hours, that is CFS, from SFS when there is a quite interval between seizure attacks. Therefore, predicting recurrence of seizure within 24 hours in FS patients is crucial, based on different prognosis and treatment strategies between CFS and SFS.

The prognostic value of lactate measurements has been investigated in systemic inflammation including sepsis [5, 6]. A recent study showed that lactate may be an important metabolite and implicated in the production of interleukin (IL)-6, which is a pro-inflammatory cytokine involved in the induction of acute-phase inflammation [7]. FS patients had significantly higher serum IL-6 levels compared to febrile patients without seizures [8]. The suppression of lactate dehydrogenase exerts anti-inflammatory effects by reducing the production of IL-6, indicating that lactate may be an important metabolite and implicated in the production of IL-6 and the regulation of the inflammatory response [7]. Elevated levels of inflammatory cytokine are associated with the development of FS, and lactate levels have a close relationship with production of some inflammatory cytokines [7, 8]. Lactate levels can be rapidly and easily obtained in most emergency departments (ED).

The role of blood examination in children with FS is still controversial [4]. But several studies have reported that measurements of neutrophil-to-lymphocyte ratio (NLR), red cell distribution width (RDW) and C-reactive protein (CRP), which are markers related to inflammation, are helpful in predicting CFS [9–11]. The purpose of this study was to investigate the role of lactate level as a factor in predicting recurrence of seizure within 24 hours in SFS patients. In addition, previously studied inflammatory markers were also reinvestigated.

2. Materials and methods

2.1 Settings

This was a retrospective cohort study of patients with febrile seizures at a single urban tertiary pediatric ED between January 2017 and February 2020. Electronic medical records (EMRs) of all patients presenting with febrile seizures were reviewed. The study cases were identified with inclusion and exclusion criteria below.

2.2 Data sources

All patients with EMRs available during the study period were evaluated for inclusion in the study. We included 6 to 60-month-old patients with FS. The definition of FS used in this study was a seizure accompanied by fever, without central nervous system infection in a patient without a history of seizures or neurologic dysfunction. The body temperature of patients was documented at 38.0 or higher in the pre-hospital period or the ED. Seizures were classified as complex if they met any one of the following criteria: focal seizure, prolonged duration of >15 minutes, and/or multiple seizures within 24 hours.

Patients who were diagnosed with CFS at other hospital and transferred to our facility were excluded from this study. And patients with focal seizures and seizures longer than 15 minutes as a chief complaint at the ED arrival were excluded, because CFS was diagnosed at the first ED visit. The exclusion criteria included prematurity (age at birth <37 weeks and age under one year), a history of afebrile seizure, abnormalities in brain imaging, electrolyte disorders, central nervous system (CNS) infection (encephalitis and meningitis, including viral infection), mental retardation, inborn errors of metabolism and developmental delay. Patients with acute or chronic systemic disease, cancer, and hematologic or rheumatologic disorders, were also excluded. Patients who did not receive blood tests including lactate levels within thirty minutes after ED arrival were excluded, either. The decision to measure lactate was based on the emergency physician's discretion.

Data obtained in the ED was searched in the EMRs. The specific data extracted included age, gender, body temperature, past medical history including prior febrile seizures, semiology, the time elapsed between the first and the second seizure within 24 hours and the results of imaging studies during hospitalization. Collected laboratory data were blood cell count, blood gas analysis, venous lactate (Normal reference value, 0.5–2.2 mmoL/L), the NLR, the RDW and CRP at the first ED visit.

We divided the patients into the recurrence group and the SFS group according to the recurrence of seizures. If the seizure happens again in a patient during ED monitoring or a patient returned to the ED due to relapse of seizure within 24 hours after discharge, they were defined as the recurrence group. All other patients discharged without seizure recurrence during ED monitoring were defined as the SFS group. We calculated odds ratios of various clinical and laboratory variables to evaluate which factor could predict recurrence of seizures in patients. Multivariable analysis was performed to confirm whether lactate levels could be an independent factor in predicting seizure relapse within 24 hours in SFS patients. Additionally, we investigated whether the factors that could predict recurrence were correlated with the elapsed time until recurrence.

2.3 Data analysis

Comparisons between the recurrence and SFS groups were performed using the student's *t*-test or the Mann-Whitney U test for continuous variables after the Kolmogorov-Smirnov test. The Chi-squared test or Fisher's exact test was performed for the categorical variables. Youden's index was measured to determine the cut-off value. Multivariable logistic regression model analysis was performed on variables with *p*-values of less than 0.1 to estimate the odds ratios (ORs) for seizure recurrences with 95% confidence intervals (CIs). The receiver operating characteristic (ROC) curve was used to measure efficacy of variables with significant differences. A *p*-value of less than 0.05 was considered statistically significant. International Business Machines (IBM), Statistical Package for the Social Sciences (SPSS) Statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analyses.

3. Results

During 38 months of the study period, a total of 427 patients with FS visited the ED. Of them, 250 patients were excluded due to prematurity (two patients), a history of epilepsy (three patients), abnormalities in brain imaging (two patients), electrolyte disorders (four patients), CNS infections (four patients), mental retardation (one patient), transfer from other hospital (twenty-four patients), seizure duration >15 minutes (four patients) and no lactate measurements (206 patients). A total of 177 patients were included in the study (Fig. 1).

There were 38 patients (21.5%) in the recurrence group and 139 (78.5%) in the SFS group. Gender, prior FS events, and seizure duration did not differ between the two groups. Median age was 12 months in the CFS group, significantly younger than 24 months in the SFS group ($p = 0.003$). Body temperature was 38.8 ℃ in the recurrence group, significantly lower than the 39.1 ℃ in the SFS group ($p = 0.008$). The time from the seizure to the ED visit and the time from the seizure to blood exam were significantly longer in the recurrence group (60 minutes *vs.* 30 minutes, $p < 0.001$; 93 minutes *vs.* 51 minutes, $p < 0.001$).

In laboratory findings, there was a significant difference between the recurrence group and SFS group in pH (7.42 *vs.* 7.39, $p = 0.029$), base excess (–1.45 *vs.* –2.40 mmoL/L, $p = 0.034$) and lactate (2.46 *vs.* 1.78 mmoL/L, $p < 0.001$). NLR, RDW and CRP were not shown significant difference between those groups. Table 1 shows comparisons between the recurrence and the SFS group.

Univariable logistic regression analysis was performed on variables with *p*-values less than 0.1 among variables including sex. Sex, age, lactate, CRP, base excess, and pH were analyzed by univariable logistic regression to identify the factors in predicting recurrence of seizure within 24 hours in SFS patients. Regression was done by univariable and multivariable analyses. The cutoff values determined by Youden's index for age, lactate, CRP, base excess, and pH were 18 months, 2.21

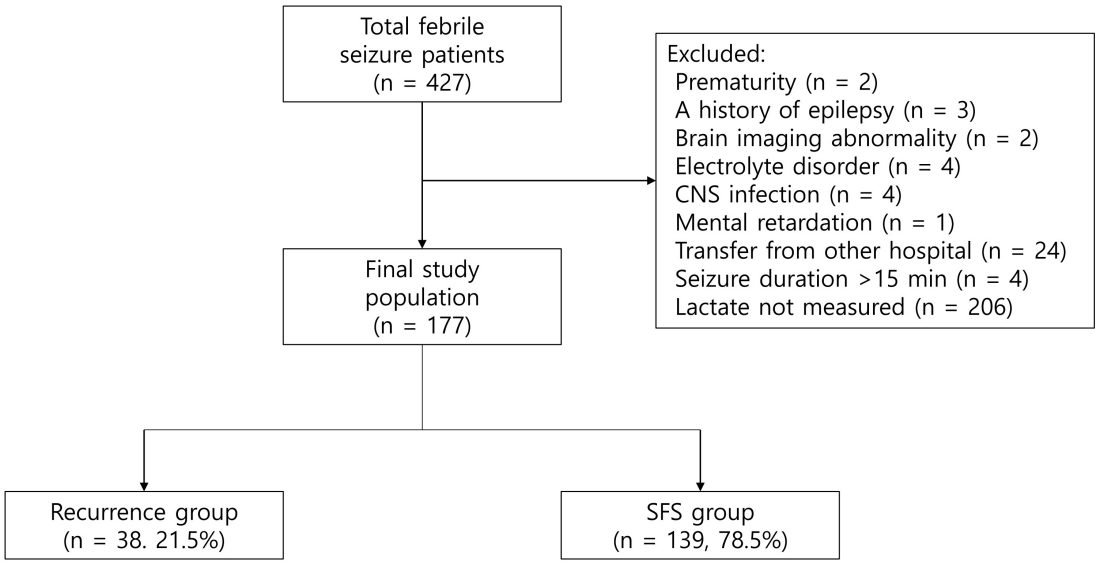

FIGURE 1. Inclusion and exclusion flow chart of study population. CNS, central nervous system; SFS, simple febrile seizure.

TABLE 1. Clinical characteristics of the study population.

	Recurrence group (n = 38)	Simple febrile seizure group (n = 139)	*p*
Male sex (%)	19 (50.0)	81 (58.3)	0.362
Age (months)	12 (10–24)	24 (12–36)	0.003
Prior event of FS (%)	23 (60.5)	64 (46.4)	0.173
Time from seizure to ED visit (minutes)	60 (30–100)	30 (25–60)	<0.001
Time from seizure to blood exam (minutes)	93 (48–125)	51 (40–75)	<0.001
Seizure duration (minutes)	4.51 ± 4.25	3.64 ± 3.68	0.254
Body temperature (°C)	38.80 (38.20–39.20)	39.10 (38.50–39.63)	0.008
Laboratory findings			
Neutrophil ($10^3/\mu L$)	8.46 ± 5.59	8.65 ± 5.33	0.850
Lymphocyte ($10^3/\mu L$)	2.74 ± 2.01	2.85 ± 1.86	0.763
Platelet ($10^3/\mu L$)	289.39 ± 96.15	290.36 ± 102.21	0.957
NLR	5.28 ± 7.57	4.39 ± 4.35	0.491
RDW (%)	13.13 ± 1.24	12.99 ± 1.29	0.533
MPV (fL)	9.01 ± 0.69	8.99 ± 0.68	0.898
pH	7.42 (7.38–7.47)	7.39 (7.36–7.43)	0.029
PO_2(mmHg)	54.89 ± 19.74	52.55 ± 19.03	0.516
PCO_2(mmHg)	36.45 ± 9.32	37.70 ± 8.91	0.462
Base excess (mmoL/L)	−1.45 (−2.65–−0.35)	−2.40 (−3.80–−0.55)	0.034
CRP (mg/dL)	18.61 ± 24.63	10.41 ± 11.00	0.053
Lactate (mmoL/L)	2.46 (2.08–2.83)	1.78 (1.31–2.41)	<0.001

FS, febrile seizure; ED, emergency department; NLR, neutrophil-lymphocyte ratio; RDW, red cell distribution width; MPV, mean platelet volume; CRP, C-reactive protein. Data are presented as mean ± SD, variables not met normality criteria, are presented as median (interquartile range).

mmoL/L, 7.18 mg/dL, –1.85 mmoL/L, and 7.415, respectively. Lactate, base excess, pH had a *p*-value of less than 0.1 and multivariable logistic regression analysis was performed with sex, age and these variables. Lactate (Odds ratio (OR) = 1.45; 95% Confidence interval (CI): 1.04–2.03, $p = 0.031$) and base excess (OR = 1.38; 95% CI: 1.08–1.74, $p = 0.009$) were found to be significant factors in predicting recurrence of seizure within 24 hours in SFS patients (Table 2). The areas under the ROC curve for lactate and base excess were 0.733 (95% CI: 0.635–0.831) and 0.612 (95% CI: 0.507–0.717), respectively

(Fig. 2). The performance of lactate and base excess at the selected thresholds is summarized in Table 3.

The median time elapsed between the first and the second seizure within 24 hours of recurrence group was 6.5 hours (interquartile range 5–12), and was analyzed through the ROC curves with lactate and base excess, which were significant in predicting recurrence of seizure. The areas under the ROC curve for lactate and base excess were 0.453 (95% CI: 0.294–0.611) and 0.496 (95% CI: 0.327–0.665), respectively.

TABLE 2. Univariable and multivariable logistic regression analysis for variables predicting recurrence of seizure within 24 h.

	Odds ratio (95% CI)	*p*
Univariable		
Male sex	1.59 (0.84–2.98)	0.153
Age >18 mon	0.55 (0.27–1.14)	0.109
Lactate >2.21 mmoL/L	4.60 (2.14–9.86)	<0.001
CRP >7.18 mg/dL	1.03 (0.50–2.13)	0.933
Base excess >−1.85 mmoL/L	2.11 (1.02–4.38)	0.044
pH >7.415	2.02 (0.98–4.18)	0.058
Multivariable		
Male sex	1.37 (0.70–2.66)	0.354
Age >18 mon	0.74 (0.54–1.00)	0.056
Lactate >2.21 mmoL/L	1.45 (1.04–2.03)	0.031
Base excess >−1.85 mmoL/L	1.38 (1.08–1.74)	0.009
pH >7.415	1.32 (0.82–2.13)	0.259

CI, confidence interval; CRP, C-reactive protein.

4. Discussion

This study is, to the best of our knowledge, the first report predicting the recurrence of seizure within 24 hours using lactate levels. In our study, lactate levels were found to be useful in predicting recurrence of seizure within 24 hours in SFS patients. Multivariable logistic regression analysis showed that lactate and base excess were independent variables in predicting recurrence of seizure within 24 hours in SFS patients. Base excess was also useful, but lactate levels were a better variable in the ROC analysis. In this study, the 2.21 mmoL/L lactate cutoff value was not significantly different from 2–2.5 mmoL/ L, as previously reported [12]. However, measurement of lactate was not useful in predicting the time elapsed between the first and the second seizure within 24 hours.

Although a lot of researches have been done on the recognition of factors causing FSs in children, the pathophysiology of FS is not clearly understood [13, 14]. Existing researches suggest a link between FS and inflammation [15, 16]. IL-1β, tumor necrosis factor-alpha (TNF-α), and IL-6 are important cytokines in the development of FS [16–18]. One of the important roles of these cytokines is the direct and indirect regulatory effects on neurons and neurotoxic neurotransmitters released during excitation or inflammation [19]. Previous studies supported the hypothesis that increased cytokines play an important role in the development of FS. However, it is not convenient or efficient to measure cytokines in various ED environments.

There have been several studies on laboratory factors for the differential diagnosis of CFS and SFS. Goksugur *et al.* [9] suggested that the NLR and the RDW were objective indicators for the differential diagnosis. Several studies also suggested that the mean NLR levels were higher in CFS than in SFS, and the differences were statistically significant [10, 11]. Elevated NLR is associated with an increased risk of FS, and this increase is seen as an indicator of inflammation [10].

The NLR is a measure of the proportion of systemic neutrophils and lymphocytes and is considered a parameter reflecting systemic inflammation. Neutrophils can induce the secretion of several inflammatory cytokines, especially IL-1β and TNF-α associated with the risk of FS [16, 20]. This study, consistent with other studies [10, 11], found that the recurrence group had higher NLR levels than those with the SFS group but the differences were not statistically significant.

The RDW is an indicator of variations in the size of red blood cells and has been widely used to investigate the cause of anemia [21]. The RDW was reported to be positively correlated with inflammatory markers [9], but the exact mechanisms that underlie the association between RDW and these diseases remain unknown. Goksugur *et al.* [9] reported that RDW was effective in differentiating FS types. However, in our study, RDW showed no role in predicting recurrence of seizure, like other studies [10, 11].

CRP is considered a useful marker of systemic inflammation. In several studies, CRP levels were significantly lower in FS patients compared to patients without FS [10, 22]. It can be suspected that patients with FS develop inflammatory process quickly enough that CRP levels do not reach their highest value [10]. However, no studies have shown statistically significant differences in CRP between patients with CFS and SFS, consistent with the results of our study [9–11].

Lactate is produced by most tissues, with the highest level of production found in muscles [23, 24]. Lactate is the end-product of non-oxidative glycolysis, and is accumulated at the sites of inflammation [25]. Additionally, lactate has begun to be recognized as an active molecule that regulates the immune response and as an indicator of the cell metabolism status [26]. Increases in lactate levels following a seizure are thought to be due to local muscle hypoxia during the seizure [27]. Once the seizure has resolved, the production of lactate ceases and lactate is rapidly removed through the kidneys and liver.

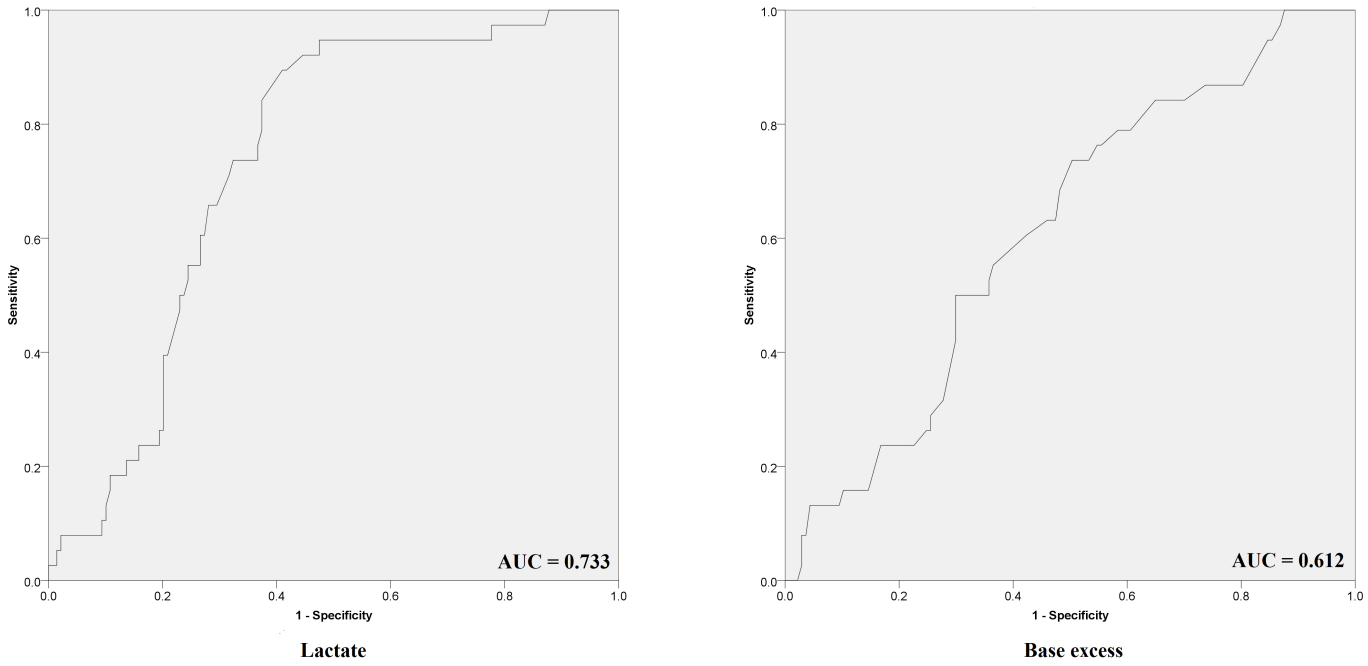

FIGURE 2. ROC curve of lactate and base excess in predicting recurrence of seizure within 24 hours. AUC, area under the curve; AUC of lactate = 0.733 (95% CI (confidence interval), 0.635–0.831), AUC of base excess = 0.612 (95% CI, 0.507–0.717).

TABLE 3. Sensitivity, specificity, and likelihood ratio values for predicting recurrence of seizure within 24 h.

Threshold	Sensitivity	Specificity	LR+	LR−	PPV	NPV
Lactate >2.21	65.8 (48.5–79.8)	70.5 (62.1–77.8)	2.23 (1.58–3.15)	0.48 (0.31–0.76)	37	62.7
Base excess >−1.85	57.8 (40.9–73.3)	60.6 (51.9–68.7)	1.47 (1.04–2.07)	0.69 (0.47–1.02)	43.4	56.6

LR, Likelihood ratio; PPV, positive predictive value; NPV, negative predictive value.

Persistently elevated lactate more than 1–2 hours following a seizure may suggest a different or concomitant underlying etiology and requires further consideration [27, 28]. In this study, the time from seizure to ED arrival and the time from the seizure to blood exam were significantly longer in the recurrence group than in the SFS group, whereas lactate levels were significantly higher in the recurrence group. The possibility of elevations in lactate levels due to systemic inflammation, not seizure should be considered in patients with recurrence of seizure within 24 hours.

Although there is a result that abnormalities on magnetic resonance imaging can predict overlap of seizures, it is difficult to implement in ED [29]. A blood examination in ED is easy to perform, but the role of blood examination in children with FS is still controversial [4]. But prehospital capillary lactate in children was useful in differentiating epileptic seizures from febrile seizures, syncope, and psychogenic nonepileptic seizures [30]. And Costea *et al.* [31] found that high lactate level in FS patients was useful in predicting the stress hyperglycemia causing CFS. Glucose and lactate are closely related in metabolism, and stress hyperglycemia appears to be one of the pathologies associated with lactate in patients with CFS [31, 32]. Further studies on the metabolic factors of febrile seizures are needed. Based on these studies and the results of this study, lactate measurement in ED in FS patients may be useful in predicting the course of the disease. But considering its low sensitivity, specificity, positive predictive value, and negative predictive value, diagnostic utility is limited and predicting recurrence based on lactate measurement alone should be avoided. In addition, patients with SFS with high levels of lactate may require monitoring in the observation unit of the ED.

This study had several limitations. First, this study was designed as a retrospective medical record review. The patient's semiology was not observed by health care providers; the chart may contain inaccurate information. Second, this was a single-center study. The criteria and threshold for laboratory tests after FS may vary from institution to institution. The decision to measure lactate was based on the subjective discretion of the emergency physician based on the semiology of seizures and physical examination findings. In particular, nearly half of patients were excluded because of subjective discretion, which may increase the likelihood of selection bias. There was no analysis of patients who were excluded from the study because they were diagnosed with CFS during the observation due to high lactate. And the results are difficult to generalize to all patients with FS due to the small sample size of the study. Third, some of the SFS group may have been diagnosed with CFS in other hospital with recurrence of seizure within 24 hours. And lactate was not measured at revisit due to recurrence of seizure within 24 hours. Further studies involving serial measurement of lactate are needed. Fourth, because there were no cytokine measurements, the correlation between cytokine and lactate levels in FS patients could not be revealed. A prospective

multicenter study with a larger number of patients may be needed to confirm the results.

5. Conclusion

In this retrospective single-center study, high lactate levels were shown to be associated with recurrence of seizure within 24 hours in SFS patients. High lactate levels seem to be a useful predictor for recurrence of seizure within 24 hours in SFS patients. Further research is needed to address the limitations and support this conclusion.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

DL, HN, HYJ and YSC—contributed to the concept and design of study. DL, HJM, HJL DJ, and HJK—contributed to the collection, analysis and interpretation of data. DL— contributed to the drafting of the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Soonchunhyang University Institutional Review Board (IRB No. 2020-06-012). The IRB approved a request to waive the documentation of informed consent.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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