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Associations Between Time to Administration of Antiseizure Medications and Short-Term Clinical Outcomes in Adults With Status Epilepticus

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Background: Status epilepticus (SE) is a time-sensitive emergency that requires immediate treatment.

Objective: To analyze the associations between time to administration of antiseizure medications (ASM) and short-term clinical outcomes.

Methods: From January 1, 2014, to December 31, 2020, we performed a retrospective cohort study in adult patients who presented with SE. The primary objective was to analyze the association between the timing of ASM administration and mortality. The second and third objectives were to determine the relationship between the timing of ASM administration and length of hospital stay along with the modified Rankin Scale (mRS) at discharge, respectively.

Results: A total of 83 patients were enrolled. The mean age was 57 years. The mean length of hospital stay was 32 days. Benzodiazepine (BDZ) was prescribed as the first ASM in 79 (95.2%) patients. Levetiracetam was the second most frequently administered ASM (39, [47%]), followed by phenytoin (28 [33.7%]) and valproate (13 [15.7%]). Seventy-one patients (85.5%) had a seizure duration longer than t_2 period. Therapy delay in SE and underdosing of ASM were noted in both alive and dead groups. Although the mortality rate was 20.5% and was highest in super-refractory SE (15 [88.2%]), we found no statistically significant difference between in-hospital mortality and timing of ASM administration. For secondary outcomes, including length of hospital stay and mRS, a statistically significant finding was only noted in the category of timing of seizure onset to the first ASM ($P = .002$ and $P = .004$, respectively).

Conclusions: This study showed no significant association between timing of ASM administration and in-hospital mortality. Prolonged duration of SE tends to be associated with increased mortality. SE guidelines were not followed in a substantial proportion of SE patients.

Keywords: Status epilepticus, Mortality, Antiseizure medications, mRS

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Introduction

Status epilepticus (SE) is a life-threatening and time-sensitive emergency that requires immediate treatment. The definition of SE has varied over time. In 2015, a new conceptual definition of SE with 2 operational dimensions (t_1 and t_2) were proposed by the International League Against Epilepsy (ILAE) Task Force.[1] Time point t_1 indicates when treatment should be initiated, and t_2 indicates when long-term consequences may occur, including neuronal death, neuronal injury, and alteration of neuronal networks. The Task Force also proposes a new classification of SE that will provide a framework for clinical diagnosis and therapeutic approaches for each patient. For convulsive tonic-clonic SE, both time points have been estimated at 5 minutes and 30 minutes, respectively. For focal SE with impaired consciousness, t_1 is 10 minutes and t_2 is 60 minutes. Prolonged SE may lead to changes in the composition and location of gamma-aminobutyric acid A receptors and N-Methyl-D-aspartic acid receptors, leading to progressive resistance to benzodiazepines (BZD), development of refractory SE (RSE), and subsequently super-refractory SE (SRSE).[2-5]

Aforementioned, timing in the treatment of convulsive SE (CSE) is probably the most relevant and modifiable prognostic factor and influences CSE duration, SE-related morbidity, and mortality according to previous studies.[6, 7] However, one study showed only the subgroup of '>30 min' antiseizure medications (ASM) administration was associated with high in-hospital mortality.[8] This is important to clarify the adequate timing of performing ASM administration.

Thus, the aim of our study was to analyze the associations between time to administration of ASM and short-term clinical outcomes in adult with CSE as well as delays in treatment when compared to current SE guidelines.[9]

Methods

Participants

We searched the *International Classification of Diseases, Tenth Revision (ICD-10)* code G40 epilepsy and G41 SE in Ramathibodi's electronic medical record (EMR) from January 1, 2014, to December 31, 2020. All subjects must meet the eligibility criteria to be included in the study. Inclusion criteria consisted of adult patients (age ≥ 18) who were initially presented with SE with prominent motor symptoms according to a definition and classification of SE.[1] Exclusion criteria were as follows: patients who initially presented with nonconvulsive SE, psychogenic nonepileptic seizure, and incomplete clinical data.

Outcomes

The primary outcome measure was to analyze the association between the timing of ASM administration and in-hospital mortality. Secondary outcome measures were to determine the relationship between timing of ASM administration and length of hospital stay, usage of anesthetic agent, and modified Rankin Scale (mRS) at discharge, respectively. Appropriate dosing and delays of ASM compared to current guidelines of SE were retrospectively reviewed, as well as their impact on SE prognosis.

Study Design

This was a retrospective cohort analysis of the associations between time to administration of ASM and short-term clinical outcomes in SE patients who initially presented with prominent motor symptoms.[1] According to the guidelines, BDZ is the initial therapy of choice and should be given within the first 5 to 20 minutes of SE onset. If SE is refractory to BDZ, a stepwise ASM treatment is recommended. Thus, second line and third line ASM should be administered within 20 to 40 minutes and

40 to 60 minutes of seizure onset, respectively.[9] Timing was recorded in minutes and documented by reviewing EMR. In our study, duration of SE was categorized into 2 groups: within t_2, and more than t_2 period. Timing of seizure onset to first ASM administration were classified (< 10, 10 - 60, and > 60 minutes). Timing of seizure onset to second ASM and timing of first ASM to second ASM were categorized (≤ 60 and > 60 minutes). We obtained patient demographic data (age, sex, and history of epilepsy) and clinical variables. Collected clinical variables included SE semiology (axis 1 of ILAE classification of SE), SE etiology (axis 2), seizure duration, information on ASM (type of ASM, calculated dosage by bodyweight-based dosing and renal clearance adjustment according to the SE guidelines,[9] timing of ASM administration, and ASM-related complications), in-hospital mortality, mRS at discharge, length of stay, and complications. In addition, adequate ASM dosage were defined as bodyweight-based and renal clearance adjustment corresponding to SE guidelines.[9]

Statistical Analysis

Demographics and baseline clinical characteristics between patients who were alive or dead following SE were compared using the Mann-Whitney *U* test for continuous variables and chi-square test for categorical variables. Continuous and categorical data are displayed as mean (range) and numbers (percentage), respectively. Associations between timing of sequence of ASM administration and short-term clinical outcomes were analyzed by logistic regression analysis.

The Kruskal-Wallis test was used to analyze the association between the duration from the onset of seizure to time of sequential ASM administration and mRS scores at discharge. Statistical significance was set at a *P* value less than .05 ($P < .05$). Statistical analysis was performed using SPSS Software, version 26 (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp; 2019).

Results

Demographic and Clinical Variables

From January 1, 2014, to December 31, 2020, 2569 patients were found by searching *ICD-10* code G40 and G41 in EMR. Of 258 SE patients, 83 SE patients met all the criteria and subsequently were enrolled in this study. Demographic and clinical variables were summarized (Table 1). Mean age of the cohort was 57 years, and 39 (47%) were male. A history of epilepsy was found in 9 (10.8%) patients. Mean (range) length of hospital stay was 32 (3 - 183) days.

Interestingly, there were 71 (85.5%) patients who initially presented to the emergency department (ED) with a seizure duration longer than the t_2 period. There were 20 (24.1%) established SE patients, 14 (16.9%) patients diagnosed with RSE, and 49 (59.0%) patients with SRSE. As a result of a seizure duration longer than the t_2 period, the refractory nature of SE as time lapses and in-hospital mortality had been demonstrated in most of our patients ($P = .018$). Of the 17 mortality, 15 (88.2%) patients died from SRSE. There were only 12 (14.5%) patients whose duration of SE was within the t_2 period. Timing of seizure onset to first ASM, timing of seizure onset to second ASM, and timing of first ASM to second ASM were not statistically different between the alive and dead groups of patients. SE ILAE semiology (axis 1) and SE ILAE etiology (axis 2) were summarized (Table 1). The majority of our patients were CSE (71 [85.6%]), followed by myoclonic SE with coma (12 [14.5%]). Acute symptomatic seizure (62 [74.6%]) was the most common etiology of SE found in this study.

BDZ was prescribed as the first ASM in 79 (95.2%) patients. Four patients (4.8%) had non-BDZ as their first ASM. Levetiracetam was the second ASM most frequently administered (39 [47%]), followed by phenytoin (28 [33.7%]) and valproate (13 [15.7%]), respectively. There were only 3 patients who presented to the ED

before the t_2 period, and were successfully treated with their first ASM. Adequate dosage of the ASM was observed in 66 (79.5%) patients with the first ASM, and were substantially decreased with the second ASM (12 [14.5%]). Usage of ASM (not including BDZ and anesthetic agent) was not statistically different between alive and dead groups. All groups required at least 1 ASM for SE control. Continuous intravenous infusion (cIV) of an anesthetic agent was used as the third line drug in 55 (66.3%) patients with midazolam being the most frequent (52 [62.7%]). There were 28 (33.7%) patients who did not require the usage of anesthetic agents for SE control. Comparing between both groups, the usage of anesthetic agents and its complications including systemic hypotension requiring vasopressors and inotropes were significantly higher in the dead group ($P = .03$ and $P < .001$, respectively). Most of our patients had a high mRS (score 3 - 6) at discharge. The mortality rate was 20.5%.

Association Between Timing of ASM Administration and Outcome Variables

We found no statistically significant difference between in-hospital mortality and timing of ASM administration (Table 2). A statistically significant correlation was found between the timing of seizure onset to the first ASM and length of hospital stay ($P = .002$). But, its relationship to the timing of seizure onset to second ASM, and the timing of the first ASM to second ASM were not statistically significant (Table 3).

Association between the timing of ASM administration and mRS at discharge was summarized (Table 4). The timing of seizure onset to first ASM was the only category that was statistically significant ($P = .004$).

Table 1. Demographic and Clinical Variables

Characteristic	No. (%)			
	All (N = 83)	Alive (n = 66)	Dead (n = 17)	*P* Value*
Demographics				
Age, mean (range), y	57 (18 - 95)	57 (18 - 95)	58 (19 - 88)	.592
Male Gender	39 (47)	33 (50)	6 (35.3)	.279
History of epilepsy	9 (10.8)	8 (12.1)	1 (5.9)	.461
Length of hospital stay, mean (range), d	32 (3 - 183)	32 (3 - 145)	32 (3 - 183)	.531
Duration of SE				
Less than t_2	12 (14.5)	11 (16.7)	1 (5.9)	.260
Longer than t_2	71 (85.5)	55 (83.3)	16 (94.1)	-
Timing of treatment with ASM				
Timing of seizure onset to first ASM, mean (range), min	43 (2 - 420)	48.58 (2 - 420)	21.35 (2 - 122)	.134
< 10	40 (48.2)	28 (42.4)	12 (70.6)	.116
10 - 60	18 (21.7)	16 (24.2)	2 (11.8)	-
> 60	25 (30.1)	22 (33.3)	3 (17.6)	-

Table 1. Demographic and Clinical Variables (Continued)

Characteristic	No. (%)			
	All (N = 83)	Alive (n = 66)	Dead (n = 17)	*P* Value*
Timing of seizure onset to first ASM, mean (range), min	132.79 (17 - 1310)	140.17 (17 - 1310)	105.41 (29 - 303)	.134
≤ 60	19 (22.9)	15 (22.7)	4 (23.5)	.981
> 60	61 (73.5)	48 (72.7)	13 (76.5)	-
Timing of first ASM to second ASM, mean (range), min	94.59 (9 - 1005)	97.57 (9 - 1005)	83.53 (10 - 300)	.729
≤ 60	53 (63.9)	42 (63.6)	11 (64.7)	.879
> 60	27 (32.5)	21 (31.8)	6 (35.3)	-
Timing of ED arrival to first ASM, mean (range), min	17.59 (2 - 215)	17.38 (2 - 215)	19.5 (2 - 67)	.923
< 10	32 (38.6)	29 (43.9)	3 (17.6)	.449
10 - 60	5 (6)	5 (7.6)	0	-
> 60	4 (4.8)	3 (4.5)	1 (5.9)	-
Timing of ED arrival to second ASM, mean (range), min	127.57 (12 - 1220)	133.85 (12 - 1220)	75.75 (12 - 174)	.638
≤ 60	20 (24.1)	18 (27.3)	2 (11.8)	.863
> 60	17 (20.5)	15 (22.7)	2 (11.8)	-
Axis 1: Classification of SE with prominent motor symptoms				
Generalized CSE	36 (43.4)	31 (47)	5 (29.4)	.118
Focal onset evolving into bilateral CSE	35 (42.2)	28 (42.4)	7 (41.2)	-
Myoclonic SE with coma	12 (14.5)	7 (10.6)	5 (29.4)	-
Stage of SE				
Established SE	20 (24.1)	18 (27.3%)	2 (11.8)	.018
RSE	14 (16.9)	14 (21.2%)	0	-
SRSE	49 (59)	34 (51.5%)	15 (88.2)	-
Axis 2: Etiology of SE				
Acute symptomatic seizure				
Acute ischemic stroke	5 (6)	4 (6.1)	1 (5.9)	.735
Acute hemorrhagic stroke	8 (9.6)	7 (10.6)	1 (5.9)	-
Metabolic disturbance	7 (8.4)	5 (7.6)	2 (11.8)	-
Drug induced seizure	1 (1.2)	1 (1.5)	0	-
Hypoxic brain injury	12 (14.5)	7 (10.6)	5 (29.4)	-
CNS infection	8 (9.6)	5 (7.6)	3 (17.6)	-
Systemic infection	7 (8.4)	6 (9.1)	1 (5.9)	-

Table 1. Demographic and Clinical Variables (Continued)

Characteristic	No. (%)			
	All (N = 83)	Alive (n = 66)	Dead (n = 17)	*P* Value*
CNS autoimmune disease	6 (7.2)	5 (7.6)	1 (5.9)	-
Systemic autoimmune disease	4 (4.8)	3 (4.5)	1 (5.9)	-
Poor ASM compliance	3 (3.6)	3 (4.5)	0	-
Substance intoxication	1 (1.2)	1 (1.5)	0	-
Remote symptomatic seizure				
Postischemic stroke lesion	7 (8.4)	7 (10.6)	0	-
Posthemorrhagic stroke lesion	3 (3.6)	3 (4.5)	0	-
Progressive symptomatic seizure				
Brain tumor	11 (13.3)	9 (13.6)	2 (11.8)	-
ASM				
Type of first ASM				
Benzodiazepine	79 (95.2)	62 (93.9)	17 (100)	.582
Levetiracetam	3 (3.6)	3 (4.5)	0	-
Valproate	1 (1.2)	1 (1.5)	0	-
Adequate dose of first ASM according to SE guideline	66 (79.5)	52 (78.8)	14 (82.4)	.745
Type of second ASM				
Levetiracetam	39 (47)	27 (40.9)	12 (70.6)	.161
Valproate	13 (15.7)	11 (16.7)	2 (11.8)	-
Phenytoin	28 (33.7)	25 (37.9)	3 (17.6)	-
No usage of second ASM	3 (3.6)	3 (4.5)	0	-
Adequate dose of second ASM according to SE guideline	12 (14.5)	10 (15.2)	2 (11.8)	.674
Usage of ASM (not including benzodiazepine and anesthetic agent)				
1 ASM	19 (22.9)	18 (27.3)	1 (5.9)	.151
2 ASMs	24 (28.9)	19 (28.8)	5 (29.4)	-
3 ASMs	20 (24.1)	16 (24.2)	4 (23.5)	-
≥ 4 ASMs	20 (24.1)	13 (19.7)	7 (41.2)	-
Anesthetic agent				
Usage of anesthetic agent	55 (66.3)	40 (60.6)	15 (88.2)	.032
Midazolam	52 (62.7)	37 (56.1)	15 (88.2)	.014
Propofol	7 (8.4)	3 (4.5)	4 (23.5)	.012
Thiopental	2 (2.4)	1 (1.5)	1 (5.9)	.295

Table 1. Demographic and Clinical Variables (Continued)

Characteristic	No. (%)			
	All (N = 83)	Alive (n = 66)	Dead (n = 17)	*P* Value*
Use 1 type of anesthetic agent	50 (60.2)	50 (60.2)	11 (64.7)	.001
Use ≥ 2 types of anesthetic agents	5 (6)	5 (6)	4 (23.5)	-
No usage of anesthetic agent	28 (33.7)	28 (33.7)	2 (11.8)	-
Baseline mRS				
1	0	-	-	-
2	5 (6)	-	-	-
3	13 (15.7)	-	-	-
4	27 (32.5)	-	-	-
5	21 (25.3)	-	-	-
6	17 (20.5)	-	-	-
Complications				
Systemic hypotension requiring vasopressive agent	40 (48.2)	24 (36.4)	16 (94.1)	< .001
Nosocomial infection	45 (54.2)	34 (51.5)	11 (64.7)	.330

Abbreviations: ASM; antiseizure medication, CNS, central nervous system; CSE, convulsive status epilepticus; ED, emergency department; mRS, modified Rankin Scale; RSE, refractory status epilepticus; SE, status epilepticus; SRSE, super-refractory status epilepticus.

* $P < .05$ was statistically significance.

Table 2. Association Between Timing of ASM Administration and In-Hospital Mortality

Period	Dead, No (%) (n = 17)	OR (95%CI)	*P* Value*
Timing of seizure onset to first ASM, min			
< 10	12 (70.6)	Reference	1
10 - 60	2 (11.8)	0.29 (0.06 - 1.47)	.136
> 60	3 (17.6)	0.32 (0.08 - 1.27)	.105
Timing of seizure onset to second ASM, min			
≤ 60	4 (23.5)	Reference	1
> 60	13 (76.5)	1.02 (0.29 - 3.59)	.981
Timing of first ASM to second ASM, min			
≤ 60	11 (64.7)	Reference	1
> 60	6 (35.3)	1.09 (0.35 - 3.36)	.879

Table 2. Association Between Timing of ASM Administration and In-Hospital Mortality (Continued)

Period	Dead, No (%) (n = 17)	OR (95%CI)	*P* Value*
Timing of ED arrival to first ASM, min			
< 10	3 (17.6)	Reference	1
10 - 60	0	0 (0 - 1)	1
> 60	1 (5.9)	3.22 (0.25 - 41.53)	.370
Timing of ED arrival to second ASM, min			
≤ 60	2 (11.8)	Reference	1
> 60	2 (11.8)	1.20 (0.15 - 9.57)	.863

Abbreviations: ASM, antiseizure medication; CI, confidence interval; ED, emergency department; OR, odds ratio.

* $P < .05$ was statistically significance.

Table 3. Association Between Timing of ASM Administration and Length of Hospital Stay

Period	Length of Hospital Stay, Median (IQR), d	*P* Value*
Timing of seizure onset to first ASM, min		
< 10	25.5 (15.5 - 53)	
10 - 60	22 (9 - 46)	.002
> 60	14 (6 - 21)	
Timing of seizure onset to second ASM, min		
≤ 60	17 (9 - 58)	.553
> 60	21 (10 - 42)	
Timing of first ASM to second ASM, min		
≤ 60	20 (11 - 46)	.278
> 60	17 (6 - 41)	
Timing of ED arrival to first ASM, min		
< 10	16 (8.5 - 21.5)	
10 - 60	21 (4 - 23)	.062
> 60	4.5 (3 - 10)	
Timing of ED arrival to second ASM, min		
≤ 60	16.5 (9.5 - 22.5)	.156
> 60	14 (6 - 21)	

Abbreviations: ASM, antiseizure medication; ED, emergency department; IQR, interquartile range.

* $P < .05$ was statistically significance.

Table 4. Association Between Timing of ASM Administration and mRS at Discharge

Period	mRS (Score 0 - 5) at Discharge, Median (IQR)	*P* Value*
Timing of seizure onset to first ASM, min		
< 10	5 (4 - 6)	.004
10 - 60	4 (4 - 5)	
> 60	4 (3 - 4)	
Timing of seizure onset to second ASM, min		
≤ 60	4 (4 - 5)	.677
> 60	4 (4 - 5)	
Timing of first ASM to second ASM, min		
≤ 60	4 (4 - 5)	.804
> 60	5 (3 - 5)	
Timing of ED arrival to first ASM, min		
< 10	4 (4 - 5)	.188
10 - 60	4 (3 - 4)	
> 60	2.5 (2 - 4.5)	
Timing of ED arrival to second ASM, min		
≤ 60	4 (4 - 5)	.545
> 60	4 (3 - 5)	

Abbreviations: ASM, antiseizure medication; ED, emergency department; mRS, modified Rankin Scale; IQR, interquartile range.
* $P < .05$ was statistically significance.

Discussion

This is a 7-year retrospective cohort study to analyze the associations between time to administration of ASM and short-term clinical outcomes in adult with CSE. For the primary outcome, the precise relationship between timing of seizure onset to first ASM (< 10, 10 - 60, and > 60 minutes) and in-hospital mortality was not significantly demonstrated in our study. The mortality rate was 20.5% and significantly depended on the stage of SE, with the highest mortality in patients with SRSE. Of the 17 dead patients, the vast majority of them (16 [94.1%]) had a seizure duration longer than the t_2 period and subsequently developed SRSE (15 [88.2%]). Moreover, despite receiving their immediate first ASM treatment in less than 10 minutes after seizure onset (12 [70.6%]), these SE patients still had ongoing SE and a further seizure duration longer than the t_2 period. Although not statistically significant, there were 13 (76.5%) patients who had a timing of seizure onset to second ASM of more than 60 minutes, and subsequently had a prolonged duration of SE. Clinical data on axis 1 (semiology) and axis 2 (etiology of SE) did not statistically show a difference between both groups. The majority of our patients did not have history of epilepsy. The most common etiology of SE was acute symptomatic seizure.

Comparing our data to the recommended guidelines, we thoroughly reviewed EMR and identified therapy

delay in SE, underdosing of first ASM, and inappropriate dosage of second ASM in both alive and dead groups. BDZ (79 [95.2%]) was most frequently used as the first ASM in our study. A selected choice of second ASM included levetiracetam (39 [47%]), phenytoin (28 [33.7%]), and valproate (13 [15.7%]), respectively. The appropriate dosage of ASM was seen in 66 (79.5%) patients with their first ASM and 12 (14.5%) patients with their second ASM, respectively.

A longer SE duration, therapy delay in SE, and inadequate ASM dosage was associated with refractoriness of SE and increased mortality. Our findings were similar to the results of SENSE registry of SE.[10] In SENSE registry, SE guidelines were not consistently followed. Moreover, underdosing of ASMs (first-line ASM [15%] and second-line ASM [41%]) and inappropriate selection of ASM were observed in SENSE registry.

However, our study showed no statistical association, the possible explanation being that other confounders, such as poor baseline mRS, acute and severe etiology of SE in admission, or several comorbidities may be causing a higher frequency of death, the mentioned therapy delay tending to be more prevalent in dead groups. This is crucial to stringently follow the SE guidelines.

For secondary outcomes including length of hospital stay and mRS, a statistically significant finding was only observed in the category of timing of seizure onset to first ASM ($P = .002$ and $P = .004$, respectively). Regarding to the length of hospital stay, this may be explained by the severity of RSE and SRSE and treatment delay in SE patients, which led to more severe cases and earlier mortality. This is an explanation for shorter length of hospital stay in delayed treatment group.

Regarding mRS, the majority of our patients (71 [85.5%]) initially presented to the ED with a seizure duration longer than t_2 period. Therefore, these SE patients were likely to develop SE refractoriness and long-term consequences. This resulted in a short length of hospital stay and a high mRS (score 3 - 5) at discharge.

The strength of our study includes the usage of the new ILAE 2015 definition and classification of SE and the current definitions of different stages of SE.[1] This provides more awareness of SE and makes this study more comparable to others. From ED arrival to discharge, we thoroughly reviewed EMR and identified factors that can help us to improve clinical outcomes and the prognosis of SE.

The limitations of this study include its retrospective design, the relatively small sample size, and a single site cohort study. Thus, our results may not be readily generalized to populations. Continuous electroencephalography monitoring was not performed at the ED and were not immediately available on admission in some cases. Our study did not include all semiology in axis 1, in-hospital SE, and patients with incomplete data.

Future Application

Achieving seizure control within the first 1 to 2 hours after seizure onset is a significant determinant of outcome.[10, 11] Despite well established guidelines, a culture of initial underdosing and therapy delay in SE had been demonstrated in ESETT study, SENSE registry, and our study. In clinical practice, SE guidelines were not followed in a substantial proportion of SE patients. Importantly, our study provides relevant information on quality improvement in SE management.

Conclusions

Although this study showed no significant association between timing of ASM administration and in-hospital mortality resulted from several comorbidities, prolonged duration of SE tends to be associated with increased mortality up to 20.5%. The majority cause is

that SE guidelines needed to be followed in a substantial proportion of SE patient

Article Information

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Ethics Approval

The research protocol was approved by the Human Research Ethic Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand (MURA 2021/874 on October 21, 2021).

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Conflict of Interest

The authors declare no conflict of interest.

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