

ORIGINAL ARTICLE

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Cost analysis on status epilepticus patients treated in intensive care units **Hamit Celik,**  **Ahmet Yardim***Buhara Hospital, Department of Neurology, Erzurum, Turkey*

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Abstract

Costs need to be analyzed for an effective provision of healthcare services. In our country, there are insufficient number of studies on cost analysis of the treatment of Status Epilepticus (SE). In this study, we aimed to investigate the treatment costs of patients admitted to intensive care units due to SE and contribute to the relevant data in our country. We conducted a retrospective review of patients who were admitted to the intensive care unit with a definitive diagnosis of SE between August 2018 and August 2019. We evaluated the demographic data, duration of hospitalization in the intensive care unit, the type of SE, the treatments given before and during hospitalization, inpatient medications and total costs and mortality rates in patients with SE. The mean age of 16 patients with SE was 41.1 ± 26.0 years, with a female/male ratio of 7/9. The patients were divided into three groups: 8 patients with primary generalized convulsive SE, 6 patients with focal onset generalized convulsive SE and 2 patients with non-convulsive SE. The average number of days of hospitalization in the intensive care unit was 7.44. Two of the patients died during the follow-up period. The average cost of medicines was 1344.25 TL (224.60 USD) and the total treatment cost was 4197.02 TL (701.25 USD). Analysis of costs in the field of healthcare provides sustainable and predictable health expenditures. A linear relationship has been shown between the number of days of hospitalization in the intensive care unit and the costs of medicines. An advanced age and acute symptomatic seizures are the leading causes of increase in the number of days of hospitalization. Multicenter studies with a higher number of participants are needed for a more accurate understanding of this data in our country.

Keywords: Status epilepticus, cost, intensive care unit, inpatient treatment**Introduction**

Status Epilepticus (SE) is a common neurological condition with high morbidity and mortality rates, requiring urgent diagnosis and early treatment. Epidemiological studies have reported the incidence of SE as 10-50/100000 / year [1]. Despite the new medical treatment, neurostimulation and surgical treatment approaches that have been used in the last 30 years, SE still has high mortality and morbidity rates. The mortality rate of SE is still around 20% [2]. SE has high treatment costs due to its high incidence, morbidity and mortality rates. Cost analyzes in epilepsy and status epilepticus have been frequently investigated in western countries [3-4]. In our country, Kutlu et al. discussed the annual treatment costs in their study examining the economic burden of epileptic patients. This study found a positive correlation between treatment costs and therapeutic response and disease severity in epileptic patients, and also showed that the cost of the medicines accounted for most of the treatment costs [5].

A study conducted by Güler et al.[6] examining inpatient treatment costs of SE reported that acute damage to the central nervous system and advanced age are factors that increase treatment costs. SE is an emergency situation that requires hospitalization. Our study evaluated the costs of drugs and inpatient treatment of SE patients hospitalized in intensive care units. In our study, we aimed to contribute to national data by evaluating inpatient treatment costs of SE patients admitted to intensive care units.

Materials and Methods

We conducted a retrospective review of patients who were admitted to the intensive care unit with a definitive diagnosis of SE between August 2018 and August 2019. Our study, which covers a certain period of time, has a cross-sectional study design. Our study included patients with convulsive or non-convulsive SE, aged 16 years or older, who were admitted to the intensive care unit with a definitive diagnosis of SE, but did not include patients with focal SE. The Classification of Status Epilepticus by Trinka et al. was used to establish the diagnosis of SE[7]. If a convulsive (tonic-clonic) seizure lasts 5 minutes or more and an absence seizure lasts 15 minutes or more, then it is defined as status epilepticus. We recorded and evaluated the demographic data of patients, any previous diagnosis of epilepsy, antiepileptic drugs

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currently used or started during hospitalization, SE treatments given during hospitalization, duration of hospitalization, mortality rate, concomitant diseases, medications used, and the total cost of inpatient treatment. In our study, we excluded the costs of examinations and medical care in the emergency department and included the costs after hospitalization in the intensive care unit. The etiology of SE included non-compliance with treatment recommendations (discontinuation, non-use of the drug, skipping dose and irregular use), infections, high fever, metabolic causes, the use of drugs that lower the seizure threshold, diseases that cause acute damage to the central nervous system, and late symptomatic seizures. In addition, we detected patients who had status epilepticus in the first episode of seizures and calculated SE-induced mortality rates. Ethical approval of the study was obtained from the Ethics Committee of Erzurum Regional Training and Research Hospital (ethics committee number 2019/16-154).

The examination of the regression models between the duration of hospitalization and drug costs of the patients in the intensive care unit showed that the highest determination coefficient was obtained by the linear regression model ($R^2 = 0.99$). In addition, the regression equation for this model was: $y = 564.613 + 256.654 \times \text{days}$. Similarly, the examination of the regression models for the correlation between hospitalization times and total costs in the intensive care unit showed that the highest determination coefficient was obtained by the linear regression model ($R^2 = 0.97$), and the regression equation for this model was: $y = 1221.221 + 728.503 \times \text{days}$.

Statistical analysis

For establishing the regression models between the duration of stay in the intensive care unit and the costs of medicines and the total cost, curve estimation approach including Linear, Quadratic, Compound, Growth, Logarithmic, Cubic, Inverse, and Power were all tested. Thus, the model with the highest determination coefficient (R^2) was chosen from the candidate models.

Results

The mean age of the patients was 41.1 ± 26.0 years. Nine of these patients were male (56.3%) and 7 were female (43.8%), with a female / male ratio of 7/9 (Table 1). Thirteen patients (81.25%) had a previous diagnosis of epilepsy. Moreover, 3 (18.25%) patients had status epilepticus in the first episode of seizures. Two of the patients died during the follow-up period. The mortality rate was 12.5%. One patient was discharged with sequelae. The first patient (patient number 10 in Table 2) died on the 11th day of hospitalization due to SE developing after acute complete MCA infarction and the second patient (patient 11 in Table 2) died on the 15th day of hospitalization due to SE, who previously had lymphoma and acute posterior system stroke. All patients had at least one radiological neuroimaging study (Brain CT, MRI or both). Hypertension was the most common concomitant disease. The average number of days of hospitalization in the intensive care unit is 7.44 with an interval of 1-35 days (Table 1). Eight (50.0%) of patients had primary generalized convulsive SE (PrGTCS), 6 (37.5%) had secondary generalized convulsive SE (Sec-

GTCS) and 2 (12.5%) had non-convulsive SE. One of the patients with non-convulsive SE had typical absence SE, while the other had atypical absence SE (Table 2). The most common etiological causes of SE were lack of drug compliance in 4 patients, systemic or local infections and related high fever in 3 patients, acute symptomatic seizure in 3 patients (due to acute stroke), post-stroke seizures (PSSE) in 2 patients, metabolic causes in 1 patient, use of medications that lower seizure threshold in 1 patient, idiopathic causes in 1 patient, and systemic infection coexistent with lack of drug compliance in 1 patient (Table 3). All patients were given benzodiazepines as the primary treatment of SE in the emergency room. Diazepam (DZP) was given to 11 patients (68.8%) and midazolam (MDZ) to 6 patients (31.3%). Loading therapy was given to all patients. All patients were given a loading treatment including levetiracetam (LEV) in 14 patients (87.5%) and valproic acid in 2 patients (12.5%) (Table 4). Acute symptomatic seizures were identified in three of the patients (patients 5, 10 and 11 in table 2). One patient had bilateral posterior cerebral artery (PCA) infarction (patient number 11) and the other two (patients' number 5 and 10) had extensive middle cerebral artery (MCA) infarction. All inpatient examination and treatment costs of these patients were reflected in the total cost. Two of the patients died during follow-up (patients' number 10 and 11), one of whom had posterior system infarction and the other had complete MCA infarction. Thirteen patients (81.25%) had a previous diagnosis of epilepsy and 3 (18.25%) of these patients had status epilepticus in the first episode of seizures. (Table 3). The average drug cost of a patient in an intensive care unit was 1344.25 TL (224.60 USD) and the average total treatment cost was 4197.02 TL (701.25 USD). The highest number of hospitalization days was determined in elderly patients hospitalized for acute damage to the central nervous system. In addition, there were higher hospitalization days and cost rates in hospitalizations due to convulsive SE. Among patients hospitalized for SE, the use of levetiracetam was detected in 12 (92.30%) of 13 patients who had a previous diagnosis of epilepsy and were therefore receiving an antiepileptic treatment (Table 3). Electroencephalography (EEG) was performed in 12 of the patients (Figure 1).

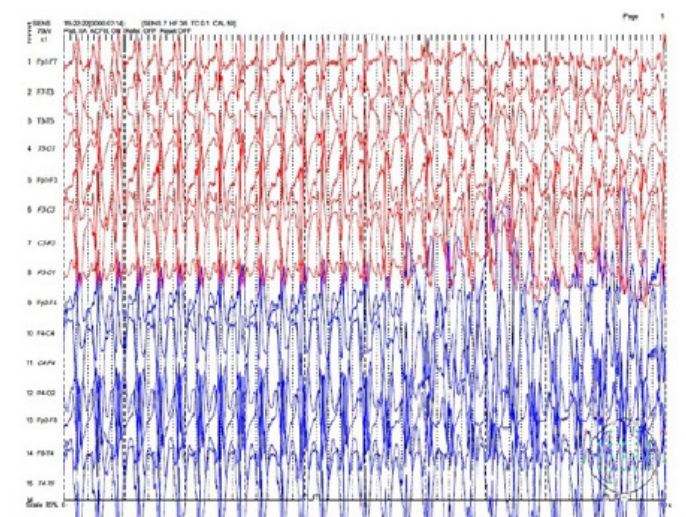


Figure 1. Graphical relationship between the number of days of hospitalization in the intensive care unit and drug costs in SE patients

Table 1. Demographic features, length of stay in the intensive care unit, drug and total costs.

Age / Year	
Mean	41.06
Median	24.5
Range	17-89
Gender / Number of people (%)	
Male	9 (15.3%)
Female	7 (3.8%)
Duration of Stay in Intensive Care / Day	
Mean	7.44
Median	5.5
Range	1-35
Drug cost / TL (USD)	
Mean	1344.25 (224.60)
Median	688 (114.95)
Minimum	90 (15.04)
Maximum	8600 (1436.90)
Total Cost (TL) "Dollar"	
Mean	4197.02 (701.25)
Median	2755.50 (460.39)
Minimum	534.88 (89.37)
Maximum	25414.0 (4246.21)

Table 2. Numerical values of the Types of Status Epilepticus

	Frequency	Percent	Valid Percent	Cumulative Percent
Valid				
Non-Conv.	2	12.5	12.5	12.5
Pri-GTCS	8	50.0	50.0	62.5
Sec-GTCS	6	37.5	37.5	100.0
Total	16	100.0	100.0	

Table 4. First-line treatments of SE and the frequency of drugs used in loading treatment

First-line drug for SE	Frequency	Percent	Valid Percent	Cumulative Percent
DZP	11	68.8	68.8	68.8
Drugs Used MDZ	5	31.3	31.3	100
Total	16	100	100	

Loading treatment of SE	Frequency	Percent	Valid Percent	Cumulative Percent
LEV	14	87.5	87.5	87.5
Drugs Used VPA	2	12.5	12.5	100
Total	16	100	100	

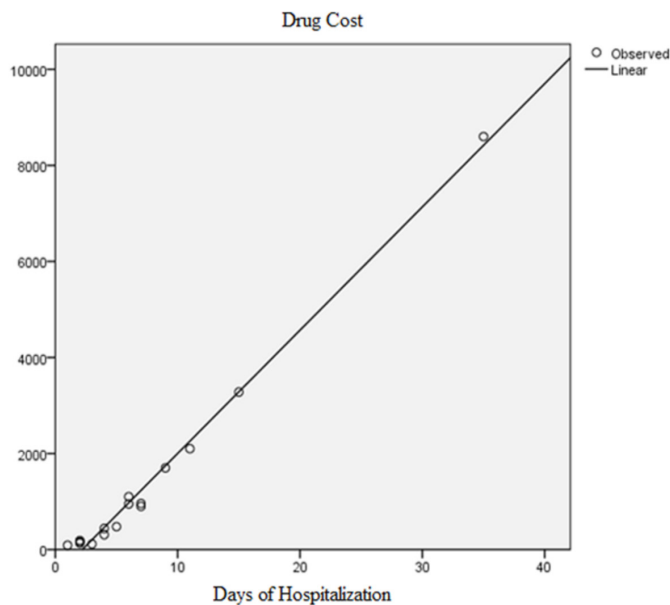
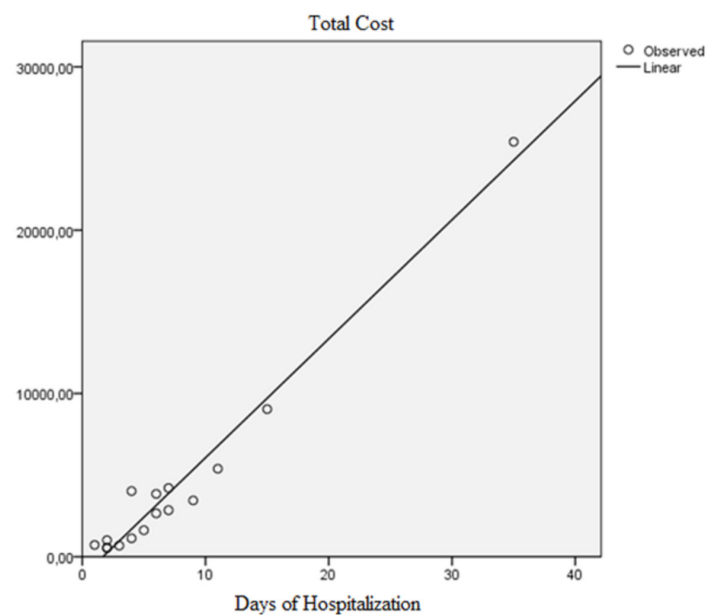
**Figure 2.** Graphical relationship between the number of days of hospitalization in the intensive care unit and the cost of inpatient treatment in SE patients**Figure 3.** EEG recording of a patient with SE

Table 3. Demographic characteristics of patients, clinical features of SE

Patient No	Age	Gender	Etiology	Type of SE	AED used by the patient before SE	Loading treatment of SE	Discharge Status	Concomitant Disease	Days of hospitalization	Drug Cost	Total Cost	Presence of Diagnosis of Epilepsy Before SE
1	21	F	Non-compliance with drugs	PRI-GTCS	LCM+LEV+	LEV	Discharged	-	6	950	2658	Y
2	17	F	Pneumonia	SEC-GTCS	VPA + LMT	LEV	Discharged	-	4	310	4020	Y
3	65	M	Hyponatremia	Non-conv.	LEV	LEV	Discharged	HT	3	116	683,28	Y
4	18	M	Non-compliance with drugs	Pri-GTCS	LEV+VPA+TPM	VPA	Discharged	MR	5	476	1625	Y
5	89	F	Acute Symptomatic Seizure	Pri-GTCS	LEV	VPA	Discharged	HT+DM	4	440	1128	Y
6	22	M	Acute Gastroenteritis	Pri-GTCS	LEV+LMT+VPA	LEV	Discharged	-	2	190	534,88	Y
7	23	F	UTI	Pri-GTCS	LEV+LCM	LEV	Discharged	-	2	136	566,49	Y
8	25	F	Idiopathic	SEC-GTCS	No	LEV	Discharged	-	1	90	723,98	No
9	23	M	Non-compliance with drugs	SEC-GTCS	LEV	LEV	Discharged	-	7	900	2853	Y
10	84	F	Acute Symptomatic Seizure	SEC-GTCS	LEV+VPA+PHT	LEV	Dead	HT + IPH	11	2100	5388	Y
11	63	M	Acute Symptomatic Seizure	SEC-GTCS	LEV	LEV	Dead	HT+Lymphoma	15	3280	9039	Y
12	24	M	Non-compliance with drugs+Pneumonia	Pri-GTCS	LEV+LTG	LEV	Discharged	-	35	8600	25414	Y
13	64	M	Late Symptomatic Seizure	SEC-GTCS	LEV	LEV	Discharged	HT+DM	2	160	1015	Y
14	69	F	Non-compliance with drugs	Non-conv.	LEV+VPA	LEV	Discharged	VP SHUNT+HT	7	960	4208	Y
15	21	M	Drugs that lower the seizure threshold	Pri-GTCS	No	LEV	Discharged	-	6	1100	3848	No
16	29	M	Urosepsis	Pri-GTCS	No	LEV	Discharged	-	9	1700	3447,67	No

Discussion

In order to ensure sustainable health expenditures, the amount and types of expenses should be analyzed in detail, by associating them with health care services. For effective use of health resources, the costs of diseases must be analyzed on a scientific basis [8]. According to the data of Turkish Statistical Institute (TurkStat), health expenditures in 2018 were 165 billion 234 million TL, which increased by 17.5% compared to the previous year [9]. In addition, the healthcare expenses tend to increase every year. Our study evaluated the cost of inpatient treatments and medications in SE patients treated in the intensive care unit. A linear relationship has been shown between the number of days of hospitalization in the intensive care unit and the costs of medicines and the total costs. Electroencephalography (EEG) was performed in 12 of the patients (Figure 2, Figure 3). In our study, the average cost of medications for an SE patient in the intensive care unit was 1344.25 TL (224.60 USD) and the average total cost of inpatient treatment was 4197.02 TL (701.25 USD). In the United States (USA), the cost of a single SE episode was an average of \$ 8,417 and the average cost per day of hospitalization was \$ 1458 [10]. In a study examining the inpatient treatment costs of SE patients in the USA and Germany, the average cost of treatment was 18.834 dollars and 8347 Euros, respectively [11]. There are also differences in the costs determined in studies conducted in the same countries. In another study conducted in Germany, examining the inpatient treatment costs of non-refractory, refractory and super-refractory SE, the average cost of inpatient treatment was € 4.063 (€) for non-refractory SE, € 4.581 for refractory SE and € 32,706 for super refractory SE [12]. Variations in costs can also be attributed to differences in pricing determined by health institutions and insurance companies of different countries. In our country, treatment costs are determined according to the Health Practice Communiqué (HPC), which is the main reason for the difference with other countries. The criteria in HPC have not been revised for many years, which has resulted in large differences in treatment costs in our country and western countries. In the literature, there is no publication investigating only SE patients in intensive care units. The limitations of our study included a one-year study period, limited number of patients, exclusion of patients under 16 years of age, and a single-center study design. Similar to previous studies in our country, our study reported higher numbers of hospitalization days and treatment costs in patients with acute symptomatic seizures. Two of the three patients (patients numbered 12, 11 and 10 in Table 3) with the highest cost and number of hospitalization days (patients numbered 10 and 11) were elderly patients with acute symptomatic seizures. In our study, the lack of drug compliance was the most common etiological cause of SE. Lack of drug compliance (skipping the dose, discontinuation of the drug or reduction of the dose without the supervision of the physician, etc.) is an important cause of SE, especially in developing societies [13]. Epileptic patients and their relatives should be insistently informed about the importance of regular use of medications and what to do if a dose is missed. In our study, infections were detected as another important etiological cause of SE. Epileptic patients should be made conscious about the importance of urgent application to health institutions in case

of high fever and infections. The mortality rate in our study was 2/16, which was consistent with the studies in the literature [2-14]. In our study, the rate of patients who had status epilepticus in the first episode of seizures was 3/16. This rate was found to be close to one third in the literature studies [15-16].

Conclusion

In conclusion, due to the high incidence and mortality rates of SE, studies on the cost of inpatient treatment of SE are important for making cost estimates. In this study, we evaluated the medications and total costs of SE patients hospitalized in the intensive care unit and thus analyzed the cost burden of these patients on our health care system. For cost analysis of SE, there is a need for further multicenter studies involving all age groups and with a higher number of participants.

Conflict of interests

The authors declare that they have no conflict of interest.

Financial Disclosure

All authors declare no financial support.

Ethical approval

Ethical approval of the study was obtained from the Ethics Committee of Erzurum Regional Training and Research Hospital (ethics committee number 2019/16-154).

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