

[ORIGINAL ARTICLE]

The Prehospital Predictors of Tracheal Intubation for in Patients who Experience Convulsive Seizures in the Emergency Department

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Abstract:

Objective To identify the prehospital factors predicting the performance of tracheal intubation (TI) at the emergency department (ED) in patients with convulsive seizure or epilepsy.

Methods We performed a retrospective analysis of seizure patients who underwent TI at the ED soon after arrival. The clinical variables obtained in the prehospital setting were reviewed.

Patients The study population included consecutive adult patients who were transported to an urban tertiary care ED due to convulsive seizure between August 2010 and September 2015.

Results Among the 822 eligible patients, 59 patients (7.2%) underwent TI at the ED. Four independent prehospital predictors were identified using multivariate analysis: age ≥ 50 years (+1 point), meeting the definition of convulsive status epilepticus (+4 points), and an on-scene heart rate of ≥ 120 bpm (+1 point) led to a higher likelihood of TI, while a higher on-scene (alert or confused) level of consciousness (-3 points) led to a lower likelihood of TI. The derived prediction rule (the sum of all points) had good predictive performance with an area under the curve of 0.88 (95% confidence interval: 0.79-0.97), a sensitivity of 0.62, a specificity of 0.91, and a positive likelihood ratio of 10.6, when the cut-off value was set to 5 points.

Conclusion We constructed a simple prehospital prediction rule to help predict the need for TI in seizure patients, even in the prehospital phase. This may possibly lead to the more effective management of seizure patients in the ED.

Key words: convulsive seizure, tracheal intubation, endotracheal intubation, prehospital prediction, convulsive status epilepticus

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Introduction

In the emergency treatment of patients with generalized seizure, especially those with status epilepticus, tracheal intubation (TI) is sometimes required in order to secure the airway and support respiration (1). For example, multicenter studies have reported that approximately 14-20% of patients with convulsive status epilepticus undergo TI at the emergency department (ED) (2-6). It was also reported that older or male patients, or those with ongoing seizure upon

arrival at the ED are more likely to be intubated (6). Some earlier guidelines have proposed conditions that may indicate the need for TI, including (1, 7): continuous status epilepticus (CSE), even after use of sufficient benzodiazepines; hypoxia ($\text{SaO}_2 < 90\%$) or respiratory failure due to hypoventilation or airway obstruction, the need for airway control during the sedation accompanying antiepileptic drug infusion, and severe consciousness disturbance.

The earlier identification of patients who are potential candidates for TI may lead to an earlier decision and in turn, more effective seizure treatment. This is especially im-

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Table 1. Basic Characteristics (Derivation Subgroup, N=620).

variables	odds ratio (95% CI)	not intubated (n=574)	intubated (n=46)	p value	
age (y/o)	-	38 (25-55)	57 (49.3-67.8)	<0.001	***
age≥50 (yes)	6.49 (3.19-14.1)	174	34	<0.001	***
sex (male)	1.10 (0.56-2.30)	387	32	0.87	
CSE ^a (yes)	21.8 (6.86-111.5)	227	43	<0.001	***
maximum duration of convulsion (min)	-	3 (1-5)	30 (20-30)	<0.001	***
maximum duration of convulsion≥30 min (yes)	40.9 (19.0-93.6)	33	33	<0.001	***
concurrent alcohol use (yes)	1.03 (0.35-2.56)	73	6	1	
first convulsion (yes)	1.01 (0.51-1.95)	211	17	1	
head/neck trauma following seizure (yes)	0.09 (0.002-0.55)	112	1	0.001	**
known CNS ^b lesions (yes)	3.64 (1.89-7.06)	132	24	<0.001	***
taking AED ^c (yes)	1.25 (0.64-2.39)	207	19	0.53	
taking antidepressants/antipsychotics (yes)	0.60 (0.18-1.57)	97	5	0.41	

a: convulsive status epilepticus, b: central nervous system, c: antiepileptic drugs

portant for physicians in countries or regions where it is difficult to perform TI or administer anticonvulsants in the pre-hospital setting due to legal restrictions. To the best of our knowledge, however, the prehospital predictors of possible indications for TI have never been investigated, even in a single-center study. Thus, we aimed to identify the prehospital predictors of TI in the ED based on the limited information that can be obtained by emergency medical services (EMS) in the prehospital setting. This information includes the on-scene level of consciousness and vital signs.

Materials and Methods

In the present single-center retrospective study, we performed univariate and multivariate analyses of cases in which TI was performed in the ED for patients with convulsive seizure or epilepsy. The ED of the National Center for Global Health and Medicine hospital is an urban, tertiary care department in the central region of Tokyo, Japan that treats over 10,000 patients annually.

We reviewed the cases of 822 consecutive adult patients who were transported to the ED and who were treated for convulsive seizure [generalized convulsive seizure or secondary generalized seizure (regardless of the presence of partial symptoms at the onset of seizure) (8)] between August 2010 and September 2015. Patients with convulsions due to syncope, cardiovascular or psychogenic causes, involuntary movement, or shivering were excluded from the study. The patients in whom intubation was performed for the exclusive purpose of subsequent surgery (e.g. subarachnoid hemorrhage) were also excluded. Anticonvulsants were not administered prior to by the EMS staff in any cases due to legal restrictions for ambulance crews in Japan. None of the patients had undergone prehospital TI.

The patients' basic characteristics, on-scene vital signs, and levels of consciousness were measured by the EMS staff and the other clinical data that were collected are shown in Table 1. The on-scene level of consciousness was

measured using the Japan Coma Scale (JCS), which is an easy tool for assessing a patient's level of consciousness (in Japan the JCS is the scale that is most frequently used to assess the level of consciousness) (9). Simply, JCS 0 corresponds to an alert state, JCS I corresponds to a confused state, JCS II corresponds to a somnolent or stuporous state, and JCS III indicates a comatose state. Although we preferred using the Glasgow Coma Scale (GCS), we had to rely on the JCS as a measurement of the level of consciousness, as EMS personnel in Japan use the JCS more frequently than the GCS. If the patient had consumed alcohol within 4 hours of the onset of seizure, we presumed the concurrent use of alcohol. The maximum duration of the convulsion was based on estimations by bystanders, the EMS staff, or the hospital staff. Here, CSE was defined as (1) a continuous seizure of 5 minutes or longer; or (2) repeated seizures between which there was an incomplete recovery of consciousness, as defined in the International League Against Epilepsy (ILAE) report of 2015 (10). The diagnosis in each case was confirmed retrospectively by two or more neurologists in our hospital.

In the present study, neurologists estimated the etiologies of the seizures with reference to the ILAE classifications (11). As such, a provoked seizure was defined as "seizures occurring in close temporal association with an acute systemic, metabolic, or toxic insult or in association with an acute central nervous system (CNS) insult (infection, stroke, cranial trauma, or acute alcohol intoxication or withdrawal)". An unprovoked, remote symptomatic etiology refers to seizure occurring after stroke, trauma (post-head injury or post-surgery), CNS infection or inflammation, chronic alcohol abuse without apparent evidence of alcohol withdrawal or other similar conditions. An unprovoked, progressive symptomatic etiology refers to seizures occurring due to brain tumors, autoimmune CNS disorders, or neurodegenerative diseases such as Alzheimer's disease. Unprovoked, idiopathic epilepsy refers to seizures that occur without any identifiable causes (other than symptomatic eti-

ologies) or in patients who have already been diagnosed with epilepsy. An unprovoked, cryptogenic etiology is defined as a single seizure in which the apparent cause is identified.

Primary outcome measure

The primary endpoint was set as the performance of TI in the ED. The decision to perform TI and start mechanical ventilation is usually made by emergency physicians soon after the patient's arrival, in parallel with the standard evaluation and treatment for the seizure. The facility's rough indications for TI in patients with convulsions include the following: repeated or continuous seizure that does not terminate even with the use of sufficient doses of benzodiazepines, respiratory failure due to hypoventilation or airway obstruction, the requirement of airway control due to sedation accompanying antiepileptic drug infusion, or severe consciousness disturbances (total GCS score: ≤ 8). Many of the patients exhibited two or more of the conditions listed above, and some medical records did not clearly indicate why TI was performed. All of the intubation procedures were performed at the ED by well-trained emergency physicians. No detailed data were available on intubation failure; however, the rates of intubation failure are usually very low. Some of the intubated patients were extubated during the initial treatment at the ED following the termination of the seizure after they their consciousness recovered and when they had sufficient spontaneous respiration.

Statistical analysis

We analyzed the cases in which TI was performed at the ED. The 822 eligible patients were randomly divided into derivation and validation subgroups at a ratio of approximately 3:1 (derivation subgroup, $n=620$; validation subgroup, $n=202$).

We performed a univariate analysis for the derivation subgroup. Fisher's exact test was used to analyze bimodal variables and the Mann-Whitney U test was used to analyze continuous variables. The values of each variable are shown as the median and interquartile range (IQR). The continuous variables were also converted to bimodal variables with the use of appropriate cut-off values.

We next performed a multivariate logistic regression analysis. Variables that were identified as being clinically favorable and/or significant in the univariate analysis were included in the multivariate analysis. A stepwise selection procedure was used to create a best-fitting model. The final number of variables was limited to ≤ 4 in order to achieve adequate statistical power. An analysis of deviance revealed that the model significantly fit the data ($p < 0.0001$). We confirmed that there were no problems with the multicovariation analysis by ensuring that all of the variance inflation factors for each variable were < 5 . Adjusted odds ratios (ORs), 95% confidence intervals (CIs), and p values were calculated for each independent variable. The validity of the final model that was used in the derivation subgroup

was evaluated using a receiver-operating characteristic (ROC) curve. We calculated the area under the curve (AUC). Estimate-weighted adequate integer points were assigned for each derived independent variable in the final model to construct a prediction rule. This rule was evaluated in the validation subgroup, and the appropriate cut-off point was selected in order to achieve a highly specific cut-off point. The AUC, sensitivity, specificity, positive likelihood ratio, and positive predictive value were calculated.

All of the statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for the R software program (The R Foundation for Statistical Computing, Vienna, Austria) (12).

Study approval

The data collection and the analysis in this study were approved by the institutional review board. This study was a retrospective observational study that was performed without obtaining written informed consent from the patients.

Results

Among the 822 eligible patients, 59 patients (7.2%) underwent TI at the ED. In addition, among the 270 patients with CSE, 43 patients (15.9%) underwent TI. None of the patients received non-invasive ventilation support soon after their arrival at the ED.

Tables 1 and 2 show the basic descriptions and the on-scene EMS characteristics, respectively, of the patients in the derivation subgroup ($n = 620$). In the derivation subgroup, 46 patients (7.4%) underwent TI. The patients who were significantly more likely to be intubated at the ED included those who were older, patients with known CNS lesions, patients with longer maximum durations of convulsion, patients with higher on-scene heart rates, systolic blood pressures and peripheral capillary oxygen saturation (SpO_2), and patients with lower levels of consciousness. Among the factors that are usually available to the EMS staff at the time of ambulance transportation, meeting the definition of CSE or an on-scene comatose state were most likely to result in TI. On the other hand, patients with higher levels of consciousness or head or neck trauma following the seizure were less likely to undergo TI. In addition, patients who underwent TI took significantly longer to be transported to the ED than those without TI—the median duration in intubated patients was 9.5 minutes (IQR, 7.0-12.8), while that in non-intubated patients was 8 minutes (IQR, 5.0-11.0) (Mann-Whitney U test, $p < 0.01$).

Table 3 summarizes the estimated etiologies of seizures in the whole study population (both the derivation and validation subgroups). Patients with seizures with remote or progressive symptomatic etiologies were significantly more likely to be intubated, while those with idiopathic epilepsy were less likely to be intubated.

Eight variables that were significant in the univariate

Table 2. On-scene EMS^a Characteristics (Derivation Subgroup, N=620).

variables	odds ratio (95% CI)	not intubated (n=574)	intubated (n=46)	p value	
HR ^b (bpm)	-	108 (90-120)	120 (108-139.5)	<0.001	***
HR ^b ≥120 (yes)	3.39 (1.75-6.75)	192	29	<0.001	***
SBP ^c (mmHg)	-	132 (120-153.5)	160 (132.5-187)	<0.001	***
SBP ^c ≥150 (yes)	3.70 (1.91-7.37)	181	29	<0.001	***
SpO ₂ ^d (%)	-	96 (95-98)	95 (91-97)	<0.001	***
JCS ^e 0 (alert): (yes)	0.12 (0.003-0.70)	92	1	0.008	**
JCS I (confused): (yes)	0.12 (0.05-0.25)	403	10	<0.001	***
JCS 0 or I (yes)	0.05 (0.02-0.11)	495	11	<0.001	***
JCS II (somnolent/stuporous): (yes)	2.11 (0.75-5.14)	45	7	0.094	
JCS III (comatose): (yes)	24.4 (11.8-52.0)	34	28	<0.001	***
Time from call for EMS ^a to the arrival of EMS ^a at the scene (min)	-	6 (5-8)	7 (5-9)	0.623	
Time required for transportation to the ED ^f (min)	-	8 (5-11)	9.5 (7-13)	0.006	**

a: emergency medical service, b: heart rate, c: systolic blood pressure, d: peripheral capillary oxygen saturation, e: Japan Coma Scale, f: emergency department

Table 3. Estimated Etiology (All Patients, N=822).

etiology	odds ratio (95% CI)	not intubated (n=763)	intubated (n=59)	p value	
provoked	1.67 (0.73-3.50)	83	10	0.196	
remote/progressive symptomatic	3.48 (1.96-6.27)	225	35	<0.001	***
unprovoked idiopathic epilepsy	0.09 (0.02-0.29)	278	3	<0.001	***
cryptogenic etiology	0.76 (0.35-1.52)	177	11	0.520	

Table 4. Final Model.

variables	adjusted odds ratio	lower 0.95	upper 0.95	p value	
(Intercept)	0.02	0.004	0.071	<0.001	
age 50 or older (yes/no)	2.62	1.19	5.75	0.016	*
CSE ^a (yes/no)	11.1	3.28	37.8	<0.001	***
on-scene HR ^b ≥120 (yes/no)	2.84	1.37	5.89	0.005	**
on-scene JCS ^c 0 or I (yes/no)	0.12	0.05	0.26	<0.001	***

a: convulsive status epilepticus, b: heart rate, c: Japan Coma Scale

JCS 0 or I corresponds to clear (JCS 0) or confused (JCS I) level of consciousness.

Table 5. Prediction Rule.

predictor	points
50 years or older (yes)	+1
CSE ^a (yes)	+4
on-scene HR ^b ≥120 (yes)	+1
on-scene clear or confused level of consciousness (yes)	-3

a: convulsive status epilepticus, b: heart rate

analysis were simultaneously included in the multivariate logistic regression analysis. We did not include the on-scene SpO₂ in the analysis, because of the inconsistency in the amounts of oxygen given to each patients during in the pre-hospital setting, which could have been a confounding in the multivariate analysis. Patients with higher on-scene levels of consciousness were analyzed in the same category (“on-

scene JCS 0 or I”). After a stepwise selection procedure, the final model was derived (Table 4). The following independent variables were identified: older age (≥50 years), adjusted OR 2.62 (95% CI: 1.19-5.75); meeting the definition of CSE, adjusted OR 11.1 (95% CI: 3.28-37.8); higher on-scene HR (120 bpm or higher), adjusted OR 2.84 (95% CI: 1.37-5.89); and higher on-scene level of consciousness (JCS 0 or I), adjusted OR 0.12 (95% CI: 0.05-0.26). This final model fit the data well and had good prediction performance. In the derivation subgroup, the AUC of the ROC was 0.91 (95% CI: 0.87-0.95).

The prediction rule, which was constructed by assigning appropriate integer points to each of the independent variables is shown in Table 5 [≥50 years, +1; CSE, +4; on-scene HR ≥120 bpm, +1; higher on-scene level of consciousness (clear or confused state), -3]. In the validation phase, this

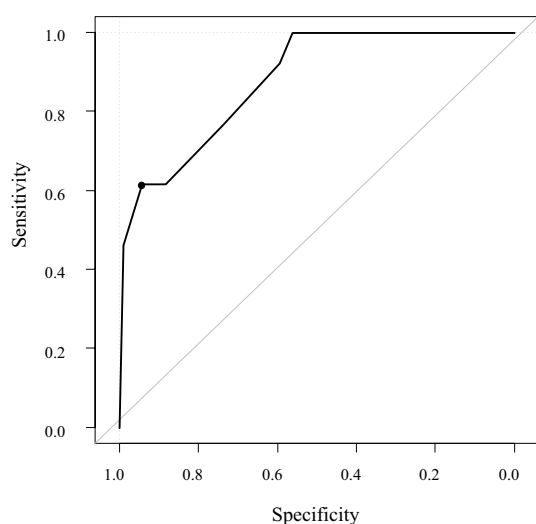


Figure 1. The receiver operating characteristic (ROC) curve of the prediction rule in the validation subgroup (n=202). This prediction rule showed good prediction performance with an area under the ROC curve of 0.88 (95% CI: 0.79-0.97).

prediction rule was applied to the validation subgroup, which yielded the ROCs shown in Fig. 1. This prediction rule had good prediction performance: the AUC of the ROC of 0.88 (95% CI: 0.79-0.97). The total cut-off score was set to ≥ 5 , which led to relatively specific performance. The sensitivity, specificity, and positive likelihood ratio were 0.62, 0.91, and 10.6, respectively. The positive predictive value was 0.46.

Fig. 2 shows the distribution of the frequency of intubation according to the prediction rule score in the total patient cohort. The prevalence of TI was approximately proportionate to the score.

Discussion

We described the clinical characteristics of patients who underwent TI and the independent prehospital factors that predicted TI. Our model reliably predicted the need for TI soon after arrival at the ED with almost excellent performance. It may help to estimate the likelihood of a need for airway control in the prehospital setting, and thereby lead to the more effective management of seizures in the emergency department.

Our results were generally consistent with those of an earlier study investigating the characteristics of patients with prehospital CSE that were associated with a need for TI (6), in which older age, male sex, and the seizure etiology of CNS tumors or stroke were identified in a univariate analysis as factors that predicted the need for TI. The greater need for respiratory support in older patients is backed by a higher mortality rate in the elderly seizure patients (13). The cut-off value for “older age” is a matter that requires further investigation, or it may be determined in each facility according to the patient’s attributes. The results of both ictal tachycardia (14) and excessive muscle exercise, such as limb

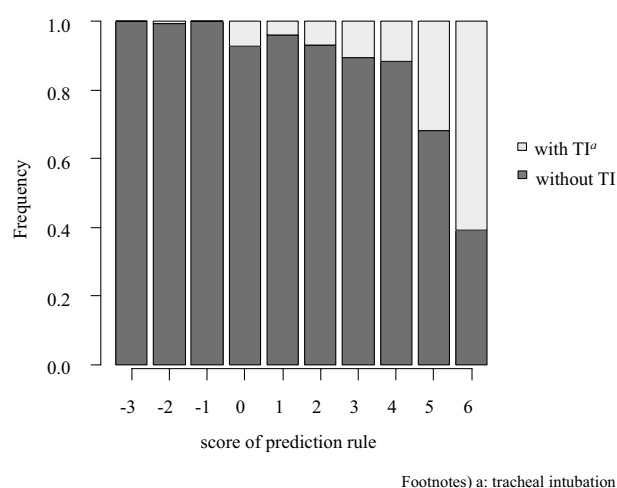


Figure 2. The distribution of scores in patients who underwent tracheal intubation (TI) among the entire cohort (n=822). The total score was approximately proportionate to the prevalence of TI.

convulsion could partly explain why a higher heart rate was found to be a predictor. In addition, did not include factors that reflect the respiratory status (such as SpO₂) because of their potential confounding influence—a higher heart rate can also be surrogate marker of hypoxia due to continuous seizure.

The fact that CSE was identified as having the largest OR for TI among the independent predictors highlights the importance of identifying this potentially clinical emergent state at an earlier stage—even before the patient reaches the hospital. Since time between the call and the arrival of the EMS staff at the scene was approximately 5-9 minutes, it is possible to recognize, even at the prehospital stage, whether or not a patient meets the definition of CSE.

We arbitrarily set the cut-off value of the model to 5 points. This resulted in a model in which patients with convulsions in the CSE state with lower levels of consciousness on the scene were more likely to undergo TI if they were older or had a higher heart rate on arrival. If we set the cut-off value to 6 points, the model would have become more specific but less sensitive, and would not have been able to predict the need for TI in younger patients. The question as to which of the cut-off values is more useful, leads to us another question: what kinds of patients or clinical situations would benefit the most from TI? Thus far, the indications for TI have not been established with sufficient evidence. Emergency physicians must decide whether to intubate a patient in a very short time under difficult circumstances. The information available in the emergency setting is limited, the patient’s level of consciousness might recover soon after the termination of the seizure, and unnecessary intubation has the potential to cause respiratory compromise. Furthermore, the impact that TI has on the short-term and long-term outcomes of seizures after acute-phase treatment remains uncertain.

The external validity of the indication for TI may be a

confounding factor in this study, as the study population was limited to patients with seizures who were treated in our ED. In other words, our results may merely reflect our facility's specific indications for TI (described in the Methods) and may not be applicable to other hospitals. In the present study, TI was performed for 15.9% of the patients with CSE, which is similar to the rates reported in earlier studies (2-6). In these studies, TI was performed in approximately 14-20% of the enrolled patients who met the definition of CSE. Although the results of the present study cannot be simply compared to those of these earlier randomized controlled trials, which compared the prehospital administration of anticonvulsants or a placebo (2-6), we suspect that the clinical practice of TI in our facility might be similar to those of other facilities. The external validation of our prediction rule is expected.

Although they were not prehospital factors, the underlying etiology of the seizure had a significant influence on the need for TI. The OR for TI in patients with a remote or progressive symptomatic etiology (including stroke and brain tumor) was high, while that for patients with idiopathic epilepsy was low. Since the former etiology increases with age (13) and the latter is frequently seen in younger patients, the difference in the prevalence of TI may be attributed to age. The exact reason why patients with idiopathic epilepsy were less likely to undergo TI remains unclear.

The actual number of patients in whom intubation was attempted but failed because of difficulties in intubation was unknown. However, earlier studies have reported that the rate of failed intubation in the ED is approximately 1-5% (15-18). Thus, we suspect that the influence of this on our results was limited.

Conclusion

We identified the prehospital factors that predicted the need for TI at the ED in patients with convulsive seizures and created a prediction rule. This prediction rule showed good performance, and may lead to the more effective management of seizure patients. Some questions remain regarding the clinical importance of our study, with respect to the external validity of the current results and the best indication for TI. Focused investigations are expected in the future.

The authors state that they have no Conflict of Interest (COI).

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