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ORIGINAL RESEARCH

Factors Influencing the Length of Emergency Intensive Care Unit Stay in Adult Tetanus Patients

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Objective: Tetanus remains a public health problem in developing countries. Patients with severe tetanus require long-term access to emergency medical resources. Here, we identified the risk factors for a prolonged length of stay (LOS) in the emergency intensive care unit (EICU) in adult tetanus patients.

Methods: We conducted a retrospective study using data from adult tetanus patients admitted to the EICU in our hospitals. K–M analysis was used for LOS analysis in the EICU, and the Log rank test was used for comparisons between groups. Cox proportional hazards regression model analyses were used to assess significant factors associated with LOS in the EICU.

Results: A total of 81 tetanus patients were included in the study. The patients had an average age of 59.39 ± 10.90 years (SD). The mean LOS was 18.1 days (median, 16.0 days; range, 0.6 days to 50.0 days). From 15 related factors, we identified two independent factors for prolonging the LOS of tetanus patients in the EICU: tracheotomy and mechanical ventilation. The risk of EICU retention in patients with mechanical ventilation was 55.3% greater than that in patients without mechanical ventilation (HR=0.447, 95% CI: 0.227–0.880, P=0.020); the risk of EICU retention was 86.2% greater in patients with tracheotomy than in those without tracheotomy (HR=0.138, 95% CI: 0.058–0.328, P<0.001).

Conclusion: Tracheotomy and mechanical ventilation support were associated with increased LOS in the EICU in adult tetanus patients, independent of the tetanus antitoxin dose. Clinicians must focus on spasm control and optimize airway management in tetanus patients in the EICU.

Keywords: tetanus, intensive care unit, length of stay, influencing factor, tracheotomy, mechanical ventilation

Introduction

Tetanus is a rare life-threatening disease that is often accompanied by paroxysmal spasm, autonomic dysfunction and even respiratory failure and has a high fatality rate. Tetanus is a vaccine-preventable noncommunicable disease, and the global tetanus vaccination initiative has achieved considerable success, with particularly significant declines in neonatal and maternal tetanus incidence.[1] To maintain protection, CDC recommends all adults get vaccinated against tetanus every 10 years. Once an adult has received a dose of Tdap, they can get Td or Tdap for their booster doses.[2] But vaccination rates among seniors are extremely low, and the incidence rate of tetanus is alarmingly high, which remains a critical public health problem.[3] The therapeutic aim of tetanus is to control spasticity and reduce the occurrence of cardiovascular instability events.[4] To achieve an optimal prognosis, patients with severe tetanus need long-term intensive care, longer hospital stays[5,6] and more expensive treatment costs[7] which places a large financial burden on their families.

Current research primarily focuses on the impact of factors on tetanus mortality rates, while a limited number of studies have documented that patients with greater tetanus severity, advanced age, prolonged mechanical ventilation, complications, and tracheostomy tend to have longer ICU stays.[8–10] Notably, while the mortality rate among tetanus patients is declining with advancing medical technology, their length of stay in the ICU is also increasing.[11,12] Therefore, in clinical practice, mastering the factors affecting the LOS in the EICU of tetanus patients and providing targeted interventions will help to optimize the

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clinical pathway of the ICU, improve the utilization of medical resources, and shorten the LOS in the ICU. Reducing the economic burden of patients' families and providing better diagnosis and treatment services for patients are highly important.

At present, there are few studies specifically on the factors influencing the length of ICU stay in tetanus patients. Therefore, this study retrospectively analyzed the case data of 81 tetanus patients admitted to the EICU of Xiangya Hospital, Central South University, over a 10-year period (2012–2022) and analyzed the factors affecting the LOS in the EICU, aiming to provide a basis for optimizing the diagnosis and treatment of tetanus and shortening the LOS of patients.

Materials and Methods

Ethics Approval and Consent to Participate

This retrospective study did not involve the collection of patients' private information and imposed no additional medical costs or physical distress on participants. All data were anonymized to safeguard participant privacy and prevent disclosure of personal identifiers, in strict adherence to confidentiality principles. The Ethics Committee of Xiangya Hospital, Central South University, approved this study with a waiver of informed consent (No. 202306134). All the methods were carried out in accordance with the Declaration of Helsinki.

Study Design

We retrospectively analyzed tetanus patients in the EICU. The Ethics Committee of Xiangya Hospital, Central South University, approved this study with a waiver of informed consent (No. 202306134).

Setting

Patients with tetanus admitted to the EICU of Xiangya Hospital, Central South University, from January 2012 to December 2022 were retrospectively enrolled as the study subjects.

Data Collection and Processing

Clinical data were collected from the electronic medical records system. A total of 15 factors that may influence the LOS were included, such as sex, age, underlying disease (hypertension, coronary heart disease, diabetes mellitus, chronic bronchial disease, chronic liver disease), and clinical score at the time of admission to the EICU (mild, moderate, severe, extremely severe). Events related to hospitalization in the EICU, such as cardiopulmonary resuscitation (CPR), mechanical ventilation, tracheotomy, total dose of benzodiazepines and tetanus antitoxin, complications (pneumonia, disuse atrophy of limbs, sepsis, multiple organ dysfunction syndrome, hypoxic-ischemic encephalopathy, septic shock, rhabdomyolysis, urinary tract infection, acute cerebral infarction, deep vein thrombosis of lower limb), vasoactive drugs (dopamine, norepinephrine, epinephrine, dobutamine, cedilanid, desmopressin, sodium nitroprusside, urapidil), combinations of other sedative drugs (propofol, phenobarbital sodium, dexmedetomidine, baclofen), analgesics (dezocine, pentazocine, fentanyl, remifentanil), antiarrhythmic drugs, and mean serum albumin (ALB) concentration, were reviewed. All the data were reviewed by two researchers (X.J. and S.C.S).

Selection of Participants

The inclusion criteria were as follows: 1) age at clinical diagnosis of tetanus ≥18 years and 2) need for intensive care according to the severity of the tetanus condition or the aggravation of underlying diseases caused by tetanus or the existence of critical complications at admission. The exclusion criteria were patients who were diagnosed with tetanus in other hospitals and who were transferred to our EICU more than 24 hours after treatment. Finally, 81 patients were included. The selection process of the study subjects is shown in Figure 1.

Outcome Measures

The purpose of this analysis was to identify the confounding factors affecting the LOS in the EICU for tetanus patients. The LOS in the EICU is defined as the time difference between the start of the patient's registration for admission to the EICU electronic medical record system and the time of departure from the EICU, which is also called the EICU lag time.

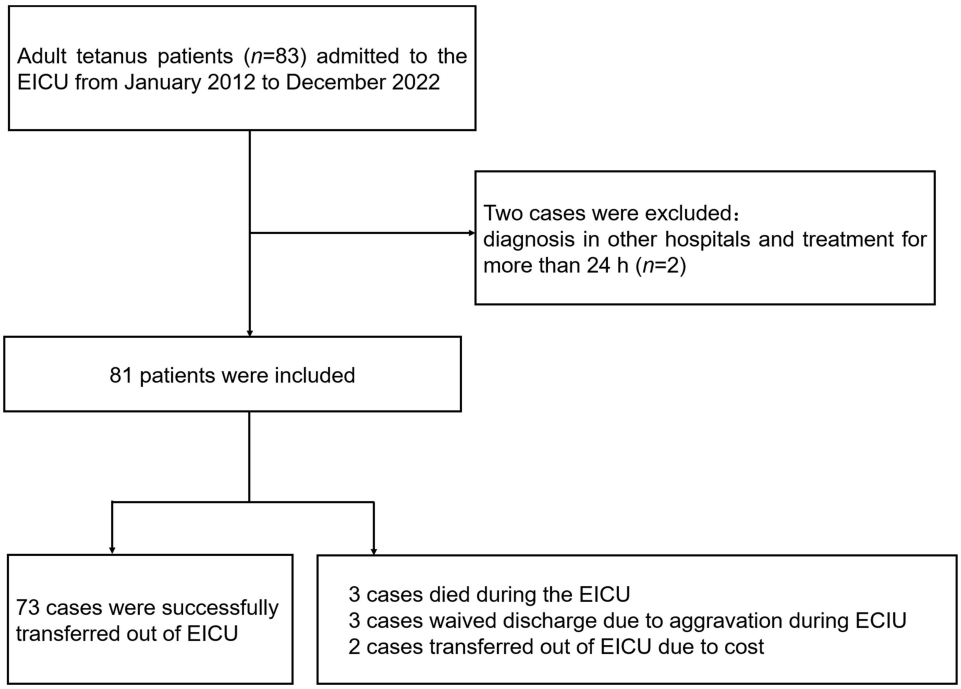

Figure 1 Selection process for the study subjects.
Abbreviation: EICU, emergency intensive care unit.

The factors affecting the LOS of tetanus patients in the EICU are complex. In this study, 15 factors that seemed reasonable for tetanus patients were selected from the hospital electronic medical records system for initial screening, including the controversial total dose of tetanus antitoxin and nutritional status.

Statistical Analysis

Data processing was performed using SPSS 26.0 statistical software. Normally distributed measurement data are expressed as the mean ± standard deviation, and nonnormally distributed measurement data are expressed as the median (interquartile range). Enumeration data are expressed as frequencies and percentages (%). K–M analysis was used for LOS analysis in the EICU, and the Log rank test was used for comparison of LOS in the EICU between groups. A total of nine influencing factors met the Cox proportional hazards assumption. Univariate Cox regression analysis revealed that six out of nine factors were associated with the LOS in the EICU. Multivariate Cox proportional hazards regression model analyses were used to assess six significant factors associated with the LOS in the EICU. In the process of multivariate Cox regression analysis, some missing data were filled by multiple interpolation. If the survival function curve after filling almost coincides with the original data, the data after multiple interpolation are basically consistent with the original data. A p value <0.05 was considered to indicate statistical significance.

Results

Characteristics of Study Subjects

A total of 81 tetanus patients were included in this study, with an average age of 59.39 ± 10.90 years (SD); 25 (30.9%) patients were > 65 years old, and 56 (69.1%) patients were ≤65 years old. There were 54 (66.7%) males and 27 females (33.3%). Over the 10-year period, the mean LOS was 18.1 days (median, 16.0 days; range, 14 hours to 50.0 days). After treatment, 73 (90.1%) patients were transferred to the general ward.

Main Results

A total of 9 factors that met the Cox proportional hazards assumption of P <0.05 were identified. Age, mechanical ventilation, tracheotomy, combination with other sedative drugs, analgesic drugs, clinical score grading at the time of

admission to the EICU, use of antiarrhythmic drugs, mean ALB concentration, and total dose of tetanus antitoxin were recorded, as shown in Table 1.

Univariate Cox regression analysis was performed on the 9 influencing factors, and the results showed that age, mechanical ventilation, tracheotomy, clinical score at the time of admission to the EICU, mean ALB concentration, and total dose of tetanus antitoxin had statistically significant effects on the LOS in the EICU (all P <0.05), as shown in Table 2.

The six factors in Table 2 with statistically significant differences were included to construct a multivariate Cox proportional hazards regression model. The analysis revealed that mechanical ventilation and tracheotomy had a statistically significant impact on the LOS in the EICU (all P <0.05), as shown in Table 3. The Kaplan-Meier curves for mechanical ventilation and tracheotomy are shown in Figure 2. The risk of EICU retention in patients on mechanical

Table 1 Preliminary Screening Factors for Cox Regression Analysis of the LOS in the EICU Among Tetanus Patients

Variables	N (%)	LOS in EICU (mean±SD, h)	log-rankχ^2	*P value*
Sex				
Man	54 (66.7)	456.5±295.6	1.918	0.166
Woman	27 (33.3)	391.3±281.4		
Age (years)				
>65	25 (30.9)	566.3±318.9	5.557	0.018
≤65	56 (69.1)	376.0±259.3		
Underlying diseases				
Yes	31 (38.3)	511.6±333.2	2.987	0.084
No	50 (61.7)	387.1±252.8		
CPR				
Yes	7 (8.6)	396.7±220.9	3.469	0.063
No	74 (91.4)	438.3±298.2		
Total dose of benzodiazepines [mg/(kg·h)]				
<0.22	56 (69.1)	440.2±295.3	0.384	0.536
≥0.22	25 (30.9)	423.2±286.2		
Complications				
Yes	61 (75.3)	449.0±303.1	1.643	0.200
No	20 (24.7)	391.3±252.9		
Mechanical ventilation				
Yes	34 (42.0)	606.7±266.4	28.637	<0.001
No	47 (58.0)	310.3±243.5		
Tracheotomy				
Yes	52 (64.2)	586.7±245.5	94.445	<0.001
No	29 (35.8)	162.2±123.8		
Vasoactive drugs				
Yes	18 (22.2)	584.0±318.0	2.666	0.081
No	63 (77.8)	392.1±270.1		

(*Continued*)

Table 1 (Continued).

Variables	N (%)	LOS in EICU (mean±SD, h)	log-rankχ^2	*P value*
Combination with other sedative drugs				
Yes	54 (66.7)	543.2±277.4	35.634	<0.001
No	27 (33.3)	217.8±188.6		
Analgesics				
Yes	48 (59.3)	547.4±301.2	33.716	<0.001
No	33 (40.7)	270.8±181.1		
Clinical score grading at the time of EICU admission				
Mild-moderate	65 (80.2)	387.3±276.9	7.150	0.007
Severe-extremely severe	16 (19.8)	627.4±274.8		
Antiarrhythmic drugs				
Yes	24 (29.6)	561.7±284.1	6.590	0.010
No	57 (70.4)	281.3±279.3		
Mean ALB concentration (g/L)				
<35	43 (53.1)	587.5±270.4	36.634	<0.001
≥35	38 (46.9)	261.8±208.4		
Total dose of tetanus antitoxin (U)				
<100,000	56 (69.1)	397.3±277.4	7.604	0.006
≥100,000	16 (19.8)	650.9±308.6		

Abbreviations: LOS, length of stay; EICU, emergency intensive care unit; CPR, cardiopulmonary resuscitation; ALB, serum albumin.

Table 2 Univariate Cox Regression Analysis of Factors Associated with the LOS in the EICU Among Tetanus Patients

Factors	*B*	*SE*	Waldχ^2	HR (95% CI)	*P value*
Age (≤65 years old as reference)					
> 65 years old	−0.606	0.261	5.417	0.545(0.327–0.909)	0.020
Mechanical ventilation (Yes/No)*	−1.315	0.260	25.568	0.269(0.161–0.447)	<0.001
Tracheotomy (Yes/No) *	−2.947	0.369	63.895	0.053(0.025–0.108)	<0.001
Combination with other sedative drugs (Yes/No)*	−0.315	0.374	3.618	0.620(0.329–1.076)	0.082
Analgesics (Yes/No) *	−0.362	0.389	3.724	0.611(0.319–1.060)	0.076
Clinical score grading at the time of EICU admission (mild-moderate as reference)					
Severe-extremely severe	−0.814	0.312	6.803	0.443(0.241–0.817)	0.009
Antiarrhythmic drugs (Yes/No) *	−0.382	0.371	3.856	0.575(0.297–1.019)	0.067
Mean ALB concentration (≥35 g/L as reference)					
<35 g/L	−1.532	0.272	31.794	0.216(0.127–0.368)	<0.001
Total dose of tetanus antitoxin (<100000U as reference)					
≥100000U	−0.838	0.311	7.290	0.432(0.235–0.795)	0.007

Note: *, using "NO" as a reference.
Abbreviations: LOS, length of stay; EICU, emergency intensive care unit; ALB, serum albumin.

Table 3 Cox Multivariate Regression Analysis of Factors Associated with the LOS in the EICU Among Tetanus Patients

Factors	*B*	*SE*	HR (95% CI)	*P value*
Age (≤65 years old as reference)				
> 65 years old	−0.379	0.308	0.685(0.374–1.253)	0.219
Clinical score grading at the time of EICU admission (mild-moderate as reference)				
Severe-extremely severe	−0.388	0.344	0.679(0.346–1.331)	0.259
Total dose of tetanus antitoxin (<100000U as reference)				
≥100000U	−0.506	0.343	0.603(0.308–1.182)	0.141
Mechanical ventilation (Yes/No) **	−0.805	0.346	0.447(0.227–0.880)	0.020
Tracheotomy (Yes/No) **	−1.983	0.442	0.138(0.058–0.328)	<0.001
Mean ALB concentration (≥35 g/L as reference)				
<35 g/L	0.302	0.399	1.353(0.619–2.956)	0.449

Note: ** using "NO" as a reference.
Abbreviations: LOS, length of stay; EICU, emergency intensive care unit; ALB, serum albumin.

ventilation was 55.3% (HR=0.447, 95% CI: 0.227–0.880, P=0.020) greater than that in patients not on mechanical ventilation. The risk of EICU retention in patients who underwent tracheotomy was 86.2% (HR=0.138, 95% CI: 0.058–0.328, P<0.001) greater than that in patients who did not undergo tracheotomy. Other factors had no significant influence on the LOS in the EICU among tetanus patients (P > 0.05).

Discussion

Tetanus is a specific infection in which *Clostridium tetani* enters the body through damaged skin or mucosa, grows and reproduces in an anoxic environment, and produces toxins, causing paroxysmal myoclonus. Because *Clostridium tetani* is widespread in the surrounding environment, it is impossible to eliminate tetanus, and this disease can occur at any age.[13] Despite comprehensive medical treatment, the fatality rate of tetanus is still 15%-30% globally.[14] As of October 2021, 47 (80%) of the 59 countries identified as having the highest risk of maternal and neonatal tetanus have been confirmed to be free of maternal and neonatal tetanus.[15–17] Among adult tetanus patients, elderly individuals, females, and farmers are the

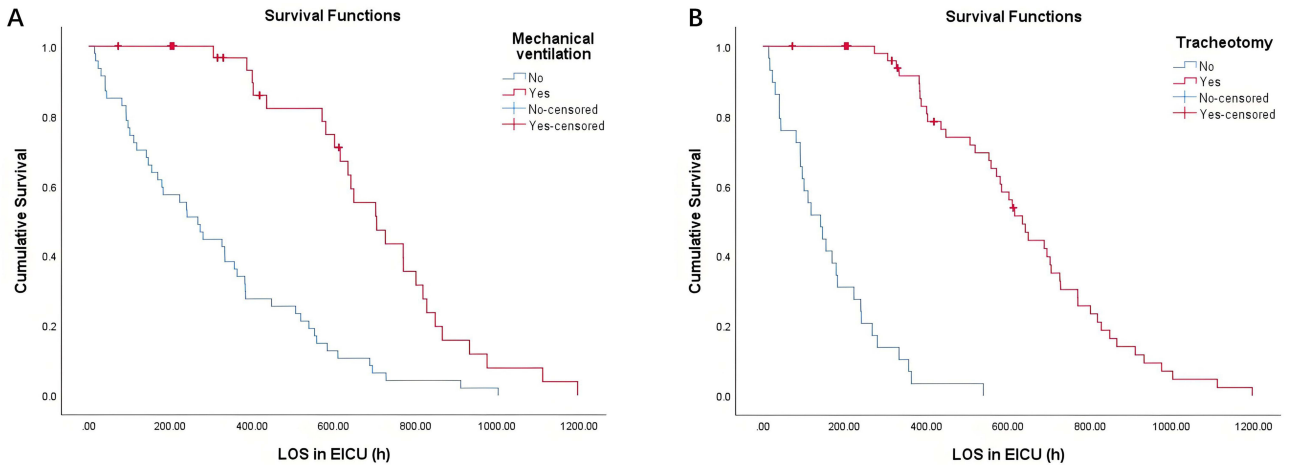

Figure 2 The Kaplan-Meier curves for mechanical ventilation and tracheotomy. (**A**) the Kaplan-Meier curves for mechanical ventilation; (**B**) the Kaplan-Meier curves for tracheotomy.
Abbreviations: LOS, length of stay; EICU, emergency intensive care unit.

main affected populations.[18,19] People who have been vaccinated against tetanus have an increased risk of tetanus infection when the level of tetanus antibody in the body decreases.[20,21] Since the implementation of the immunization program in China, the incidence rate of tetanus in China has decreased significantly, but elderly patients who have not been vaccinated against tetanus have become a group with a high incidence of tetanus at present. Therefore, reducing the mortality rate and shortening the hospitalization period in the clinical treatment of tetanus has become the focus of many scholars.

There are few studies on the impact of clinical interventions on the LOS of tetanus patients in the ICU. Our study revealed that tracheotomy significantly affected the LOS in the EICU for adults with tetanus. This finding is partially consistent with the finding that tracheotomy prolongs the ICU stay in a multicenter study of tetanus patients in Fujian Province, China.[10] A single-center retrospective observational study from Pakistan demonstrated improved survival rates in tetanus patients receiving early tracheostomy, along with reduced risks of mechanical ventilation and ventilator-associated pneumonia.[22] However, this study has not analyzed whether early tracheostomy reduces ICU length of stay in tetanus patients. Therefore, the impact of tracheostomy on ICU hospitalization duration in tetanus patients remains unclear. In our study, tracheotomy intervention significantly increased the risk of prolonged EICU retention by 86.2%. Respiratory failure due to restricted mouth opening, laryngeal muscle spasm, sputum obstruction or ventilation dysfunction may be the main reason for tracheotomy. For high-risk airway patients, when tracheotomy cannot be avoided, the optimal time for tracheotomy is controversial in clinical practice. Whether the timing of tracheotomy has an impact on prognosis and LOS in the ICU needs further research.

This study also revealed that mechanical ventilation intervention significantly increased the risk of prolonged EICU retention by 55.3%. These findings are similar to those of a French multicenter tetanus study.[9] We concluded that mechanically ventilated patients who are severely ill and who require stronger sedative and analgesic medications in this group will subsequently experience a series of possible complications that may lead to a prolonged stay in the EICU.[23]

Among the studies on related factors affecting the death of tetanus patients, there was a significant correlation between age and tetanus death.[9,24,25] Due to the small number of tetanus deaths in our center (a total of 88 cases, 6 deaths, a mortality rate of 6.8%), no correlation analysis was conducted. Our study revealed no significant correlation between age and LOS in the EICU. A Vietnamese study revealed that the severity of the disease was associated with the need for mechanical ventilation in tetanus patients in the ICU.[26] Although our study adopted Japan's modified rating scale for the severity and prognosis of tetanus to conduct clinical quantitative grading of Ablett's disease, no correlation was detected.[13,27] From the clinical data, it was found that some patients with an initial score of mild-moderate on admission rapidly progressed to severe disease, and such few patients remained unrecognized early in the initial assessment.

Treatment interventions for adult patients with tetanus involve many factors, such as tetanus antitoxin, antibiotics, sedative and analgesic drugs, nutritional support, and airway care.[4,28–30] Nepal et al reported that magnesium sulfate combined with diazepam effectively reduced spasms.[31] High-calorie nutritional support and dexmedetomidine reduced tetanus mortality and improved the prognosis of adult patients with moderate/severe systemic tetanus.[32] Benzodiazepines (diazepam, midazolam) were mainly used to control spasms, and in some patients, benzodiazepines were combined with other sedative drugs in our research. The timing of the clinical combination of other sedatives depends on the degree of spasm control of patients, and the type of combination depends on the clinician's personal decision, so whether different sedatives affect the LOS of the EICU needs further prospective study. The mean ALB concentration was used to reflect the nutritional status of tetanus patients during their EICU stay in our study, and we did not find that the ALB concentration had a significant effect on the EICU duration. At present, the optimal dose of tetanus antitoxin for tetanus patients is still controversial.[29,33,34] Our center observed that in clinical decision-making, increasing the dose of tetanus antitoxin was limited to patients whose spasticity remained poorly controlled with high doses of benzodiazepines, and the present study did not find that the total dose of tetanus antitoxin had an effect on the length of the EICU stay.

In summary, more attention should be given to the clinical management of tetanus patients who undergo subsequent tracheotomy combined with mechanical ventilation support or only tracheotomy. Therefore, the mortality rate of patients with tetanus may decline, the economic burden of patients may decrease, and the utilization rate of ICU medical resources may improve.

Limitations

The limitation of this study is that it was a single-center retrospective study with a small number of patients. In this study, despite adjusting for various possible factors and patient characteristics, the effect of residual confounders could not be excluded. Although the included tetanus patients were not found to have underlying neuromuscular-related diseases, the type and number of diseases underlying each patient may have had an unknown bias on the results. The 15 seemingly plausible influencing factors included may have data for some variables that did not satisfy the conditions of the Cox analysis due to insufficient sample size, resulting in the possible exclusion of some variables from the Cox risk model. In addition, the time between the onset of illness and tracheotomy varied among patients, and the timing of tracheotomy was not analyzed further in depth in this study due to the limited sample size, which may have affected the occurrence of complications in the clinic and thus affected the LOS in the EICU. The specific timing of the use of mechanical ventilation was also different for patients using mechanical ventilation, and the impact on the results is also unknown. Decisions on additional tetanus antitoxin dosage were found to be based on the spasm control status of the tetanus patient from the electronic medical record system physician chart notes, and the timing of its addition was a relatively uncontrollable influence. Moreover, the initial dose of tetanus antitoxin administered and subsequent additional doses and time intervals differed for each patient, so there was an unknown bias in the effect of the dose of tetanus antitoxin administered on the LOS in the EICU. Finally, relevant correlates of tetanus patient care, such as the frequency of acoustic or nursing manipulation stimuli and the frequency of spasmodic episodes in patients, were not included because of the limited sample size. Future research should focus on expanding the sample size, reorganizing data for subgroup analysis, and applying propensity score matching (PSM) reduce to potential bias and variables confounding.

Conclusions

Tracheotomy and mechanical ventilation support were associated with increased LOS in the EICU in adult tetanus patients. Future multicenter or prospective studies are anticipated to validate the aforementioned findings. Clinicians must focus on spasm control and optimize airway management in tetanus patients in the EICU. More efficient methods should be sought for the management of artificial airway establishment and mechanical ventilation to wean patients as soon as possible, promote recovery, and shorten the LOS in the EICU. Furthermore, we call for strengthened tetanus vaccination efforts among adults to reduce the incidence of tetanus.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare for this work.

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