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Original Contribution

Prognostic factors for generalized tetanus in adults: A retrospective study in a Chinese hospital

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ABSTRACT

Background: We evaluated factors associated with mortality in patients with moderate/severe generalized tetanus.
Methods: This retrospective study included patients with moderate/severe generalized tetanus admitted to the Affiliated Hospital of Nantong University (China) between January 2005 and January 2017. Clinical data were extracted from medical records. Patients were divided into two groups based on outcome (survival or death). Factors associated with mortality were analyzed using univariate and multivariate logistic regression.
Results: Seventy-five patients were included (57.3% male; age, 57.9 ± 18.4 years; APACHE II score, 10.6 ± 3.4; severe tetanus, 49.3%; mortality, 25.3%). Multivariate analysis identified severe tetanus (odds ratio [OR], 30.364; 95% confidence interval [CI], 2.459–374.896) and APACHE II score (OR, 1.536; 95%CI, 1.051–2.243) as positively associated with mortality, whereas high-calorie nutrition (OR, 0.027; 95%CI, 0.002–0.359) and dexmedetomidine use (OR, 0.035; 95%CI, 0.003–0.467) were negatively associated with mortality (all $P < 0.05$).
Conclusion: Tetanus severity and APACHE II score were associated with mortality in patients with generalized tetanus, whereas high-calorie nutrition and dexmedetomidine use reduced the odds of death. High-calorie nutrition and dexmedetomidine administration may improve prognosis in adult patients with moderate/severe generalized tetanus.

1. Introduction

Tetanus is a potentially fatal infectious disease caused by *Clostridium tetani* that exist widely in the environment. Tetanus remains an important health threat in some developing countries such as Africa and in other underdeveloped areas after large-scale natural disasters [1]. Tetanus has become rare in industrialized countries and developed areas due to the popularity of effective immunization programs. As a result, some clinicians are unable to identify tetanus at the early stages of the disease and can only make a diagnosis when the clinical manifestations become obvious, leading to a delay in treatment [2]. There is a report that some doctors lack experience and knowledge in the diagnosis and treatment of tetanus, resulting in inappropriate early-stage treatment, failure of therapy and even death after worsening of the patient's condition [3].

For logical and ethical reasons, it has been difficult to carry out clinical trials of different treatment strategies for tetanus [2]. The rarity of cases has also impeded the progress of clinical research such as randomized controlled trials [4]. Nevertheless, it remains necessary to improve the early diagnosis and treatment of tetanus and promote evidence-based guidelines in order to maximize the prognosis of the disease [4]. One approach that may help to identify those patients with tetanus who are at risk of a poor prognosis and thus in need of particular clinical vigilance is to identify the demographic and clinical factors, including treatment-related factors, that are associated with mortality.

The aim of the present study was to identify the demographic, clinical and therapeutic factors that influenced the survival of patients with tetanus. Therefore, this study retrospectively analyzed the clinical data of 75 adult patients with moderate or severe tetanus admitted to the Affiliated Hospital of Nantong University (a tertiary hospital with comprehensive healthcare facilities located in eastern China) between January 2005 and January 2017. It was anticipated that the findings would provide new data of interest to clinicians that could potentially help to improve future management strategies for moderate and severe tetanus.

2. Patients and methods

2.1. Study population

This study retrospectively analyzed the clinical data of all adult patients with tetanus admitted to the Affiliated Hospital of Nantong

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University between January 2005 and January 2017. Our hospital is a regional, tertiary hospital with an intensive care unit (ICU) located in eastern China that has 2100 beds and treats about 90,000 hospitalized patients and >200,000 outpatients per year. In order to ensure the representativeness of the cases included in the study, we selected only the most typical cases with moderate and severe generalized tetanus according to the diagnostic criteria for tetanus [5]. The inclusion criteria were: (1) age ≥ 18 years old; (2) typical symptoms of tetanus such as difficulty opening the mouth, risus sardonicus, difficulty swallowing, neck stiffness, muscle spasm and/or convulsions; (3) other nervous system diseases or precipitating factors were excluded; and (3) generalized tetanus (the most common form) was diagnosed and considered to be either moderate or severe in severity. The exclusion criteria were: (1) family members chose to discharge the patient within 24 h after admission due to worsening of the patient's condition, inability to pay the treatment costs or other reasons; (2) the patient had complications that could potentially have an impact on the prognosis, such as multiple or combined injuries; (3) the patient had underlying diseases that could potentially have an impact on the prognosis, such as chronic renal insufficiency, liver cirrhosis, autoimmune rheumatic diseases or malignant tumors; or (4) incomplete data in the medical records. The research ethics committee of the Affiliated Hospital of Nantong University approved the study.

2.2. Clinical data

Demographic and clinical data, including information regarding the diagnosis and treatment, were extracted from the hospital's electronic medical record system and medical record files. The demographic and clinical characteristics included age, gender, disease severity, acute physiology and chronic health evaluation II (APACHE II) score, location of the wound, wound type, early wound cleaning, incubation period (the time from injury to initial symptoms), onset time (the time from initial symptoms to first seizure) and hospital department to which the patient was admitted.

Most of the patients had received diphtheria-pertussis-tetanus (DPT) immunization, although a small number of older patients could not recall whether or not they had been immunized. All patients with tetanus received tetanus immune globulin on admission to our hospital and were treated in accordance with the current, widely accepted principles of treatment of tetanus which include reduction of muscle spasms, muscle tension and autonomic nerve disorders, provision of ventilatory support as necessary, neutralization of tetanus toxin, debridement of the wound and use of antibiotics [2]. Our analysis also included some therapeutic parameters that differed between patients, including debridement after admission, type of antibiotic used, calorie level of the nutrition provided, use of hemodynamic monitoring, use of mechanical ventilation, type of sedative (dexmedetomidine or propofol) used in combination with midazolam and use of muscle relaxants. The dose of midazolam used was 0.06–0.12 mg/kg/h when combined with dexmedetomidine and 0.08–0.15 mg/kg/h when combined with propofol.

For most patients in our study, the dosing for dexmedetomidine infusion was 0.2–0.7 μg/kg/h, in line with the current recommendations of the US Food and Drug Administration (FDA). However, our clinical experience during the past decade has indicated that dosing up to 1 μg/kg/h is also safe with no obvious adverse effects. Therefore, the dose of dexmedetomidine used in our patients was 0.2–1 μg/kg/h, and the dose was dynamically adjusted according to the sedation score and sedation goal. The sedation scale used was the Richmond Agitation-Sedation Scale (RASS), which gives a score that ranges from −5 to +4 [6]. Our sedation goals were to maintain moderate to deep sedation during the onset of typical symptoms (i.e. RASS maintained at −3 to −4 points) and subsequently to maintain light sedation (i.e. RASS maintained at −1 to −2 points) when the symptoms (such as convulsions) had improved and there were no significant fluctuations in vital signs. Dexmedetomidine infusion was continued when the patient's tetanus-related symptoms occurred frequently at the early stage. After the improvement of the symptoms, the dose of dexmedetomidine was then gradually reduced, using the minimum dose required, until there was sufficient recovery in the patient's condition for the drug to be discontinued. The duration of dexmedetomidine infusion in about 60% of patients was ≤7 days, and infusion for >7 days was required in about 40% of patients.

Vital signs, including heart rate, arterial blood pressure, respiratory rate and body temperature were monitored regularly in all patients. Continuous arterial pressure and central venous pressure were monitored in patients with unstable hemodynamics. If these techniques were considered insufficient due to substantial variability in the patient's hemodynamics, femoral artery catheterization was performed to enable use of the pulse-indicated continuous cardiac output (PiCCO) technique. The PiCCO technique permitted measurement of parameters such as the cardiac index, extravascular lung water index, systemic vascular resistance index and intrathoracic blood volume index.

2.3. Definitions

The patients were divided into two groups (survived or died) according to the clinical outcome at the time of hospital discharge. The survived group was defined as patients who were cured and discharged from our hospital or patients whose symptoms of tetanus had significantly improved (with almost complete disappearance of typical symptoms and recovery of vital signs to stable levels), who no longer needed further monitoring and organ support therapy, and who were transferred to local community medical institutions to continue receiving restorative therapy. The died group was defined as patients who died in the hospital after systemic therapy or patients whose condition had deteriorated further, in whom it was difficult to correct organ failure and maintain vital signs, who were discharged on the wishes of family members and who died within 24 h after discharge.

2.4. Statistical analysis

Statistical analysis was performed using SPSS 23.0 (IBM Corporation, Chicago, IL, USA). Normality of distribution was evaluated using the Kolmogorov-Smirnov test. Variables with a normal distribution were compared using Student's *t*-test, and values are presented as means ± standard deviations. Categorical variables are presented as frequencies and were analyzed using the Chi-squared test or Fisher's exact test, as appropriate. Factors that differed significantly between patients who survived and those who died were entered into a univariate logistic regression analysis, and crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Factors that were significant in the univariate analysis were entered into a multivariate logistic regression analysis to identify factors independently associated with mortality; adjusted ORs and 95% CIs were calculated. Two-sided P-values < 0.05 were considered to be statistically significant.

3. Results

In this study, 108 cases of adult tetanus were reviewed and 24 cases were excluded (mild tetanus, n = 7; localized tetanus, n = 4; incomplete data, n = 2; and discharged within 24 h due to rapid deterioration after admission, inability to pay for treatment costs or other reasons, n = 11). A further 9 cases were excluded due to the presence of severe complications or underlying diseases. Therefore, 75 cases were included in the final analysis (Fig. 1).

The average age of the patients included in the study was 57.9 ± 18.4 years, and the mean incubation period and mean onset time were 10.0 ± 7.5 days and 2.9 ± 2.6 days, respectively. Compared with the group who survived, the group who died included more patients with severe tetanus (P = 0.018), had fewer patients who received

early wound cleaning (P = 0.009) and contained patients with a significantly higher APACHE II score (P = 0.006) (Table 1). There were no significant differences between the two groups in age, gender, location of the wound, wound type, incubation period, onset time and department to which admitted (Table 1).

The rate of wound debridement after admission was 62.7% overall and was significantly higher in patients who survived than in those who died (P = 0.004). Penicillin was the most commonly used antibiotic (50.7%) followed by metronidazole (16%), and both drugs were used together in 33.3% of the patients. However, there was no significant difference between groups in the type of antibiotic used (P = 0.346). High-calorie nutrition (30–35 kcal/kg/day) was received by 48% of patients and was more commonly used in the group of patients who survived than in those who died (P = 0.001). With regard to sedative use, all patients were administered a benzodiazepine (midazolam) to control convulsions and maintain basic sedation. Midazolam was combined with propofol in 61.3% of patients and dexmedetomidine in 38.7% of patients, and the rate of dexmedetomidine use was higher in the group of patients who survived (46.4%) than in those who died (15.8%) (P = 0.015). Hemodynamic monitoring, use of mechanical ventilation and use of muscle relaxants showed no significant differences between the two groups (Table 2).

Univariate logistic regression analysis identified six variables significantly associated with mortality, including severity of disease, early wound cleaning, APACHE II score, debridement after admission, combined use of dexmedetomidine with midazolam and high-calorie nutrition (Table 3). In multivariate logistic regression analysis (Fig. 2), severe tetanus and higher APACHE II score at admission were significantly associated with greater odds of death (OR values > 1), while the use of dexmedetomidine (vs. propofol) as a sedative (in combination with midazolam) and high-calorie nutrition were associated with lower odds of death (OR values < 1). However, early wound cleaning (pre-admission) and wound debridement after admission were not significant factors in the multivariate regression analysis (Fig. 2).

Table 1
Demographic and clinical characteristics of the patients in the study.

Characteristic	All (n = 75)	Died (n = 19)	Survived (n = 56)	P
Age (years)				0.245
<40	14 (18.7%)	2 (10.5%)	12 (21.4%)	
≥40	61 (81.3%)	17 (89.5%)	44 (78.6%)	
Gender				0.414
Male	43 (57.3%)	10 (52.6%)	33 (58.9%)	
Female	32 (42.7%)	9 (47.4%)	23 (41.1%)	
Severity				0.018
Moderate	38 (50.7%)	4 (21.1%)	34 (60.7%)	
Severe	37 (49.3%)	15 (78.9%)	22 (39.3%)	
Location of wound				0.357
Head and neck	4 (5.3%)	2 (10.5%)	2 (3.5%)	
Trunk	3 (4.0%)	–	3 (5.4%)	
Upper limbs	30 (40.0%)	10 (52.6%)	20 (35.7%)	
Lower limbs	34 (45.4%)	6 (31.6%)	28 (50.0%)	
Not identified	4 (5.3%)	1 (5.3%)	3 (5.4%)	
Wound type				0.826
Puncture by metal	32 (42.7%)	8 (42.1%)	24 (42.9%)	
Deep incision	16 (21.3%)	4 (21.0%)	12 (21.4%)	
Stabbed by thorns	11 (14.7%)	3 (15.8%)	8 (14.3%)	
Contaminated abrasion (by soil)	7 (9.3%)	3 (15.8%)	4 (7.1%)	
Animal bite	3 (4.0%)	–	3 (5.4%)	
Blast injury (by firecracker)	2 (2.7%)	–	2 (3.5%)	
Not identified	4 (5.3%)	1 (5.3%)	3 (5.4%)	
Wound cleaning				0.009
Yes	35 (46.7%)	4 (21.1%)	31 (55.4%)	
No	40 (53.3%)	15 (78.9%)	25 (44.6%)	
Incubation period (days)[a]				0.864
<7	31 (41.3%)	7 (36.8%)	24 (42.9%)	
≥7	37 (49.3%)	9 (47.4%)	28 (50.0%)	
Onset time (days)[a]				0.544
<3	36 (48.0%)	10 (52.6%)	26 (46.4%)	
≥3	34 (45.3%)	8 (42.1%)	26 (46.4%)	
APACHE II score	10.6 ± 3.4	12.8 ± 4.6	9.9 ± 2.6	0.006
Department to which admitted				0.722
Intensive care unit	29 (38.7%)	8 (42.1%)	21 (37.5%)	
Ward	46 (61.3%)	11 (57.9%)	35 (62.5%)	

Data presented as n (%) or mean ± standard deviation. APACHE II: acute physiology and chronic health evaluation II.
[a] Incubation period and onset time could not be definitively determined in some cases.

4. Discussion

Tetanus is a potentially fatal disease, and its mortality rate has been reported to be around 35%, with a higher fatality rate in hospitals without formal intensive care facilities [7,8]. It has been pointed out that the treatment of tetanus requires a fully functional ICU as a guarantee [9]. In this study, the mortality rate of patients with tetanus was 25.3%, which was lower than that in previous studies. A possible reason for this was that our patients received appropriately graded management after admission according to the severity of their condition. Patients with non-severe tetanus were admitted to surgical isolation wards with

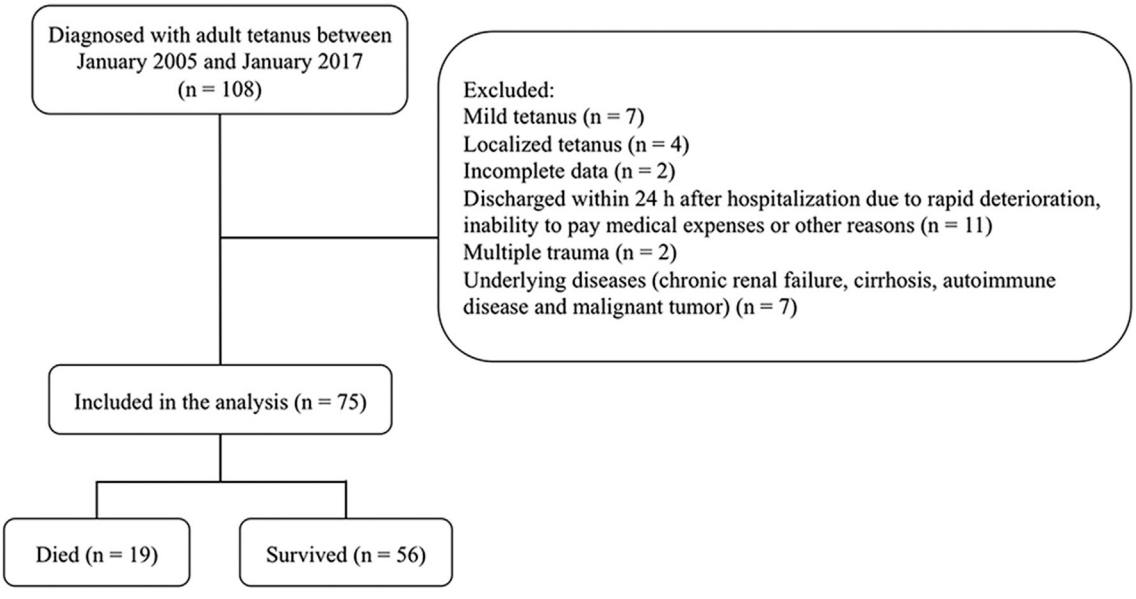

Fig. 1. Flow chart of the study population.

Table 2
Comparison of therapeutic parameters between patients who survived and patients who died.

Variable	All (n = 75)	Died (n = 19)	Survived (n = 56)	P
Debridement after admission				0.004
Yes	47 (62.7%)	7 (36.8%)	40 (71.4%)	
No	28 (37.3%)	12 (63.2%)	16 (28.6%)	
Antibiotic type				0.346
Penicillin	38 (50.7%)	10 (52.6%)	29 (51.8%)	
Metronidazole	12 (16.0%)	1 (5.3%)	10 (17.9%)	
Combined use	25 (33.3%)	8 (42.1%)	17 (30.4%)	
High-calorie nutrition[a]				0.001
Yes	36 (48.0%)	3 (15.8%)	33 (60.7%)	
No	39 (52.0%)	16 (84.2%)	22 (39.3%)	
Hemodynamic monitoring				0.487
Yes	26 (34.7%)	6 (31.6%)	20 (35.7%)	
No	49 (65.3%)	13 (68.4%)	36 (64.3%)	
Mechanical ventilation				0.851
Yes	50 (66.7%)	13 (68.4%)	37 (66.1%)	
No	25 (33.3%)	6 (31.6%)	19 (33.9%)	
Sedative used with midazolam[b]				0.015
Propofol	46 (61.3%)	16 (84.2%)	30 (53.6%)	
Dexmedetomidine	29 (38.7%)	3 (15.8%)	26 (46.4%)	
Muscle relaxant				0.217
Yes	10 (13.3%)	1 (5.3%)	9 (16.1%)	
No	65 (86.7%)	18 (94.7%)	47 (83.9%)	

Data are presented as n (%).
[a] High-calorie nutrition was defined as the provision of 30–35 kcal/kg/day.
[b] All patients received a sedative benzodiazepine (midazolam) to control spasms and maintain essential sedation; propofol or dexmedetomidine were used in combination with midazolam.

conventional rescue facilities, whereas patients with severe disease or deteriorating health status were admitted to the ICU, which was fully equipped and had comprehensive rescue measures for the treatment of tetanus.

Previous studies exploring predictors of mortality in patients with tetanus [8,10-13] have identified age, other demographic characteristics, incubation period, clinical features, laboratory indicators and severity of tetanus as prognostic indicators, but there has been little research into the influence of therapeutic factors on the prognosis of tetanus. With gradual improvement and diversification of monitoring and treatment technologies in recent years, it is likely that differences in therapeutic methods will affect the prognosis of tetanus in some way. The present study was based on previous research and included the assessment of APACHE II score, which has often been used to assess and predict mortality in critically ill patients [14]. In addition, we evaluated whether certain therapeutic factors were predictors of prognosis in patients with tetanus. Our data showed that the factors independently associated with the mortality of patients with moderate or severe generalized tetanus were disease severity and APACHE II score at admission, whereas a more active nutritional strategy (with higher calorie intake) and administration of dexmedetomidine as a sedative (in combination with midazolam) were beneficial at improving clinical outcome.

Patients with tetanus are likely to have an impaired basal diet due to limitation of mouth opening and difficulty swallowing, while their energy consumption would be expected to be higher than that of healthy individuals because of convulsions, sympathetic excitement and a high metabolic rate. Therefore, nutritional support is an important therapy for patients with tetanus. At present, uncertainties and debates remain about the optimal caloric intake for critically ill patients [15]. The most commonly used straightforward method for determining the energy requirements of critically ill patients is the weight formula. The current American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines suggest an intake of 20–35 kcal/kg/day depending on the disease, and the commonly recommended range is 25–30 kcal/kg/day [16]. During the diagnosis and treatment of our patients, we came to realize that moderate and severe tetanus were often accompanied by high energy consumption. Therefore, in recent years we have used enhanced nutritional support with an increased daily calorie intake of 30–35 kcal/kg/day. Furthermore, enteral nutrition is the preferred method in our hospital, with moderate levels of parenteral nutrition used as a supplement according to the patient's gastrointestinal tolerance. Our observation that high-calorie nutrition was associated with reduced mortality in patients with moderate/severe tetanus is consistent with other studies in critically ill patients, which showed that better nutrition was associated with reduced mortality [17] whereas malnutrition was closely associated with increased mortality [18]. Furthermore, in patients on long-term mechanical ventilation, an increased nutritional intake at an early stage was associated with longer survival time and faster rate of physical recovery [19]. In addition, the use of calorie-enhanced nutrition in the ICU was associated with an increase in the rate of successful discharge [20].

Controlling convulsions and reducing autonomic nerve disorders are important aims in the treatment of tetanus. The most commonly used drugs for controlling convulsions in patients with tetanus are benzodiazepines, mainly because of their beneficial properties as a sedative, anticonvulsant and muscle relaxant [2]. Opioid analgesics, epidural blocking agents and clonidine have been reported to have benefits for the control of autonomic nerve disorders, but more evidence from randomized controlled trials is needed before these agents are recommended as standard therapies [2]. Dexmedetomidine has become a widely used sedative in the ICU and is now recommended as a priority sedative by the management of pain, agitation and delirium in adult patients in the ICU (IPAD) guidelines [21]. Dexmedetomidine, an α_2-adrenergic receptor agonist, exerts a sedative effect as well as other actions, including analgesia and inhibition of transmitter release from sympathetic nerves [22]. In recent years we have increasingly used dexmedetomidine in combination with a benzodiazepine (midazolam) to produce sedation in patients with tetanus. In a small number of previously described cases, dexmedetomidine has been reported to have advantages with regard to controlling sympathetic overactivity, stabilizing hemodynamic parameters, decreasing the frequency of convulsions and reducing the use of sedatives and muscle relaxants in patients with tetanus [23,24]. In fact, the main cause of death in patients with tetanus in the ICU is sudden cardiac arrest or circulatory failure due to autonomic nerve abnormalities [25]. Thus, dexmedetomidine may have important advantages when used in the management of patients with tetanus. Our experience also indicated that dexmedetomidine was safe to use in patients with tetanus, and in general, obvious adverse

Table 3
Univariate logistic regression analysis of factors associated with mortality.

Factor	Unit change	Crude OR (95% CI)	P
Severity	Severe vs. moderate	4.017 (1.270–12.708)	0.018
Wound cleaning pre-admission	Yes vs. no	0.215 (0.063–0.730)	0.014
APACHE II score	+1	1.305 (1.081–1.576)	0.006
Debridement after admission	Yes vs. no	0.176 (0.058–0.540)	0.002
High-calorie nutrition[a]	Yes vs. no	0.121 (0.032–0.466)	0.002
Sedative combined with midazolam	Dexmedetomidine vs. propofol	0.216 (0.057–0.826)	0.025

APACHE II: acute physiology and chronic health evaluation II; CI: confidence interval; OR: odds ratio.
[a] High-calorie nutrition was defined as the provision of 30–35 kcal/kg/day.

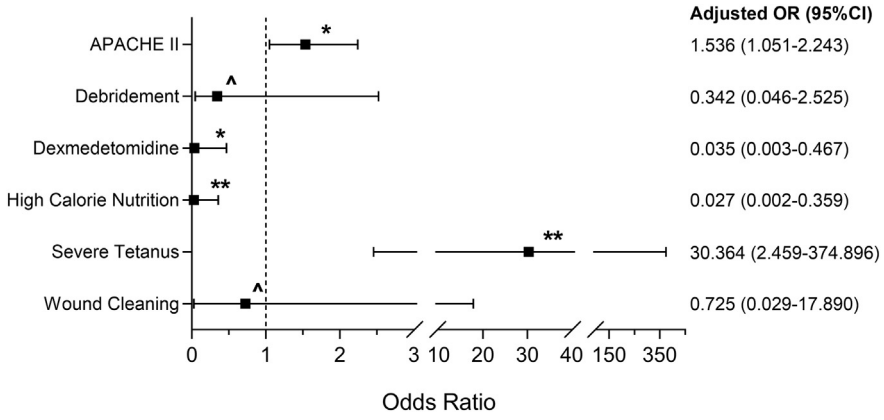

Fig. 2. Multivariate logistic regression analysis of factors independently associated with mortality. APACHE II: acute physiology and chronic health evaluation II; CI: confidence interval; OR: odds ratio. *P < 0.05; **P < 0.01; ^not significant.

events were not observed. The only commonly encountered adverse effect was bradycardia, which was more apparent when a loading dose of dexmedetomidine was administered. Since only mild bradycardia occurred during continuous infusion of dexmedetomidine at the maintenance dose, we generally avoided the use of an intravenous loading dose. We found that continuous intravenous use of dexmedetomidine was safe for patients without bradycardia at baseline. Although dexmedetomidine also caused temporary hypotension in a few cases, this effect was much smaller than that seen with other sedatives commonly used (such as propofol and benzodiazepines).

Our study found that patients treated with dexmedetomidine in combination with midazolam had a better prognosis than those treated with propofol and midazolam. This apparent benefit of dexmedetomidine over propofol may be explained by the known advantages of α_2-adrenoceptor agonists, including sedation, anti-sympathetic effects and stabilization of circulatory function. Although dexmedetomidine and propofol are both recommended by the IPAD guidelines for use in critically ill patients, each has its characteristics and advantages. The depth of sedation with propofol is dose-dependent, and propofol has a faster onset and shorter half-life than dexmedetomidine. However, propofol has disadvantages that it shares with many other sedatives. In particular, propofol exerts an effect on the cardiovascular system and can cause hypotension, especially in patients with poor cardiac reserve and hypovolemia; this adverse effect is also dose-dependent. We speculate that there are two possible reasons for the poorer prognosis of patients in the propofol group, as compared with the dexmedetomidine group. Firstly, hypovolemia may not have been obvious in patients with tetanus at the onset of their symptoms (due to enhanced sympathetic nervous system activity) and hence may have been missed. As a result, the hypotensive adverse effect of propofol may have been exacerbated in these patients, especially as a large dose of propofol (up to 1.5–2 mg/kg/h) was often needed to ensure adequate sedation and control of tetanus-related symptoms. Furthermore, propofol's hypotensive effect may also have been exacerbated by its co-administration with midazolam, which also impacts on the circulation. Secondly, the disease course in patients with tetanus is long and includes autonomic nervous system dysfunction and variations in vital signs. Therefore, a long-lasting deep sedation was needed until recovery. Since propofol is a short-acting sedative, frequent additional loads were often required in our patients to maintain long-term deep sedation, while discontinuation of propofol was also sometimes needed due to circulation-related problems. The frequent fluctuations in symptoms and hemodynamics may have interfered to some extent with the systematic treatment of tetanus and the recovery of the patient. Subsequently, some inappropriate adjustments of therapy may also have been factors that affected patient prognosis. In contrast, dexmedetomidine has a slower onset and half-life than propofol, exerts only small inhibitory effects on the cardiovascular system and has the obvious advantage of stabilizing hemodynamics. The anti-sympathetic effects of dexmedetomidine reduce the risk of sudden fluctuations in heart rate or blood pressure in patients with tetanus. In addition, when dexmedetomidine is used in combination with midazolam, a lower dose of the benzodiazepine drug can be used due to synergism between the two agents. We suggest that compared with the combination of propofol and midazolam, co-administration of dexmedetomidine and midazolam produces a sustained and more stable deep sedation and results in more stable hemodynamics. These are favorable factors that are beneficial to the clinical management of patients with tetanus and thus would be expected to improve prognosis, as was observed in our study.

Complete debridement can potentially clear out any *Clostridium tetani* that remain in the wound, thereby removing the source of tetanus toxin. Failure to treat the wound or incomplete debridement can have serious consequences [3]. However, there are no unified guidelines concerning wound debridement in patients with tetanus. Some minor wounds can be difficult to debride. Furthermore, for deep wounds or those that have healed, thorough expanding debridement would cause intense pain and potentially aggravate the patient's condition. Our study found that although the proportion of patients who underwent wound cleaning and debridement was higher in the group of survivors, wound cleaning and debridement was not an independent factor predicting survival. In part, this might be related to exacerbation of the symptoms of tetanus due to the intense stimulation caused by treatment of the wound itself. However, the lack of a significant effect may also be related to the small sample size, which resulted in a relatively large confidence interval in the multivariate regression analysis. Regarding the early debridement of tetanus-prone wounds, we believe that clinicians should adopt a proactive attitude but should pay attention to the impact of debridement itself on the symptoms of tetanus. Debridement may be more beneficial to patients if their airway is already opened, their condition has stabilized and adequate analgesia has been administered.

With regard to other interventions used in the treatment of tetanus, antibiotic type, administration of muscle relaxants, hemodynamic monitoring and use of mechanical ventilatory support (when necessary) were not found to have a significant relationship with prognosis. We did not find that penicillin or metronidazole use showed any advantages with regard to prognosis, in agreement with previous reports [2,7]. With regard to muscle relaxants, our principle was that they were only administered to treat uncontrolled convulsions after adequate sedation and were not used routinely. In fact, the sustained use of muscle relaxants has been reported to be an independent risk factor for increased mortality [26]. Because patients with tetanus have frequent convulsions, substantial secretion of sweat, apparent increased levels of invisible water loss and autonomic dysfunction, it is helpful to use hemodynamic monitoring to evaluate circulatory function and guide rehydration therapy. Of course, hemodynamic monitoring is

usually performed in patients with an unstable circulation. Although hemodynamic monitoring can better guide clinical treatment and rescue, it was not shown to have a significant impact on prognosis in our study, which might be related to the fact that patients with hemodynamic monitoring were more likely to have more severe tetanus. Mechanical ventilation has become more widely adopted in China, hence patients with tetanus can now receive effective ventilatory support if required.

This study also had some limitations. First, this was a retrospective study, so the level of evidence is inferior to that of a prospective study. In addition, the retrospective design may have introduced some selection bias or recall bias. Secondly, this was a single-center study and the sample size was relatively small. Third, other risk factors may have been present that were not measured, thus the possible influences of these other confounding factors remain unknown. Although there are difficulties in carrying out a large prospective cohort study of patients with tetanus, it will be worth performing further studies with larger sample sizes in order to better characterize the prognostic factors in patients with tetanus.

Taken together, the findings of our study revealed that the severity of tetanus and APACHE II score at admission were associated with increased mortality, while the use of dexmedetomidine and more active nutritional supplementation were important therapeutic factors associated with an improved prognosis. It is our view that patients with tetanus should be treated depending on disease severity using a hierarchical approach to clinical management in a hospital with a fully-equipped ICU.

Funds

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Conflict of interests

There are no conflicts of interests to declare.

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