

# BMJ Open Using competing risk and multistate model to estimate the impact of nosocomial infection on length of stay and mortality in burn patients in Southeast China

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## ABSTRACT

**Objective** Due to the defects in skin barrier function and immune response, burn patients who survive the acute phase of a burn injury are at a high risk of nosocomial infection (NI). The aim of this study is to evaluate the impacts of NI on length of stay (LOS) and hospital mortality in burn patients using a multistate model.

**Design and setting** A retrospective observational study was conducted in burn unit and intensive care unit in the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China.

**Participants** Data were obtained from 1143 records of patients admitted with burn between 1 January 2013 and 31 December 2016.

**Methods** Risk factors for NIs were determined by binary logistic regression. The extended Cox model with time-varying covariates was used to determine the impact of NIs on hospital mortality, and cumulative incidence functions were calculated. Multiple linear regression analysis was applied to detect the variables associated with LOS. Using a multistate model, the extra LOS due to NI were determined.

**Results** 15.8% of total burn patients suffered from NIs and incidence density of NIs was 9.6 per 1000 patient-days. NIs significantly increased the rate of death (HR 4.266, 95% CI 2.218 to 8.208,  $p=0.000$ ). The cumulative probability of death for patients with NI was greater than for those without NI. The extra LOS due to NIs was 17.68 days (95% CI 11.31 to 24.05).

**Conclusions** Using appropriate statistical methods, the present study further illustrated that NIs were associated with the increased cumulative incidence of burn death and increased LOS in burn patients.

## INTRODUCTION

Burn injury, as a common cause of morbidity and mortality, has been recognised as a global public health problem. According to the data from WHO, burns account for an estimated 300 000 deaths each year.<sup>1</sup> Previous evidence illustrated that burn shock and inhalation injury were the major cause of early death

## Strengths and limitations of this study

- Using multistate and competing risks analysis, the present study assessed the impact of nosocomial infections (NIs) on hospital mortality and length of stay (LOS) in burn patients.
- Some potential factors, such as nursing protocols and the history of immunosuppression drugs, that may be associated with NI, LOS and mortality were not recorded.
- This study was performed in a single centre and the results need to be further confirmed by multiple centre trials.

among patients with burn injury.<sup>2,3</sup> Due to the advance in fluid resuscitation, surgical approach, organ function protection, antibiotic innovation and other adjunct strategies, the early mortality of burn patients decreased dramatically over the last 30 years.<sup>4,5</sup> On the other hand, because of the defects in skin barrier function and immune response, burn patients who survive the acute phase of a burn injury are at a high risk of acquiring nosocomial infection (NI).<sup>6</sup>

It has been reported that about 30%–80% of burn patients suffered from NIs.<sup>7–9</sup> Nevertheless, the exact impact of NIs on the length of stay (LOS) and mortality of burn patients remains elusive. Williams *et al*<sup>10</sup> investigated the predominant causes of death in burned paediatric patients. They found that infection is the leading cause of death after burn injury. A recent study reported an incidence density of 14.7 infections/1000 patient-days in burn patients.<sup>11</sup> Nevertheless, the study illustrated that NIs were not a risk factor for mortality, using logistic regression, after adjusting for confound variables.<sup>11</sup> It should be noted that NI is a time-varying factor, and it can develop

at any time after admission. Matched cohort study is the most commonly used method for estimating LOS associated with NIs. However, different matching factors were used in different studies, and it may be difficult to identify appropriate matching factors for NIs.<sup>12</sup> More importantly, the time-dependent characteristics of NIs imply that infection can impact on LOS only after the infection has started.<sup>12 13</sup> So, appropriate statistical methods for estimating the risk of death and LOS due to NI among burn patients would be helpful in making medical decisions and developing policy. Multistate modelling is a method to avoid time-dependent bias, and it is a useful way of describing a process in which a patient moves through a series of states in continuous time.<sup>12 13</sup> The aim of this study was to determine the impacts of NI on LOS and hospital mortality in burn patients using a multistate model.

## MATERIALS AND METHODS

### Patients

A retrospective study was conducted in burn unit and intensive care unit (ICU) in the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China. The burn unit has 72 beds and there are 50 beds in the ICU. After approval by the Institutional Review Board of the First Affiliated Hospital of Wenzhou Medical University, data of total 1143 patients admitted with burn were collected during January 2013 to December 2016. Inclusion criteria: (1) age of 0–99 years; (2) admission to hospital no later than 3 days postburn; (3) LOS >48 hours. As the present study was an observational and retrospective study, informed consent was waived by the Medical Ethics Committee.

### Data collection

NI in burn patients was defined as infection occurring 48 hours after hospital admission. There were four main types of NIs (burn wound infection (BWI), bloodstream infection (BSI), pneumonia, urinary tract infection, UTI) according to the criteria of the Centers for Disease Control and Prevention (CDC).<sup>14</sup> Briefly, BWI was defined as patient has a change in burn wound appearance, such as rapid eschar separation, dark brown, black or violaceous discolouration of eschar and at least one of the following: histological examination of burn biopsy shows invasion of organisms into adjacent viable tissue or positive blood culture without other identifiable infection. BSI includes laboratory-confirmed BSI and clinical sepsis. Patient with laboratory-confirmed BSI must have a recognised pathogen cultured from one or more blood cultures and organism cultured from blood is not related to an infection at another site. Clinical sepsis must meet the following clinical signs or symptoms with no other recognised cause: fever ( $T > 38^{\circ}\text{C}$ ), hypotension (systolic pressure  $\leq 90$  mm Hg) or oliguria ( $< 20 \text{ cm}^3/\text{hour}$ ); blood culture not done or no organisms or antigen detected in blood; and no apparent infection at another site and

physician instituted treatment for sepsis. Patients had rales or dullness to percussion on physical examination of the chest or a chest radiographic examination that showed new or progressive infiltrate or consolidation, cavitation, or pleural effusion and new onset of purulent sputum or change in character of sputum were diagnosed with pneumonia. Finally, UTI patient with the following signs or symptoms with no other recognisable cause: fever ( $T > 38^{\circ}\text{C}$ ), urgency, frequency, dysuria or suprapubic tenderness and at least one of the following: (1) positive dipstick for leucocyte esterase and/or nitrate; (2) positive urine microscopy or urine culture.

Patients with a history of smoke or fire exposure in a closed space or maxillofacial burn were suspected to have inhalation injury. The diagnosis of inhalation injury was made if the suspected patients had physical findings including changes in voice and carbonaceous sputum production or had bronchoscopic evidence.<sup>15</sup>

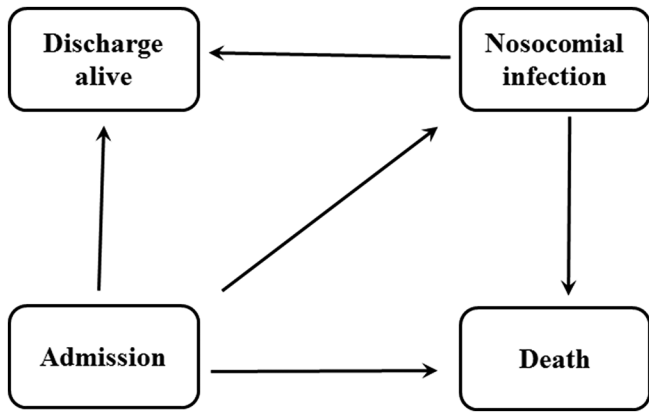
The characteristics of NI including time, site and pathogen were recorded. For patients with NI at the same site, only the first episode of it was analysed. The potential factors which are associated with NIs, LOS and mortality were collected, including gender, age, history of diabetes, date of admission, burn types (flame, scalding, electric and others), burn size and depth and inhalation injury.<sup>7–9</sup> Additionally, the dates of discharge and death were also recorded.

### Management

Resuscitation was performed according to the modified Evans (Ruijin) formula as described by the previous paper.<sup>16 17</sup> Dressings were changed every 1–3 days by doctors. Silver sulfadiazine was applied on deep partial-thickness and full-thickness burns. For full-thickness burns, early surgical excision of burn eschar and biological closure were performed when the patients' condition permits. Prophylactic antibiotic therapy was performed in patients who needing surgical intervention (perioperative period of debridement or auto skin grafting) or requiring mechanical ventilation. The strategy of prophylactic antibiotic therapy was mainly based on the advice of doctors from the department of microbiology and infectious diseases and the previous antibiotic susceptibility pattern of the centre. Additionally, patients met CDC criteria were treated with antibiotics. When a pathogen was identified, antibiotics were adjusted according to the results of isolate's susceptibility. The duration of antibiotics therapy is decided by the treating physician based on clinical symptoms, blood culture results as well as other infection markers.

### Statistical analysis

Data are presented as a percentage of a percentage of total or IQRs (25th and 75th percentiles), as appropriate. Mann-Whitney U test is used to analysis continuous variables while categorical variables were analysed by the  $\chi^2$  test. Univariate analysis was performed to assess the potential variables associated with NI and hospital



**Figure 1** Multistate model. Our model including four states: admission, nosocomial infection, discharge alive and death. After admission, patients may be infected or not, then they may be discharge alive or die.

mortality. Variables included in the univariate analysis were age, sex, diabetes, burn types (flame, scalding, electric and others), total body surface area (TBSA) (<10%, 10%–29%, ≥30%), full thickness of burn and inhalation injury. The variables with  $p < 0.05$  were used for further analysis. A Cox model was used to determine the risk factors for NI and death. In the Cox model, NI was modelled as a time-varying covariate by the ‘survival’ package in R. Cumulative incidence functions were calculated by the ‘cmprsk’ package. Additionally, linear regression analysis was applied to detect the variables associated with hospital LOS. The ‘etm’ package in R was performed to calculate the difference in LOS between patients with and without NI. The code used in the present study was

available at <https://CRAN.R-project.org/>. There are four states in our multistate model: admission (state 0), NI (state 1), discharge alive (state 2) and death (state 3). After admission, patients with NIs move from state 0 to state 1, then state 2 or state 3, while non-infected patients directly move from state 0 to state 2 or state 3. The detail information about this multistate model is shown in figure 1. R V.3.4.1 software and SPSS V.18.0 were used to prepare and analysis the data. Statistical significance was expressed as both  $p$  values and 95% CIs. A two-sided  $p < 0.05$  was considered statistically significant.

**Patient and public involvement**

No patients were involved in developing the hypothesis or research questions. No patients were involved in the development of the outcome measures. No patients were involved in developing plans for design or implementation of the study. There are no plans to disseminate the results of the research to study participants.

**RESULTS**

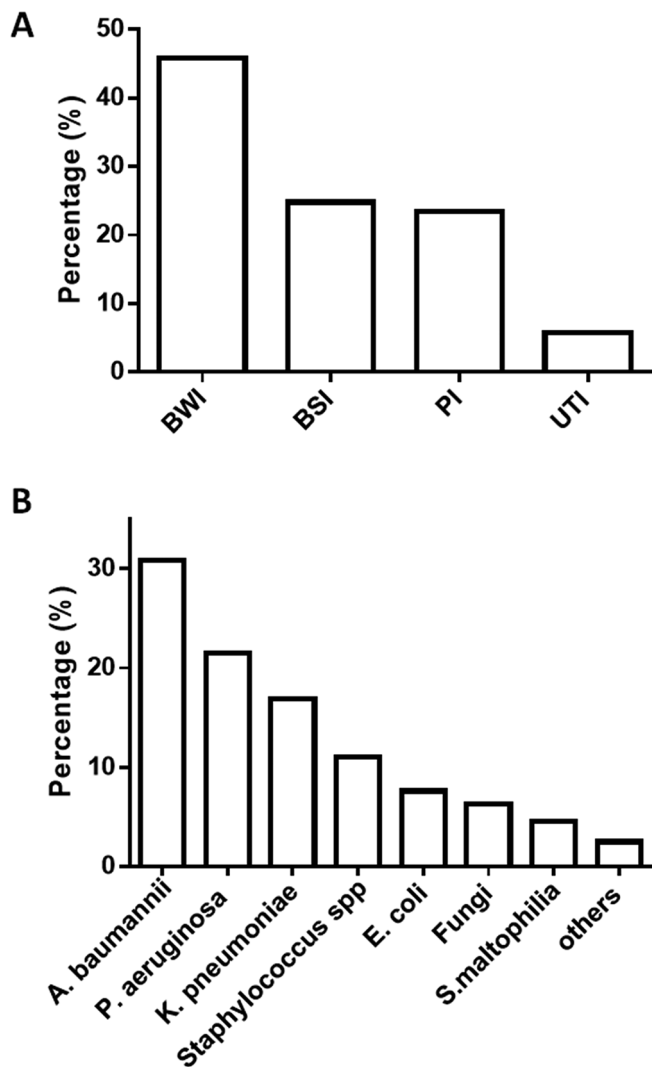
**Patient characteristics**

During the study period, a total of 1143 burn patients were admitted to the hospital. One hundred and fifty-seven burn patients were ineligible by exclusion criteria and 986 patients were included in the final analysis. Demographic and burn-related characteristics are shown in table 1. 65.1% of the patients were men and 34.9% were women. The median age was 37 (IQR, 18–49) years and 7.1% were elderly patients (65 years and older). 47.6% of the patients had <10% TBSA burn, 30.8% had

**Table 1** Demographics and clinical characteristic of burn patients with and without NI

Variables	Total n=986	NI n=156	No-NI n=830	P values
Male, n (%)	642 (65.1)	105 (64.7)	537 (67.3)	0.530
Age (years), median (25th, 75th)	37 (18, 49)	37 (17, 49)	37 (24, 37)	0.470
Diabetes, n (%)	38 (3.9)	11 (7.1)	27 (3.3)	<b>0.024</b>
TBSA, n (%)				
<10%	469 (47.6)	55 (35.3)	414 (49.9)	<b>0.031</b>
10%–29%	304 (30.8)	38 (24.4)	266 (32.0)	0.056
≥30%	213 (21.6)	63 (40.3)	150 (18.1)	<b>0.000</b>
Full thickness burn, n (%)	221 (22.4)	60 (38.5)	161 (19.4)	<b>0.000</b>
Inhalation injury, n (%)	46 (4.7)	38 (24.3)	8 (1.0)	<b>0.000</b>
Burn type, n (%)				
Flame	771 (78.2)	118 (75.6)	653 (84.7)	0.400
Scalding	96 (9.7)	11 (7.1)	85 (10.2)	0.218
Electric	73 (7.4)	15 (9.6)	58 (7.0)	0.250
Others	46 (4.7)	12 (7.7)	34 (4.1)	0.051
Length of hospital stay median (25th, 75th)	14 (8, 28)	27 (13.25, 57.75)	13 (7, 24)	<b>0.000</b>
In-hospital mortality, n (%)	54 (5.5)	25 (16.0)	29 (3.5)	<b>0.000</b>

Values of  $P < 0.05$  are given in bold. NI, nosocomial infection; TBSA, total body surface area.



**Figure 2** Characteristics of nosocomial infections. BWI, burn wound infection; BSI, bloodstream infection; PI, pulmonary infection; UTI, urinary tract infection.

10%–29% TBSA burn and 21.6% of burn patients with TBSA more than 30%. The main burn type is flame (78.2%), followed by scalding (9.7%), electric (7.4%) and other types (4.7%). There were 46 (4.7%) patients had inhalation injury. The hospital mortality was 5.5% (54/986) and the median length of hospital stay was 14 (IQR 8–28).

### Characteristics of NIs

One hundred and fifty-six burn patients had 209 NIs, and the median time from admission to the NI was 7 days (IQR 5–10). Over all NI rate was 9.6 per 1000 patient-days. Among all NIs, BWI was the most frequent infection (45.9%), followed by BSI (24.8%), pneumonia (23.4%) and UTI (5.7%) (figure 2A). As shown in figure 2B a total of 237 micro-organisms were isolated. The most common pathogens was *Acinetobacter baumannii* (30.8%), followed by *Pseudomonas aeruginosa* (21.5%), *Klebsiella pneumoniae* (16.9%) and *Staphylococcus spp* (11%) (figure 2B).

Univariate analysis indicated that there were significant differences in diabetes, TBSA <10%, TBSA ≥30%,

**Table 2** Results of the Cox proportional hazard analysis of nosocomial infection

Variables	HR	95% CI	P values
LOS	1.002	0.996 to 1.007	0.547
TBSA	1.189	1.005 to 1.407	<b>0.043</b>
Full thickness burn	1.799	1.289 to 2.511	<b>0.000</b>
Inhalation injury	3.326	2.169 to 5.102	<b>0.000</b>
Diabetes	1.586	0.856 to 2.939	0.143

Values of P<0.05 are given in bold.

LOS, length of stay; TBSA, total body surface area.

full thickness burn, inhalation injury and LOS between burn patients with and without NIs (table 1). Using a Cox regression model, there was a statistically significant increased OR for NI in patients with full thickness burn (HR 1.799; 95% CI 1.288 to 2.511, p=0.000) and inhalation injury (OR 3.326; 95% CI 2.169 to 5.102, p=0.000), TBSA (HR 1.189; 95% CI 1.005 to 1.407, p=0.043) (table 2).

### Impact of NIs on hospital death of burn patients

As shown in table 1, the hospital mortality of patients with and without NI was 16.0% and 3.5%, respectively. Univariate analysis indicated that the hospital mortality of patients with NIs was higher than those without NIs (online supplementary table S1). Using a Cox regression model with NI modelled as a time-varying covariate, we found the risk of hospital death for patients with NI was 5.92 times higher than that for patients without it (95% CI 3.098 to 11.310, p<0.001). After adjusting for age, gender, TBSA and inhalation injury, the risk of hospital death for patients with NI was 4.266 times higher than for patients without NI (95% CI 2.218 to 8.208, p=0.000) (table 3, online supplementary table S1). Cumulative incidence functions for death were shown in figure 3A. The cumulative probability of discharge was consistently lesser for an infected patient (figure 3A). As shown in figure 3B, the cumulative probability of death for a patient with NI was greater than that for a patient without NI.

### Extra LOS

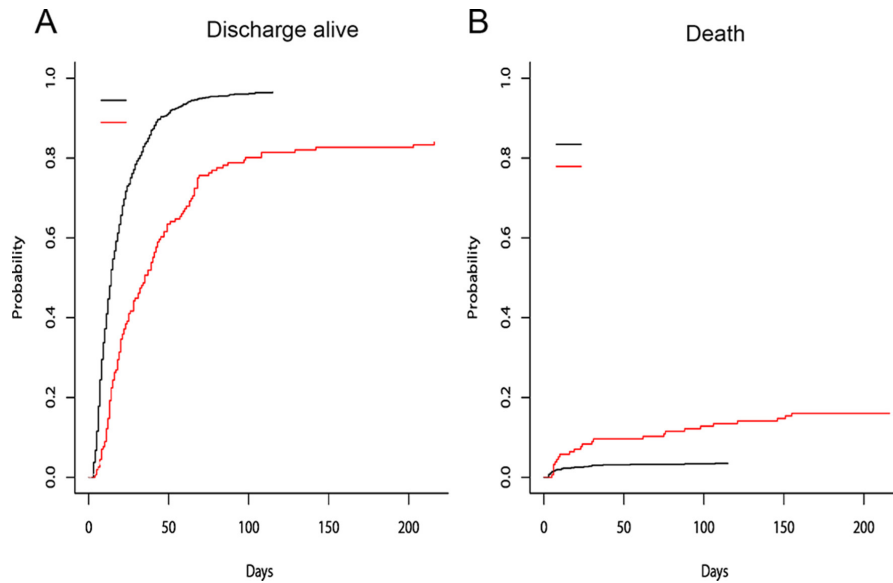
As shown in figure 1, the median LOS for patients without NI was 13 days (IQR 7–24). For patients with NI, the median LOS was 27 days (IQR 13.25–57.75). Because the

**Table 3** Results of the Cox proportional hazard analysis of hospital death

Variables	HR	95% CI	P values
Nosocomial infection	4.266	2.218 to 8.208	<b>0.000</b>
TBSA	1.374	1.034 to 1.825	<b>0.028</b>
Inhalation injury	2.824	1.448 to 5.508	<b>0.002</b>
Age	1.003	0.991 to 1.016	0.608
Gender	1.212	0.667 to 2.201	0.528

Values of P<0.05 are given in bold.

TBSA, total body surface area.



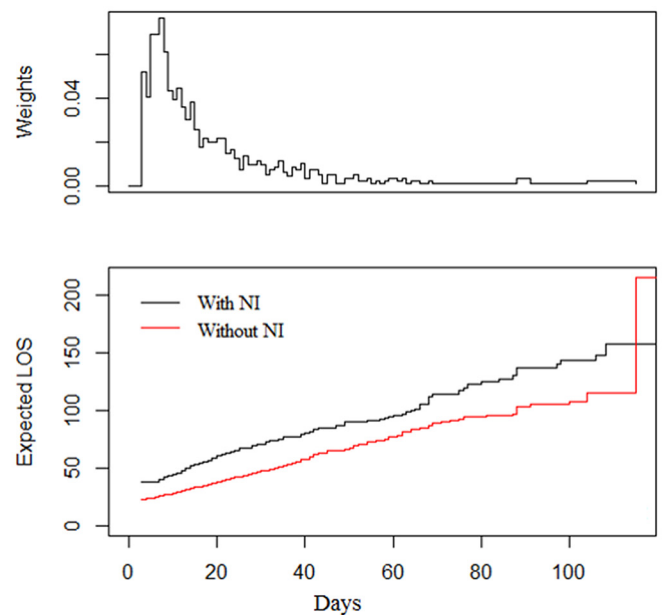
**Figure 3** Cumulative incidence functions for discharge (A) and death (B) in burn patients. Red lines: nosocomial infection; black lines: no nosocomial infection.

LOS distribution is positively skewed, the logarithm (base 10) of LOS was used as the response variable in multiple linear regressions. Based on the results of multiple linear regressions, NI was associated with increased LOS in burn patients. Other variables associated with LOS were TBSA, electric burn, flame burn, full thickness (table 4). Using a multistate model, the extra LOS due to NI was 17.68 days (95% CI 11.31 to 24.05, SE 3.25,  $p < 0.001$ ) (figure 4).

## DISCUSSION

Burn patients are at high risk for local and systemic infections. Although infection control programme has been performed in most burn centres and hospitals, the incidence of NI remains high. Alp *et al* reported that 11% of burn patients were suffered from NI and incidence density was 14.7 per 1000 patient-days.<sup>11</sup> Recently, a prospective cohort study was conducted in six major US burn centres to determine the association between burn size and the morbidity and mortality of burns. It found that in patients who have  $>20\%$  TBSA burn and need for surgical intervention, the incidence of NI was 70%.<sup>18</sup> In the present study, incidence density of NI was 9.6 per 1000 patient-days which was less than that reported by

Alp *et al* and Jeschke *et al*. BWI was the most common infections in our burn centre. *A. baumannii* and *P. aeruginosa* accounted for about 50% of total isolates, and *A. baumannii* was the predominant pathogen. Previously study illustrated that *A. baumannii* was the most common Gram-negative pathogen in burn patients.<sup>9</sup> According to the data published by Alp *et al*,<sup>11</sup> 57% of isolates from burns was *A. baumannii* in 2009. Nowadays, *A. baumannii* has emerged as an important pathogen causing NIs in China. Rigorous antibiotic stewardship and infection control measures were applied to prevent the spread of *A. baumannii* infections.<sup>19</sup>



**Figure 4** Extra LOS in patients without (red line) and with (black line) infection. LOS, length of stay; NI, nosocomial infection.

**Table 4** Results of multiple linear regressions analysis of length of stay (days)

Variables	B	95% CI	P values
TBSA	0.085	0.056 to 0.113	0.000
Full thickness burn	0.105	0.052 to 0.157	0.000
Electric burn	0.228	0.129 to 0.328	0.000
Flame burn	0.093	0.031 to 0.155	0.003
Nosocomial infection	0.244	0.184 to 0.305	0.000

TBSA, total body surface area.

Many factors contribute to NIs in burns, including burn injury-induced immunosuppression.<sup>6–9</sup> Clinical and experimental evidence illustrated that severe systemic inflammation after burn injuries can lead to a compensatory anti-inflammatory response, which is characterised by decreased number of T helper lymphocytes, increased suppressive activity of regulatory T cells (Tregs) which specialised for immune suppression, as well as elevated levels of anti-inflammatory cytokines.<sup>20–22</sup> Inhibition of Tregs attenuates postburn sepsis has been confirmed by an experimental study.<sup>23</sup> In addition, we also observed that full thickness burn, TBSA and inhalation injury are the risk factors for NIs in burn patients. The most notable finding in this study was the association between NIs and hospital mortality in burn patients. It has been reported that, in patients with more than 40% TBSA, over 70% of deaths were related to sepsis resulting from BWIs and other infection complications.<sup>6 8 9 11 24</sup> Nevertheless, a study illustrated that NI was a risk factor for mortality in univariate analysis, but it was not found as a risk factor for mortality in the stepwise forward logistic regression undertaken to control effect of confound variables.<sup>11</sup> The different statistical method may contribute to the different results. In the present study, NI was modelled as a time-varying factor in a competing risk model. The results illustrated that the risk of hospital death for burns with NI was 4.266 times higher than that for non-infected patients, and the cumulative probability of discharge was consistently lesser for an infected patient. Burn size was the strongest predictor of mortality in burns, as illustrated by previous studies.<sup>18 25 26</sup> In the present study, we found that TBSA is a risk factor for hospital death in burn patients. Additionally, inhalation injury usually causes pulmonary and systemic complications which greatly increases the risk of death after burn and the results of our study confirmed this.<sup>25 26</sup>

The association between NI and LOS has been illustrated by many studies. The median LOS was about twofold higher in patients with trauma with NI compared with patients without infection.<sup>27</sup> Among patients with critical illness, NI increased the LOS by approximately 18 days per patients.<sup>28</sup> NI after burn has been considered as a risk factor for prolonged LOS. Shupp *et al* reported that BSI was associated with longer hospital LOS in burn patients.<sup>29</sup> Nevertheless, there were no studies to assess the exact impact of NIs on LOS in burns. Additionally, the time-dependent nature of NIs implies that infection can impact on LOS only after the infection has started. While analysing the impact of NIs on LOS, the duration of hospitalisation prior to the NIs should be considered. So, a multistate model was used in the present study to estimation of extra LOS caused by NI. We found that the extra LOS due to NI in burn patients was 17.68 days.

There are some limitations in the present study. Initially, efforts used to prevent NI, such as antibiotic treatment and surgery, may have been started before the diagnosis was made. So, our assessment of the impact of NI on LOS and hospital mortality should be regarded as a lower estimate.

Second, as an observational and retrospective study, some potential factors, such as nursing protocols and the use of antipeptic ulcer or immunosuppression drugs, that may be associated with NIs, LOS and death were not available. Furthermore, factors, including mechanical ventilation and application of antibiotics, may also influence the incidence of NIs. These factors need to be taken into consideration in the prospective studies. Additionally, the present study was performed in a single centre and the results need to be further confirmed by multiple centre trials. Finally, there were no patients and public involved in this retrospective observational study. As patient and public involvement is important for a clinical research,<sup>30</sup> it needs to be done in the future studies.

## CONCLUSION

The present study provided additional information about the impact of NI on LOS and hospital mortality in burn patients. Using competing risk and multistate model, we found that NI was associated with the increased cumulative incidence of burn death. The expected extra LOS due to NIs among burn patients was 17.68 days. The model used in the present study may help to improve the accuracy of estimates of LOS and incidence of death due to NIs in burns.

**Contributors** H-LG and Z-JL wrote the protocol, participated in the data analysis and contributed to writing this manuscript. G-JZ, X-WL, J-JX and C-JL collected the data. All authors read and approved the final manuscript.

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**Competing interests** None declared.

**Patient consent** Not required.

**Ethics approval** Institutional Review Board of the First Affiliated Hospital of Wenzhou Medical University.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data are available.

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