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Original Article

Does early bloodstream infection pose a significant risk of in-hospital mortality in adults with burns?

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KEYWORDS
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Abstract *Background/purpose:* Bloodstream infections (BSI) are common in patients with major burns, but its effect on mortality remains controversial. This study was aimed to investigate if BSI is significant risk factor of mortality?
Methods: This is a retrospective chart review study included 266 adult patients admitted to our burn center from 2000 to 2019. Age, sex, inhalation injuries, total burn surface area (TBSA), duration of stay in intensive care unit, BSI and mortality were variables studied. Fisher exact test, Mann—Whitney test and logistic regression was used for statistical analysis.
Results: There were 234 survivors and 32 non-survivors. Male was predominant. The overall incidence of BSI was 18.8%, and the overall crude mortality was 12%. Burns $\geq$ 30% TBSA and BSI were significant risk factors. A predictive function based on 30% TBSA and BSI within 14 days after the onset of burns (BSI-14) was derived. The function has a sensitivity of 0.97, specificity of 0.42 and achieved a maximum Youden Index at functional value $\geq$ 0.05727. The mortality probability of BSI-14 in burns $\geq$ 30% TBSA was 40.8%.
Conclusions: BSI and burns $\geq$ 30% TBSA were significant risk factors of mortality. Early detection of BSI-14 is critical in burn care as its probability of mortality can be as high as 40% in patients $\geq$ 30% TBSA of burns. To reduce the risk of mortality, early in ventilator withdrawal, invasive lines and tubes removal, and early grafting should be emphasized besides infection control and appropriate use of antibiotics.

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Introduction

In the past decades, there are abundant research on investigating the risk factors of burn mortality as its prediction is important in modern burn care. Studies have shown that burn size, patient age and the presence of inhalation injury are significant risk factors of mortality.[1–4] Although blood stream infections (BSIs) are common in burns with mortality ranging between 30.0% and 36%,[5,6] however, it is seldom used as a risk factor to predict mortality. This is because results in various study are controversial.[7–10] Previous report indicated that patients with positive blood cultures were 12 times more likely to die during hospitalization than patients without positive blood cultures.[11]

Compared with patients without BSIs, Tang CQ et al. showed that patients who developed BSIs had a larger burn size and depth.[12] Similarly, Chen et al. stated that among patients with a TBSA over 50%, non-survivors had larger burn sizes and were also more likely to have microorganism-positive blood and sputum cultures compared with survivors.[13] Also, studies had shown that most of the first BSI episodes were diagnosed during the first week of hospitalization, and majority of the clinical burn deaths occurred within several days after injury.[14,15] Based on these facts, this study was aimed to investigate the probability of mortality in severe burn patients with early BSI episodes.

Materials and methods

Hospital setting

This retrospective study was conducted at the National Taiwan University Hospital (NTUH), a 2,500-bed tertiary-care center in northern Taiwan. From the 2000 to 2019, only adult (elderly than 20 years) patients admitted to Burn Centre of NTUH were included in this study. There are 4 intensive care unit beds and 10 ordinary beds in the burn center. This study was approved by the Ethic Committee of NTUH. (IRB/REC no. 201407007RINB).

Study design

Using chart review, age, gender, inhalation injuries, total burn surface area (TBSA), duration of stay in intensive care unit, BSI and mortality were variables collected. The authors would like to emphasize that the mortality concerned in this manuscript is in-hospital all-cause or crude mortality. Blood cultures (Bactec 9240 system, Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA) were performed when the clinical signs and symptoms of BSI were present. All isolates, including bacteria and *Candida* species, obtained from positive blood cultures were initially identified by the automated system, Vitek 2 system (bio-Merieux, Vitek, Hazelwood, MO, USA) prior to 2015 and by the Bruker Biotyper matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) system since 2016.

Definition

An episode of bacteremia or fungemia was defined by a positive blood culture, which must have occurred >2 days after any previous positive result unless it was clear to the investigator that the new positive was part of the same episode.[16] The diagnosis of BSI was also confirmed when blood cultures obtained from two different puncture sites yielded the same microorganism.[17,18] If the cultured bacteria were common micro-organisms in normal skin flora, they were considered as true pathogens when the same pathogens were cultured two or more times.[6] Polymicrobial episodes were defined as having >1 clinically significant blood culture isolate occurring within 2 days of each other.[17] Multidrug resistance is defined as resistance to at least three classes of antimicrobial agents. For either three of penicillins, cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, tigecycline, polymyxins for gram-negative bacteria, and glycopeptides, oxacillin (penicillin), erythromycin, clindamycin, trimethoprim-sulfamethoxazole, linezolid, daptomycin, aminoglycoside (gentamicin), tetracyclines (tetracycline or minocycline) for gram-positive bacteria. BSI within 14 days after the onset of burns was termed as BSI-14. The rationale of not defining early BSI as that defined by Raz-Pasteur et al. who defined early BSI as BSI in the first week of burns was due to small sample size of BSI patients in the first week of burns in our study.

Statistical analysis

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean ± SD or median. Quantitative variables were compared using Mann–Whitney test, while qualitative variables were correlated using chi-square test/Fisher's exact test. The association of mortality with various parameter was assessed using univariate and multivariate Firth's logistic regression. A predictive function was derived and receiver operating characteristic (ROC) curve was plotted and the areas under the curve (AUC) were calculated for prediction ability. Two-tailed P values $< 0{\cdot}05$ were considered significant. All statistical analyses were performed with SAS version 9·2 (Cary, NC, USA).

Results

A total of 266 patients were included in the study. The patient demographic characteristic is shown in Table 1. Male was predominant. There were 234 survivors and 32 non-survivors. The overall mortality rate was 12.0% in which flame burn was the most common type of burns injuries. Burn size in term of total surface of burns (TBSA) was significantly larger in the non-survivors. The male: female sex ratio was 2:1 in the survivors, but increased to 4:1 in the non-survivors. The mean age was 36.5 years in the survivors, younger than that in the non-survivors although the difference was statistically insignificant. The overall incidence of BSI was 18.8% (50/266). A total of 50 patients had BSI attacks, 39 in the survivors and 11 in the non-survivors. BSI-14 occurred in 13 of the survivors, and 6 in the non-

Table 1 Demographic characteristic of the survivors and the non-survivors.

Variables	Survivors (n = 234)	Non-survivors (n = 32)	*p*-value
Sex, M (%)	157 (67.1)	26 (81.3)	0.1050
Age (mean, SD)	36.45 (19.92)	42.84 (21.11)	0.1014[a]
Inhalation injuries (%)	16 (59.3)	6 (85.7)	0.5448[b]
TBSA (mean, sd)	38.82 (19.16)	71.63 (25.42)	<0.0001[a]
Burns ≥ 30% TBSA (%)	131 (55.98)	30 (93.75)	<0.0001
ICU stay (median, min—max)	24 (3—474)	17 (0—208)	0.5524[a]
BSI (%)			0.0223[b]
In the first week after burns	5 (2.1)	2 (6.3)	
In the second week after burns	8 (3.4)	4 (12.5)	
After second week of burns	26 (11.1)	5 (15.6)	
No of BSI episodes in a month			0.020[b]
1	33 (14.1)	9 (28.1)	
2	6 (2.6)	1 (3.1)	
3	0 (0)	1 (3.1)	

[a] Mann-Whitney Test for continuous variables.
[b] Fisher exact test was used for category variables.
BSI, bloodstream infection; ICU, intensive care unit; SD, standard deviation; TBSA, total burn surface area.

survivors. 15% of the non-survivors had BSI 14 days after the onset of burns.

In univariate analysis, inhalation, TBSA, and BSI were significant independent risk factors of mortality, but further analysis in multivariate disclosed that burns ≥ 30% TBSA and BSI were the only mortality risk factors (Table 2). A predictive function was derived. At $\hat{p}$ value 0.05727, the maximum Youden index value was achieved with sensitivity 0.96875 and specificity 0.42308 (Fig. 1 and Fig. 2).

A risk stratification based on burns ≥ 30% TBSA and BSI-14 was defined (Table 3). The probability of mortality was 1.7% in patients of burns <30% TBSA without BSI-14, but increased to 5.7% if there was. In the absence of BSI, the mortality risk in burns ≥ 30% TBSA was 16 times higher than that less than. However, the probability of mortality was 40.8% when BSI-14 occurred in patients with burns ≥ 30% TBSA.

The microbiological profile of the isolates from blood cultures is shown in Table 4. Methicillin-resistant *Staphylococcus aureus* was the most common causative pathogen, followed by *Enterobacter cloacae*. However, *E. cloacae* was the most common pathogen in the non-survivors. *Bacillus thuringiensis* and *Micrococcus* species, microorganisms normally found in the normal skin flora, were considered as true pathogens in three patients. One patient had blood cultures of *B. thuringiensis*, sampling from the artery and venous lines. Meanwhile, *Micrococcus* species were cultured in the blood streams of two patients in addition to the burned wounds.

Discussion

Our results demonstrated that the overall incidence of BSI episodes was 19% (50/266) compared to 4% - 46·5% as reported in the literature.[10,14] In the non-survivors, it was about twice as high as that in the survivors (34.4% vs. 16.7%). A comparison of the demographic characteristic between these two groups showed that there were significant differences in the data related to TBSA and BSI. However, unlike other results of previous studies,[19—22] our analysis did not show that age and gender significantly differ between the survivors and the non-survivors. While Olaitan et al.[22] stated that the mortality in males (20.8%) was higher than in females (18.6%), Taylor et al.[20] described that seniors had greater increase in mortality

Table 2 Univariate and multivariate analysis of risk factors for burn mortality.

Variable	Univariate				Multivariate			
	Estimation	OR	OR 95% CI	*p*-value	Estimation	OR	OR 95% CI	*p*-value
Sex, M	−0.7539	0.471	(0.186, 1.191)	0.1116				
Age	0.0155	1.016	(0.997, 1.034)	0.0941				
Inhalation injuries	1.1458	3.145	(1.131, 8.744)	0.0281*				
Burns ≥ 30% TBSA (%)	2.4676	11.794	(2.754, 50.502)	0.0009*	2.4293	11.351	(2.639, 48.819)	0.0011*
Burn size	0.0587	1.060	(1.041, 1.080)	<0.0001*				
ICU stay	0.00314	1.003	(0.996, 1.010)	0.3945				
Early BSI	1.3671	3.924	(1.374, 11.204)	0.0107*	1.2482	3.484	(1.151, 10.547)	0.0272*

BSI, bloodstream infection; CI, confidence interval; ICU, intensive care unit, M, male; OR, odds ratio; TBSA, total body surface area.
Early BSI was defined as BSI occurred in 14 days of burns.

$$\hat{p} = \frac{e^{-4.0492+2.4293 \quad Burns \geq 30\% \text{ TBSA}+1.2482 early \ BSI}}{1 + e^{-4.0492+2.4293 \quad Burns \geq 30\% \text{ TBSA}+1.2482 early \ BSI}}$$

$\hat{p}$	Sensitivity	Specificity	PPV	NPV	Youden
0.05727	0.96875	0.42308	0.18675	0.99000	0.39183

Figure 1. A derived functional equation for mortality prediction.

per 1% increment in burn size and one year increase in age than other ages.

Inhalation, TBSA, and BSI were independent predictors of mortality in univariate logistic regression analysis. Although previous studies disclosed that inhalation was associated with mortality,[23–25] in our study, it was not a significant risk factor in multivariate analysis. In other words, this study showed that inhalation was a variable that is significant univariate but not significant multivariate due to its associations with other predictors. TBSA was the strongest risk factor in the present study, as mentioned by Dhopte et al., who stated that TBSA was the most important factor predicting mortality in pediatric burns,[19] and Olaitan and Jiburum mentioned that survival decreased with increasing percentage burn surface areas.[22]

In the multivariate analysis, this study showed that BSI-14 increased the risk of mortality in burns with $\geq$ 30% TBSA. The authors considered BSI occurring in 14 days after the

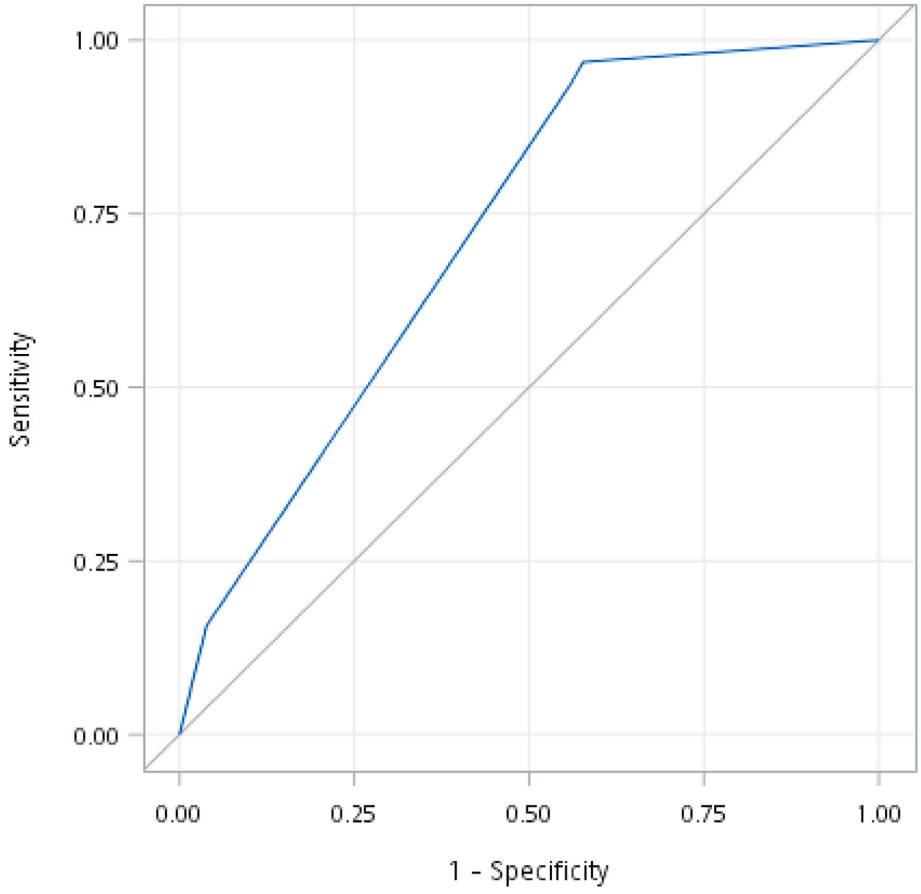

Figure 2. Receiver operating characteristic (ROC) curve for multivariate logistic regression model.

Table 3 Risk stratification of burn patients with bloodstream infections.

Burn ≥30%	BSI	$\widehat{p}$	Mortality rate
0	0	0.017	1.7%
0	1	0.057	5.7%
1	0	0.165	16.5%
1	1	0.408	40.8%

onset of burns as early BSI. This is different from Raz-Pasteur et al., who defined early BSI as BSI in the first week of burns and late BSI as that in the second week and beyond. He stated that most BSI episodes were diagnosed during the first week of hospitalization.[14] In a study of 137,061 burn patients, Zavlin et al. reported that most fatal outcomes (52.0%) occurred within 7 days after injury.[25]

Table 4 Comparison of the microbiological profiles of patients with bloodstream infection between the survivals and the non-survivals.

Isolate	No. of patients (n = 50)	
	Survivals (n = 39)	Non-survivals (n = 11)
Gram-positive bacteria		
Methicillin resistant *Staphylococcus aureus*	7	2
Staphylococcus epidermidis	2	0
Enterococcus species	3	2
Gram-negative bacteria		
Escherichia coli	2	0
Enterobacter cloacae	5	5
Bacillus thuringiensis	1	0
[a]*Micrococcus* species	2	0
[a]*Enterobacter aerogenes*	1	0
Enterobacter species	1	0
Serratia marcescens	1	1
Salmonella serogroup O4	1	0
Acinetobacter baumannii	6	1
Burkholderia cepacia complex	2	0
Stenotrophomonas maltophilia	1	1
Klebsiella pneumoniae	1	2
Pseudomonas aeruginosa	4	0
Bacteroides fragilis	0	1
Coagulase neg. staphylococci	6	0
Elizabethkingia	0	1
Fungi		
Candida parapsilopsis	2	0
Candida tropicalis	1	2
Candida alblican	3	0
Polymicrobial	18	5
[b]**Multidrug resistant**	12	5

[a] Bacillus thuringiensis and Micrococcus species which are microorganisms normally found in the normal skin flora are considered as true pathogens in three patients.

[b] A strain that is resistant to three or more than 3 antibiotics is considered as multidrug resistant strain.

In our study, 19% (6/32) of the non-survivors had BSI-14 which had an incidence of 7% (19/266), As above-mentioned, the effects of BSI on mortality remains controversial in the literature. In 2011, Patel et al. reported that BSI was a significant predictor of mortality in 2,364 patients.[10] Similarly, Shupp et al.[9] found that patients with BSI had higher mortality only when TBSA was <50%. On the contrary, in a study comparing the mortality of 76 BSI and 103 non-BSI patients, Brusselaers et al.[7] concluded that BSI did not adversely affect survival. In fact, inter-study comparisons were difficult because there was a wide spectrum in burn severity, in addition to variations in the quality of care and the absence of standard of care among different burn centers.

The risk stratification table shows that BSI-14 and burns surface area ≥ 30% TBSA are critical factors in predicting mortality. In the non-survivors, the mean surface area of burns was significantly larger than the survivors. This is compatible to the statement that the risk of BSI is higher in patients with larger burn size.[12,13] Tang et al. stated that patients who developed BSIs had a greater illness severity at admission to the intensive care unit, and worse outcomes.[12]

This could be explained by the facts that patients in this subgroup are associated with a higher risk of sepsis due to intense systemic burn response and immune suppression, in addition to a need for prolonged intubation and insertion of the central lines to maintain hemodynamic and respiratory stability. In addition, Brusselaers et al.[7] reported that BSI was significantly associated with longer hospitalization duration and mechanical ventilation which led to high mortality risk.

Although age and inhalation were not risk factors of mortality in multivariate analysis, however, these factors adversely affected the prognosis of BSI, besides the size of burns. Poor nutrition and immunity in the aged, impaired lung functions caused by inhalation, and persistent systemic inflammatory response in large burns with limited skin donors for grafting aggravate the clinical course of BSI. In addition, prompt treatments of BSI in these subgroups of burned patients is not easy as there is no unanimity as to which signs or symptoms are of utility for the early diagnosis of BSI or sepsis.[26]

The prophylactic use of systemic antibiotic has been a debate issue in burn care. Although their benefits are controversial,[27—30] in our burn center, empirical antibiotic is routinely used in severe burns patients on admission. In cases suspicious of BSI, prior to the availability of the culture results, broad-spectrum antibiotics are usually used empirically and changed to narrow spectrum when test results of the blood cultures are available. Frequently, empirical antifungal agent is recommended in cases without any clinical improvement despite the administration of broad-spectrum antibiotics.

Our study highlighted the importance of early diagnosis of BSI-14. The authors would like to emphasize that clinical pictures of burn BSI differ from that found in the general population.[25] In severe burns, the continuous exposure to pathogens due to the loss of skin barrier and the persistent systemic inflammatory response due to prolonged open wounds complicated the sepsis profile found in the general population. A diagnostic guideline was provided in a

consensus which was obtained from American Burn Association defining burn sepsis in the following criteria: 1) temperature >39 °C or <36.5 °C, 2) progressive tachycardia >110 beats per minute, 3) progressive tachypnea >25 breaths per minute or minute ventilation >12 L/min, 4) thrombocytopenia <100,000/mcl (does not apply until 3 days after burn), 5) hyperglycemia in the absence of pre-existing diabetes mellitus and 6) inability to continue enteral feedings >24 h. Burn sepsis is considered in the presence of three or more of the abovementioned criteria.[25]

Prompt identification of burns wound infections, ventilator related pneumonia, central line associated BSI (CLABSI), enteral bacterial translocation or urinary tract infections as the possible sources of secondary BSI is paramount,[31–39] allowing early source control and initiation of appropriate antibiotic regimens. Of these, CLABSI is always a challenging problem in severe burns due to limited unburned site for placement for the central line. In addition, the burns wounds are always colonized with pathogens. In a study of 177 severe burns patients, CRBSI accounted for 41.5% of the BSI episodes.[12] A delay in the diagnosis may result in mortality. Prevention is mandatory. Besides strict infection control and appropriate antibiotic use,[40–43] early in burn excision and grafting, ventilator withdrawal and removal of invasive lines and tubes are critical preventive measures in reducing the risks of becoming the sources of secondary BSI.

Our study has limitations. First, relative lower BSI rates and small sample size of the mortality group may reflect good clinical care in the study. Another limitation was that the impacts of BSI in the late stage of burns were not investigated in the study. Finally, only adult patients and one center experience was included in the study.

In conclusion, BSI and burn size were significant risk factors of mortality in multivariate analysis. Early diagnosis of BSI-14 is critical in burn care as its probability of mortality can be as high as 40% in patients ≥ 30% TBSA of burns. Inhalation is an independent risk factor. To reduce the risk of mortality, early in ventilator withdrawal, invasive lines and tubes removal, and early grafting should be emphasized besides infection control and appropriate use of antibiotics.

Data statement

The research data is available in National Taiwan University Hospital Burn Center. Data is available via application to Medical Research Center.

Declaration of competing interest

The authors declare no conflict of interest.

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