

Bloodstream infection as a predictor for mortality in severe burn patients: an 11-year study

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*Received 24 April 2013; Final revision 8 September 2013; Accepted 8 September 2013;
first published online 7 October 2013*

SUMMARY

In this study we collected and analysed data of the severe burn patients at our institution over an 11-year period in order to shed light on the controversial role of bloodstream infection (BSI) as a predictive factor for mortality in this burn population. The factors examined were age, total body surface area, smoke inhalation, presence of BSI, and BSI with resistant bacteria. In total 1081 burn patients were hospitalized from 2001 to 2011, of whom 4% died. We focused here on 158 severe burn patients, 74 of whom developed BSI, and 35 who died. Using univariate analysis, it appeared that the BSI group had a threefold greater chance of mortality compared to the non-BSI group. Patients with a Ryan score 3 had a 100% chance of mortality and those with a score 0 had 0%. Thus, focusing only on Ryan score 1 and score 2 patients, BSI did not contribute to mortality, nor was it shown to contribute to mortality in a multivariate analysis in which the score and BSI were included together. When BSI did occur, it predicted longer hospitalization periods. We conclude that BSI predicts longer length of hospitalization stay but does not contribute to the prediction of mortality beyond that offered by the Ryan score in a severe burn population.

Key words: Antibiotic resistance, bloodstream infections, hospital microbiology, infectious disease epidemiology.

INTRODUCTION

Advances in intensive care and burn care have substantially improved survival outcomes for patients with severe burn injuries in the last 10 years, with the recent literature quoting mortality rates of between 1·4% and 18% [1]. The ability to predict mortality is important, as it enables caregivers, the patient and

family members to address the prognosis of each burn patient. Since Baux's paper, published in French in 1961 [2], the percentage of burn area and patient's age have been the primary predictors of mortality after thermal injury. The Prognostic Burns Index (PBI) and Acute Burns Severity Index (ABSI), published in 1982 [3], made important contributions towards increasing the specificity of burn prognostic scoring, placing emphasis mainly on age and percentage of burn area. In 1998, Ryan's retrospective review of 1665 patients resulted in an easy to use and very specific prognostic tool based on three risk factors: age, total body surface area (TBSA) and

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inhalational injury. The predicted mortality rates in the Ryan scoring model are: 0=0.3%, 1=3%, 2=33%, 3=90% [4].

Prognostic scoring was further refined by the Belgium Outcome in Burns Injury Study in 2009, with a review of over 5000 burns, where patients were subdivided according to age and TBSA, thus improving the predictive value of the Ryan score [5]. These recently developed, multifactorial models of burn mortality, however, have not included microbiological aspects of burn wounds in their calculations [2–5].

There is still a lack of consensus regarding the contribution of BSI to death, as some studies found a correlation between the two, while others did not [1, 6–9].

Burn patients are at a high risk of BSI, and the causes for infection are many, including: alterations in cellular and humoral immune responses, extensive skin barrier disruption and a large cutaneous bacterial load, the possibility of gastrointestinal bacterial translocation, prolonged hospitalization, and invasive diagnostic/therapeutic procedures [10, 11]. The chances of BSI occurrence increase with burn size and depth. Early debridement and wound closure are advocated to decrease infection risk, but bacterial colonization of burns remains difficult to avoid, potentially leading to systemic infections [12–14]. Furthermore, the global rise in antibiotic-resistant bacteria strains in burn injuries is also reflected in the growing prevalence of BSI with such strains [14, 15], which might be associated with an increase in mortality rates.

In this study we collected data on severe burn patients admitted to our hospital between 2001 and 2011 and examined whether BSI contributes to the prediction of death by adding this as an additional factor to Ryan's scoring method.

METHODS

Study setting

All medical records of the burn patients admitted to the Rambam Healthcare Campus (RHC) Burn Unit and Intensive Care Unit (ICU) during the years 2001–2011 were retrospectively retrieved from a computerized, hospital-wide database. Only severe burn patients were included in the study, defined as TBSA > 10% when the burn areas included hands or face, or TBSA >20% not including hands or face.

Permission for this review was obtained from the hospital's Helsinki Committee.

The RHC Burn Unit is one of four burn units in Israel, and is the admitting centre for all severe burn cases in the north of Israel, with a total population of two million. At RHC there are 948 beds of which 18 are in the ICU. The Burn Unit, associated with the Plastic Surgery Department, is an eight-bed facility with mean annual admissions of around 200 burn patients. Burn patients who need mechanical ventilation are hospitalized in the ICU. Once extubated, they are transferred to the Burn Unit in the Plastic Surgery Department. Burn patients who do not require mechanical ventilation upon admission are hospitalized in the Burn Unit. Patient records were analysed throughout their hospitalization period, including both the ICU and Burn Unit hospitalization periods.

Assessment and management of burn patients

Superficial and mid-dermal burns not requiring surgery, and deep, full-thickness burns prior to surgery, are typically dressed with NaOHCl solution 1:10, silver sulfadiazine cream, or Aquacel Ag dressing to achieve an aseptic wound condition. Early burn excision and skin grafting of third-degree burns (2–7 days post-burn) is practised in our Burn Unit, as soon as the patient is surgically fit, until all areas of the burn are grafted. We defined smoke inhalation in a patient as when the cause of the burn was a fire in an enclosed place, and signs of burns on the face particularly in the mouth and nose identified by the presence of carbon sputum, subsequently leading to patient intubation.

Study design and mortality assessment

Data were collected on the demographic and clinical characteristics of the patients, TBSA and smoke inhalation, as well as mortality rate and timing of death during the hospitalization period. The mortality rate of the study population was examined according to Ryan's scoring system, assigning each one a score of 0, 1, 2, or 3 according to the following criteria: age >60 years, TBSA >40%, and the presence of smoke inhalation. Meeting each one of these criteria gained 1 point [4]. All the microbiological data from blood cultures in these patients were collected and patients were presumed to have a BSI if microorganisms were grown from their blood cultures. If a patient had more than one episode of BSI with the same pathogen, only the first BSI episode was used in the analysis.

For the analysis of whether the presence of BSI, and particularly BSI with resistant bacteria, contributed to mortality, patients who died within 72 h of admission were excluded. The reason for this was to take into account the high probability that death during this period could have resulted from other factors besides sepsis, such as systemic inflammatory response syndrome (SIRS). We also analysed which factors contributed to longer length of stay (LOS), including Ryan score, TBSA, smoke inhalation, BSI and age. LOS included the combined hospitalization period in the ICU and/or the Burns Unit.

Microbiological methods and definitions

All blood cultures were taken when any sign of sepsis was observed, and were processed by the hospital microbiology laboratory using a Bactec 9240 system (Becton Dickinson, USA). Antibiotic resistance (minimum inhibitory concentration) was determined according to the criteria of the Clinical and Laboratory Standards Institute (CLSI) [16].

BSI was defined as the isolation of bacteria that are not normally known to colonize the skin, such as Gram-negative bacilli, certain pathogens such as *Staphylococcus aureus* or fungi from at least one blood culture, or coagulase-negative staphylococci (CoNS) in at least two separate positive blood cultures and where the isolates shared the same antibiogram. Antimicrobial resistance was defined as resistance to methicillin for *S. aureus* (MRSA), resistance to carbapenems (imipenem) for *Pseudomonas aeruginosa* (PSE-IMP), *Acinetobacter baumannii* complex (ACI-IMP), and *Klebsiella pneumoniae* (CRKP).

Statistical methodology

To identify parameters associated with increased in-hospital mortality, binary logistic regressions were used for the calculation of the odds ratios (ORs) with 95% confidence intervals (CIs) and *P* values in bivariate analysis. The variants examined were Ryan score, TBSA, age, smoke inhalation, gender, and BSI. All variables with a *P* < 0.2 on bivariate analyses were considered for inclusion in a multivariable explanatory model. The area under the receiver-operating characteristic (ROC) curve was used as a measure of model discrimination. The Hosmer–Lemeshow goodness-of-fit statistic was calculated. Two-tailed *P* values ≤ 0.05 were considered as statistically significant. Comparison of the mortality rate between

presence or absence of BSI in score 1 and 2 groups was done by χ^2 test. The LOS of the different score groups was compared using analysis of variance [ANOVA, *post-hoc* (Bonferroni)], followed by the multi-way univariate ANOVA method, to analyse the role of BSI on LOS. Statistical analyses were performed using SPSS v. 18.0 software (SPSS Inc., USA).

RESULTS

One thousand and eighty-one patients were admitted to the RHC Burn Unit and ICU during the 11-year period from 2001 to 2011, of which 35 (4%) died. One hundred and seventy-four were classified as having severe burns and included in the study and of these 83 had a Ryan score of 0, 41 a score of 1, 40 a score of 2 and 10 a score of 3. Seventy-three per cent (*n* = 128) were male. The mean age was 42 ± 19 years (range 17–89 years). The mean TBSA was 34 ± 23% (range 10–100%) and 38% had smoke inhalation. The median LOS was 28 ± 34 days (range 1–216 days).

To examine the association of patient characteristics and BSI, those patients who died within the first 3 days of hospitalization were excluded, assuming that in this period there is no BSI. Also excluded were patients who were discharged during the first 3 days. Thus, 16 patients were eliminated, six who were discharged and 10 who died during that period, leaving 158 patients in the study. Of the latter patients, 35 (22%) died, and 75 (48%) had BSI. Twenty-six of the 75 patients who had BSI died (34%) compared to 9/83 patients who did not have BSI (10%); (*P* < 0.001, OR 4.2, 95% CI 1.8–9.8). In this bivariate analysis, the risk of dying was more than threefold greater in the BSI group.

BSI was present in 21% of the Ryan score 0 patients; 67% of score 1, 88% of score 2 and only 43% of score 3 patients. There was a significant increase in BSI occurrence in Ryan scores 1 and 2 compared to score 0 patients (OR 7.5, 95% CI 3.22–17.8 *P* < 0.001; OR 28.1, 95% CI 8.6–91.5, *P* < 0.001, respectively). However, for Ryan score 3, there was less BSI occurrence and the difference was not significant (Table 1).

Of the 35 patients who died, all had a Ryan score of ≥ 1 (23% chance of death in score 1; 56% in score 2; and 100% in score 3) (*P* < 0.001); score 0 had 0% of death cases (Fig 1, Table 1). In the score 3 group, all deaths occurred within the first 2 weeks of admission and this rapid mortality rate explains the low rate of BSI in this group. However, in the score 1 and 2 groups,

Table 1. Association between patients' characteristics, BSI and in-hospital mortality

		Total	BSI					In-hospital mortality				
			N	%	OR	95% CI	P	N	%	OR	95% CI	P
Age, yr	≤60	130	57	44	1			19	15	1		
	>60	28	18	64	2.2	1.0–5.2	0.062	16	57	7.6	3.1–18.7	<0.001
TBSA, %	≤40	115	40	35	1.0			15	13	1.0		
	>40	43	35	81	8.0	3.4–18.9	<0.001	20	46	5.7	2.5–12.8	<0.001
Inhalation injury	No	101	33	33	1.0			3	3	1.0		
	Yes	57	42	74	5.6	2.7–11.5	<0.001	32	56	41.0	11.6–144.8	<0.001
Score	0	78	16	21	1.0			0	0%			<0.001
	1	39	26	67	7.5	3.2–17.8	<0.001	9	23			
	2	34	30	88	28.1	8.6–91.5	<0.001	19	56			
	3	7	3	43	2.8	0.6–13.9	0.204	7	100			
BSI	No	83						9	11	1.0		
	Yes	75						26	35	4.2	1.8–9.8	<0.001
Sex	M	117	49	42	1.0			23	20	1.0		
	F	41	26	63	2.3	1.1–4.9	<0.001	12	29	1.7	0.7–3.7	0.2

BSI, Bloodstream infection; OR, odds ratio; CI, confidence interval; TBSA, total body surface area.

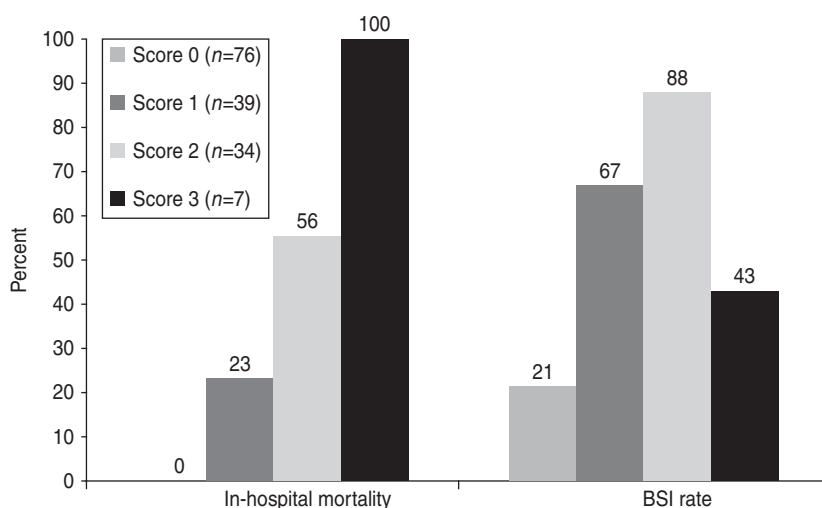


Fig. 1. Mortality rate and bloodstream infection (BSI) rate in the different score groups.

death occurred more gradually over the hospitalization period (Fig 2).

In a bivariate analysis, an age >60 years, smoke inhalation and burn severity were found to be strong predictors of mortality. The mortality rate of patients aged ≤60 years was 15%, and for patients aged >60 years it was 57% (OR 7.6, 95% CI 3.1–18.7, P<0.001). Mortality in patients with TBSA ≤40% was 13%, and for those with TBSA >40% it was 47% (OR 5.7, 95% CI 2.5–12.8, P<0.001). Mortality in patients without smoke inhalation was 3%, compared to 56% in patients who had smoke

inhalation (OR 41, 95% CI 11.6–144.8, P<0.001) (Table 1).

In the multivariate analysis we found that mortality was predicted very well with the combination of risk factors used in Ryan's scoring. The Hosmer–Lemeshow goodness-of-fit result of 0.8 showed good calibration and the area under the curve of 0.921 was indicative of a high predictive power. However the addition of BSI as our variable of interest left the prediction capacity almost unchanged as with or without BSI, the area under the curve was almost identical (Table 2).

Table 2. Multivariable model including variable of interest (BSI)

	Model without BSI			Model with BSI		
	aOR	95% CI	P value	aOR	95% CI	P value
Smoke	35.5	9.3–135.3	0.000	39.3	10.0–154.0	0.000
Age >60 yr	13.9	3.6–53.9	0.000	14.8	3.7–58.7	0.000
TBSA >40%	3.7	1.4–10.0	0.009	4.1	1.5–11.4	0.007
BSI				0.6	0.2–1.8	0.399
Hosmer & Lemeshow test						
Without BSI		0.08				
With BSI		0.345				
Area under the curve						
Model with BSI		0.926	Asymptotic 95% CI			
Model without BSI		0.921	0.884–0.967			
			0.877–0.956			

BSI, Bloodstream infection; aOR, adjusted odds ratio; CI, confidence interval; TBSA, total body surface area.

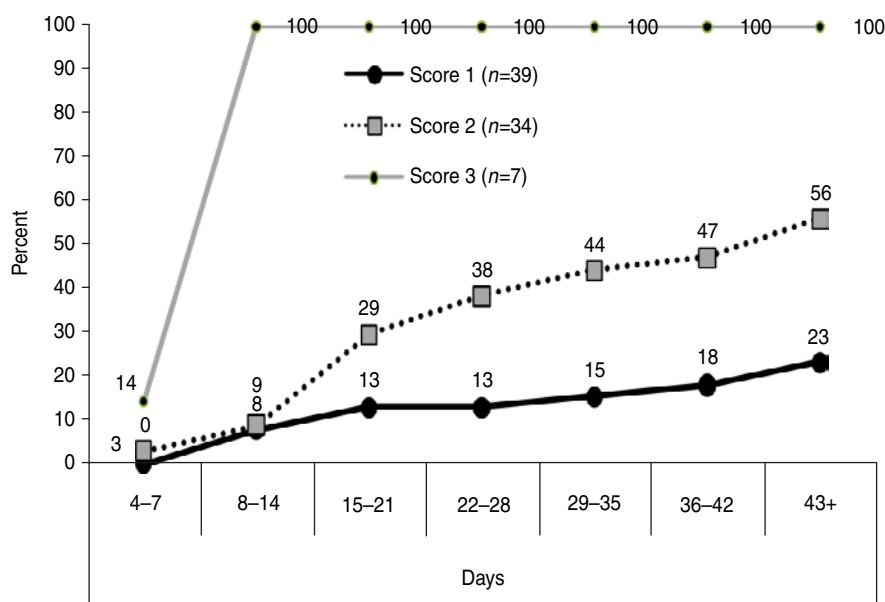


Fig. 2. Time to mortality in each of the score groups.

Furthermore, because BSI cannot reduce or add respectively to mortality rates of 0% and 100%, an additional bivariate analysis was conducted which excluded patients with Ryan scores 0 and 3 using χ^2 test to determine whether BSI was a predictor of death only in the Ryan score 1 and 2 groups. No significant difference in mortality rate was found when BSI was present (Table 3). Similarly no significant difference in mortality was observed when BSI was associated with antibiotic-resistant bacteria, and no difference was found between specific bacterial groups, or with fungi. This analysis underscored the finding that BSI in any of its forms was not a

significant factor for prediction of mortality in this patient group (Table 3).

An analysis of variance was used to examine whether BSI contributed to LOS, relating only to patients who survived. The factors found to be associated with longer hospitalization were high Ryan score, high TBSA, smoke inhalation, age and BSI. Subsequently, median LOS was plotted using a multivariate analysis against TBSA, which proved to be the strongest factor. An interaction between TBSA, BSI and LOS was evident and in general the higher the TBSA, the longer the LOS, and more specifically, in TBSA $\leq 40\%$, BSI was significantly correlated to

Table 3. Association between patients' characteristics and mortality rates for Ryan scores 1 and 2

	BSI		Without BSI		P		
	N	%	N	%			
Score 1	26	27	13	15	0.69		
Score 2	30	53	4	75	0.61		
	KLB		No KLB		P		
	N	%	N	%			
Score 1	12	33	27	19	0.42		
Score 2	13	62	21	52	0.73		
	CRKP		No CRKP		P		
	N	%	N	%			
Score 1	2	50	37	22	0.41		
Score 2	4	75	30	53	0.61		
	PSE		No PSE		P		
	N	%	N	%			
Score 1	7	0	32	28	0.17		
Score 2	13	46	21	62	0.48		
	PSE-IMP		No PSE-IMP		P		
	N	%	N	%			
Score 1	5	0	34	26	0.31		
Score 2	8	38	26	62	0.42		
	MRSA		No MRSA		P		
	N	%	N	%			
Score 1	7	29	32	22	0.65		
Score 2	9	33	25	64	0.14		
	Fungi		No fungi		P		
	N	%	N	%			
Score 1	2	50	37	22	0.41		
Score 2	6	33	28	50	0.37		
	BSI without RES		BSI with RES		Without BSI		P
	N	%	N	%	N	%	
Score 1	12	25	14	29	13	15	0.71
Score 2	12	58	18	50	4	75	0.65

BSI, Bloodstream infection; KLB, *K. pneumoniae*; CRKP, carbapenem-resistant *K. pneumoniae*; PSE, *P. aeruginosa*; PSE-IMP, carbapenem-resistant *P. aeruginosa*; MRSA, methicillin-resistant *S. aureus*; RES, resistant bacteria.

Table 4. Association between patient characteristics and LOS

		No (mortality)	Mean (days)	Median (days)	s.d. (days)	Min. (days)	Max. (days)	<i>P</i>
Score	0	82	28·6	26·5	22·7	1	116	<0·001*
	1	32	47·7	43·0	33·7	1	145	
	2	15	86·8	74·0	55·3	21	216	
Age, yr	≤60	116	39·1	33·0	34·7	1	216	0·5
	>60	13	49·5	36·0	45·9	3	141	
TBSA, %	<20	62	25·7	26·0	17·8	1	93	<0·001
	20–40	44	41·2	38·0	34·1	1	139	
	>40	23	77·0	60·0	48·5	21	216	
Smoke inhalation	No	103	33·6	30·0	28·4	1	145	<0·001
	Yes	26	66·0	47·0	49·5	1	216	
BSI	Without	80	24·0	23·5	16·8	1	93	<0·001
	With	49	66·4	50·0	42·9	6	216	

TBSA, total body surface area; BSI, bloodstream infection.

* Score 1 vs. 0 ($P=0\cdot01$); score 1 vs. 2 ($P<0\cdot001$), score 2 vs. 0 ($P<0\cdot001$)

longer LOS. However, in TBSA >40%, absence of BSI was extremely rare, and thus it is difficult to confirm a causal connection between BSI and LOS (Table 4).

DISCUSSION

Infectious complications in burns are common, and the development of infection during the course of hospitalization, particularly BSI, could intuitively be considered to be a harbinger of a poor outcome. The Ryan model for the prediction of mortality is based on risk factors present at admission. In this study we asked whether including a complication such as BSI, which can develop over the course of the hospitalization period, can improve the prediction model in the severe burn population. Ultimately, we did not find that including BSI improved the prediction of mortality, whether using a multivariate analysis or when focusing only on patients with Ryan scores 1 and 2. While BSI is one of the major factors leading to mortality in severe burn patients, it did not prove to be statistically significant as a predictor of mortality.

There is consensus that the most common factors for predicting mortality in burn patients are those used in Ryan's scoring: age, TBSA, and smoke inhalation [2, 4]. These three factors are so strong statistically that any other factor such as BSI does not add to the prediction of mortality. Taking this into account, it is clear that there is no justification for changing the diagnostic and therapeutic approaches. Still, this

observation should not detract from the importance of diagnosing sepsis as soon as possible, and the need to administer the appropriate antibiotic treatment for the appropriate period.

Regarding the prediction of BSI, we found that in scores 1 and 2, compared to score 0, the rate of BSI increases. Ryan score 0 patients had only 20% BSI and 0% mortality, indicating that the younger population with less severe burns have lower chances of developing BSI, and subsequent mortality. Patients with Ryan scores 1 and 2 had BSI rates of 66% and 88%, respectively, suggesting that as burn severity and age increase, so does the chance of contracting BSI. In fact, most of the patients with score 2 had positive BSI, and only 1/10 did not have BSI during their hospitalization period. Interestingly, in the most severely burned, score 3 patients with 100% mortality, all of whom died within the first 2 weeks, only 43% had positive BSI. Thus, we can presume that they did not have time to become infected and the causes of death were other than infection.

There is no consensus in the literature regarding the actual contribution of BSI to mortality [8–10]. Patel *et al.* [9] found that the mortality rate for patients with BSI was higher than for patients without BSI, and Wisplinghoff *et al.* [15] also found that BSI with *Acinetobacter baumannii* complex was a risk factor for mortality in their burn patients. However, both of these studies only used a univariate analysis. Contrary to the above and similar to our own observation, Brusselaers *et al.* [1] also did not

find that BSI contributed to mortality, even in the case of resistant bacteria. They did find, however, that BSI contributed to increased LOS which was also found here, and observed that patients with BSI had a greater need for vasopressors or inotropic agents and longer durations of ventilator dependency and hospitalization. Generally, it is difficult to prove whether BSI is a predictor of death because BSI usually occurs in the more severely burned patients and it is hard to distinguish whether their death was caused by the BSI or from other factors correlated to the severity of the trauma.

Another interesting finding was that in the Ryan score 3 group, mortality occurred quickly, within the first 2 weeks, which may explain why the rate of BSI in this group is half that of the score 2 group, while the cases of death in score 1 and 2 groups occurred gradually over the course of hospitalization.

As more data are collected in the future, the statistical validity of the conclusions of this study will increase. In the meantime, we have found that burn severity, smoke inhalation and older age are much more important for the prediction of death, than the presence or absence of BSI. It is important to note that, in spite of the long study period, the fact that we chose to focus only on severe burn patients resulted in a relatively small number of cases in each of the study groups, which made it difficult to find statistical evidence of differences between them. A further limitation of the study was that we did not examine the appropriateness of the antibiotic therapy for the species of bacteria recovered from blood culture. Last, the definition we used for 'severe burn' patients was one that is used in our Burn Unit, and not according to standard international criteria.

In conclusion while many approaches for predicting burn prognosis have been presented in the literature, the debate over which formula is best for predicting mortality in severe burn patients, and the specific role of BSI, is ongoing. We confirm that in severe burn patients hospitalized over a relatively long period of time, the Ryan score is an excellent tool for this patient cohort. Most of the patients in the score ≥ 1 groups will have BSI at some point in their hospitalization period, but its occurrence does not predict a higher chance of mortality, although it is associated with a longer LOS.

ACKNOWLEDGEMENTS

We acknowledge the contribution of Abbie Rosner in the editing of this manuscript.

DECLARATION OF INTEREST

None.

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