Burn injury outcomes in patients with pre-existing diabetic mellitus: Risk of hospital-acquired infections and inpatient mortality☆

Laquanda Knowlin [a,b], *Paula D. Strassle* [a,c], *Felicia N. Williams* [a,b], *Richard Thompson* [a,b], *Samuel Jones* [a,b], *David J. Weber* [d], *David van Duin* [d], *Bruce A. Cairns* [a,b], *Anthony Charles* [a,b,*]

[a] *Department of Surgery, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States*
[b] *North Carolina Jaycee Burn Center, Chapel Hill, NC, United States*
[c] *Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States*
[d] *Division of Adult Infectious Diseases, University of North Carolina, Chapel Hill, NC, United States*

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ABSTRACT

Background: Diabetes mellitus (DM) is a major cause of illness and death in the United States, and diabetic patients are at increased risk for burn injury. We therefore sought to examine the impact of pre-existing DM on the risk of inpatient mortality and hospital acquired infections (HAI) among burn patients.

Methods: Adult patients (≥18 years old) admitted from 2004 to 2013 were analyzed. Weighted Kaplan–Meier survival curves – adjusting for patient demographics, burn mechanism, presence of inhalation injury, total body surface area, additional comorbidities, and differential lengths of stay– were used to estimate the 30-day and 60-day risk of mortality and HAIs.

Results: A total of 5539 adult patients were admitted and included in this study during the study period. 655 (11.8%) had a pre-existing DM. The crude incidence of HAIs and in-hospital mortality for the whole burn cohort was 8.5% (n=378) and 4.4% (n=243), respectively. Diabetic patients were more likely to be older, female, have additional comorbidities, inhalational injury, and contact burns. After adjusting for patient and burn characteristics, the 60-day risk of HAI among patients with DM was significantly higher, compared to non-diabetic patients (RR 2.07, 95% CI 1.28, 6.79). However, no significant difference was seen in the 60-day risk of mortality (RR 1.34, 95% CI 0.44, 3.10).

Conclusions: Pre-existing DM significantly increases the risk of developing an HAI in patients following burn injury, but does not significantly impact the risk of inpatient mortality. Further understanding of the immune modulatory mechanism of burn injury and DM is imperative to better attenuate the acquisition of HAIs.

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* *Corresponding author at*: UNC School of Medicine, University of North Carolina, 4008 Burnett Womack Building, Chapel Hill, NC CB 7228, United States. Fax: +1 919 9660369.
E-mail address: anthchar@med.unc.edu (A. Charles).

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1. Introduction

Diabetes mellitus (DM) affects roughly 12% of adults in the United States, or 29.1 million people, and represents a major burden to the healthcare system. The cost of DM care due to increased health care utilization and lost productivity was approximately $245 billion in 2012 [1]. Over the past 3 decades, the prevalence of adults diagnosed with DM in the US has increased substantially [2]. Diabetics are at increased risk for burn injury due to peripheral neuropathy, which is associated with decreased sensory and motor function and leads to the inability to quickly withdraw extremities from heat source [3–5]. Subsequently, a substantial proportion of patients admitted to burn centers are diabetic [6].

Burn injuries are often associated with complications, even in otherwise healthy individuals. Diabetics may be at increased risk for complications and mortality. For example, diabetics have a predilection for atherosclerotic occlusion in small and large vessels thus facilitating development of ischemic extremities. Diabetics also exhibit wound repair failures and infections [5,7,8]. This is commonly attributable to microangiopathy and altered neutrophil migration [9] with reduced bacteriocidal activity and impaired phagocytosis [10,11]. With increased longevity of the US population and the concomitant rise in the number of diagnosed diabetics, it is likely that the number of diabetics admitted to the hospital following burn that may indicate intensive medical or surgical care will also increase. While existing data suggests that tight glycemic control following burn injury improves complication and mortality rates, it is unclear whether pre-existing DM impacts patient outcomes after burn injury [12,13].

Thus, the primary objective of this study is to estimate the impact of diabetes on the risk of hospital acquired infections (HAIs) and inpatient mortality after being hospitalized for burn injury.

2. Methods

Patients were identified using the North Carolina Jaycee Burn Center registry, which consists of data collected on all admitted patients in real-time for reporting to the National Burn Repository. Adult (≥18 years old) patients admitted with burn injury including inhalation injury only between January 1, 2004 and December 31, 2013, were eligible for inclusion. Only a patient's first hospitalization, for their first burn, within the time period was included for analysis.

Registry data was then linked to the Carolina Data Warehouse for Health (CDW-H), which is a central repository for clinical and administrative data from the entire UNC Healthcare System, which includes the Jaycee Burn Center [14]. Registry data were validated using CDW-H data and manual chart review. Missing and illogical registry data were abstracted using similar methods. Patients were excluded if discharge date could not be determined (n=37).

Diabetes mellitus was identified using both the comorbidities recorded in the burn registry and International Statistical Classification of Diseases and Related Health Problems (ICD-9) diagnostic codes attached to the inpatient billing records (ICD-9-CM 250). Mortality during the inpatient hospitalization was also captured using both the registry and CDW-H records. Hospital-acquired infections (HAIs) were identified using the UNC Hospital Epidemiology database, which documents HAIs identified through real-time, hospital-wide surveillance. Surveillance is performed in accordance with the Centers of Disease Control and Prevention (CDC) criteria and definitions [15]. Only a patient's first HAI was included in analyses.

Bivariate analyses comparing demographics, comorbidities, burn characteristics, and patient outcomes (inpatient mortality, HAIs, length of stay) between diabetic and non-diabetic patients were performed using Chi-square and Wilcoxon–Mann–Whitney tests, where appropriate. Comorbidities were identified using inpatient ICD-9-CM diagnostic codes and included prior myocardial infarction (412–412.9), congestive heart failure (428–428.9), peripheral vascular disease (441–441.9, 443.9, 785.4, and V43.4), cerebrovascular disease (438–438.9), pulmonary disease (490.0–496.9, 500–505.9, and 506.4), and renal disease (582–582.9, 583–583.7, 585–586.9, and 588–588.9). Yearly admit rates of diabetic patients were calculated using Poisson regression. A p-value <0.05 was considered statistically significant. Revised Baux scores were calculated as described by Osler et al. [16]. Multivariable linear regression, adjusting for demographics, comorbidities, and burn characteristics, was used to estimate the average effect diabetes had on length of stay.

Kaplan–Meier survival curves were used to estimate the cumulative 30-day and 60-day risks of mortality among patients with and without DM. An Aalen-Johansen estimator was used to estimate the 30-day and 60-day cumulative incidence of HAIs in order to account for mortality as a competing risk [17]. Both risk differences (RDs) and risk ratios (RRs) were calculated. Only patients admitted for at least 2 days (i.e. at risk for an HAI as per CDC criteria) were included in HAI analyses. Weighted survival curves were used to estimate the standardized, cumulative 30-day and 60-day risk for both mortality and HAIs [18,19]. Standardized estimates were adjusted using inverse-probability of treatment weights (IPTW) to account for confounding and inverse-probability of censoring weights to account for potentially informative censoring.

Briefly, the IPTW for each patient was estimated using logistic regression which modeling the probability of DM using admit year (categorized into tertiles, 2004–2007, 2008–2010, and 2011–2013), patient age (modeled as a linear spline with knots at 30, 45, 60, and 75 years old), gender, race/ethnicity, comorbidities, burn mechanism, total burn surface area (modeled as a linear spline with knots at 20, 35, 50 and 65), and inhalational injury. Weights were stabilized using the marginal (i.e. overall) probability of having diabetes in the cohort. The inverse-probability of censoring weights was also estimated using logistic regression. The probability of censoring (i.e. being discharged alive) was estimated using DM status and all covariates included in the IPTW model. These weights were also stabilized using the marginal probability of being censored. Weights were then multiplied together to obtain a final weight for each patient and truncated at 5% and 95%.

Confidence intervals for both the crude and standardized cumulative incidence measures were calculated using a nonparametric bootstrap. Specifically, 500 resamples with

replacement were conducted and the RD and RR were calculated using the above procedures. The 95% confidence intervals (CI) were determined using the 2.5 and 97.5 percentile cut points for each effect estimate.

All analyses were performed using SAS 9.4 (SAS Inc., Cary, NC). Institutional Review Board (IRB) approval was obtained from the University of North Carolina.

3. Results

5539 patients met the inclusion criteria. 655 (11.8%) had a diabetes mellitus (DM) diagnosis. A significant increase in the proportion, and absolute number, of diabetic patients treated has increased over time, p=0.01. Diabetic patients were significantly more likely to be female (34.1% vs. 26.6%, p<0.0001), African American (36.9% vs. 26.0%, p<0.0001), older (median age 56.7 years old vs. 39.9 years old, p<0.0001), and have comorbidities (40.3% vs. 10.6%, p<0.0001) compared to non-diabetic patients (Table 1). Additionally, diabetic patients were more likely to have contact burns (8.9% vs. 4.7%, p≤0.0001) and inhalational injury (11.0% vs. 8.1%, p=0.01). Although the incidence of flame was similar in diabetics and non-diabetics, the association of inhalational injury is situational and likely not related to diabetic comorbidity. No differences were seen in median burn size (4.0% vs. 4.0%, p=0.44). Due to the older age of diabetic patients and higher incidence of inhalational injury, the median revised Baux scores was substantially higher among diabetics (64.0 vs. 47.6), p<0.0001.

One-third (n=1838) of patients were admitted to the intensive care unit (ICU); patients with DM were more likely to be admitted to the burn ICU (40.3% vs. 32.3%, p<0.0001). However, after adjusting for patient and burn characteristics, no significant difference in the odds of ICU admission was seen in diabetic patients (OR 1.03, 95% CI 0.81, 1.30), p=0.81. Patients with diabetes were hospitalized for a median 11 days (interquartile range [IQR] 4–26), compared to a median 7 days (IQR 2–13) for patients without diabetes, p<0.0001. Even after adjusting for patient demographics, comorbidities, and burn characteristics, patients with diabetes were hospitalized for, on average, 3.3 days longer (95% confidence interval [CI] 1.21,

Table 1 – Patient demographics and burn characteristics of adult patients, stratified by pre-existing diabetes mellitus (DM) status.

	DM 655 (11.8%)	No DM 4884 (88.2%)	p-value[a]
Hospitalization year, n (%)			
2004–2007	155 (23.7)	1354 (27.7)	**0.03**
2008–2010	181 (27.6)	1410 (28.9)	0.51
2011–2013	319 (48.7)	2120 (43.4)	**0.01**
Gender, n (%)			
Male	432 (66.0)	3588 (73.5)	**<0.0001**
Female	223 (34.1)	1296 (26.6)	–
Race/ethnicity, n (%)			
African American	234 (36.9)	1233 (26.0)	**<0.0001**
Caucasian	311 (49.1)	2651 (56.0)	**0.001**
Hispanic	22 (3.5)	287 (6.1)	**0.009**
Other	67 (10.6)	567 (12.0)	0.31
Unknown	21	146	
Age, in years, median (IQR)	56.7 (48.3–66.2)	39.9 (28.5–52.3)	**<0.0001**
Comorbidities, n (%)			
Myocardial infarction	58 (8.9)	82 (1.7)	**<0.0001**
Congestive heart failure	76 (11.6)	64 (1.3)	**<0.0001**
Peripheral vascular disease	53 (8.1)	28 (0.6)	**<0.0001**
Cerebrovascular disease	22 (3.6)	32 (0.7)	**<0.0001**
Pulmonary disease	114 (17.4)	365 (7.5)	**<0.0001**
Renal disease	86 (13.1)	55 (1.1)	**<0.0001**
Burn mechanism, n (%)			
Flame	343 (52.5)	2604 (53.6)	0.65
Scald	197 (30.2)	1508 (31.0)	0.68
Contact	58 (8.9)	230 (4.7)	**<0.0001**
Other burn	55 (8.4)	519 (10.7)	0.08
Unknown	2	23	
TBSA, median (IQR)	4.0 (2–9)	4.0 (2–10)	0.44
Baux score, median (IQR)	64.0 (53.6–77.3)	47.6 (34.4–62.5)	**<0.0001**
Inhalation injury, n (%)			
Yes	72 (11.0)	394 (8.1)	**0.01**
No	583 (89.0)	4489 (91.9)	–

Abbreviations: DM, diabetes mellitus; IQR, interquartile range; TBSA, total burn surface area.

[a] Chi-square and Wilcoxon-Mann-Whitney tests were used to calculate p-values; p<0.05 are in bold.

5.38). Only 242 patients (4.4%) were hospitalized longer than 60 days and administratively censored prior to discharge or death.

Overall, 243 (4.4%) died during their inpatient hospitalization. The unadjusted cumulative mortality rates for both diabetic and non-diabetic patients are depicted in Fig. 1a. No significant differences were seen at the 30-day or 60-day cumulative incidence (Table 2). The 60-day cumulative mortality among patients with DM was 16.2%, compared to 13.9% among patients without DM (RR 1.17, 95% CI 0.68, 1.90). After adjusting for confounding and potentially informative censoring through weighting, there was still no significant difference in the 30-day and 60-day mortality rates (Fig. 1b). After 30 days, diabetic patients had a lower mortality risk (RR 0.54, 95% CI 0.08, 2.28) and, after 60 days, a higher risk of mortality (RR 1.34, 95% CI 0.44, 3.10) compared to non-diabetic patients but both were not statistically significant (Table 2).

Of the 4,426 patients (79.9%) hospitalized for at least 2 days and at risk for infection, 378 (8.5%) developed at least one HAI. Among patients with an HAI, skin infections (n=127, 33.6%) were the most common, followed by respiratory infections (n=95, 25.1%), bloodstream infections (n=72, 19.1%), and urinary tract infections (n=67, 17.2%). While more diabetic patients developed at least one HAI (9.9% vs. 6.4%, p=0.0008), no significant difference in the overall number of infections, among those with at least one HAI, were seen between the two groups (p=0.96).

The unadjusted cumulative incidence of HAIs is depicted in Fig. 2a. No significant differences were seen between the two

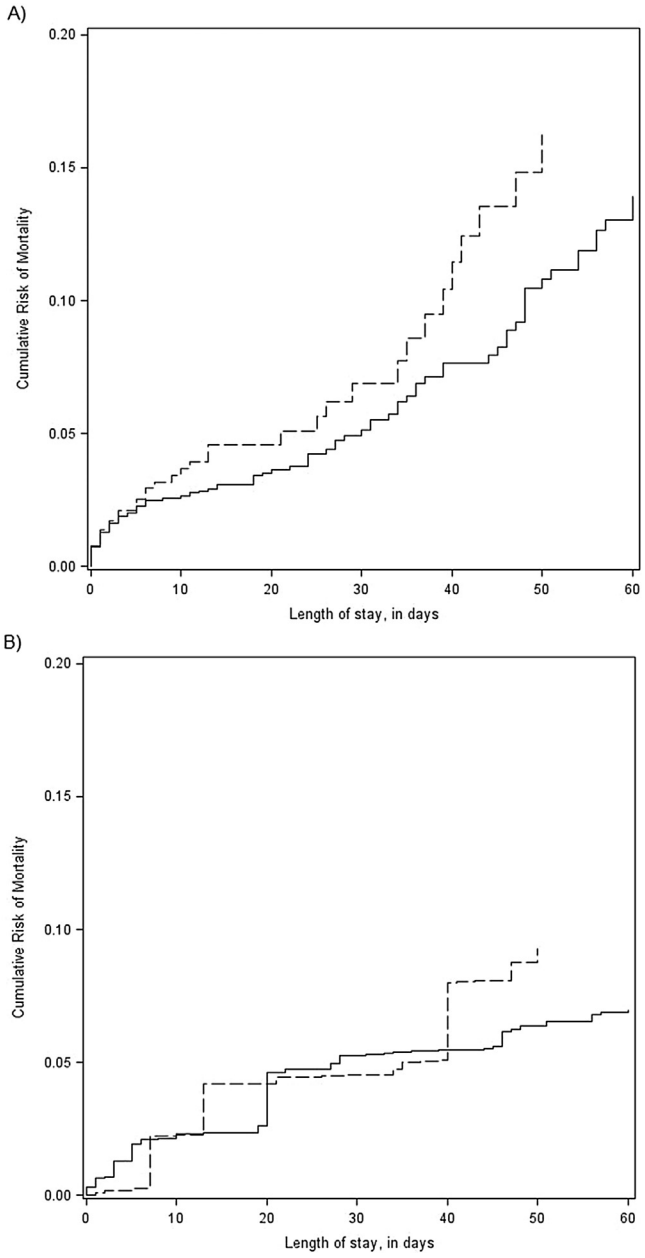

Fig. 1 – (A) Crude and (B) stabilized 60-day cumulative incidence of inpatient mortality among patients with diabetes (dashed) and without diabetes (solid).

Table 2 – Crude and standardized 60-day risk of mortality by diabetes mellitus (DM) status among adult burn patients.

	Mortality, %		Risk difference	95% CI[a]	Risk ratio	95% CI[a]
	DM	No DM				
Crude						
30-day	6.9	5.1	0.02	−0.01, 0.05	1.34	0.77, 2.12
60-day	16.2	13.9	0.02	−0.05, 0.11	1.17	0.68, 1.90
Standardized[b]						
30-day	3.2	5.8	−0.03	−0.11, 0.03	0.54	0.08, 2.28
60-day	9.3	7.0	0.02	−0.06, 0.13	1.34	0.44, 3.10

Abbreviations: DM, diabetes mellitus; CI, confidence interval.

[a] CIs determined using 2.5 and 97.5 percentile cutpoints from 500 nonparametric bootstrap resamples.

[b] Standardized for admit year (categorized into tertiles, 2004–2007, 2008–2010, and 2011–2013), patient age (modeled as a linear spline with knots at 30, 45, 60, and 75 years old), gender, race/ethnicity, comorbidities, burn mechanism, total burn surface area (modeled as a linear spline with knots at 20, 35, 50 and 65), and inhalational injury.

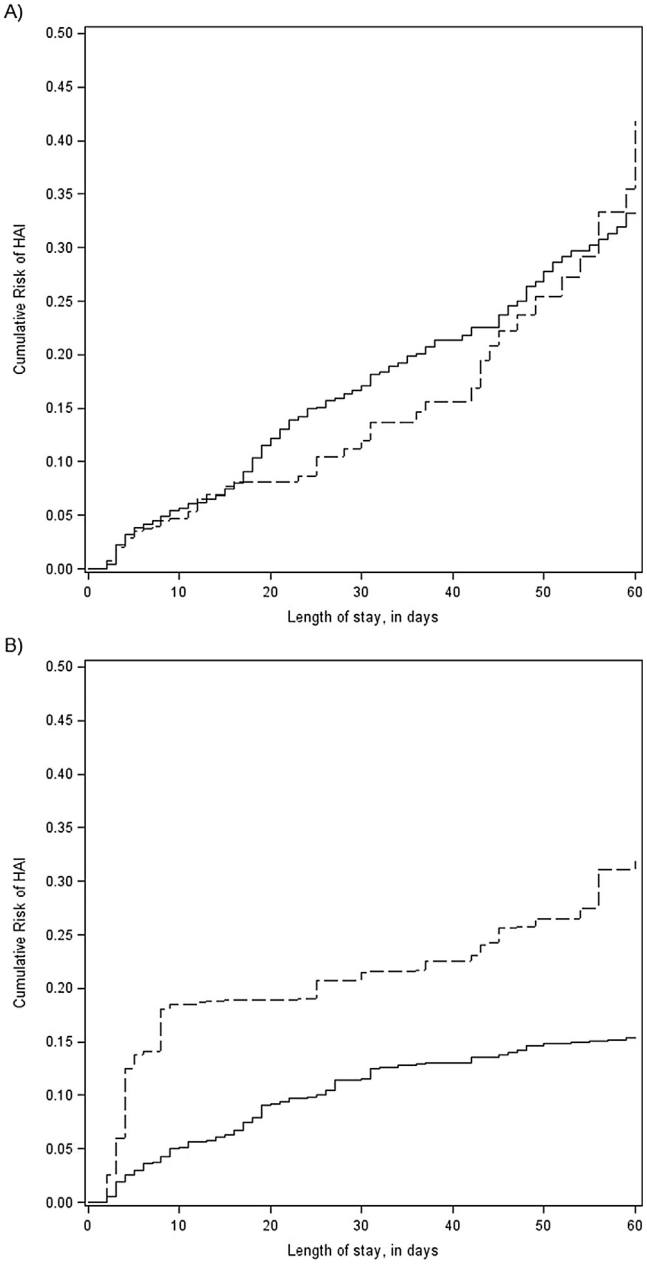

Fig. 2 – (A) Crude and (B) stabilized 60-day cumulative risk of hospital-acquired infection (HAI) among patients with diabetes (dashed) and without diabetes (solid) among adult burn patients admitted to the unit for ≥2 days.

Table 3 – Crude and standardized 60-day cumulative incidence of hospital-acquired infections (HAIs) by diabetes mellitus (DM) status among adult burn patients.

	HAI incidence, %		Risk difference	95% CI[a]	Risk ratio	95% CI[a]
	DM	No DM				
Crude						
30-day	12.1	20.2	−0.08	−0.18, 0.18	0.60	0.36, 2.03
60-day	41.8	33.2	0.09	−0.07, 0.59	1.26	0.80, 2.73
Standardized[b]						
30-day	18.6	11.1	0.07	−0.03, 0.39	1.67	0.74, 10.79
60-day	31.8	15.4	0.15	0.04, 0.84	2.07	1.28, 6.79

Abbreviations: HAI, hospital-acquired infection; DM, diabetes mellitus; CI, confidence interval

[a] CIs determined using 2.5 and 97.5 percentile cutpoints from 500 nonparametric bootstrap resamples.

[b] Standardized for admit year (categorized into tertiles, 2004–2007, 2008–2010, and 2011–2013), patient age (modeled as a linear spline with knots at 30, 45, 60, and 75 years old), gender, race/ethnicity, comorbidities, burn mechanism, total burn surface area (modeled as a linear spline with knots at 20, 35, 50 and 65), and inhalational injury.

groups. After 30 days, the crude cumulative incidence of HAIs among diabetic patients was lower (RR 0.60, 95% CI 0.36, 2.03); after 60 days the cumulative incidence of HAIs was higher among diabetic patients (RR 1.26, 95% CI 0.80, 2.73) (Table 3). After adjusting for confounding and differential hospitalization lengths, patients with DM were significantly more likely to have at least one HAI after 60 days (Fig. 2b). Specifically, after 60 days, patients with DM were over 2 times more likely (95% CI 1.28, 6.79) to get an infection, compared to non-diabetics (Table 3). Similarly, while patients with DM were also more likely to have an HAI at 30-days, the result was not significant (RR 1.67, 95% CI 0.74, 10.79).

4. Discussion

In this study, we found that pre-existing DM increased the risk of developing an HAI, even after adjusting for patient demographics, additional comorbidities, burn characteristics, and differential lengths of stay. However, despite the increased risk of HAIs, no difference in the risk of inpatient mortality was seen. Our findings support previous research which found that DM increased the average length of stay and the incidence of complications (which include infections) [20–23].

Memmel et al. found that the diabetic burn population was more susceptible to infections compared to non-diabetic patients (14.9% vs 8.1%, $P<0.001$). In addition, others have found diabetic patients had higher incidences of bacteremia (9.2% vs 2.5%), urinary tract infection (11% vs. 3%), pneumonia (9.2% vs. 6.3%), burn wound cellulitis (27% vs. 11%), and nosocomial burn wound infection (8% vs. 4%) [24]. Diabetic patients have predisposition for both acute and chronic infections. Previous studies have linked skin/soft tissue infections [25] and pulmonary infections [26] to chronic hyperglycemia. Interestingly, multiple organisms are have been found in diabetic burn wounds, with the most common organism being *Staphylococcus aureus*, whereas single organisms are more likely to infect wounds in non-diabetic individuals [24,27].

While we found no difference in inpatient mortality between patients with and without DM, previous studies in trauma patients have been mixed. In a retrospective analysis of the National Trauma Data Bank, Liou et al. found that DM was an independent predictor of higher mortality [28]. On the other hand in a systematic review of complications and outcomes of diabetic patients with burn trauma, diabetic patients had a higher odds of sustaining wound infections, local infections and urinary tract infection. However, diabetic patients did not have higher odds of mortality [29]. Early burn mortality is attributable to acute infections leading to sepsis, however early excision and grafting and the use of ICU protocols such as ventilator and sepsis bundles has led to the reduction of early sepsis associated burn mortality [30].

The body's response following burn injury has been described in two phases, resuscitation and hypermetabolic. It is during the hypermetabolic state that burn patients develop insulin resistance and hyperglycemia, and contribute to the increase morbidity and mortality seen in burn patients [31]. Advancement over the last three decades in burn care such growth hormones [32], use of B-blockers [33,34], and testosterone [35] have helped attenuate the burn hypermetabolic response; however, there still remains a challenge to combat stress-induced hyperglycemia that may be magnified in patients with pre-existing DM [36].

Potential strategies to mitigate poor outcomes in burn patients with pre-existing diabetes include glycemic control with insulin therapy, vigilant wound management, and the early recognition of sepsis. For hyperglycemia associated with the hypermetabolic response, maintaining blood glucose levels below 110 mg/dl with intensive insulin therapy are recommended, but care should be taken to prevent hypoglycemia (i.e blood glucose <60 mg/dl). In severely burned pediatric patients, a target blood glucose of 130 mg/dl is suggested to prevent the additional risk and detrimental outcomes from hypoglycemia [37]. Alternative therapies such as metformin and fenofibrate may be utilized with monitoring for unwanted side effects, like lactic acidosis [38,39]. Early intervention in cases of sepsis in burned diabetic patients is imperative to reduce progression to septic shock and increase mortality [40]. Our widespread adoption of appropriate glycemic control and early recognition and treatment of sepsis using goal-directed therapy and ICU sepsis bundles may explain why we did not find a significant increase in inpatient mortality among diabetics in our study.

This study is not without limitations. First, pre-existing diabetes and comorbidities were identified using ICD-9 codes, which likely underestimates the true incidence and may be subject to interpretation. Furthermore, we do not have glycated hemoglobin levels to determine level of preexisting diabetic control. Second, only inpatient mortality was able to be measured and represents on a portion of all deaths caused by burn injury. Future studies should include measures of long-term morbidity and mortality outside of the initial hospitalizations. Patients were also observed for differing lengths of time and could be associated with both the risk of HAI and inpatient mortality. However, inverse-probability of censor weighting was used to account for differing lengths of stay in order to minimize this potential bias. We were also able to account for the potential confounding by age, additional comorbidities, and burn characteristics using treatment weights, which allows us to estimate the direct effect of diabetes on inpatient mortality and HAIs (assuming no unmeasured confounding variables). Finally, this analysis only includes patients from one burn center, and results may not be generalizable to other hospitals.

5. Conclusion

Pre-existing diabetes mellitus significantly increases the risk of developing hospital-acquired infections, but does not increase inpatient mortality following burn injury. Our findings emphasize that advancements in burn care such as early insulin use and appropriate glycemic control to prevent burn mortality in diabetic patients and improve other burn outcomes have been successful. However, further understanding of the immune modulatory mechanism of burn injury and diabetes mellitus is imperative to better attenuate the acquisition of hospital-acquired infections.

Conflict of interest

The authors declare no conflict of interest.

Authors' contributions

Laquanda Knowlin: study design, data collection, data interpretation, literature search, and writing. Paula D. Strassle: study design, data collection, data analysis, data interpretation, literature search, and writing. Felicia N. Williams: critical revision and literature search. Lindsay Stanford: literature search. Richard Thompson: data collection, data analysis. Samuel Jones: critical revision and literature search. David J. Weber: critical revision. David van Duin: critical revision. Bruce A Cairns: critical revision. Anthony Charles: study design, data collection, data interpretation, literature search, and writing.

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