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World J Surg. Author manuscript; available in PMC 2020 December 01.

Published in final edited form as:

World J Surg. 2019 December ; 43(12): 3035–3043. doi:10.1007/s00268-019-05165-x.

Sex-Based Differences in Inpatient Burn Mortality

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Abstract

Background: Among burn patients, research is conflicted, but may suggest that females are at increased risk of mortality, despite the opposite being true in non-burn trauma. Our objective was to determine if sex-based differences in burn mortality exist, and assess whether patient demographics, co-morbid conditions, and injury characteristics explain said differences.

Methods: Adult patients admitted with burn injury-including inhalation injury only-between 2004 and 2013 were included. Inverse-probability of treatment weights (IPTW) and inverse-probability of censor weights (IPCW) were calculated using admit year, patient demographics, co-morbid conditions, and injury characteristics to adjust for potential confounding and informative censoring. Standardized Kaplan-Meier survival curves, weighted by both IPTW and IPCW, were used to estimate the 30-day and 60day risk of inpatient mortality across sex.

Results: Females were older (median age 44 vs. 41 years old, $p<0.0001$), and more likely to be Black (32% vs. 25%, $p<0.0001$), have diabetes (14% vs. 10%, $p<0.0001$), pulmonary disease (14% vs. 7%, $p<0.0001$), heart failure (4% vs. 2%, $p=0.001$), scald burns (45% vs. 26%, $p<0.0001$), and inhalational injuries (10% vs. 8%, $p=0.04$). Even after weighting, females were still over twice as likely to die after 60 days (RR 2.87, 95% CI 1.09, 7.51).

Conclusions: Female burn patients have a significantly higher risk of 60-day mortality, even after accounting for demographics, co-morbid conditions, burn size, and inhalational injury. Future research efforts and treatments to attenuate mortality should account for these sex-based

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The authors have no conflict of Interests.

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differences. The project was supported by the National Institutes of Health, Grant Number UL1TR001111.

Keywords

sex-based; mortality; burns

Introduction

There is no greater metabolically demanding trauma to the body than a severe burn injury [1, 2]. They lead to severe physiologic derangements that effect every organ system, increase risk for infection, multi-system organ failure, and death [2]. The most common algorithms used to predict mortality post-burn use age, total body surface area (TBSA) burn, and the presence of inhalation injury [3–6]. While at least two algorithms include sex in their prediction models, the actual effects of sex are often conflicting, with one model assigning increased risk to males, and the other, to females [7, 8].

Some studies conclude that females have increased mortality risks post-burn, despite the opposite being true in non-burn trauma.[9–12] With conflicting evidence, we sought to assess whether sex-based differences in burn mortality exist, and whether these differences could be explained by differences in patient demographics, co-morbid conditions, and or injury characteristics.

Materials and Methods

Adult patients admitted with burn injury between January 1, 2004 and December 31, 2013 were eligible for inclusion. Patients were identified using the institutional Burn Center registry and then linked to a central repository for clinical data from the Healthcare System.

Bivariate analyses comparing patient demographics, co-morbid conditions, burn characteristics, and inpatient mortality across sex and race were performed using Chi-square and Wilcoxon-Mann-Whitney tests, where appropriate. Yearly admission rates were calculated using Poisson regression. A p-value <0.05 was considered statistically significant. Co-morbid conditions of interest were measured using International Classification of Diseases, 9^{th} Revision, Clinical Modification (ICD-9-CM) codes. Revised Baux scores were calculated as described by Osler et al (2010) [13].

Kaplan-Meier survival curves were used to estimate the cumulative 30-day and 60-day risk of inpatient mortality. Both risk differences (RDs) and risk ratios (RRs) were calculated. Weighted survival curves were used to estimate the standardized, cumulative 30-day and 60-day risk for mortality [14]. Standardized estimates were weighted using inverse-probability of treatment weights (IPTW) to account for confounding and inverse-probability of censoring weights (IPCW) to account for informative censoring. The propensity score (PS) for each patient was estimated using logistic regression which modeled the probability of being female, compared to male, using admit year, patient age, race, co-morbid conditions, burn mechanism, TBSA and inhalational injury, as well as for interaction between admit year, TBSA, and inhalational injury. TBSA was confirmed by experienced senior medical

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staff. Inhalation injury was diagnosed by bronchoscopy. Variables for the IPTW models were chosen by identifying potential confounders and causes of mortality using directed-acyclic graphs (DAGs) and previous research in this cohort [15–18]. Weights were stabilized using the marginal probability of being female (probability of being female / probability of being female, given their covariates [i.e. PS]). IPTW removes confounding similar to traditional multivariable modeling with several advantages, namely that weighted, unbiased Kaplan-Meier curves can be created, since traditional adjustment is not possible [14].

The IPCW were also estimated using logistic regression. Among patients censored, length of stay was partitioned into quintiles, and a pooled, multivariable logistic regression model was used to estimate the probability of each patient being censored in each time period, adjusting for the aforementioned variables. Weights were scaled by the marginal probability of being censored in each time period (probability of being censored during quintile / probability of being censored during quintile, given covariates). Therefore, each patient had up to five censor weights calculated for their hospital stay, depending on their total LOS. The IPTW and IPCW were then multiplied together to obtain a final weight for each patient, for each time period, and truncated at the 5^{th} and 95^{th} percentiles.

In order to account for the weighting, confidence intervals for both the crude and standardized cumulative incidence measures were calculated using a nonparametric bootstrap. The 95% confidence intervals (95% CI) were calculated using the standard error estimated from the bootstraps. Interaction terms and likelihood ratio tests were used to assess whether the sex-inpatient mortality relationship was different across age and inhalational injury.

Two secondary analyses were performed to look at the effect of sex on inpatient mortality among patients ≤50 year old (i.e. pre-menopausal females) and >50 years old (i.e. post-menopausal females), and on patients admitted for ≥25 days. New IPTW and IPCW models were fit for each subset analysis, separately, using the same methods described above.

All analyses were performed using SAS 9.4 (SAS Inc., Cary, NC). Institutional Review Board (IRB) approval was obtained.

Results

5,539 patients were included in the analyses and 243 (4.4%) died during their inpatient hospitalization. 1,838 patients (33.3%) were admitted to the burn intensive care unit (ICU). Only 4.4% of patients (n=242) had a length of stay (LOS) longer than 60 days.

Females represented 27% of all patients admitted (n=1,519) and, were more likely to be black, have scald burns, have smaller burns, and have inhalational injuries (Table 1). Males were most likely to be white and have flame burns. The proportion of female patients admitted to the burn center has increased between 2004 and 2013 (Figure 1).

The cumulative 60-day inpatient mortality for females and males was 21.7% and 11.4%, respectively (Figure 2a). No differences were seen in 25-day mortality. After stratifying patients by both LOS and sex, 52 (4%) females hospitalized for <25 days died, 93 males

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hospitalized <25 days (3%) died, 20 (10%) females hospitalized ≥25 days died, and 26 (5%) males hospitalized ≥25 days died. Differences in patient demographics and burn characteristics between these 4 groups can be seen in Table 2.

Prior to adjustment, female patients were about twice as likely to die within both 30 days (risk ratio [RR] 2.10, 95% confidence interval [CI] 1.36, 3.24) and 60 days (RR 1.91, 95% CI 1.24, 2.93). After accounting for potential confounding and differential LOS, females were still over twice as likely to die at 60 days (RR 2.87, 95% CI 1.09, 7.51) (Figure 2b, Table 3). After weighting the difference in 30-day mortality (RR 2.24, 95% CI 0.86, 5.87) was no longer significant. No significant modification of the sex-60day mortality relationship was seen by either inhalational injury or age.

Sixty-four percent of females (n=974) and 70% of males (n=2,806) were ≤50 year old. Minimal differences in the effect of sex on inpatient mortality were seen across age groups. Both females ≤50 years old and females >50 years old were still twice as likely to die when compared to their male counterparts in their age group (RR 2.13, 95% CI 0.49, 9.20 and RR 2.43, 95% CI 0.98, 6.02, respectively), although the effect of sex was no longer statistically significant (Table 4). Moreover, when the analysis was subset to only patients with LOS ≥25 days, females were still over twice as likely to die at 60 days (RR 2.21, 95% CI 1.02, 4.80).

Discussion

We found significant differences in patient demographics, co-morbid conditions, and injury characteristics between females and males in our study. Females were more likely to be black, older, have diabetes, pulmonary disease, heart failure, cerebrovascular disease, and have inhalational injury. Our initial hypothesis was that co-morbid conditions and burn characteristics would explain any sex-based disparities in mortality. For example, in prior analyses we found that pre-existing pulmonary disease, cardiovascular disease, and diabetes increased mortality in adult burn patients [15, 17, 19]. We have also shown that the Charlson Comorbidity Index score is predictive of inpatient mortality, even after adjusting for patient age, TBSA, and inhalational injury [18, 19]. Additionally, inhalational injury, with or without the presence of a cutaneous burn, is known to significantly increase mortality[13].

However, even after accounting for patient demographics, co-morbid conditions, burn mechanism, TBSA, and inhalational injury, females were over twice as likely to die as males. These effects were also consistent across age and inhalational injury. Interestingly, in both the unadjusted and weighted analyses, the increase in mortality among females was only observed after the length of stay exceeded 25 days. Longer hospital courses are typically for patients with larger sized burns, inhalation injuries, multiple co-morbid conditions, challenging wounds and/or challenging dispositions. While these patients have higher risks of hospital acquired infections, multi-system organ failure, and sepsis which increase their mortality risk, it is unclear why mortality in these patients would be differential across sex. When we restricted our analyses to patients hospitalized for ≥25 days and adjusted our weights to account for greater prevalence of these risk factors, the disparity still persisted.

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In non-burn trauma, estrogen has been shown to be protective and improve cardiac function and the immune response[1, 9, 20–23]. Additionally, female trauma patients with high Injury Severity Scores have been shown to have fewer infectious complications than their male counterparts [24], to be more responsive to therapeutic interventions [20], and have improved survival [25]. Unfortunately, estrogen does not appear to be protective in burns[1, 8, 10–12, 22, 26]. Animal models to explain the physiologic findings demonstrate that estrogen mitigates the immune system post-burn by decreasing local and systemic pro-inflammatory cytokines, and preventing the infiltration of neutrophils [27, 28]. Testosterone has been shown to dampen the immune response, whereas estrogen has been shown to enhance the activity of humoral and cellular immune function [26, 27, 29]. Estrogen also modulates lymphocyte and macrophage function. The extent of activation of the humoral and cellular immune system by estrogen has been proposed as a possible mechanism for why females are at greater risk for developing autoimmune diseases, and also as a possible explanation of why females do better after trauma and septic shock; however, this does not explain the observed incidence in inpatient mortality after burns in females [26, 27, 29]. The true impact of estrogen on burn-related trauma requires a more comprehensive evaluation of the inflammatory and immunological modulation post injury.

The hormonal milieu has also been used to explain sex-based differences in burns. Hormonal deficiencies in postmenopausal females may influence the various stages of wound healing and replacement may improve outcomes, especially since females who present with burns tend to be older [30, 31]. However, when we assessed whether the effect was differential across age – as a surrogate for menopausal state-the estimated effect of female sex on mortality remained consistent. This suggests a consistent effect across all ages – similar to findings by Kerby et al [32]. While George et al claimed the effect of sex on inpatient mortality was different across age, they did not actually test this assertion and they did not account for length of stay in their analyses, which impacted the effect of sex in our analysis, as differences were only found in stays >25 days [33].

Another postulated mechanism for the sex-based differences relates to sexspecific expression of pro-and anti-inflammatory cytokines, with estrogen decreasing the pro-inflammatory cytokines [26, 28, 29]. Specifically, estradiol production mediates IL-6 production, greatly influencing the milieu after burn injury, for both sexes [1, 29, 34]. Multiple studies have shown differences in the levels of pro-inflammatory cytokines, e.g. IL-6, which correlates with the severity of sepsis [9, 28, 29, 34–38]. IL-6 enhances immune function, which may explain the survival benefit in females after other forms of trauma and septic shock, but, unfortunately, IL-6 is not protective in burns [26, 29, 34].

Although obesity, and/or body mass index (BMI) was not measured in this analysis, deposition or accumulation of adipose tissue may also play a role in these sex-based differences in inpatient mortality [26]. The distribution of fat is different between sexes, with females having a greater amount of subcutaneous tissue and lower body fat as compared to males whom have greater visceral accumulation of adipose tissue. Adipose tissue is a metabolically active endocrine organ. Adipose tissue releases pro-inflammatory hormones, e.g. TNFα, IL-6, as well as aromatase, which peripherally converts androgens to estrogen. Researchers have hypothesized that adipose tissue modulates the immune response after

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traumatic injury, which can be further modified by androgens. Obesity leads to a state of chronic low-grade inflammation, in which there is up-regulation of pro-inflammatory cytokines. Visceral and subcutaneous fat each have different metabolic profiles and responses to androgens, which may explain some of the differences in immune response after injury [25, 39–41].

Finally, sex-based differences in morbidity and mortality may not be fully explained by the aforementioned immunologic, metabolic and endocrine interactions. While not studied here, socioeconomic factors may contribute more than we can measure [10, 42–44]. Females who are burned are more likely to be single, divorced or widowed, living with children, and of a lower socioeconomic status when compared to age-matched males [44]. In addition, females twice as likely to have pre-existing neurologic or psychiatric conditions[45]. Even after accounting for demographic variables, females have been found to have greater impairments, worse quality of life, and greater psychological stress 12 months after injury [46]. Wasiak et al. found that females were more likely to be older, have more chronic health problems, and tended to take longer to present for medical care than males [47]. The latter is a major determinant of mortality in burns [48]. However, no patient should receive a lower standard of care due to race, sex, socioeconomic status or comorbid conditions [49].

Many of the published studies to date have conflicting conclusions on the impact of sex in burns due to inadequate power, misinterpretation of accepted scoring systems, (e.g. the Abbreviated Burn Severity Index [ABSI]), or are likely biased due to unaccounted for confounding variables. For example, the study performed by Gomez et al, which provides the FLAMES score, identified female sex as an independent predictor of mortality, but they were unable to control for age (female patients were older) or burn mechanism [7]. Forster et al. re-evaluated ABSI as a prediction model, but unlike the original study, they assigned male sex a value of 1 in the score (i.e. they were at increased risk of mortality), and female sex a value of zero [50]. While they concluded that original study remained valid, this misinterpretation of the original study makes interpreting the effect of sex in these contradicting models difficult.

To the best of our knowledge, this is the largest and most comprehensive single center analysis demonstrating a consistent sex-based difference in inpatient mortality. It is also the first analysis to include co-morbid conditions when assessing the impact of sex on inpatient mortality after burn injury, and incorporated several sensitivity analyses in an attempt to identify a cause for these observed sex-based differences in mortality.

This study does have limitations. First, only inpatient, all-cause mortality was able to be captured in this analysis; however, we believe that the number of deaths occurring after discharge would be minimal. We also utilized inverse-probability of censor weighting to account for differential lengths of stay and informative censoring to minimize the impact of differences in follow-up time between patients. Future studies should assess whether causes of death differ between sexes, as this may help to elucidate why a mortality difference exists. Additionally, patient co-morbid conditions were measured using ICD-9-CM codes attached to the inpatient hospitalization, which means that some co-morbid conditions were likely missed, but we expect that the misclassification of co-morbid patients as not having the

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condition would be non-differential with respect to sex, and would bias results towards the null. We are also missing other potential risk factors for mortality, like obesity, burn depth and frailty, which are known to be associated with increased mortality risk. Finally, this is a single-center analysis and results may not be generalizable, particularly if the patient population and burn characteristics differ.

Conclusion

Females have a significantly higher risk of 60-day mortality, even after accounting for demographics, co-morbid conditions, burn size, mechanism, and presence of inhalation injury. Future research should focus on potential genomic, proteomic, or immunological responses to burns that may explain sex-based mortality risks.

Acknowledgments

The project described was supported by the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through Grant Award Number UL1TR001111. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

The study was approved by our institutional review board (IRB).

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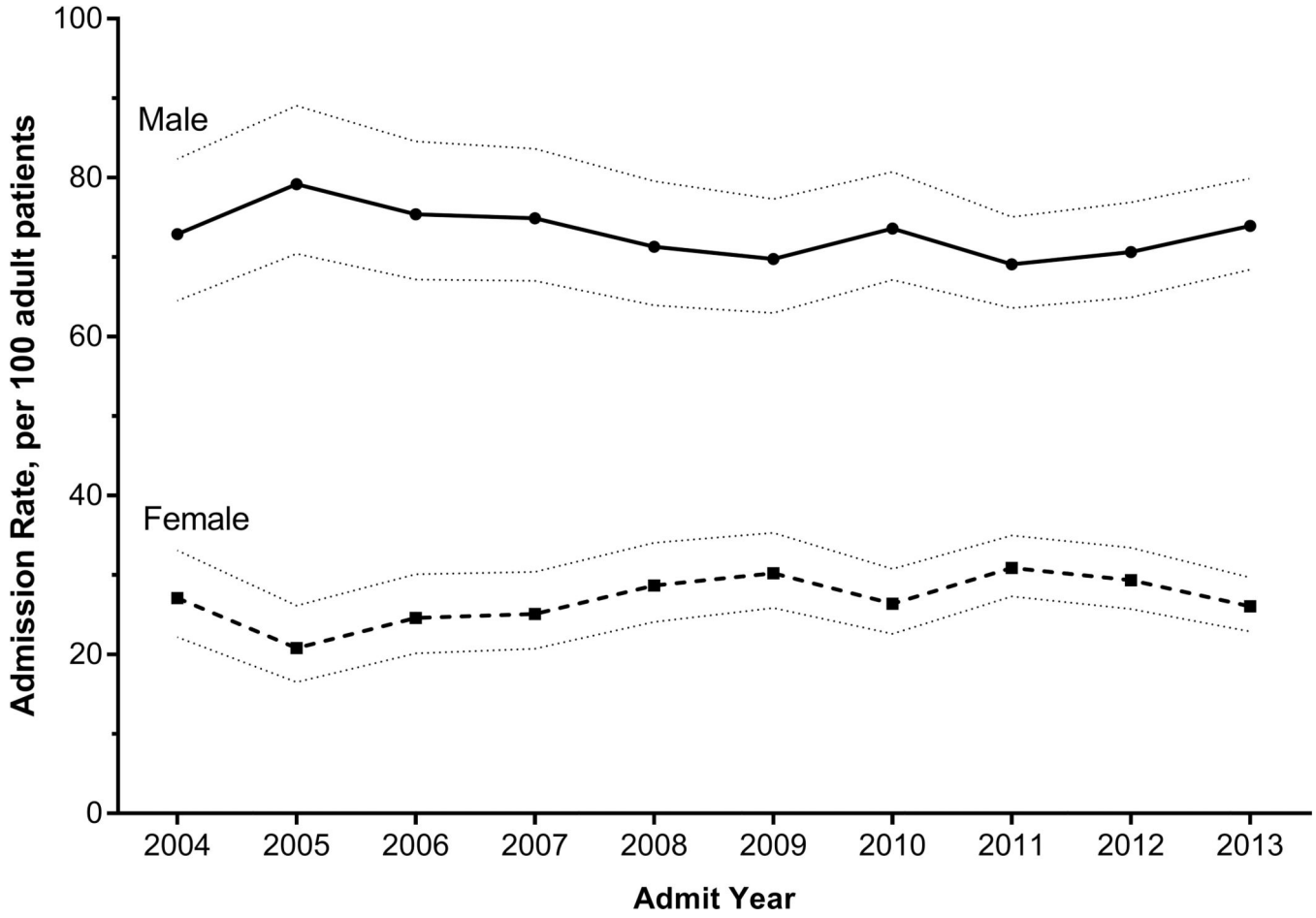

Figure 1.
Yearly rate of burn admissions, per 100 patients, stratified by sex.

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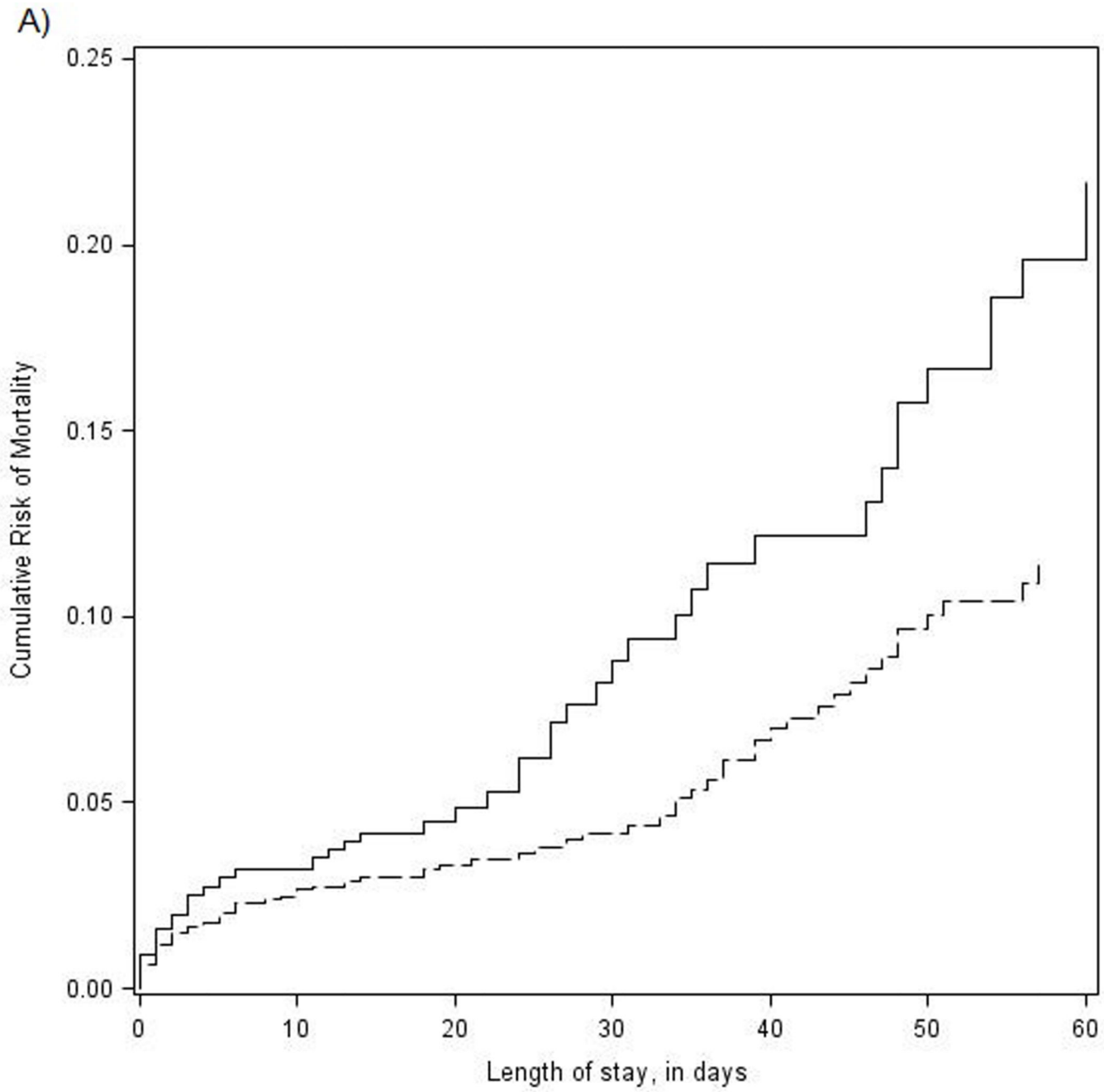

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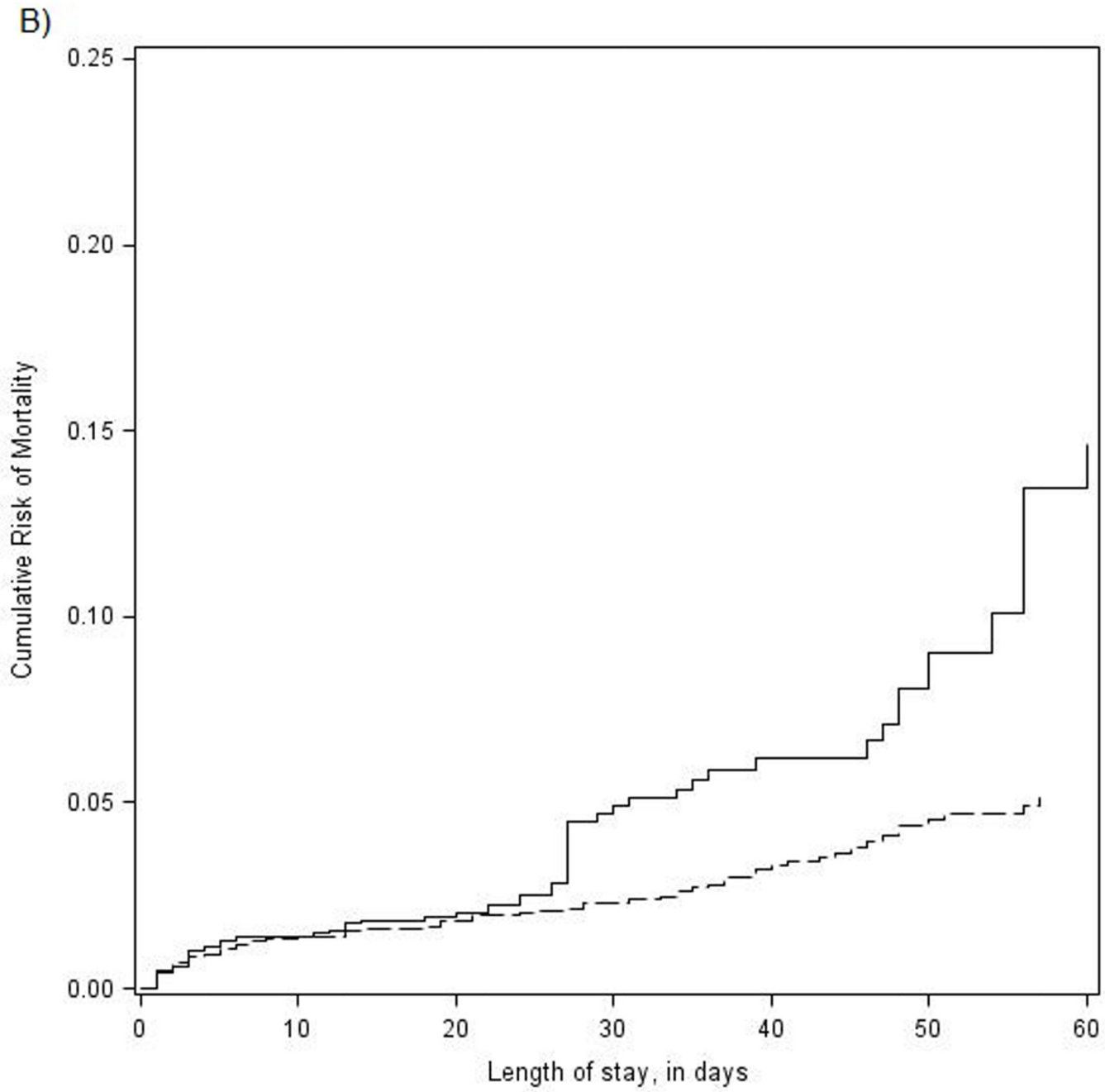

Figure 2.

A) Crude and B) standardized 60-day cumulative incidence of inpatient. mortality among female (solid) and male (dashed) adult burn patients.

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Table 1.

Patient demographics and burn characteristics of adult patients admitted for burn injury, stratified by sex.

	Female 1,519 (27.4%)	**Male 4,020 (72.6%)**	**p-value[a]**
Admit year, n (%)			
2004–2007	369 (24.3)	1,140 (28.4)	**0.002**
2008–2010	450 (29.6)	1,141 (28.4)	0.36
2011–2013	700 (46.1)	1,739 (43.3)	0.06
Race, n (%)			
Black	477 (32.3)	990 (25.4)	**<0.0001**
White	743 (50.3)	2,219 (57.0)	**<0.0001**
Other	256 (17.3)	687 (17.6)	0.80
Missing	43	124	–
Age, in years, median (IQR)	44 (31 – 58)	41 (30 – 54)	**<0.0001**
Co-morbid conditions, n (%)			
Diabetes	216 (14.2)	412 (10.3)	**<0.0001**
Pulmonary disease	217 (14.3)	262 (6.5)	**<0.0001**
Heart failure	55 (3.6)	85 (2.1)	**0.001**
Prior MI	26 (1.7)	114 (2.8)	**0.02**
Renal disease	36 (2.4)	105 (2.6)	0.61
PVD	22 (1.5)	59 (1.5)	0.96
Cerebrovascular disease	18 (1.2)	36 (0.9)	0.33
Burn mechanism, n (%)			
Flame	634 (41.9)	2,313 (57.8)	**<0.0001**
Scald	676 (44.7)	1,029 (25.7)	**<0.0001**
Contact	111 (7.3)	177 (4.4)	**<0.0001**
Other burn	92 (6.1)	482 (12.1)	**<0.0001**
TBSA, median (IQR)	3 (1 – 8)	5 (2 – 10)	**<0.0001**
Inhalation injury, n (%)	147 (9.7)	319 (7.9)	**0.04**
Baux score, median (IQR)	51 (36 – 67)	50 (36 – 64)	**0.009**

Abbreviations: IQR, interquartile range; MI, myocardial infarction; PVD, peripheral vascular disease; 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**

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Table 2.

Patient demographics and burn characteristics, stratified by length of stay and sex.

	LOS <25 Days 4,764 (86%)		LOS ≥25 Days 775 (14%)	
	Female 1,318 (28%)	**Male 3,446 (72%)**	**Female 201 (25%)**	**Male 574 (74%)**
Admit year, n (%)				
2004–2007	290 (22)	932 (27)	79 (39)	208 (36)
2008–2010	380 (29)	963 (28)	70 (35)	178 (31)
2011–2013	648 (49)	1,551 (45)	52 (26)	188 (33)
Race, n (%)				
Black	397 (31)	797 (24)	80 (41)	193 (34)
White	650 (51)	1,935 (58)	93 (47)	284 (50)
Other	232 (18)	599 (18)	24 (12)	88 (16)
Missing	39	115	4	9
Age, in years, median (IQR)	42 (29 – 55)	40 (28 – 52)	54 (41 – 66)	49 (36 – 61)
Co-morbid conditions, n (%)				
Diabetes	160 (12)	299 (9)	56 (28)	113 (20)
Pulmonary disease	173 (13)	195 (6)	44 (22)	67 (12)
Heart failure	33 (3)	54 (2)	22 (11)	31 (5)
Prior MI	18 (1)	70 (2)	8 (4)	35 (6)
Renal disease	22 (2)	49 (1)	14 (7)	56 (10)
PVD	11 (1)	30 (1)	11 (5)	29 (5)
Cerebrovascular disease	11 (1)	21 (1)	7 (3)	15 (3)
Burn mechanism, n (%)				
Flame	493 (38)	1,908 (56)	141 (70)	405 (71)
Scald	636 (48)	957 (28)	40 (19)	72 (13)
Contact	97 (7)	156 (5)	14 (7)	21 (4)
Other burn	86 (7)	410 (12)	6 (3)	72 (13)
TBSA, median (IQR)	3 (1 – 6)	4 (2 – 8)	15 (7 – 26)	16 (7 – 28)
Inhalation injury, n (%)	85 (6)	154 (4)	62 (31)	165 (29)
Baux score, median (IQR)	48 (34 – 62)	47 (34 – 59)	76 (62 – 92)	74 (59 – 89)

Abbreviations: LOS, length of stay; IQR, interquartile range; MI, myocardial infarction; PVD, peripheral vascular disease; TBSA, total burn surface area

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Table 3.

Crude and standardized 60-day risk of inpatient mortality between male and female adult burn patients.

	Mortality, %		Risk		Risk	
	Female	Male	Difference	95% CI[a]	Ratio	95% CI[a]
Crude						
30-day	8.8%	4.2%	0.05	0.01, 0.08	2.10	1.36, 3.24
60-day	21.7%	11.4%	0.10	0.03, 0.18	1.91	1.24, 2.93
Standardized[b]						
30-day	4.9%	2.2%	0.03	−0.01, 0.07	2.24	0.86, 5.87
60-day	14.6%	5.1%	0.10	0.05, 0.14	2.87	1.09, 7.51

Abbreviations: CI, confidence interval

[a]CIs determined using 2.5 and 97.5 percentile cut points from 500 nonparametric bootstrap resamples

[b]Standardized by inverse-probability of treatment weights (IPTW) and inverse probability of censor weights (IPCW) to account for potential confounding and differential lengths of stay, respectively; IPTW models adjusted for admit year (categorized into terciles, 2004 – 2007, 2008 – 2010, and 2011 – 2013), patient age (modeled as a linear spline with knots at 30, 45, 60, and 75 years old), race, diabetes, chronic pulmonary disease, congestive heart failure, prior myocardial infarction, renal disease, peripheral vascular disease, and cerebrovascular disease burn mechanism, total burn surface area (TBSA, modeled as a linear spline with knots at 20, 35, 50 and 65), and inhalational injury, as well as interaction between admit year and TBSA, admit year and inhalational injury, and TBSA and inhalational injury; IPCW models adjusted for admit year, age, sex, race, co-morbid conditions, TBSA, and inhalational injury

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Table 4.

Standardized 60-day risk of inpatient mortality between male and female adult burn patients, stratified by age and among patients admitted for >25 days, respectively.

	Mortality[a], %		Risk		Risk	
	Female	Male	Difference	95% CI[b]	Ratio	95% CI[b]
Age						
≤50 years old	4.4	2.0	0.02	0.00, 0.05	2.13	0.49, 9.20
>50 years old	24.3	10.0	0.14	−0.01, 0.30	2.43	0.98, 6.02
Hospitalized ≥25 days	12.0	5.4	0.07	0.00, 0.14	2.21	1.02, 4.80

Abbreviations: CI, confidence interval

[a]Standardized by inverse-probability of treatment weights (IPTW) and inverse probability of censor weights (IPCW) to account for potential confounding and differential lengths of stay, respectively; IPTW models adjusted for admit year (categorized into terciles, 2004 – 2007, 2008 – 2010, and 2011 – 2013), patient age (modeled as a linear spline with knots at 30, 45, 60, and 75 years old), race, diabetes, chronic pulmonary disease, congestive heart failure, prior myocardial infarction, renal disease, peripheral vascular disease, and cerebrovascular disease burn mechanism, total burn surface area (TBSA, modeled as a linear spline with knots at 20, 35, 50 and 65), and inhalational injury, as well as interaction between admit year and TBSA, admit year and inhalational injury, and TBSA and inhalational injury; IPCW models adjusted for admit year, age, sex, race, co-morbid conditions, TBSA, and inhalational injury

[b]CIs determined using 2.5 and 97.5 percentile cut points from 500 nonparametric bootstrap resamples