Short and long-term patient outcomes following inhalation injury among burn patients

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A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2017

Committee:

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Program Authorized to Offer Degree:

Epidemiology

University of Washington

Abstract

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Objective: Our aim was to assess the effect of inhalation injury on in-hospital and post-discharge morbidity and mortality among burn patients.

Summary of background data: There has been no systematic assessment of long-term outcomes following inhalation injury. Additionally, the literature remains sparse regarding many non-mortality in-hospital outcomes.

Methods: This was a retrospective cohort study of burn patients admitted to our state's regional burn center from 2009-2015, with or without inhalation injury. Records were linked to statewide discharge and vital statistics records to assess post-discharge outcomes. Adjustment variables included age, total body surface area burned and presence of comorbidities.

Results: From 2009-2015, there were 4,463 admissions for cutaneous burns, including 206 with inhalation injury. In-hospital mortality was 31% in inhalation injury patients compared to 1% in non-inhalation injury patients; the adjusted relative risk was 4.85 (95% CI 3.18, 7.40). Inhalation injury was also associated with a significant increase in adjusted risk of in-hospital pneumonia, acute respiratory distress syndrome, aspiration, and tracheostomy ($p<0.05$ for all). There was no significant difference in post-discharge all-cause mortality, all-cause readmission, readmission for pulmonary diagnosis, or readmission requiring mechanical ventilation.

Conclusions: Inhalation injury is associated with increased early morbidity and mortality, but is not significantly associated with post-discharge mortality or inpatient readmission. This is important for inpatient management and counseling burn patients.

Background

Inhalation injury occurs in 3.5-15% of burn patients,[1-7] and burn patients sustaining inhalation injury have an increased risk for in-hospital mortality compared to patients without inhalation injury.[1-6] Presence of inhalation injury, in addition to patient age and burn size, is used to calculate the revised Baux Score, a validated scoring tool which predicts in-hospital mortality.[2]

In addition to mortality, several studies have demonstrated elevated pneumonia risk. A 1987 study identified pneumonia in 38% of inhalation injury patients compared to 9% of non-inhalation injury patients,[8] and a 2007 study demonstrated pneumonia in 27% of inhalation injury patients.[9] Additionally, inhalation injury was a risk factor for pneumonia in burn patients age 55 and older.[10] Inhalation injury has also been associated with longer hospital length of stay.[6] However, data remains sparse on other in-hospital outcomes such as discharge to intermediate care facilities and need for tracheostomy, which are critical for counseling patients and families on post-injury expectations and care needs.

Regarding long-term outcomes, the existing literature is predominated by case series, small sample sizes, and variable follow-up. In a case series of 13 patients injured in a building fire in Bangalore, India who had isolated inhalation injury requiring intubation, there was a high frequency of delayed airway complications.[11] Three required placement of long-term artificial airways at 11 weeks, four months and eight months post-discharge; one of these underwent surgical release of subglottic stenosis, mitomycin application and subsequent bronchoscopic dilation. An additional patient developed exertional stridor eight weeks after discharge and required bronchoscopic dilation of tracheal stenosis, although did not require placement of an artificial airway.[11] In a study of 23 survivors of smoke inhalation injury reevaluated between one and seven years after injury, six reported subjective symptoms of dyspnea, cough and phlegm that were new since injury; 17 underwent spirometry testing which showed no evidence of significant obstructive lung disease, and normal bronchial response to histamine challenge in all tested patients.[12] Another case series evaluated 17 pediatric burn patients eight years after sustaining severe thermal inhalation injury and variable total body surface burned (mean 67%, SD 29%) with spirometry; all had abnormal lung function wherein two had obstructive disease, five had restrictive disease, nine had both obstructive and restrictive, and one had a diffusion abnormality.[13] Finally, a study of pediatric patients with (n=51) and without (n=72) inhalation injury assessed disability and quality of life at least 5 years post injury (mean 9 years) using the World Health Organization Disability Assessment Scale II (WHODAS II) and the Burn Specific Health Scale-Brief (BSHS B). While outcome measures correlated with TBSA, percent 3rd degree burn and ventilator days, multivariable models did not show inhalation injury to be associated with poorer outcomes.[14]

Given a lack of systematic data assessing long-term outcomes following inhalation injury, the primary goal of this study was to assess long-term outcomes for burn patients with inhalation injury compared to those without inhalation injury, focusing on mortality, readmissions, readmissions for pulmonary causes, and readmissions requiring intubation. We also sought to compare in-hospital outcomes between these groups of patients, including mortality, tracheostomy, discharge to intermediate care facilities, and pulmonary complications. Our aim was to test the hypothesis that inhalation injury would be an independent risk factor for poor outcomes among burn patients, and to quantify observed differences in outcomes between those with and without inhalation injury.

Methods

Study design, population, and setting

This was a retrospective cohort study which included admitted patients of all ages with cutaneous burns, with or without inhalation injury, admitted at Harborview Medical Center between 1/1/2009 and 12/31/2015. Harborview is the only American Burn Association verified burn center in Washington State, and serves as the regional referral center. As such, the institution manages almost all severely burned patients in this large catchment area. We excluded patients transferred to our institution who arrived more than 48 hours after injury. The study was approved by the University of Washington Institutional Review Board.

The primary exposure was presence of inhalation injury. This was coded by trained burn research nurses for our institutional burn registry; in addition, manual medical record review was performed to verify correct coding. Manual verification was performed for all patients coded as having inhalation injury, as well as a random selection of 50 intubated patients not coded to have inhalation injury. For the purpose of this study, inhalation injury was assigned on the basis of bronchoscopic findings; when bronchoscopy was not performed, carboxyhemoglobin levels above 10% and clinical history were assessed. Patients with elevated carboxyhemoglobin levels who had no evidence of inhalation injury on bronchoscopy were considered unexposed.

For outcome assessments, we assessed several different outcome time points as described below. This approach required use of specific cohorts for various portions of analysis; this is elucidated in **Figure 1.**

In-hospital outcomes

In-hospital outcomes included mortality, hospital length of stay, intensive care unit (ICU) utilization, ventilator requirement, hospital disposition, tracheostomy, pneumonia, ventilator-associated pneumonia, aspiration, empyema and pulmonary embolism. These were ascertained using our institutional burn and ICU registries, hospital billing data and the Amalga Unified Intelligence System (Microsoft, Redmond, WA) platform for medical record query.

Post-discharge outcomes

We analyzed long-term all-cause mortality in two ways: (1) beginning at the time of hospital arrival to the end of follow-up (12/31/15; "any-time") and (2) among patients surviving to hospital discharge, beginning at the time of discharge to the end of follow-up (12/31/15; "post-discharge"). Among patients surviving to hospital discharge, we also assessed all-cause readmission, readmission with respiratory diagnosis and readmission requiring mechanical ventilation.

Post-discharge outcomes through 12/31/2015 were assessed based on statewide rehospitalization records from the Washington State Comprehensive Hospital Abstract Reporting System (CHARS) and statewide vital statistics records, provided by the Washington State Department of Health. Given that our institution treats some patients from outside of Washington State, all assessments of long-term outcomes were limited to those patients who had Washington State zip codes for their residence upon index burn hospitalization admission. Included patients were probabilistically linked to CHARS and vital statistics records using LinkPlus version 2.0 (Centers for Disease Control and Prevention, Atlanta, GA) on the basis of first name, middle initial, last name, date of birth, sex, and zip code, then manually verified.

Readmission with respiratory diagnosis and readmission with mechanical ventilation were ascertained using International Classification of Diseases (ICD)-9 and ICD-10 diagnosis codes from the statewide discharge data. Respiratory diagnoses were defined as ICD-9 codes 460-519, or ICD-10 codes J00-J99. Readmission with intubation or mechanical ventilation was defined as presence of ICD-9 procedure codes 96.04, 96.05, 96.70, 96.71 or 96.72, or ICD-10 procedures codes 0BH17EZ, 5A1935Z, 5A1945Z, or 5A1955Z. Causes of post-discharge death were based on ICD-10 Cause-of-Death codes from vital statistics data.

Secondary analysis

Since not all patients in the inhalation injury cohort received bronchoscopy, a secondary analysis was performed on patients with bronchoscopy-confirmed inhalation injury compared to patients without inhalation injury. In addition, we assessed whether higher bronchoscopic grade was associated with mortality from the date of hospital arrival to the end of follow-up (12/31/15).

Data analysis:

Descriptive data to compare sociodemographic and injury characteristics were tabulated. For in-hospital outcomes, Poisson regression with robust standard errors were used to provide unadjusted and adjusted estimates of the relative risks of outcomes for burn patients with inhalation injury compared to burn patients without inhalation injury. To topographically demonstrate the impact of inhalation injury on mortality at varying ages and TBSAs and to allow conceptualization of patient-specific risks, we generated contour plots based on thin plate spines.

For long-term outcomes, survival analysis methods using proportional hazards regression models were used. For non-mortality outcomes, competing risk regression was employed to account for death as a competing risk. All multivariable models adjusted for TBSA and age; we also adjusted for preexisting comorbidities relevant to each outcome (cardiovascular comorbidities for mortality outcomes, pulmonary comorbidities for respiratory outcomes, and any comorbidity for all-cause readmission). Multivariable Cox proportional hazards regression models estimated adjusted hazard ratios (aHR), while adjusted models from competing risk regression models estimated subhazard ratios (sHR).

Statistical analysis was conducted using Stata version 14 (StataCorp LP, College Station, TX), and contour plots were generated in R version 3.3.1 (The R Foundation for Statistical Computing Platform, Vienna, Austria).

Results

From 1/1/2009 to 12/31/2015, there were 4,463 admissions for cutaneous burns. Of these, 206 had burns with inhalation injury, and 4,257 had burns without inhalation injury. **Table 1** tabulates patient characteristics and injury data, as well as basic outcome data. Mean age was higher in the burn with inhalation cohort, and the inhalation cohort had evidence of more severe injury marked by higher TBSA, longer length of stay, more frequent ICU and ventilator requirements.

In-hospital outcomes

In-hospital outcomes were assessed, as shown in **Table 2,** for patients with inhalation injury (n=206) compared to burn patients without inhalation injury (n=4,257)**.** In both crude and adjusted analyses, burn patients with inhalation injury had significantly greater likelihood of in-hospital mortality, tracheostomy, pneumonia and other pulmonary complications. **Figure 2** demonstrates the impact of inhalation injury on mortality at varying ages and TBSAs; the first two frames show the relationship among burn patients with and without inhalation injury, and the final frame highlights the regions of greatest difference. These suggest that inhalation injury had the greatest impact on mortality at moderate TBSAs in the extremes of age. In contrast, elderly patients with high TBSA had high predicted mortality regardless of inhalation injury.

When these analyses were repeated comparing patients with inhalation injury confirmed with bronchoscopy (n=126) compared to patients without inhalation injury (n=4,257), the results were similar: all outcomes on crude analyses, and all outcomes except pulmonary embolism on adjusted analyses, were significantly more common among inhalation injury patients.

Any-time mortality (hospital arrival through end of follow up)

Next, we considered all-cause mortality at any time (in-hospital or post-discharge) among those patients who were Washington state residents at the time of burn hospitalization (n=149 with inhalation injury and n=3,361 without inhalation injury). Cumulative mortality was 34.9% among burn patients with inhalation injury compared to 6.2% in burn patients without inhalation injury, corresponding to a crude HR of 7.48 (95% CI 5.52, 10.14) and an adjusted HR of 2.63 (95% CI 1.90, 3.63).

To assess the importance of bronchoscopic grade on any time mortality, we compared patients with grade 1 (n=53), grade 2 (n=28), and grade 3-4 (n=12) inhalation injury confirmed on bronchoscopy to burn patients without inhalation injury (n=3,361) as shown in **Supplementary Table 1**. All-cause mortality at any time was 25% in grade 3-4, 25% in grade 2, and 32% in grade 1, compared to 6.2% in patients without inhalation injury; these corresponded to adjusted HRs of 1.45 (95% CI 0.46, 4.59), 1.88 (95% CI 0.88, 4.00), and 2.35 (95% CI 1.41, 3.93), respectively relative to patients without inhalation injury.

Post-discharge outcomes

Among patients who survived to hospital discharge and had Washington State zip codes at the time of index burn admission (n=106 with inhalation injury and n=3,331 without inhalation injury), we assessed post-discharge outcomes including all-cause mortality, all-cause readmission, readmission with pulmonary diagnosis and readmission requiring mechanical ventilation. Counts, median times to outcome, unadjusted and adjusted hazards are shown in **Table 3;** additionally, plots of cumulative incidence over time are presented in **Figure 3.** After adjustment for age, TBSA and comorbidities, burn patients with inhalation injury were not at significantly higher risk of any of these outcomes, although there were trends toward higher hazards of each.

Causes of post-discharge mortality were assessed. There were nine post-discharge deaths in the inhalation injury cohort; of these, three resulted from chronic obstructive pulmonary disease, emphysema or other chronic respiratory disease, two resulted from cardiac disease, vascular disease or stroke, one from malignancy, one from accidental poisoning, one from gastrointestinal or liver disease, and one from diabetes mellitus. There were 180 post-discharge deaths in the cohort without inhalation injury; of these, 40 resulted from chronic obstructive pulmonary disease, emphysema or other chronic respiratory disease, four resulted from pneumonia or pneumonitis, two resulted from treats to breathing, and the remaining resulted from other sources (cardiac disease, vascular disease, stroke, malignancy, trauma, accidental poisoning, gastrointestinal or liver disease, diabetes mellitus, sepsis or other non-respiratory infections, cerebral disorder, other).

We repeated the above analyses on the cohort of burn patients with bronchoscopy-confirmed inhalation injury compared to those without inhalation injury (n=72 with bronchoscopy-confirmed inhalation injury and n=3,331 without inhalation injury); results were similar as shown in **Supplementary Table 2**. The adjusted HR for all-cause mortality was 1.42 (95% CI 0.61, 3.28), the subhazard ratio for all-cause readmission was 1.51 (95% CI 1.04, 2.21), the subhazard ratio for readmission with pulmonary diagnosis was 1.26 (95% CI 0.64, 2.51), and the subhazard ratio for readmission with mechanical ventilation, was 1.06 (95% CI 0.31, 3.69).

Discussion

This seven-year cohort study was studied for in-hospital and post-discharge outcomes of burn patients with inhalation injury compared to burn patients without inhalation injury, and demonstrated that inhalation injury was associated with poorer in-hospital outcomes but no significant difference in post-discharge outcomes.

In-hospital, inhalation injury was associated with significantly greater risks of mortality, discharge to an intermediate care facility, tracheostomy and pulmonary complications such as pneumonia. As demonstrated in the contour plots, while patients with advanced age and high TBSA unsurprisingly had high risk of mortality, we found that inhalation injury had the greatest impact on mortality for patients with moderate TBSAs in the oldest and youngest age ranges. While the absolute risk of pneumonia observed in the inhalation injury cohort is somewhat lower than that reported in the 1987 and 2007 studies,[8, 9] the overall effect is similar. Observed differences may result from differences in the patient populations, advancements in patient management since the timeframes of these studies, or changes in means of classifying pneumonias.

When we considered outcomes from the time of hospital arrival to the end of follow-up, inhalation injury was associated with greater risk of all-cause mortality. While there is a trend toward higher post-discharge mortality, this did not reach statistical significance. Likewise, we did not observe significant increases in risk all-cause readmission, readmission for respiratory diagnoses or readmission requiring mechanical ventilation. Thus, our data suggest that poor outcomes after inhalation injury occur acutely; if patients survive hospitalization, they are unlikely to have long-term sequelae requiring inpatient care.

In considering these results, we hypothesize that certain patient factors, such as frailty, immobility, acute intoxication or mental health conditions may be critical drivers of which patients develop inhalation injury, and such underlying patient factors may be more important factors for long-term morbidity. In addition, patients who do have long-term sequelae relating to inhalation injury may be more likely to have symptoms which are managed on an outpatient basis, which our study was unable to assess. Further study is warranted to consider such outcomes.

Interestingly, we did not observe an association between higher bronchoscopic grade and any-time mortality, although our sample size was limited particularly for higher injury grades. However, patients with severe inhalation injury who were not expected to survive may have been less likely to receive bronchoscopic grading thereby confounding these results. Still, in practice, diagnosis of higher grade injury did not clearly correlate with poorer outcome; thus, we recommend additional study of the utility of bronchoscopy for risk-stratification and guidance of patient management.

This study has several limitations which relate to its retrospective nature. Identification of inhalation injury is not always straightforward, relying on a combination of factors such as bronchoscopic findings, carboxyhemoglobin levels and clinical history. Bronchoscopy was not performed in all patients suspected to have inhalation injury in our cohort, and became used somewhat more frequently over the course of the study. While carboxyhemoglobin levels are also useful in inhalation injury diagnosis, we lacked reliable information in our retrospective records to enable back-calculation or imputation to an estimated value at the time of injury. Given these factors, there may have been some misclassification of exposure. Given careful manual chart review of all patients identified with inhalation injury we expect this definition to be quite specific; as such, we expect that any misclassification occurring would have resulted in attenuated measures of association. In addition, we assessed all post-discharge and several in-hospital outcomes using diagnosis and procedure codes, which may be imperfectly ascertained. This may have led to misclassification of outcomes; however, we expect that this would occur at similar extent in the two groups. For long-term outcomes, the length of follow-up was limited by the most recently-available CHARS data, so patients with the most recent injuries had shortest follow-up durations. Additionally, ascertainment of long-term outcomes was limited to inpatient admissions and inpatient procedures performed in Washington, which resulted in two limitations. First, we lacked data about whether individuals relocated out of Washington, so were unable to censor them at the time of out-migration. If these patients received subsequent hospitalizations or died outside of Washington, these events would have been missed. However, we expect that relocation frequency would be similar between exposure groups. Secondly, we were unable to assess outcomes which are managed on an outpatient basis, which are likely to be more common than inpatient outcomes. While we were able to assess the most severe complications, we did not have data on some outcomes which may have been important for quality of life and patient counseling such as need for pulmonary medications or home supplemental oxygen. Given that complications requiring inpatient admission are less common, our statistical power to detect differences was limited, particularly for rare events.

This was the first study to systematically study long-term clinical outcomes in patients with inhalation injury. We observed clinically significant differences in in-hospital mortality and complications, suggesting that inhalation injury requires thoughtful clinical care. However, we observed no significant difference in long-term outcomes, either for mortality or readmissions. Further study regarding whether there are differences in lower acuity outcomes, such as those which could be managed on an outpatient basis, is warranted.

Figure 1. Cohort identification

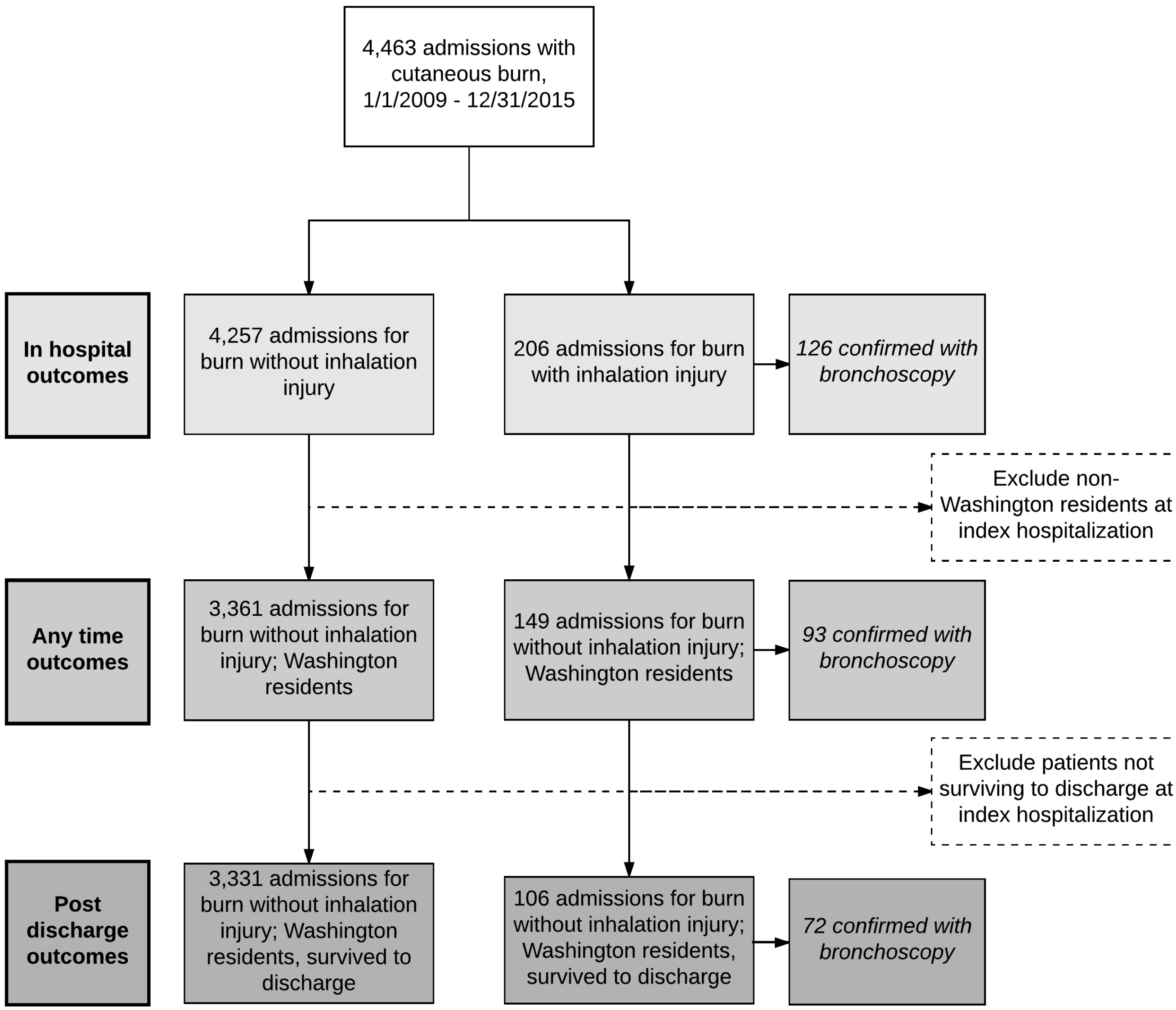


Table 1. Patient characteristics, injury data and basic outcomes for burn patients with and without inhalation injury

	Burn without inhalation (n=4257)	Burn with inhalation (n=206)
Age, median (IQR)	28.4 (5.7, 48.4)	46.6 (31.7, 57.2)
Female sex	1354 (31.8%)	64 (31.1%)
Race/ethnicity		
White	2690 (63.2%)	147 (71.4%)
Black	327 (7.7%)	8 (3.9%)
Asian	315 (7.4%)	8 (3.9%)
Hispanic or Latino	458 (10.7%)	13 (6.4%)

TBSA burned, median (IQR)	3.1 (1.2, 7.0)	23.2 (7.6, 43.7)
% Third degree burn, median (IQR)	0% (0, 0.4%)	8.3% (0, 31.6%)
Received operation	41 (1.1%)	10 (10.5%)
Admitted to ICU	887 (20.8%)	205 (99.5%)
Required ventilator	380 (8.9%)	200 (97.1%)
Ventilator days (if ventilated): median (IQR)	2 (1-6)	3 (1-15.5)
Admission COHGb: median (IQR) if tested	1.7 (0.9, 3.0)	3.1 (1.3, 8.6)
Tested in n (%)	566 (13.3%)	177 (85.9%)
Admission COHGb level >20	2 (0.1%)	22 (10.7%)
Inhalation injury confirmed with bronchoscopy	N/A	126 (61.2%)
Bronchoscopic grade: 1	N/A	66 (52.4%)
2		44 (34.9%)
3		15 (11.9%)
4		1 (0.8%)
Hospital LOS: median (IQR)	2 days (1-7)	19 days (3-41)
Hospital disposition		
Died	46 (1.1%)	63 (30.6%)
Home/self-care	4018 (94.6%)	96 (46.6%)
Extended care or skilled nursing facility	103 (2.4%)	6 (2.9%)
Rehabilitation	20 (0.5%)	14 (6.8%)
Transfer to outside hospital	37 (0.9%)	21 (10.2%)
Transfer to psychiatry	22 (0.5%)	6 (2.9%)

Abbreviations: IQR = interquartile range. TBSA = total body surface area. ICU = intensive care unit

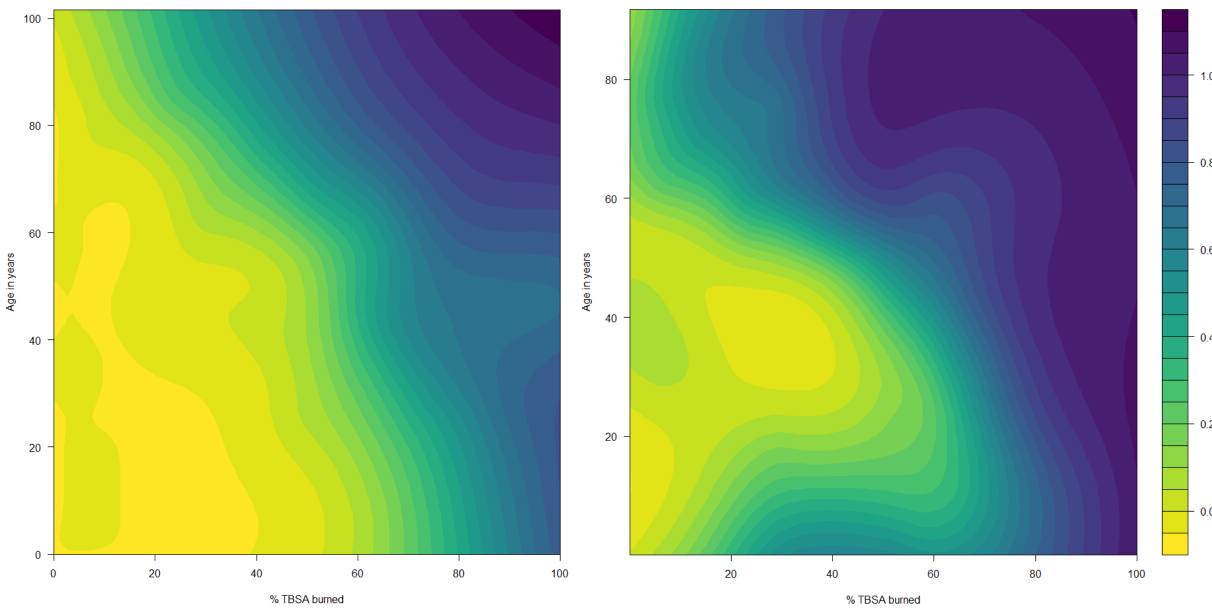
Table 2. In-hospital outcomes for burn patients with and without inhalation injury

	Burn without inhalation (n=4257)	Burn with inhalation (n=206)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]
Mortality	46 (1.1%)	63 (30.6%)	28.30 (19.87, 40.30)	4.85 (3.18, 7.40)
Discharge to intermediate care[b]	123 (2.89%)	20 (9.71%)	3.36 (2.14, 5.28)	1.47 (0.88, 2.46)
Tracheostomy	20 (0.47%)	22 (10.68%)	22.73 (12.61, 40.97)	9.70 (4.16, 22.64)
Pneumonia	65 (1.53%)	45 (21.84%)	14.30 (10.04, 20.37)	5.16 (3.02, 8.80)
Ventilator-associated pneumonia	53 (1.25%)	45 (21.84%)	17.54 (12.09, 25.44)	5.96 (3.31, 10.71)
Aspiration	19 (0.45%)	16 (7.77%)	17.39 (9.08, 33.33)	10.40 (4.59, 23.58)
Empyema	1 (0.02%)	4 (1.94%)	82.64 (9.28, 736.26)	62.01 (2.87, 1340.34)
Pulmonary embolism	9 (0.21%)	5 (2.43%)	11.48 (3.88, 33.95)	6.35 (1.15, 35.00)

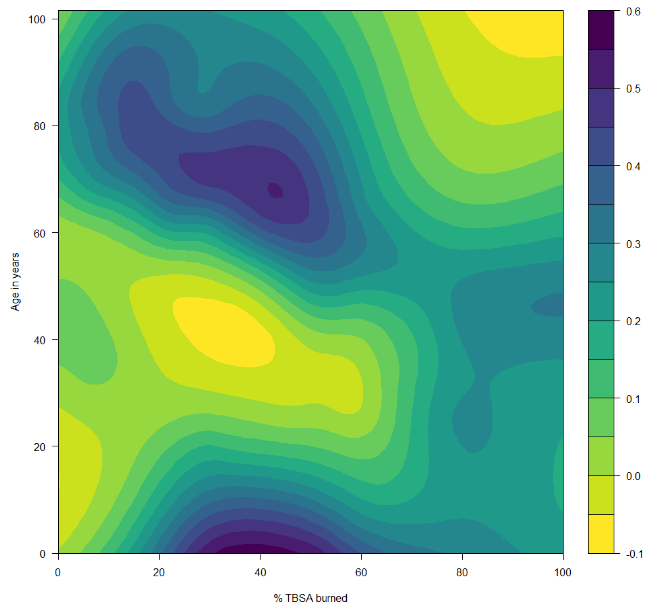
[a] *All adjusted models accounted for age and total body surface area burned. The mortality adjusted model also accounted for cardiovascular comorbidity. The discharge to intermediate care model also accounted for any comorbidity. Models for tracheostomy, pneumonia, ventilator-associated pneumonia, aspiration and empyema also accounted for respiratory comorbidity. The model for pulmonary embolism did not account for comorbidity.*
[b] *Intermediate care defined as discharge to extended care, skilled nursing or rehabilitation facility.*

Figure 2. Contour plots of predicted mortality based on total body surface area burned and age

A. No inhalation B. Inhalation



C. Difference



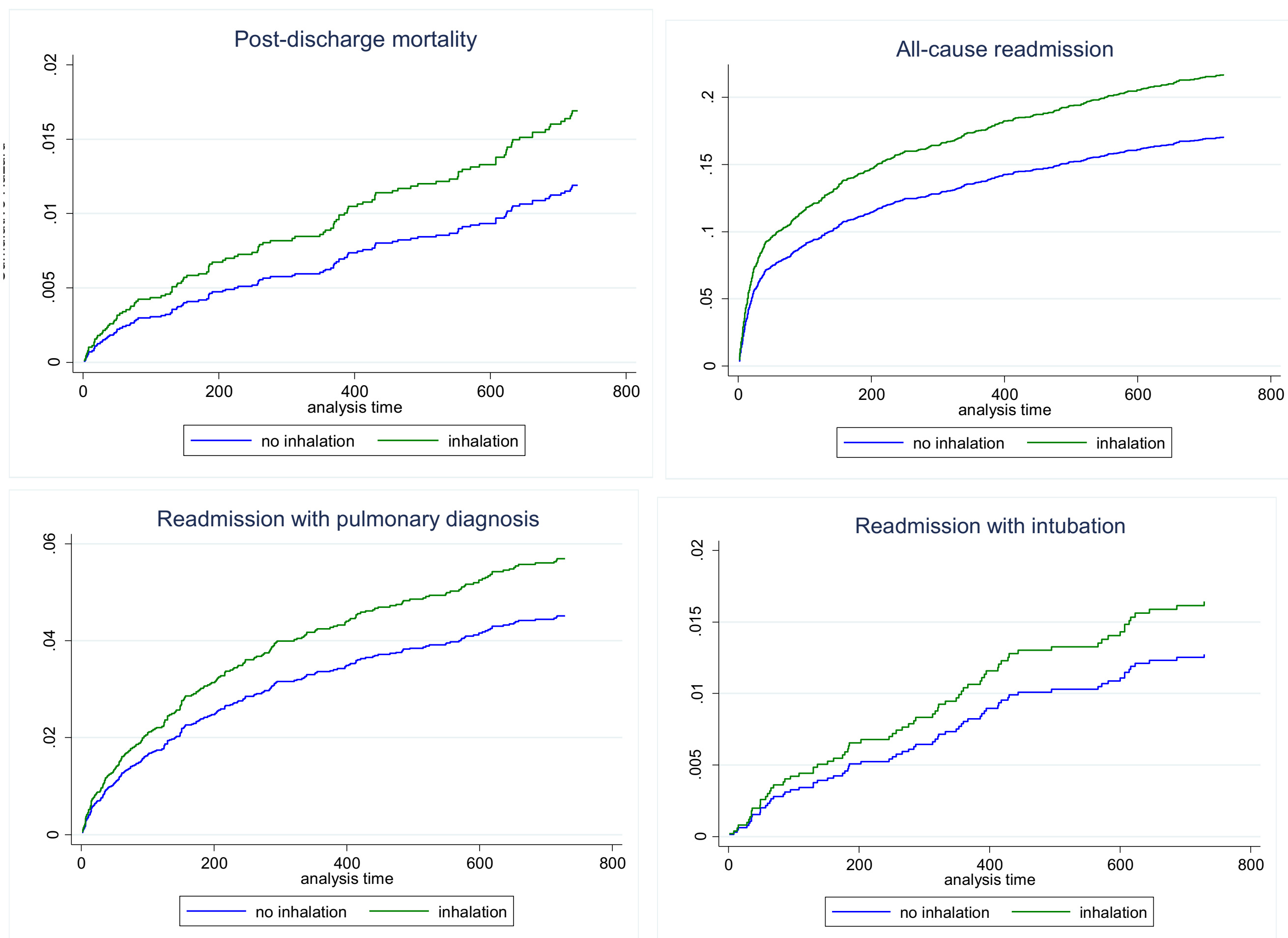
Panels A and B demonstrate the risk of mortality over varying total body surface area burned and patient age, wherein darker colors indicate greater risk of mortality. Panel C highlights the difference between these curves, wherein darker colors indicate a greater difference in predicted mortality between burn patients with inhalation injury and burn patients without inhalation injury.

Table 3. Post-discharge outcomes for burn patients with and without inhalation injury

	Burn without inhalation N=3331	**Burn with inhalation N=106**	**Median time to outcome in months, burn without inhalation (IQR)**	**Median time to outcome in months, burn with inhalation (IQR)**	**Crude hazard ratio (95% CI)**	**Adjusted hazard ratio or subhazard ratio (95% CI)** [a]
All-cause mortality	180 (5%)	9 (9%)	16.1 (4.8, 32.5)	20.1 (13.6, 28.7)	1.64 (0.84, 3.21)	aHR 1.42 (0.72, 2.82)
All-cause readmission	776 (24%)	39 (40%)	4.2 (0.6, 17.5)	4.3 (0.8, 14.5)	1.92 (1.39, 2.65)	sHR 1.31 (0.94, 1.82)
Readmission with pulmonary diagnosis	311 (9%)	15 (14%)	8.6 (2.4, 24.4)	2.6 (0.5, 7.8)	1.66 (0.99, 2.78)	sHR 1.27 (0.73, 2.21)
Readmission requiring mechanical ventilation	98 (3%)	5 (5%)	12.9 (5.3, 28.3)	10.5 (2.8, 19.8)	1.70 (0.69, 4.18)	sHR 1.29 (0.49, 3.42)

[a] *All adjusted models included TBSA and age; comorbidity-adjustment was outcome-specific. Models for the three readmission outcomes also included death as a competing risk. The comorbidity in the model for all-cause mortality was cardiovascular comorbidity, all-cause readmission was any comorbidity, readmission with pulmonary diagnosis and readmission requiring mechanical ventilation was respiratory comorbidity.*

Figure 3. Cumulative incidence of all-cause mortality, all-cause readmission, readmission with respiratory diagnosis and readmission with intubation over time.



Time is expressed in days from the time of injury.

Acknowledgements

Dr. Witt wishes to thank Dr. Monica Vavilala, Dr. Saman Arbabi, Dr. Samuel Mandell, Dr. Tam Pham, and Dr. Nicole Gibran, in addition to the thesis committee, for guidance with this project. In addition, Dr. Witt would like to acknowledge Andrea Dai, Shari Honori, Shauna Carlson, and Aaron Parker for assistance with data acquisition.

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