The effect of smoking status on burn inhalation injury mortality

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ABSTRACT

Introduction: Three factors that effect burn mortality are age, total body surface of burn (TBSA), and inhalation injury. Of the three, inhalation injury is the strongest predictor of mortality thus its inclusion in the revised Baux score (age+TBSA+17* (inhalation injury, 1=yes, 0=no)). However, the weighted contribution of specific comorbidities such as smoker status on mortality has traditionally not been accounted for nor studied in this subset of burn patients. We therefore sought to examine the impact of current tobacco and/or marijuana smoking in patients with inhalation injury.

Methods: A retrospective analysis of patients admitted to a regional burn center from 2002 to 2012. Independent variables analyzed included basic demographics, burn mechanism, presence of inhalation injury, TBSA, pre-existing comorbidities, and smoker status. Bivariate analysis was performed and logistic regression modeling using significant variables was utilized to estimate odds of mortality.

Results: There were a total of 7640 patients over the study period. 7% (n=580) of the burn cohort with inhalation injury were included in this study. In-hospital burn mortality for inhalation injury patients was 23%. Current smokers (20%) included cigarette smokers and marijuana users, 19% and 3%, respectively. Preexisting respiratory disease (17%) was present in 36% of smokers compared to 13% of non-smokers ($p<0.001$). Smokers had significantly lower mortality rate (9%) compared to non-smokers (26%, $p<0.01$). The logistic regression model for mortality outcomes identified statistically four significant variables: age, TBSA, ethnicity, and smoker status (OR=0.41, 95% CI=0.18–0.93). Presence of comorbidities, including preexisting respiratory disease, was not significant.

Conclusion: In the sub group of burn patients with inhalation injury, the odds of mortality significantly decreased in pre-existing smokers after adjusting for significant covariates. We postulate that an immune tolerance mechanism that modulates and diminishes the pro-inflammatory response confers a survival advantage in smokers after exposure to acute smoke inhalation injury. Future prospective studies in human and/or animal models are needed to confirm these findings.

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1. Introduction

Burn is one of the most devastating traumatic injuries affecting an estimated 486,000 people in the United States in 2015 [1]. Advancements over the past three decades in burn care such as measured fluid resuscitation, improved critical care management, and early excision and grafting have resulted in improved burn outcomes. Despite these advances, the three major determinants of increased burn mortality include age>60 years old, % total body surface area (%TBSA) >40%, and presence of inhalation injury [2–5]. Inhalation injury is considered to be the strongest predictor of burn mortality [2,4]. To better prognosticate burn outcomes, the Baux score was created [6,7], however, to account for the weighted contribution of inhalational injury to burn mortality, it was later revised to include this predictor variable (age+percent burn+17*) (inhalation injury, 1=yes, 0=no) [8,9]. More recently, with the recognition of increased longevity of the US population and its health related sequelae, it is paramount that future burn mortality prediction models account for pre-existing comorbidities in the prognostication of injury outcomes. Specifically the role of pre-existing respiratory disease markers such as smoking in the subset of burn patients with inhalational injury.

Smoking is the single largest preventable cause of death and disease in the United States [10]. It was estimated in 2014, that 16.8% (40 million) adults in the United States are current smokers of tobacco or marijuana. Of which 30.7 million smoked every day. Majority of smokers range between 18 and 64 years of age. There are a variety of harmful substances in tobacco smoke and marijuana that impair mucociliary clearance, damage the cell lining of the trachea, bronchus and bronchioles, and kill cells in the lungs that are responsible for removing dust and bacteria leading to more mucus production [11–15]. Toxins liberated during smoking can cause damage to lung airways and alveoli leading to emphysema, and chronic bronchitis [16,17]. Marijuana also can suppress the immune system that could lead to increased risk of lower respiratory tract infection in these smokers [16].

There have been no previous studies examining the independent effect of smoking on burn mortality in patients with inhalation injury. As the pathologic pulmonary manifestation of smoking is akin to chronic inhalational injury, we hypothesize that there will be an increased mortality in burn patients with inhalational injury that are current smokers at the time of the injury as compared to non-smokers.

2. Methods

This is a retrospective study of all burn patients admitted to the University of North Carolina Jaycee Burn Center from 2001 to 2012. The North Carolina Jaycee Burn Center at UNC was established in 1981 and averages more than 1200 acute admissions per year. The burn center is a single unit, 36-bed facility that has been verified by the American Burn Association for pediatric and adult care.

The medical records of subjects identified by the UNC Burn database query were reviewed to verify baseline demographic data, injury characteristics, and provide detailed information and associated preexisting comorbidities. Injury characteristics of interest included burn etiology, %TBSA burn, presence of inhalation injury, and intubation status on admission to the burn center. Inhalation injury diagnosis is based on history and confirmed by fiberoptic bronchoscopy examination per our clinical protocol. Per National Burn Data Standards (NBDS) created by the American Burn Association, inhalation injury is recorded in the burn registry as either absent or present with and without cutaneous burn based on medical records. Other useful modalities such as chest-computed tomography (CT), radionuclide imaging with ^{133}Xenon, carbon monoxide levels and pulmonary function testing results are not part of our inhalational injury protocol.

Preexisting comorbidities were weighted using the Charlson Comorbidity Index (CCI) score [18,19]. The score is the weighted sum of comorbid conditions. There are 17 comorbid conditions included in the score and each is assigned a weight from 1 to 6 points (Table 1). Pre-existing comorbidities were identified utilizing the National Trauma Data Bank (NTDB) from the American College of Surgeons Committee on Trauma. Current smoking status was obtained from medical records and recorded into the burn registry. Smoking status is reported from patient, family member, or persons living with the patient or with intimate knowledge of patient's smoking habits upon admission to the burn center. In addition to tobacco smoke, marijuana use information was enquired.

Our outcome of interest is in-hospital mortality in patients with inhalation injury. Baseline patient and injury characteristics were compared between groups for mortality and smoker status using Analysis of Variance for continuous variables and chi-squared for categorical variables. Kruskal–Wallis test was used to compare medians. We employed both bivariate analyses to determine the relative influence of smoking on mortality among covariates. To determine odds of mortality, we used a multivariate logistic regression model controlling for pertinent confounders (age, TBSA, ethnicity,

Table 1 – Charlson Comorbidity Index score system.

Comorbidity	Score
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatologic disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes without chronic complications	1
Diabetes with chronic complications	2
Hemiplegia or paraplegia	2
Renal disease	2
Any malignancy, including leukemia and lymphoma	2
Moderate or severe liver disease	3
AIDS/HIV	6
Metastatic solid tumor	6
Maximum comorbidity score	33

CCI, and smoker status). A comparison of Area Under the Receiver Operating Characteristic (AUROC) curve between regression models was done with current smokers and non-smokers to determine accuracy of including smoker status in predicting burn mortality. Stata/MP (Version 12) (Statacorp, College Station, TX) was used for all data management and statistical analysis. The University of North Carolina Institutional Review Board approved this study.

3. Results

3.1. *Patient demographic*

A total of 7640 patients were admitted to the hospital during the study period. Only a subset of 580 patients had inhalation injury and thus met criteria for analysis in this study. The mean age was 44±20 years and a male predominance (n=395, 68%). Caucasians made up 56% of the population. The most common mechanism of burn was flame (n=536, 93%) compared to scald and other injury, 3% and 4% respectively. The mean TBSA for this inhalation injury cohort was 22 (SD=24%) with a median of 13% (Table 2). There was no significant difference in TBSA based on ethnicity or gender. The mean length of hospitalization, ICU stay, and mechanical ventilation days was 36.9±46.4 days, 28.4±36.4 days, and 21.4 ±31.3 days respectively. Current smokers (20%) with inhalation injury included tobacco smokers and marijuana users, 19% and 3%, respectively. Thirty-two percent of inhalation injury patients had comorbidities. Preexisting respiratory disease was present in 17% of inhalation injury burn patients.

3.2. *Bivariate analysis for burn inhalation injury patients*

During the study period, the mortality rate in inhalation injury patients was 23%. The mean age of survivors vs. non-survivors was 41.2±19.1 years and 55.0±19.8 years, respectively (Table 3). TBSA was significantly associated with mortality ($p<0.001$). The average TBSA for patients who died was 46.9 ±28.3%. Men represented 61% of non-survivors compared to women at 39% ($p<0.05$). Ethnicity and mechanism of burn had no significant impact on mortality. Length of hospital stay for non-survivors was significantly shorter ($p<0.01$). ICU stay and days on mechanical ventilation were not significant.

3.3. *Smoker status analysis*

A separate bivariate analysis was performed to compare smokers and non-smokers. The mean age for current smokers vs. non-smokers was 49.0±14.5 years and 43.2±21.2 years, respectively ($p<0.001$) (Table 4). The average TBSA for smokers was significantly lower than non-smokers (12.1±16.1% vs. 24.4 ±25.3%, $p<0.001$). Current smokers had a higher CCI score (0.96±1.33) compared to non-smokers (0.61±1.26, $p<0.01$). Caucasians were predominant in both groups and were more likely to be smokers compare to minorities (68% vs. 32%, $p<0.05$). Smokers had a significantly lower mortality rate than non-smokers (9% vs. 26%, $p<0.001$). There was no statistically significant difference in gender, mechanism of injury, length

Table 2 – Patient characteristics.

Patient characteristics (n=580)	*n*	Mean (±SD) or %
Gender		
Male	395	68%
Female	184	32%
Age		
Overall mean		44.3 (±20.1)
Ethnicity		
White	323	56%
Other	256	44%
Type of burn		
Flame	536	93%
Scald	18	3%
Other	21	4%
Respiratory disease		
Pre-existing	100	17%
None	480	83%
Smoker status		
Smoker	116	20%
Non-smoker	464	80%
Comorbidities		32%
Overall		0.68 (±1.28)
TBSA		
Overall mean		22.0 (±24.2)
By gender		
Male	395	23.2 (±24.6)
Female	184	19.4 (±23.2)
By ethnicity		
White		20.0 (±23.6)
Other		24.2 (±24.3)
Survival		
Overall	448	77%
Respiratory disease		
Pre-existing	77	77%
None	371	77%
Smoker status		
Smoker	98	90%
None	350	74%
ICU stay		
Overall mean		28.4 (±36.4)
Hospital stay		
Overall mean		36.9 (±46.4)
Mechanical ventilation		
Overall mean	481	21.4 (±31.3)
By gender		
Male	329	22.9 (±31.9)
Female	150	18.4 (±29.9)
By ethnicity		
White	257	18.0 (±27.7)
Other	210	25.7 (±34.8)

TBSA: % total body surface area burn.

Table 3 – Bivariate analysis of burn patients with inhalation injury.

	Live	Dead	p-Value
Age	41.2 (±19.1)	55.0 (±19.8)	<0.001
TBSA	14.5 (SD=16.7)	46.9 (SD=28.3)	<0.001
CCI	0.60 (0–7)	0.95 (0–6)	0.004
Ethnicity			
White	54%	60%	0.236
Other	46%	40%	
Gender			
Male	70%	61%	0.035
Female	30%	39%	
Mechanism			0.137
Flame	92%	96%	
Scald	3%	3%	
Other	4%	1%	
Smoker status			
Smoker	23%	8%	<0.001
Non-smoker	77%	92%	
Respiratory disease			
Pre-existing	17%	17%	0.950
None	83%	83%	
ICU stay	29.5 (±35.9)	24.9 (±38.2)	0.187
LOS	40.4 (±47.9)	24.8 (±38.4)	<0.001
Mechanical ventilation	21.1 (±29.4)	23.0 (±37.1)	0.553

TBSA: total body surface area.
CCI: Charlson Comorbidity Index.
LOS: length of hospital stay.

Table 4 – Bivariate analysis of burn patients with inhalation injury (smokers vs. non-smokers).

	Smoker	Non-smoker	p-Value
Age	49.0 (±14.5)	43.2 (±21.2)	0.005
TBSA	12.1 (SD=16.1)	24.4 (SD=25.3)	<0.001
CCI	0.96 (±1.33)	0.61 (±1.26)	0.003
Ethnicity			
White	68%	53%	0.010
Other	32%	47%	
Gender			
Male	71%	68%	0.528
Female	29%	32%	
Mechanism			0.285
Flame	90%	94%	
Scald	4%	3%	
Other	6%	3%	
Respiratory disease			
Pre-existing	36%	13%	<0.001
None	64%	87%	
In-hospital mortality	9%	26%	<0.001
ICU stay	28.3 (±39.5)	28.4 (±35.6)	0.962
LOS	37.0 (±49.3)	36.9 (±45.6)	0.879
Mechanical ventilation	23.0 (±35.8)	21.1 (±30.1)	0.546

TBSA=total body surface area.
CCI=Charlson Comorbidity Index.
LOS=length of hospital stay.

of hospitalization, ICU stay, and days on mechanical ventilation between current smokers and non-smokers.

A multivariate logistic regression performed for mortality outcome controlling for statistically significant covariates on bivariate analysis: age, TBSA, ethnicity, comorbidities using Charlson Comorbidity Index revealed a decreased odds of mortality in smokers (OR=0.41, 95% CI=0.18–0.93) (Table 5). Examining mortality over length of hospitalization in first 100 days, the predicted mortality at 30 days is significantly lower for smokers (8%) compared to non-smokers (17%) (Fig. 1). Comparison of AUROC was done on logistic regression models with smokers and nonsmokers to determine accuracy of this variable in predicting mortality over length of hospitalization. There was a significant difference between smokers (AUROC=0.870, 95% CI=0.833–0.907) and nonsmokers (AUROC=0.899, 95% CI=0.867–0.931, $p<0.01$).

4. Discussion

No previous studies have examined the independent influence of current smoking on mortality following burn inhalation injury. In this study, we have established that in patients with burn inhalation injury, there is a 50% decrease in odds of mortality in current smokers compared to nonsmokers.

Cigarette smoke or indeed smoke from a fire produces a smoke with more than 4000 noxious and toxic components, including gas and particulate matter such as a formaldehyde, carbon monoxide, nicotine acetaldehyde, phenol and potassium cyanide. Smoke-related toxins damage epithelial and capillary endothelial cells of the airway [20]. Smoke induced irritation of the trachea and larynx and Inhaled particulate matter is deposited in the respiratory tract results in breathlessness due to swelling and narrowing of lung airways, with impairment of the pulmonary mucociliary clearance system and associated impaired bacterial clearance can lead to increased risk of pneumonia, decrease production of surfactant, and permanent damage to alveoli [21–24].

Following acute inhalation injury, the early inflammatory changes occur in the smoke naïve airway, followed by a period of diffuse exudate formation and progressive bronchiolar edema. Furthermore, the combination of necrotizing

Table 5 – Multivariate logistic regression for mortality in burn cohort.

Variable	Adjusted odds ratio, 95% confidence interval (CI)	p-Value
Age	1.06 (1.04–1.08)	<0.001
TBSA	1.08 (1.06–1.09)	<0.001
Ethnicity	2.00 (1.14–3.48)	0.015
CCI	1.16 (0.96–1.41)	0.123
Smoker status	0.41 (0.18–0.92)	0.031

TBSA=total body surface area.
CCI=Charlson Comorbidity Index.

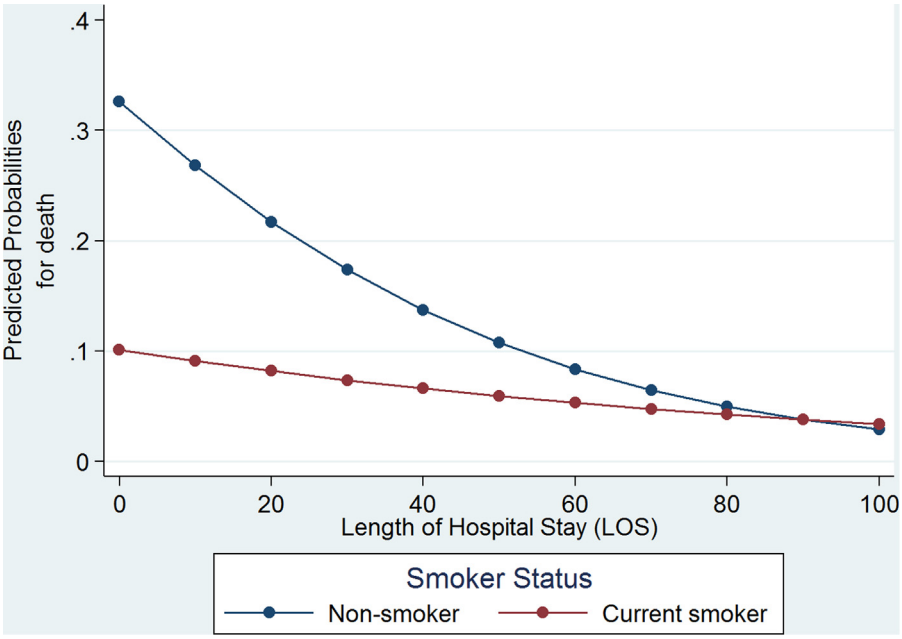

Fig. 1 – Predicted probability of mortality for current and non-smokers with inhalation injury.

bronchitis, bronchial swelling, and bronchospasm that causes obstruction of large and small airways and increased capillary permeability, which magnifies airway and pulmonary edema and increase morbidity and mortality [25–27]. This pathologic response is mediated through innate immune cells like monocytes/macrophages that detect and respond to "danger signals" (e.g. smoke, tissue damage) through pattern recognition receptors expressed on their surface and modulated by Toll like receptor 4 (TLR4) [28,29].

The detection of smoke and chemical toxins by innate immune cells triggers a robust and essential pro-inflammatory response that leads to extensive tissue damage. This early and exuberant inflammatory changes that occur in the smoke naïve airway, followed by a period of diffuse exudate formation and progressive bronchiolar edema may be absent in current smokers.

Pathophysiological adaptations to regulate over-exuberant inflammation serve as an important mechanism for host protection against toxin exposure. One of the classic examples of such a protective mechanism is endotoxin tolerance, a phenomenon in which cells or organisms exposed to low concentrations of endotoxin such as Lipopolysaccharide enter into a transient unresponsive state and are unable to respond to larger challenges with endotoxin [30,31]. We posit that in chronic smokers, this same adaptive immunologic tolerance mechanism may have developed as a result of chronic smoke exposure and is protective during acute smoke inhalation injury. Long-term smokers have demonstrated a chronic, low-grade inflammation. After long-term tobacco smoke exposure (15–84 weeks) some studies found suppressed cell-mediated immunity [32,33]. The influence of the acute inhalation of smoke particle and toxins within the milieu of a chronically smoke exposed airway and pulmonary parenchyma results in a mooted inflammatory response and a survival advantage [34,35].

Another protective mechanism that have been described previously in studies that may explain our findings is the presence of an anti-inflammatory substance found in cigarette smoke such as Carbon monoxide (CO) [36,37]. High concentrations of CO can induce apoptosis and inhibit respiratory enzyme functions [38]. However, administered at low concentrations, CO has shown to be cyto-protective and diminish the inflammatory response by down regulating pro-inflammatory cytokines and the up-regulation of the anti-inflammatory cytokine interleukin-10 [39,40]. Furthermore, Smokers have been much higher levels of Heme Oxygenase-1 (HO-1), an enzyme that oxidizes heme to CO, observed in the airways than in nonsmokers and are exposed to chronic low-levels of CO through long-term use which may explain a diminished inflammatory response following acute inhalation injury in current smokers [36]. HO-1 has been implicated in cyto-protection in many acute lung injury models [41].

The limitations of this study are those inherent to any study with a retrospective. This is a single center study, but our large sample size obviates the loss of generalizability of our findings. The contribution of frailty and its effect on outcome was not evaluated. Furthermore, the Charlson Comorbidity Index was originally based on the predictive power to estimate mortality in medicine patients and was never intended to generalizations to surgical or burn cohort. Most importantly, Inhalation injury was analyzed as an all or none variable. The degree of inhalation injury and the heterogeneity of smoke inhaled are unknown. According to the NBDS, carbon monoxide levels can provide information regarding injury severity and risk for adverse outcomes. However, a low carboxyhemoglobin does not always indicate a minimal smoke exposure because administration of oxygen at the scene of the fire can displace some of the carbon monoxide before arrival in the emergency department. We agree pre-hospital information is unavailable in our registry and there is a small likelihood of presentation or

survivor bias. Based on American Burn Association guidelines, most burns are automatic referred to our regional burn center and we believe we capture a preponderance amount of severe burn patients with and without inhalation injury. Like any other trauma surveillance registry, we do not and cannot capture death at the scene. Lastly, the chronicity of smoking and the pack year history of smokers where not controlled for in our analysis as that data was not available.

5. Conclusion

In the sub group of burn patients with inhalation injury, the odds of mortality significantly decreased in pre-existing smokers after adjusting for significant covariates. We postulate that an immune tolerance mechanism that modulates and diminishes the pro-inflammatory response confers a survival advantage in smokers after exposure to acute smoke inhalation injury. A prospective study is needed to better characterize our findings and molecular mechanism on the interaction of smoking and adaptive immune response is imperative. There needs to be future prospective studies in human and/or animal models to take in account varying degrees of inhalation injury and smoke exposure chronicity on burn outcome to confirm these findings.

Conflict of interest

None.

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