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The effect of preexisting respiratory co-morbidities on burn outcomes☆

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ABSTRACT

Introduction: Burns cause physiologic changes in multiple organ systems in the body. Burn mortality is usually attributable to pulmonary complications, which can occur in up to 41% of patients admitted to the hospital after burn. Patients with preexisting comorbidities such as chronic lung diseases may be more susceptible. We therefore sought to examine the impact of preexisting respiratory disease on burn outcomes.

Methods: A retrospective analysis of patients admitted to a regional burn center from 2002–2012. Independent variables analyzed included basic demographics, burn mechanism, presence of inhalation injury, TBSA, pre-existing comorbidities, smoker status, length of hospital stay, and days of mechanical ventilation. Bivariate analysis was performed and Cox regression modeling using significant variables was utilized to estimate hazard of progression to mechanical ventilation and mortality.

Results: There were a total of 7640 patients over the study period. Overall survival rate was 96%. 8% (n=672) had a preexisting respiratory disease. Chronic lung disease patients had a higher mortality rate (7%) compared to those without lung disease (4%, $p<0.01$). The adjusted Cox regression model to estimate the hazard of progression to mechanical ventilation in patients with respiratory disease was 21% higher compared to those without respiratory disease (HR=1.21, 95% CI=1.01–1.44). The hazard of progression to mortality is 56% higher (HR=1.56, 95% CI=1.10–2.19) for patients with pre-existing respiratory disease compared to those without respiratory disease after controlling for patient demographics and injury characteristics.

Conclusion: Preexisting chronic respiratory disease significantly increases the hazard of progression to mechanical ventilation and mortality in patients following burn. Given the increasing number of Americans with chronic respiratory diseases, there will likely be a greater number of individuals at risk for worse outcomes following burn.

1. Introduction

Burn results is significant morbidity and mortality worldwide. In the United States, an estimated 486,000 burns occurred in 2015 [1]. Following major burns, mortality is usually attributable to pulmonary complications, which can occur in up to 41% of patients admitted to the hospital after burn [2–4]. Previous

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studies over the last three decades have shown the effect of burns on the respiratory system occurs in three phases [5–9].

These three phases are the early or resuscitative phase (first 48 h), the post-resuscitative phage (2–7 days), and the late phase (beyond 7 days) after burn. Phase I is seen within minutes to hours as acute respiratory distress secondary to thermal injury from smoke inhalation, carbon monoxide poisoning, or secondary to airway obstruction. Pulmonary edema that occurs is seen as precursor to the development of ARDS in burn. The Phase II includes patients that were asymptomatic for the initial 24–48 h; however, develop symptoms of tachypnea and hypoxemia within 5 days after burn. Patients develop atelectasis, acute respiratory distress Syndrome (ARDS), analgesic related respiratory suppression, or ventilatory failure. Lastly, phase III develop late complications such as pneumonia and pulmonary emboli [8,9].

With increase in longevity of the US population, there is a concomitant rise in the number of people with health related comorbidities, particularly chronic respiratory diseases. There is a broad spectrum of respiratory diseases but they can be broadly classified as either obstructive or restrictive respiratory disease [10]. Examples of obstructive lung diseases include chronic bronchitis and emphysema, asthma, cystic fibrosis, and bronchiectasis. In contrast, restrictive lung diseases such as sarcoidosis, interstitial lung disease, pulmonary fibrosis, hypoventilation syndrome due to obesity, and amyotrophic lateral sclerosis are characterized by reduce lung volume making it difficult to fully expand to fill lungs with air [10].

Current burn mortality prediction models such as the Baux score utilize age, % total body surface area (TBSA) of burn, and presence of inhalation injury but do not account for pre-existing comorbidities such as respiratory diseases. The contribution of pre-existing chronic respiratory diseases (PCRD) on burn outcomes is currently undefined. We hypothesize that patients with PCRD will have an increased progression to mechanical ventilation and mortality following burn.

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 on medical comorbidities. Pre-existing comorbidities was obtained from information reported by patient, family, or others that intimately know the patient's history upon admission to the burn center. This are entered into the medical records. Subsequently, two dedicated burn registry nurses that collect, review and validate this data, enter the data into the University of North Carolina Burn Registry. The burn registry data is then uploaded to the National Trauma Data bank (NTDB) of the American College of Surgeons. It includes 27 different preinjury comorbidities. Smoking status for all the patients in the database was also recorded. 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 was based on history, physical examination, and/or bronchoscopic examination. The number of days on mechanical ventilation in the intensive care unit was included. All patients in the ICU were treated with the prevailing standard of care (i.e., ventilator management, fluid resuscitation, etc.) at a large academic burn center at the time of admission

To examine the effect of baseline medical comorbidities on outcome, a Charlson Comorbidity Index (CCI) score was calculated for each patient. The standardized Charlson Index has been reported to accurately predict the probability of mortality within 1 year for a number of medical conditions [11,12]. 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. The weighted sum of all comorbid conditions is the patient's Charlson score (Table 1). The CCI was also modified for this study to exclude respiratory disease to elicit the independent effect of respiratory disease on burn outcome. By removing pre-existing respiratory diseases from the CCI, we avoid controlling twice for respiratory disease in our cox proportional statistical analysis, as chronic respiratory disease was a separate independent variable. We validated the modified CCI by comparing the predictive probability of mortality of CCI with the mCCI and there was no statistical significant differences noted, as both were equally predictive (Supplementary material Figs. 1 and 2).

The outcomes of interest in this study included in-hospital mortality and need for mechanical ventilation. Patients who had withdrawal of care were included in the analysis as they

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

were admitted to the burn center. Older age (>70 years) and/or greater than 75% TBSA burn triggered a discussion with family on withdrawal care. The number of patients who had care withdrawn was small and not statistically significantly different in patients with or without PCRD.

Baseline patient and injury characteristics were compared between groups (Lived/Died) using Analysis of Variance for continuous variables and chi-squared for discrete variables. We employed both univariate and multivariate models to determine the relative influence of PCRD after controlling for covariates. To estimate the hazard of progression to mechanical ventilation and mortality, we used a multivariate cox regression model controlling for pertinent confounders (age, TBSA, mechanism of injury, presence of inhalation injury, comorbidities using CCI, and smoker status). 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

A total of 7640 patients were admitted during the study period and included in our analysis. The mean age was 32±22 years with a male predominance at 5244 (68%). Caucasians made up 3896 (51%) of the population. The most common burn mechanism was scald (n=3687, 49%) followed by flame injury (n=3453, 45%). The overall mean %TBSA for this population was 8.6±12% (Table 2). There was no significant difference in % TBSA based on race or sex. The mean hospital/ICU length of stay, and days of mechanical ventilation was 12.7±24.7 days, 5.1±20.2 days, and 3.2±15.8 days respectively ($p<0.001$). Burn patients with at least one comorbidity represented 40% of the population (n=3057). A total of 672 patients had pre-existing respiratory disease prior to burn. Chronic preexisting respiratory diseases included in this study were COPD (n=236, 35%), chronic bronchitis (n=43, 6%), emphysema (n=31, 5%), asthma (n=297, 44%), obstructive sleep apnea (n=68, 10%), sarcoidosis (n=8, 1%) and other (n=12, 2%). Concurrent smokers were 18% of burn cohort (n=1347).

3.1. *Respiratory disease*

A bivariate analysis was performed to compare patients with preexisting respiratory disease (PCRD) and without preexisting respiratory disease (NRD). The mean age for PCRD vs. NRD was 42.5±24.7 years and 30.9±21.9 years, respectively ($p<0.001$). There was a significant difference between the two groups with race and sex ($p<0.001$) but no difference was seen in % TBSA. PCRD patients had a higher modified CCI score (0.80 ±1.40) compared to NRD patients (0.30±0.86, $p<0.001$). Percentage of smokers for PCRD vs. NRD was 32% and 16%, respectively ($p<0.001$). Inhalation injury was higher in PCRD patients compared to NRD patients (15% vs. 7%, $p<0.001$). The crude mortality rate was higher for patients with PCRD (7% vs. 4%, $p<0.001$). Patients with PCRD had statistically significant increase in hospital-LOS (17.9±29.5 days vs. 12.1±24.0 days, $p<0.001$) and ICU-LOS stay (9.0±22.7 days vs. 4.7±19.9 days, $p<0.001$), and ventilator days (6.2 days vs. 2.9 days, $p<0.001$) compared to NRD patients (Table 3).

Table 2 – Patient characteristics.

Patient characteristics (n=7,640)	*n*	Mean (±SD) or %
Sex		
Male	5,244	69%
Female	2,396	31%
Age		
Overall		32.0 (±22.4)
Race		
White	3,896	51%
Other	3,742	49%
Type of burn		
Flame	3,426	45%
Scald	3,678	49%
Other	480	6%
Inhalation		
Inhalation injury	562	7%
No inhalation injury	7,078	93%
Charlson Comorbidity Index (CCI)		
Overall mean	7,640	0.906864 (±1.4)
		40%
TBSA		
Overall mean	7,640	8.6 (±12.0)
By sex		
Male	5,244	9.0 (±12.6)
Female	2,396	7.7 (±10.7)
Survival		
Overall	7,274	96%
By sex		
Male	5,017	96%
Female	2,257	94%
By race		
White	3,699	96%
Other	3,584	97%
ICU stay		
Overall mean		5.1 (±20.2)
Hospital stay		
Overall mean		12.7 (±24.7)
Mechanical ventilation		
Overall mean	956	3.2 (±15.8)

TBSA=total burn surface area.

A multivariate Cox regression model was utilized to determine increased hazard of progression to mechanical ventilation and mortality in the PCRD vs. NRD subgroups after adjusting for significant covariates on bivariate analysis. The estimated increased hazard of progression to mechanical ventilation was 21% higher (HR=1.21, 95% CI=1.01–1.44) for patients with PCRD compared to those without disease (Table 4 and Fig. 1). The estimated increased hazard of progression to mortality is 56% higher (HR=1.56 (NRD reference group), 95% confidence interval: 1.10–2.19) for patients with PCRD compared to NRD (Table 5). There is a continuous significant difference in mortality between the two groups starting at 60 days after adjusted the Kaplan Meier survival curve for significant covariates ($p<0.01$, Fig. 2).

4. Discussion

In this study, we have shown that burn patient with preexisting chronic respiratory comorbidities have an

Table 3 – Bivariate analysis of burn patients (with and without preexisting respiratory disease).

	Respiratory disease	No respiratory disease	p-Value
Age	42.5 (±24.7)	30.9 (±21.9)	<0.001
TBSA	8.4 (±11.6)	8.6 (±12.1)	0.789
mCCI	0.80 (±1.40)	0.30 (±0.86)	<0.001
Race			<0.001
White	58%	50%	
Other	42%	50%	
Sex			<0.001
Male	60%	70%	
Female	40%	30%	
Mechanism			<0.001
Flame	57%	44%	
Scald	39%	49%	
Other	4%	6%	
Smoker status			
Smoker	32%	16%	<0.001
Non-smoker	68%	84%	
Inhalation injury	15%	7%	<0.001
Mortality rate	7%	4%	<0.001
ICU stay	9.0 (±22.7)	4.7 (±19.9)	<0.001
LOS	17.9 (±29.5)	12.1 (±24.0)	<0.001
Mechanical ventilation	6.2 (±19.2)	2.9 (±15.4)	<0.001

TBSA = total body surface area.
mCCI = Charlson Comorbidity Index excluding preexisting respiratory diseases.

Table 4 – Multivariate Cox regression for mechanical ventilation in burn cohort.

Variable	Adjusted hazard ratio, 95% confidence interval (CI)	p-Value
Age	1.00 (0.99-1.00)	0.947
TBSA	0.99 (0.98-0.99)	<0.001
Mechanism		
Flame (reference group)		
Scald	0.74 (0.60-0.92)	0.005
Other	1.04 (0.78-1.38)	0.792
mCCI	0.91 (0.85-0.97)	0.002
Inhalation injury	1.36 (1.18-1.56)	<0.001
Smoker status	0.81 (0.68-0.96)	0.017
Respiratory disease	1.21 (1.01-1.44)	0.037

TBSA = total body surface area.
mCCI = Charlson Comorbidity Index excluding respiratory diseases.

increased estimated hazard of progression to mechanical ventilation and mortality compared to burn patients without pre-existing respiratory diseases after controlling for significant covariates. Furthermore, outcomes such as length of hospital/ICU stay and days on mechanical ventilation were significantly longer for patients who presented with a preexisting respiratory disease.

These findings are particularly relevant as some respiratory diseases are associated with increased risk of burn. Individuals with COPD on home oxygen are at increased risk of burn [12–14]. Sharma et al. found that the absolute risk of burn in patients prescribed oxygen therapy was 2.98 per 1000 patients compared with 1.69 per 1000 patients not prescribed oxygen during a 22-month period [15].

The only prior study evaluating the impact of preexisting comorbidities, including respiratory disease on in-hospital burn mortality utilized the National Burn Repository (NBR) on 31,338 burn records from 1995–2005. Though they showed that there was a significant increase crude mortality rate in patients with chronic pulmonary disease (14.3% vs. 6.6%, $p<0.001$) compared to those without chronic pulmonary disease, contrary to our findings, chronic pulmonary disease was not significant independent predictor of mortality but there was a trend toward greater risk of mortality as these patients tended to have additional medical comorbidities that may diminish its effect. Furthermore, similar to our study, hospital length of stay was longer (15.9 vs. 12.9, $p<0.001$) in

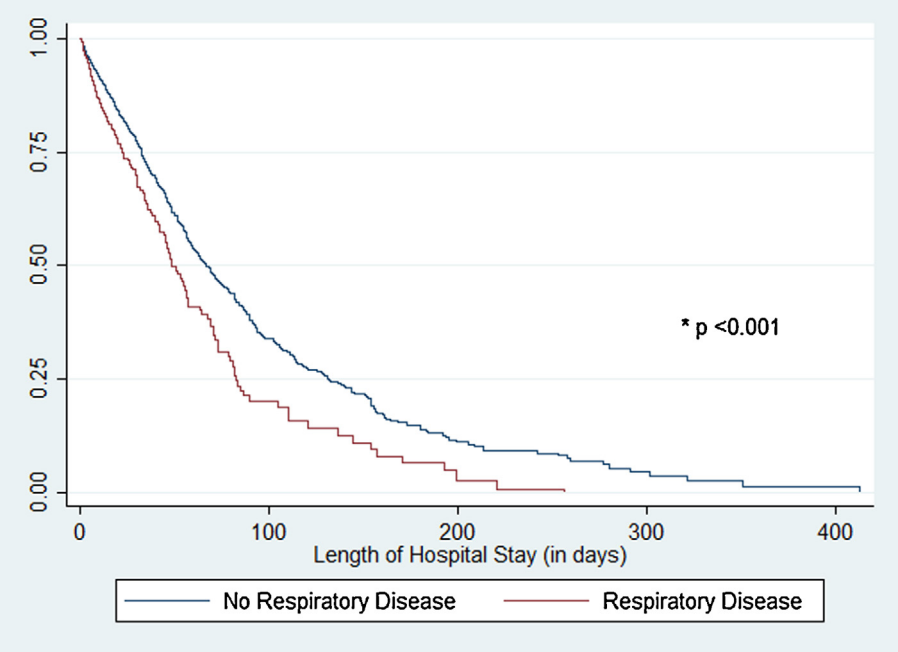

Fig. 1 – Adjusted Kaplan Meier curve for progression to mechanical ventilation comparing burn patients with and without pre-existing respiratory disease.

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

Variable	Adjusted hazard ratio, 95% confidence interval (CI)	p-Value
Age	1.05 (1.05–1.06)	<0.001
TBSA	1.06 (1.06–1.07)	<0.001
Mechanism		
Flame (reference group)		
Scald	0.54 (0.36–0.81)	0.003
Other	0.99 (0.50–1.96)	0.970
Mechanical ventilation	1.03 (1.02–1.04)	<0.001
ICU LOS	0.95 (0.94–0.96)	<0.001
mCCI	1.18 (1.09–1.28)	<0.001
Inhalation injury	1.95 (1.49–2.56)	<0.001
Smoker status	0.63 (0.44–0.91)	0.014
Respiratory disease	1.56 (1.10–2.19)	0.011

TBSA = total body surface area.
ICU LOS = intensive care unit length of stay.
mCCI = Charlson Comorbidity Index excluding respiratory diseases.

those with chronic pulmonary disease compared to patients without [16].

Majority of patients included in our study had preexisting obstructive pulmonary disease. The association between thermal burns and respiratory insufficiency is well established. There are several different mechanisms in the pathogenesis of the pulmonary complications that may be more pronounced on patients with preexisting respiratory disease and some these are time dependent. It is well known that direct heat injury to the lungs is not a major cause of lung injury in burn patients as direct burn to the respiratory tract below the larynx is unusual [17], however, the products of combustion are toxic to the airways and result in bronchospasm coupled with a diminished mucociliary clearance in the presence of preexisting obstructive airway disease may contribute to the increased mortality [18].

In burn patients with preexisting chronic respiratory disease, any associated decreased chest wall movements secondary to eschar, pain, narcotic use and altered mental status will result in shallow breathing and gradual alveolar collapse, decreased functional residual capacity and ultimately decreased lung compliance and shunting [19,20]. Furthermore, depending on the burn size and presence of inhalation injury, toxin induced chemical pulmonary edema and lack of a balanced fluid resuscitation approach may lead to increased lung water [21].

Lastly, Infectious complications are a constant threat to thermally injured patients during hospitalizations and are a

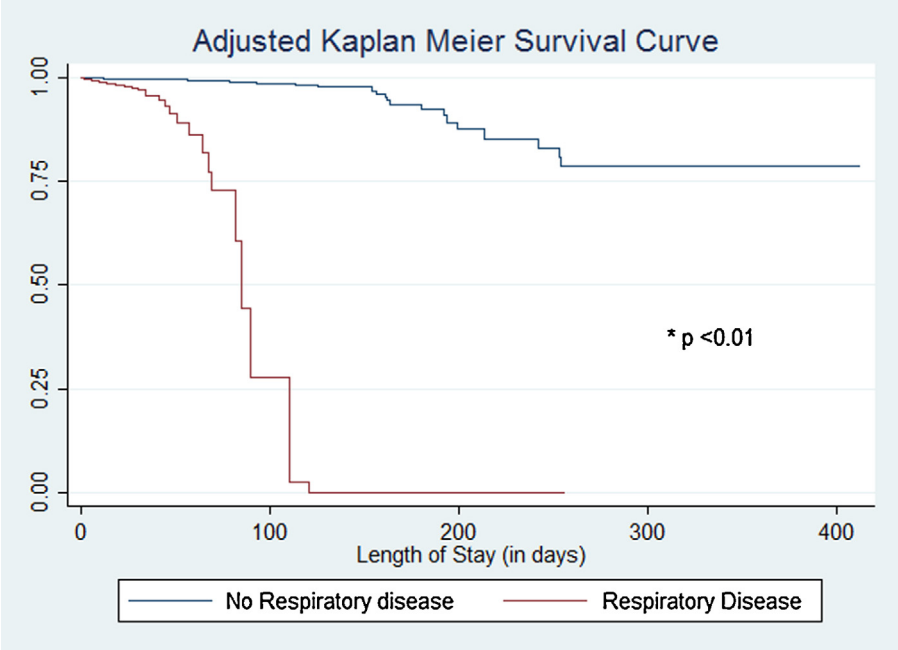

Fig. 2 – Adjusted Kaplan Meier survival curve comparing burn patients with and without pre-existing respiratory disease.

predominant cause of death. Most of the infections that develop in burn patients are nosocomial and of a pulmonary etiology. The etio-pathogenesis of pneumonia in a burn patient is multifactorial. Severely burned patients who require mechanical ventilation with or without inhalation injury have an increased pneumonia rates because of serious immunosuppression after the burn trauma [22]. Also, aspiration of contaminated oropharyngeal secretions is the first step in the pathogenesis of lower airways infections. *S. pneumoniae, H. influenzae,* and *S. aureus* are the classic community-acquired bacteria carried in the oropharynx of previously healthy individuals. They are the microorganisms involved in primary endogenous pneumonia [23]. Bacteria that most commonly cause ventilator-associated pneumonia is *Pseudomonas aeruginosa* with a prevalence of 4% [24] and mortality rate of 13.5% despite appropriate antibiotics [25]. Known risk factors for *P. aeruginosa* infections are prior antibiotic exposures and duration on mechanical ventilation greater than 5 days [26].

Patients with pre-existing respiratory diseases are certainly more susceptible to pneumonia. Previous studies have found the in-hospital mortality rate to be between 20–30% for patients requiring mechanical ventilation for COPD exacerbation [27–30]. In addition, patients with COPD have been found to have high neutrophil, macrophages, and $CD8^+$ T cells in the lungs. This creates an imbalance of pro-inflammatory and protective mediators normally found in healthy individuals as these cells release inflammatory cytokines and proteases [31–33]. Obstructive lung disease that develop with increasing age and the additive effect on immune system dysfunction in older individuals with preexisting chronic respiratory disease may be partly responsible for the increase susceptibility to pulmonary infections and/or increase mortality following burn.

The increased hazard for mortality cannot be attributed to mechanical ventilation alone and there has to be additional mechanism for the increased hazard for mortality in patients with PRCD. We postulate that in this patient population, the increased pathology of the underlying chronic respiratory disease e.g., Sarcoidosis or COPD and indeed the necessary therapeutic strategies e.g., chronic steroid use within the burn milieu are contributory. Furthermore, frailty is an important component in these patient that may be additive.

Strategies to mitigate the poor outcomes in the subset of burn patients with preexisting respiratory disease should be based on maximal medical therapy of the underlying respiratory disease. Additional steps include reducing pulmonary complications of burn and therapy. Close attention to preventing airway obstructions secondary to edema, sloughed mucosa and bronchospasm is essential. Preventing pulmonary edema with a balanced resuscitation strategy aimed at guaranteeing stable macro- and micro-hemodynamics, while avoiding excessive interstitial fluid overload is especially important in these patients. This can be achieved using a goal directed resuscitation strategy that utilizes both clinical variables such as vital signs, mean arterial pressure, urine output and hemodynamic monitoring adjuncts that combine pulse contour analysis and trans-pulmonary thermodilution technique. Also transthoracic/esophageal echocardiogram can help guide volume status [34]. For intubated patients, frequent endotracheal suctioning and therapeutic bronchoscopy may be necessary as is the use of bronchodilators. Preventing atelectasis with lung recruitment maneuvers is often necessary. Prevention of ventilator associated pneumonia and culture guided use of antibiotics must be instituted early.

The limitations of this study are those inherent to any study with a retrospective methodology. Though this is a single

center study, our sample size was robust enough not to affect the generalizability of our findings. The pre-existing comorbidities were abstracted from documented diagnosed based on ICD-9 codes and hence subject to interpretation. The contribution of frailty and its effect on to outcome was not evaluated. All respiratory diseases were groups were categorized as one entity and the individual contribution of each individual respiratory diseases and its weight on burn mortality was not analyzed. Lastly, we acknowledge that over the study period, ventilatory management has evolved with low tidal strategies and targeted use of neuromuscular blockade and we cannot entirely control for these variables. Dichotomization of our dataset into two time periods 2001–2009 and 2010-2012 did not diminish the independent effect of preexisting chronic respiratory disease on burn mortality

5. Conclusion

Preexisting chronic respiratory disease significantly increases the hazard of progression to mechanical ventilation and mortality in patients following burn. These findings re-emphasizes the need for the inclusion of comorbidities in any burn mortality prediction models so as to better inform burn mortality prognostication. Given the increasing number of Americans with acute or chronic respiratory diseases, there will likely be a greater number of individuals at risk for worse outcomes following burn.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.burns.2016.08.029.

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