Smoking is associated with an improved short-term outcome in patients with rib fractures

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Abstract

Background Smokers with cardiovascular disease have been reported to have decreased mortality compared to non-smokers. Rib fractures are associated with significant underlying injuries such as lung contusions, lacerations, and/or pneumothoraces. We hypothesized that blunt trauma patients with rib fractures who are smokers have decreased ventilator days and risk of in-hospital mortality compared to non-smokers.

Study design The Trauma Quality Improvement Program (2010–2016) was queried for patients presenting with a blunt rib fracture. Patients that died within 24 h of admission were excluded. A multivariable logistic regression model was performed.

Results From 282,986 patients with rib fractures, 57,619 (20.4%) were smokers. Compared to non-smokers with rib fractures, smokers had a higher median injury severity score (17 vs. 16, $p < 0.001$). Smokers had a higher rate of pneumonia (7.5% vs. 6.6%, $p < 0.001$), however, less ventilator days (5 vs. 6, $p = 0.04$), and lower in-hospital mortality rate (2.3% vs. 4.6%, $p < 0.001$), compared to non-smokers. After controlling for covariates, smokers with rib fractures were associated with a decreased risk for in-hospital mortality compared to non-smokers with rib fractures (OR 0.64, 0.56–0.73, $p < 0.001$).

Conclusion Despite having more severe injuries and increased rates of pneumonia, smokers with rib fractures were associated with nearly a 40% decreased risk of in-hospital mortality and one less ventilator day compared to non-smokers. The long-term detrimental effects of smoking have been widely established. However, the biologic and pathophysiologic adaptations that smokers have may confer a survival benefit when recovering in the hospital from chest wall trauma. This study was limited by the database missing the number of pack-years smoked. Future prospective studies are needed to confirm this association and elucidate the physiologic mechanisms that may explain these findings.

Keywords Trauma · Smoking · Nicotine · Mortality · Pneumonia

Introduction

Smoking continues to be a top public health epidemic. Although there has been a significant decline in per capita consumption of smoking tobacco, almost 25 trillion cigarettes have been consumed since the 1960s [1]. More than 30% of avoidable lung cancers and cardiac deaths have been attributed to smoking [2, 3]. For each person in the United States that succumbs to the ill effects of smoking, there are two new, young replacement smokers [4]. The prevalence of smoking is greatest in those with lower education, lower socioeconomic status, mental illness, and racial minority groups [5]. However, smoking does not uniformly and consistently affect all patient groups the same. More than 30 years ago, Kelly et al. reported lower mortality rates in patients with acute myocardial infarction who smoke

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compared to non-smokers [6]. This phenomenon, termed the “smoker’s paradox”, has been demonstrated in multiple subsequent studies on cardiovascular disease [7–9]. The mechanism is postulated to be multifactorial and related to changes in oxygen delivery, endothelial function, enhanced thrombolysis and inflammation; however, no conclusive data have been reported [10, 11].

Patients with fatal cardiac disease often have inadequate delivery and utilization of oxygen and the pathophysiologic adaptations in smokers may provide a survival benefit in this regard [12, 13]. Similarly, trauma patients have significant morbidity and mortality resulting from hypoxemia secondary to hypovolemia, hypotension, and/or respiratory failure [14, 15]. Thus, the trauma population, in which there is a high smoking prevalence ranging from 22 to 43%, may similarly benefit from the smoker’s paradox [16, 17]. Ferro et al. reported that trauma patients who smoke had no difference in the rate of sepsis, respiratory complications, multiorgan failure, or mortality compared to non-smokers [17]. In a subsequent study, using a large national database, Bell et al. demonstrated that trauma patients aged ≤ 65 years who smoke have a significantly less risk of mortality and major complications compared to non-smokers [18]. Both these studies included patients with a wide spectrum of injuries. Trauma patients involved in mechanisms severe enough to cause a rib fracture often have underlying lung damage (contusion, laceration, and/or pneumothorax) with subsequent pulmonary morbidity [19, 20]. The smoker’s paradox has not been evaluated in patients with rib fractures. We hypothesized that blunt trauma patients with rib fractures who are smokers have decreased ventilator days and associated with a decreased risk of mortality compared to non-smokers. We also sought to confirm the smoker’s paradox in a subset of patients with coronary artery disease (CAD).

Methods

This study was approved by the Institutional Review Board at the University of California, Irvine. A retrospective analysis of the Trauma Quality Improvement Program (TQIP) was performed between January 2010 and December 2016. All patients ≥ 18 years of age with one or more rib fractures after blunt trauma were identified using the International Classification of Diseases version-9 (ICD-9) diagnosis codes: 807–807.19 and 807.4. Patients that were current smokers were compared to non-smokers. This is listed as one of the 30-required comorbidities to be reported in the TQIP and is defined as “A patient who reports smoking cigarettes every day or some days within the last 12 months. Exclude patients who smoke cigars or pipes or use smokeless tobacco (chewing tobacco or snuff).” The primary outcomes were ventilator days and in-hospital mortality. Secondary outcomes

included total hospital length of stay (LOS), intensive care unit (ICU) LOS, blood products transfused, thoracotomy for hemorrhage control, and in-hospital complications including pneumonia, acute kidney injury (AKI), and acute respiratory distress syndrome (ARDS).

Demographic variables collected included age, comorbidities, gender, the lowest systolic blood pressure within 24 h of admission, injury severity score (ISS), incidence of associated lung or heart injuries, flail chest, and abbreviated injury scale (AIS) for the head, spine, thorax and abdomen. Lung or cardiac injuries were identified by the appropriate ICD-9 diagnosis codes. Lung injuries were defined as lung contusion, laceration, pneumothorax, and/or hemothorax. All variables were coded as present or absent. Frequency statistics were performed for all variables. A Student’s *t* test or Mann–Whitney *U* test was used to compare continuous variables and Chi square was used to compare categorical variables for bivariate analysis. Categorical data were reported as percentages, and continuous data were reported as medians with interquartile range or as means with standard deviation.

The magnitude of the association between predictor variables and mortality was first measured using a univariable logistic regression model. Covariates were chosen based on a review of the literature and included hypotension (systolic blood pressure ≤ 90 mmHg) within 24 h, age ≥ 65 years, ISS ≥ 25 , massive blood product transfusion (≥ 6 units of packed red blood cells within 4 h), severe (grade > 3) AIS for the head, spine, thorax, abdomen, in-hospital AKI, pneumonia, ARDS, thoracotomy, and history of diabetes, hypertension, chronic obstructive pulmonary disease (COPD), and cerebrovascular accident (CVA). Covariates with statistical significance ($p < 0.20$) were included in a hierarchical multivariable logistic regression model and the adjusted risk for mortality was reported with an odds ratio (OR) and 95% confidence intervals (CI). The reference group used in our analysis included blunt trauma patients with one or more rib fractures who were non-smokers. We also performed a subset analysis on patients with coronary artery disease (CAD), defined by those with history of myocardial infarction or angina within the previous 30 days. All *p* values were two sided, with a statistical significance level of < 0.05 . All analyses were performed with IBM SPSS Statistics for Windows (Version 24, IBM Corp., Armonk, NY, USA).

Results

Demographics and primary outcomes

From 282,986 patients with rib fractures, 57,619 (20.4%) were smokers and 225,367 (79.6%) were non-smokers. Compared to non-smokers, those who smoked were younger

(median age, 48 versus 54 years, $p < 0.001$), more often male (75.3% versus 66.8%, $p < 0.001$), and had a higher median ISS (17 versus 16, $p < 0.001$). The smoker group had lower rates of diabetes (9.2% versus 13.6%, $p < 0.001$) and hypertension (25.4% versus 33.6%, $p < 0.001$), but a higher rate of COPD (11.7% versus 6.6%, $p < 0.001$), compared to non-smokers. They also had a higher rate of associated lung injuries (63.3% versus 59.9%, $p < 0.001$), similar rate of flail chest ($p = 0.94$), cardiac injuries ($p = 0.18$), and a lower rate of multiple rib fractures (83.0% versus 83.4%, $p = 0.01$), compared to non-smokers (Table 1). Smokers had less ventilator days (median, 5 versus 6, $p = 0.009$) and a lower rate of in-hospital mortality (2.2% versus 4.6%, $p < 0.001$), compared to non-smokers. In a subset of patients with CAD ($n = 3870$), the in-hospital mortality rate was lower in smokers compared to non-smokers (5.0% versus 7.7%, $p = 0.018$) but both groups had similar ventilator days (median, 6 days, $p = 0.60$).

Risk of mortality in trauma patients with rib fracture

In a univariable logistic regression model, smoking was associated with a lower in-hospital mortality risk (OR 0.48, CI 0.45–0.51, $p < 0.001$). The strongest variable associated with in-hospital mortality was AKI (OR 12.38, CI

11.60–13.21, $p < 0.001$), followed by severe AIS of the head (OR 7.26, CI 7.00–7.54, $p < 0.001$). After adjusting for covariates in a multivariable logistic regression model, smoking was found to be independently associated with a lower risk for in-hospital mortality (OR 0.64, CI 0.56–0.73, $p < 0.001$). The strongest independent risk factor associated with an increased risk of in-hospital mortality remained AKI (OR 6.57, CI 5.60–7.70, $p < 0.001$) followed by severe AIS of the head (OR 4.79, CI 4.33–5.29, $p < 0.001$) (Table 2). In a subset of patients with CAD, the risk for in-hospital mortality was similar (OR 0.51, CI 0.10–2.58, $p = 0.42$).

Other clinical outcomes in trauma patients with rib fractures

Compared to non-smoking blunt trauma patients with rib fractures, smokers had no difference in median total hospital LOS ($p = 0.16$) or ICU LOS ($p = 0.37$). The smoking cohort required less red blood cells (RBCs) transfused within 4 h of admission (mean, 3.4 versus 4.1 units, $p < 0.001$), and had no difference in the rate of thoracotomies required for hemorrhage control ($p = 0.09$). Compared to non-smokers, those who smoked had a higher rate of pneumonia (7.5% versus 6.6%, $p < 0.001$) and a trend towards a lower rate of ARDS (2.2% versus 2.3%, $p = 0.06$).

Table 1 Demographics of adult blunt trauma patients with rib fractures

Characteristic	Non-smoker ($n = 225,367$)	Smoker ($n = 57,619$)	p value
Age, year, median (IQR)	54.0 (39, 68)	48.0 (34, 57)	< 0.001
Male, n (%)	150,576 (66.8%)	43,383 (75.3%)	< 0.001
ISS, median (IQR)	16.0 (10, 22)	17.0 (11, 22)	< 0.001
Lowest SBP within 24 h, median (IQR)	71.0 (35, 96)	66.0 (35, 94)	< 0.001
Multiple (≥ 2) rib fractures, n (%)	188,041 (83.4%)	47,817 (83.0%)	0.01
Flail chest, n (%)	10,684 (4.7%)	2727 (4.7%)	0.94
Comorbidities, n (%)			
Congestive heart failure	6555 (2.9%)	864 (1.5%)	< 0.001
End-stage renal disease	1920 (0.9%)	270 (0.5%)	< 0.001
Diabetes	30,682 (13.6%)	5286 (9.2%)	< 0.001
Hypertension	75,660 (33.6%)	14,644 (25.4%)	< 0.001
History of myocardial infarction	2997 (1.3%)	594 (1.0%)	< 0.001
Angina in previous 30 days	315 (0.1%)	50 (0.1%)	0.06
COPD	14,784 (6.6%)	6716 (11.7%)	< 0.001
AIS (grade > 3), n (%)			
Head	34,842 (15.5%)	7018 (12.2%)	< 0.001
Spine	4315 (1.9%)	1099 (1.9%)	0.91
Thorax	38,216 (17.0%)	9303 (16.1%)	< 0.001
Abdomen	10,934 (4.9%)	3006 (5.2%)	< 0.001
Associated injuries, n (%)			
Lung	135,003 (59.9%)	36,464 (63.3%)	< 0.001
Heart	2575 (1.1%)	620 (1.1%)	0.18

ISS injury severity score, IQR interquartile range, SBP systolic blood pressure, COPD chronic obstructive pulmonary disease, AIS abbreviated injury scale

Table 2 Multivariable logistic regression analysis for risk of mortality in adult blunt trauma patients with rib fractures

Risk factor	OR	CI	p value
Smoker	0.64	0.56–0.73	<0.001
Hypotensive (SBP < 90 mmHg) within 24 h	1.14	1.03–1.27	0.011
Age	1.03	1.03–1.03	<0.001
ISS $\geq$ 25	3.45	3.07–3.88	<0.001
PRBC transfusion $\geq$ 6 units within 4 h	2.24	1.98–2.53	<0.001
Peripheral vascular disease	1.78	0.97–3.26	0.061
End-stage renal disease	2.78	1.84–4.20	<0.001
Diabetes	1.23	1.07–1.42	0.004
Hypertension	0.74	0.66–0.83	<0.001
Chronic obstructive pulmonary disease	1.14	0.95–1.37	0.160
Severe AIS-abdomen (grade > 3)	0.88	0.77–1.00	0.052
Severe AIS-thorax (grade > 3)	1.33	1.20–1.47	<0.001
Severe AIS-head (grade > 3)	4.79	4.33–5.29	<0.001
Severe AIS-spine (grade > 3)	1.35	1.10–1.67	0.004
Acute kidney injury	6.57	5.60–7.70	<0.001
Pneumonia/VAP	0.50	0.44–0.57	<0.001
Acute respiratory distress syndrome	2.24	1.88–2.67	<0.001
Thoracotomy for hemorrhage control	2.24	1.64–3.05	<0.001
Male	1.17	1.06–1.29	0.002

SBP systolic blood pressure, ISS injury severity score, PRBC packed red blood cell transfusion, VAP ventilator-associated pneumonia, AIS abbreviated injury scale

Discussion

This retrospective analysis using 7 years of data from the TQIP found the prevalence of smoking in blunt trauma

patients with rib fractures to be 20%. Interestingly, the smoker's paradox exists in this population as we found smokers with rib fractures to be associated with nearly a 40% decreased risk of in-hospital mortality compared to non-smokers, even after controlling for many well-known risk factors of mortality in trauma. Additionally, we found smokers to require one less ventilator day compared to non-smokers. The rate of pneumonia was higher in smokers (Table 3).

Smokers with cardiovascular disease have been demonstrated to have improved outcomes compared to non-smokers with cardiovascular disease in multiple reports [6–9]. Our study suggests the smoker's paradox may also exist in blunt trauma patients with rib fractures that are recovering in the hospital. Interestingly, in a subset analysis of these patients with CAD, smoking did not confer a survival advantage after controlling for covariates. Rib fracture patients have three primary issues: (1) impaired gas exchange; (2) impaired breathing mechanics; and (3) hypoventilation/atelectasis due to pain [21]. There are several mechanisms to help explain our findings. Nicotine, a key component in most cigarettes sold in the United States, causes an increase in the activation of the sympathetic nervous system. The resultant catecholamine surge can increase the heart rate, blood pressure, and cardiac contractility—changes that may be beneficial in trauma patients presenting with hypovolemic shock and/or respiratory failure [22]. Additionally, nicotine potentiates systemic vasoconstriction which may reduce blood loss and improve blood pressure and tissue oxygen delivery [23]. This theory is supported in our findings as smokers required fewer RBCs transfused within 4 h of admission despite having a lower median SBP. In pulmonary vasculature, nicotine acts as a vasodilator which can further improve oxygen

Table 3 Clinical outcomes in adult blunt trauma patients with rib fractures

Outcome	Non-smoker (n = 225,367)	Smoker (n = 57,619)	p value
LOS, days, median (IQR)	6.0 (3, 11)	6.0 (3, 11)	0.16
ICU, days, median (IQR)	4.0 (2, 9)	4.0 (2, 9)	0.37
Ventilator, days, median (IQR)	6.0 (2, 13)	5.0 (2, 12)	0.04
PRBC units transfused within 4 h, mean (SD)	4.1 (5)	3.4 (4)	<0.001
Thoracotomy for hemorrhage control, n (%)	286 (0.1%)	57 (0.1%)	0.09
Respiratory complications, n (%)			
Pneumonia/VAP	14,825 (6.6%)	4312 (7.5%)	<0.001
Acute respiratory distress syndrome	5226 (2.3%)	1260 (2.2%)	0.06
Disposition, n (%)			
Home	135,200 (63.4%)	40,972 (74.1%)	<0.001
Acute care rehabilitation	49,201 (23.1%)	9863 (17.8%)	<0.001
Hospice	1067 (0.5%)	137 (0.2%)	<0.001
Skilled nursing facility	27,640 (13.0%)	4308 (7.8%)	<0.001
Mortality, n (%)	10,414 (4.6%)	1304 (2.3%)	<0.001

LOS length of stay, IQR interquartile range, SD standard deviation, ICU intensive care unit, PRBC packed red blood cells, VAP ventilator-associated pneumonia

utilization and alleviate the effects of pulmonary hypertension in critically ill patients [24]. Finally, although nicotine can cause chronic pain disorders, it may potentially decrease the severity of acute pain [25]. This physiologic adaptation would be beneficial in patients with parietal chest wall pain secondary to rib fractures allowing for deep breathing exercises and thereby improved oxygenation.

Smoking promotes both inflammatory and anti-inflammatory effects. Smoking one cigarette exposes the respiratory tract to 15,000–40,000 μg of particulate matter [26]. This results in oxidant stress and activation of inflammatory mediators, cytokines, and neutrophils with heightened local immune function [27]. In a non-injured patient, these changes over time result in a wide range of adverse sequelae including the destruction of alveolar walls, emphysematous changes, and COPD [28, 29]. As expected, our study demonstrated a significantly larger incidence of COPD in the smoking group. In the injured patient, these adaptations may confer a survival benefit. In the lung, catecholamines can function as immunomodulators of innate and adaptive immune cells including alveolar macrophages which can result in anti-inflammatory immune responses [30–32]. Our study supports this as we found smokers to require one less ventilator day and had a trend towards a lower rate of ARDS compared to non-smokers, although the latter finding was not statistically significant. This conflicts with prior reports demonstrating increased incidence of ARDS in smokers presenting after blunt trauma [33, 34]. Resnick et al. reported that trauma patients who smoke admitted to a level I center to spend more days on a mechanical ventilator, compared to non-smokers [35]. However, these studies focused on all critically ill patients presenting after severe trauma suggesting that smoking may not confer a similar mortality benefit for all non-thoracic injuries. Future prospective studies are needed to determine risk of ARDS in a generalizable trauma population and evaluate for potential pathophysiologic differences between smokers and non-smokers with ARDS.

Several predictors of mortality have been identified for blunt trauma patients presenting with rib fractures. These include age ≥ 65 years, hemopneumothorax, extremity fractures, and head injuries [36, 37]. However, these studies, as well as a large systematic review and meta-analysis, which reported the predictors of mortality in patients with chest wall trauma, did not address how smoking affects mortality [38]. Our study is the first to demonstrate smoking to be associated with a significantly lower rate of in-hospital mortality in blunt trauma patients with rib fractures. While the intricacies of this association will need to be examined in the laboratory, there is a possible explanation. The leading cause of death in trauma patients surviving the initial resuscitation is sepsis and multiorgan failure [39]. Although this involves a complex interplay of inflammatory mediators, receptors and cytokines, none have proved to be a useful

clinical target for intervention [40, 41]. Nicotine is considered a strong agonist for the α -7 nicotinic acetylcholine receptor (α 7NAR), and has been demonstrated to attenuate the febrile response to lipopolysaccharide promoting an anti-inflammatory effect [42]. In mouse models, nicotine activating α 7NAR has been demonstrated to improve survival in mice induced with sepsis by cecal ligation and puncture [43]. In vivo, nicotine attenuates cytokine release from macrophages improving survival in experimental models of sepsis suggesting a potential target to be exploited in the treatment of inflammatory disorders [44]. While we would not advocate for patients to smoke to prevent worse outcomes after trauma, future basic science research is needed to evaluate which components of smoking contribute to the protective effect that smoking confers to patients with rib fractures. This may allow the development of medications that augment respiratory and/or inflammatory pathophysiology in a protective manner.

Our study involves a large national database with multiple participating trauma centers; therefore, a reporting bias and coding errors are undoubtedly present. Furthermore, as a database, there were pertinent missing variables including the severity of rib fractures, such as whether the fractures were displaced or not, baseline arterial blood gas results, as well as pulmonary functional status (i.e., baseline incentive spirometer or pulmonary function testing) and interventions for analgesia such as rib fixation or an epidural catheter. In addition, limitations of the database included the number of cigarettes smoked daily as well as how many pack-years of smoking were present. Also, although the non-smoking group had not smoked within the past 12 months, the percentage of ex-smokers in this group is not available within the database. We were also not able to determine if nicotine was in the system at the time of trauma and if any changes were a result of acute nicotine withdrawal as use of nicotine-replacement therapy is also not available within the database. The cause of death is not available with the TQIP database and only information pertaining to the index-hospitalization is available. As such, we are unable to report 30-day outcomes.

Conclusion

Despite having more severe injuries and increased rates of pneumonia and hypotension, smokers with rib fractures were associated with nearly a 40% decreased risk of in-hospital mortality compared to non-smokers. Additionally, they required one less ventilator day and had no difference in total and ICU LOS. The long-term detrimental effects of smoking have been widely established. However, biologic and pathophysiologic adaptations that smokers develop may provide a survival benefit when recovering from rib fractures

after blunt trauma. Future prospective studies are needed to confirm this association, as well as basic science studies to elucidate the physiologic mechanisms that may explain these findings and develop therapeutic interventions without the long-term deleterious effects of cigarette smoking.

Compliance with ethical standards

Conflict of interest Areg Grigorian, Michael Lekawa, Matthew Dolich, Sebastian D Schubl, Andrew R Doben, Cathertine M Kuza, Cristobal Barrios, and Jeffry Nahmias declare that they have no conflict of interest.

Ethical statement This research involved humans. However, since this retrospective study was performed using a national database with de-identified patients, risk to participants is minimal. There is no consent required.

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