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Original investigation

"Smoker's Paradox" in Patients Treated for Severe Injuries: Lower Risk of Mortality After Trauma Observed in Current Smokers

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Abstract

Background: Studies evaluating the effect of smoking status on mortality outcomes in trauma patients have been limited, despite the fact that survival benefits of smoking have been reported in other critical care settings. The phenomenon "smoker's paradox" refers to the observation that following acute cardiovascular events, such as acute myocardial infarction and cardiac arrest, smokers often experience decreased mortality in the hospital setting. The objective of our study was to determine whether smoking imparts a survival benefit in patients with traumatic injuries.
Methods: We performed a retrospective cohort study that analyzed cases included in the National Trauma Data Bank research dataset. Hierarchical logistic regression analyses were used to determine whether smoking alters the risk of mortality and complications in patients who smoke.
Results: The percentage of patients experiencing mortality differed significantly between smokers (n = 38,564) and nonsmokers (n = 319,249) (1.8% vs. 4.3%, $P < .001$); however, the percentage experiencing a major complication did not (9.7% vs. 9.6%, $P = .763$). Regression analyses indicated that smokers were significantly less likely to die during the hospital stay compared to nonsmokers after adjusting for individual and hospital factors (OR = 0.15; CI = 0.10, 0.22). Additionally, smokers were also less likely to develop a major complication than nonsmokers (OR = 0.73, CI = 0.59–0.91).
Conclusions: Patients who smoke appear to have a much lower risk of in-hospital mortality than nonsmokers. Further investigation into biological mechanisms responsible for this effect should be carried out in order to potentially develop therapeutic applications.

Introduction

In the cardiology literature, the term "smoker's paradox" refers to the counterintuitive observation that following acute myocardial infarction smokers often experience decreased mortality in the hospital setting.[1–4] Over the past 25 years, additional studies have found that smoking has protective effects against in-hospital mortality in patients who experience cardiac arrest, stroke, and heart failure.[5–9] The biologic mechanisms responsible for the smoker's paradox are underdetermined. However, laboratory studies have proposed that changes in endothelial function, enhanced thrombolysis, induced inflammation, faster epicardial flow, and remodeling of cardiac gap junctions are plausible explanations for the smoking paradox.[10–14]

In the trauma setting, the effect of smoking status on mortality outcomes in trauma patients has not been well studied.[15] Considering that both traumatic injury and acute cardiac events' lethality often results from inadequate levels of oxygen delivery and utilization at the cellular level, the survival benefit of smoking on mortality outcomes in cardiac patients may be present in the injured patient population as well. However, some studies have reported that smoking increases the risk of certain complications following injury, which could negate any survival benefits.[16,17]

The objective of our study was to determine whether smoking imparts a survival benefit in patients with traumatic injuries. We hypothesized that smoking status would be a significant predictor

of in-hospital mortality following trauma. We also hypothesized that although smoking would be associated with a reduced risk of in-hospital mortality, it would be associated with increased risk of developing a major complication.

Methods

Data Source

We performed a retrospective cohort study that analyzed cases included in the National Trauma Data Bank (NTDB) research data set from years 2008–2010. Trauma centers that treated at least 200 patients per year were included in the study. Due to variation in the quality of reporting comorbidity and complication data by hospitals in the NTDB, we limited the analysis to centers that reported comorbidity data for a minimum of 80% of patients and at least one pneumonia or urinary tract infection. Two-hundred seventy-nine trauma centers were included in the analysis.

Patients between the ages of 18 and 64 with an Injury Severity Score (ISS) of 9 or greater were included in the analysis.[18] ISS is calculated by dividing the body into six regions (head/neck, face, chest, abdomen, extremities, and external). Each region is given a score of 1–6 based on injury severity, with 6 being an unsurvivable injury. ISS is calculated by taking the three most severely injured body regions and squaring the injury scores. ISS can range from 1 to 75, since patients with scores of 6 often do not receive life-preserving care due to the futility of medical treatment. The "Abbreviated Injury Scale only" patients with a principal diagnosis of trauma were included and those admitted with poisoning, drowning, burns, suffocation, overexertion, and environmental causes were excluded from the study. Patients that were dead on arrival or died in the emergency department were also excluded from analysis. A total of 391,190 patients were included in the analysis.

Outcome Variables

The two outcomes we examined were major complication and mortality. Major complications were defined as acute respiratory distress syndrome, acute renal failure, cardiovascular complications (cardiac arrest, myocardial infarction, and cerebrovascular accident), pulmonary embolism, organ/surgical site infection, pneumonia, or systemic sepsis. Mortality included only in-hospital deaths.

Statistical Analysis

We calculated means, medians, and standard deviations for continuous variables and frequencies are reported for categorical variables. Associations between patient characteristics and outcomes were examined using chi-square and *t* tests. All tests were two tailed tests with alpha set to 0.05.

Hierarchical logistic regression was used to determine patient odds ratios of complication and mortality for smokers and nonsmokers. The models incorporated hospital as a random effect in order to account for within-hospital correlation. We controlled for patient age, gender, race/ethnicity, insurance status, number of comorbidities, type of injury, ISS, head injury (Glasgow Coma Score motor score), and hypotension in both the complication and mortality models. The mortality model also included major complication as a covariate. In addition to patient-level covariates, we controlled for hospital characteristics including safety net status, as defined by the Agency for Healthcare Quality and Research, and annual patient volume, in order to account for hospital resources and provider experience.[19] Lastly we investigated interaction effects between smoking status and all other covariates. Interaction terms between smoking status and age, as well as smoking status and hypotension were significant and included in the final models. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

Because cases in the NTDB are often missing demographic, comorbidity, physiologic and outcome data, we performed multiple imputation using the SAS procedure MI to minimize potential bias from missing data.[20] Multiple imputation simulates a set of plausible values for missing data in order to account for uncertainty about the correct value to impute.[21] After creating five imputed datasets, we used the procedure MIANALYZE to pool results from the regression analyses. We performed a sensitivity analysis comparing results from an analysis using only the original dataset with only the observed values with results from the imputed dataset. We found no substantial differences in estimates. We present only results obtained from analyses using the imputed dataset.

Results

Descriptive analyses indicated that patients who smoked differed significantly from those who did not smoke on nearly every covariate included in the analysis. On average, patients who smoked were younger (mean age 39.0 vs. 39.8), more likely to be male (76.3% vs. 72.7%), more likely to be White (81.8% vs. 76.4%), and less likely to have private insurance (26.8% vs. 36.6%). Smokers also had lower injury severity scores on average (mean 15.6 vs. 16.4) and fewer experienced hypotension (3.2% vs. 3.8%). The percentage of patients experiencing in-hospital mortality was significantly lower in smokers (1.8% vs. 4.3%), however the percentage of complications was not (9.7% vs. 9.6%, Table 1).

Hierarchical logistic regression analyses found that smokers were significantly less likely to die during the hospital stay compared to nonsmokers (*OR* = 0.15, CI = 0.10, 0.22). Additionally, smokers were also less likely to develop a major complication than nonsmokers (*OR* = 0.73, CI = 0.59–0.91). Insurance status, injury severity, mechanism of injury, hypotension, Glasgow Coma Score motor score, and complication were also significantly associated with mortality. For complication analyses, we found that insurance status, gender, mechanism of injury, hypotension, and Glasgow Coma Score motor score were predictive of developing a major complication. Our model also controlled for two hospital-level characteristics, safety-net status, and annual patient volume. Safety-net status did not predict either of the outcomes that we studied, however, volume did. Higher patient volumes were associated with reduced likelihood of death, but increased likelihood of developing a complication (results not shown). Lastly, our model controlled for interactions between smoking and additional patient-level covariates. We found a significant interaction between smoking and both age and hypotension ($P < .001$ and $P = .004$, respectively). Controlling for interactions resulted in a large reduction in smoking odds ratios, with the odds ratio for mortality being 0.53 (CI = 0.48–0.58) prior to adding interactions and 0.15 (CI = 0.10–0.22) after adding interaction terms to the model (Table 2).

Discussion

Our results indicated that patients who currently smoke are significantly less likely to experience mortality and major complications following traumatic injury. Our findings differ from the only other study investigating the effect of smoking on trauma outcomes, in

Table 1. Patient Demographic and Injury Characteristics

	Nonsmokers	Smokers	*P*
Number of patients	319,249	38,564	
Mean age (*SD*)	39.8 (14.1)	39.0 (13.2)	<.001
Median age	40	39	
Female (%)	27.3%	23.7%	<.001
Race/ethnicity (%)			<.001
White	76.4%	81.8%	
Non-White	23.6%	18.2%	
Mean # comorbidities (*SD*)	0.7 (0.9)	1.7 (0.9)	<.001
ISS mean (*SD*)	16.4 (9.3)	15.6 (.2)	<.001
Type of injury (%)			<.001
Blunt	89.8%	89.2%	
Penetrating	10.2%	10.8%	
GCS			<.001
6	84.6%	89.4%	
2–5	5.7%	4.3%	
1	9.8%	6.3%	
Hypotension (%)	3.8%	3.2%	<.001
Insurance (%)			<.001
Private	36.6%	26.8%	
Public	17.1%	23.4%	
Self-pay	22.5%	27.0%	
Other	23.8%	22.8%	
Mortality			<.001
Lived	95.7%	98.2%	
Died	4.3%	1.8%	
Major complication			.763
No complication	90.4%	90.3%	
Complication	9.6%	9.7%	

GCS = Glasgow Coma Score (motor); ISS = Injury Severity Score.

Table 2. Adjusted Odds Ratios for the Occurrence of Major Complications or Death by Smoking Status

	OR (95% CI)	
	Major complication	Death
Smoking status		
Nonsmoker	Reference	
Smoker	0.73 (0.59, 0.91)	0.15 (0.10, 0.22)
Age (years)	1.03 (1.02, 1.03)	1.06 (1.05, 1.06)
Race		
White	Reference	
Non-White	1.03 (0.99, 1.07)	0.96 (0.91, 1.01)
Insurance		
Private	Reference	
Public	1.29 (1.24, 1.35)	1.18 (1.09, 1.27)
No insurance	0.79 (0.76, 0.82)	1.50 (1.42, 1.59)
Gender		
Male	Reference	
Female	0.78 (0.76, 0.81)	0.99 (0.95, 1.06)
Number of comorbidities	1.00 (1.00, 1.00)	1.00 (1.00, 1.01)
ISS	1.06 (1.05, 1.06)	1.07 (1.06, 1.07)
Mechanism		
Blunt	Reference	
Penetrating	1.16 (1.12, 1.21)	3.54 (3.35, 3.73)
Hypotension		
No hypotension	Reference	
Hypotension	1.98 (1.69, 2.33)	1.96 (1.52, 2.54)
GCS motor category		
6	Reference	
2–5	3.99 (3.84, 4.14)	6.63 (6.21, 7.08)
1	4.36 (4.23, 4.50)	20.83 (19.79, 21.92)
Major complication		
No major complication	Reference	
Major complication	NE	1.26 (1.20, 1.32)
Age × smoker		
Nonsmoker × age	Reference	
Smoker × age	1.02 (1.02, 1.03)	1.02 (1.01, 1.03)
Hypotension × smoker		
No hypotension × nonsmoker	Reference	
No hypotension × smoker	0.97 (0.95, 0.99)	0.49 (0.47, 052)
Hypotension × nonsmoker	1.68 (1.65, 1.72)	2.90 (2.82, 2.97)
Hypotension × smoker	1.92 (1.80, 2.05)	0.96 (0.86, 1.07)

CI = confidence interval; GCS = Glasgow Coma Score (motor); ISS = Injury Severity Score; NE = not estimated; *OR* = odds ratio.

which the authors reported that there were no significant differences in mortality or complication between smokers and nonsmokers.[15] However, this study analyzed 327 patients from a single hospital and only three patients died, which limits the generalizability of its findings and power of analysis.[15] Our findings are similar to studies investigating mortality outcomes in patients hospitalized for acute cardiac events, including cardiac arrest.[6–8] Although the etiology of the beneficial effect of smoking is unknown, it is possible that physiological changes associated with smoking or some component of tobacco smoke is protective during an ischemic event which can be brought on by injury, stroke, cardiac arrest, or heart attack.[7,22] For each of these conditions, with the exception of injury, current smokers were reported to have reduced in-hospital mortality by at least one study.[1,5,6] This is the first report of the smoker's paradox in the injured patient population.

Although some studies have reported that the "smoker's paradox" effect is greatly diminished or disappears after adjusting for covariates such as age, we did not find this to be the case.[23] However, our study did not include adults over 65 years of age, so the age distributions of the populations studied likely differed, particularly because cardiovascular patients are older on average than trauma patients. Chen et al.[2] evaluated the effect of smoking on clinical outcomes in patients with acute myocardial infarction who were less than 45 years of age. This study reported that the smoker's paradox phenomenon is stronger in younger patients and that smoking reduced the risk of death by 75%.[2] We also found that there was a significant interaction between age and smoking, with the protective effect of smoking being stronger in younger patients. Accounting for this interaction between smoking and age increased the magnitude of the protective effect estimate when included in the regression model. However, including interaction effects did not alter the direction of the smoking effect, which was substantial prior to including interaction terms in the model.

In addition to mortality, we also found that smoking status was predictive of developing a major complication. In contrast to some reports in the trauma literature, we found that smoking significantly reduced the likelihood of developing a major complication, although not to the extent it reduced mortality (*OR* = 0.73, CI = 0.59–0.91).[17] However, when we examined respiratory complications alone, we found that smoking neither increased nor decreased the risk of acute respiratory distress syndrome or pneumonia significantly (results not shown, *OR* = 1.06, CI = 0.73, 1.36 and *OR* = 1.07, CI = 0.84–1.37, respectively).

A number of explanations for smoker's paradox in cardiac patients have been reported; however, given that smoking has a

broad range of physiological consequences, the mechanism of action may or may not be the same in injury. Considering that adverse cardiovascular events often occur after trauma, it is possible that smoking improves mortality outcomes in injured patients by reducing the likelihood of death after cardiovascular complications. However, there may be additional physiological evidence for the relationship between smoking status and mortality. Several potential reasons for why smokers have a reduced risk of mortality following injury may relate to the hemostatic, hemodynamic, and anti-inflammatory effects of nicotine.

Hemostatic derangement is a major cause of morbidity and mortality following traumatic injury. Acute coagulopathy is present in approximately a quarter of trauma patients and, compared to patients with normal coagulation, those with coagulopathy are four times more likely to die.[24–26] Platelet dysfunction is thought to play a role in coagulopathy after trauma and insufficient fibrinogen concentration can dramatically increase mortality.[27,28] It has been known for decades that smoking induces platelet hyperactivity and produces changes such as increased aggregation, increased adhesiveness, and higher platelet counts.[29–31] Smoking may enhance functioning of the hemostatic system in injured patients by protecting against platelet dysfunction and coagulopathy after trauma. This may offer a particular survival advantage in cases where treatment in a definitive care setting or administration of blood components is delayed.

Another potential mechanism that could explain how smoking improves trauma outcomes may be due to the hemodynamic effects of smoking, which could potentially provide hemodynamic support to patients experiencing hypotension. Nicotine acts as a vasoconstrictor, which possibly helps to stabilize blood pressure in hypovolemic patients. Some studies have reported that administration of vasopressors after hemorrhagic shock improves outcomes.[32,33] Nicotine possesses vasoconstrictive properties that may help to increase pressure in blood vessels, limit tissue hypoperfusion, and reduce blood loss.[34] In addition to its vasoconstrictive effects on coronary and peripheral blood vessels, smoking also induces vasodilation in pulmonary blood vessels due to the nitric oxide and carbon monoxide content contained in cigarette smoke.[35] This effect could help mitigate the effects of hypoxia and pulmonary hypertension and as well as to improve tissue oxygen utilization.

An additional possibility for reduced mortality in smokers may relate to secondary injury. Secondary injury refers to damage that uninjured cells undergo as a result of the physiologic response to the primary injury.[36] At the cellular level, nicotine is known to have anti-inflammatory properties that are thought to be regulated by the vagus nerve via the cholinergic anti-inflammatory pathway. Animal studies have shown that nicotine improves outcomes after reperfusion injury by modulating the inflammatory response through cholinergic anti-inflammatory pathway.[37–39] This characteristic of nicotine may mediate the relationship between smoking and survival at the cellular level by interrupting ischemic cascade after injury and preventing ischemia-reperfusion injury. Ischemia-reperfusion injury is the most common precipitant of multiple organ dysfunction syndrome, which is the leading cause of death in trauma patients who survive the first 24 hours.[40]

The clinical implications of our findings suggest that it may be possible to identify a therapeutic agent (nicotine or otherwise) responsible for improving survival outcomes in smokers after trauma. Before any potential therapeutic agents are pursued, it is necessary to establish whether nicotine or an additional component of cigarette smoke is driving the reduction in mortality and that this paradox is not due to unmeasured confounding variables. Because smoking is a habit for most smokers, it is also necessary to determine whether short-term changes or long-term changes that result from smoking contribute to its protective effects. In the cardiology literature, many studies support the idea that long-term physiological changes in endothelial and cardiac tissue explain the smoking paradox.[12,14] Undoubtedly smoking does cause enduring physical changes in organ systems, however, Hung et al.[30] reported that smokers also experience acute platelet activation in as little as 5 minutes after smoking a cigarette. Schmidt and Rasmussen[41] also reported a similar fast-acting effect on platelet activation in nonsmokers after smoking a cigarette.

Although smoking has acute effects that may benefit patients who are severely injured, the duration of these effects are undetermined. Comparing the effect of smoking on early and late mortality may provide greater insight into the mechanism by which smoking improves mortality outcomes. Additionally, examining whether or not smoking is protective against certain complications such as coagulopathy or multiple organ failure, may also shed light on which physiological pathways in smokers are altered in order to improve survival.

It is important to note that the overall the aim of this study is not to establish that smoking offers long-term health benefits, rather it is interested in exploring the effects of smoking on in-hospital mortality in order to identify potential therapeutic modalities and targets for injured patients.

Limitations

This study has several limitations. The first is that determining whether or not a patient was a smoker may be difficult for trauma providers, particularly for patients who experience early mortality. We attempted to mitigate this problem by imputing missing values for smoking status. However, if providers indicated that a patient had no comorbidities instead of unknown comorbidities, then this could potentially bias the analysis. We were also unable to determine how long a patient had smoked or how many cigarettes they smoked per day from the data. Therefore, the extent of a patient's exposure to smoking is unknown. There is also uncertainty regarding exposure to smoke of nonsmokers, who could be exposed to secondhand smoke regularly or may have previously been smokers during their lifetime. Future studies should attempt to address this by quantifying smoking exposure of patients in terms of the number of years patients smoked and the number of cigarettes smoked per day.

Another limitation of this study is that the NTDB is not a nationally representative dataset, but rather a convenience sample. Additionally, data is self-reported and under-reporting of complications has been cited as a problem in the past.[42] We attempted to minimize data quality issues by excluding centers with large amounts of missing data and by performing multiple imputations on our study sample. Our study also excluded patients who were over 65 due to the fact that there is significant variation in whether or not centers report isolated hip fractures with no other injuries to the NTDB. Previous studies have found that the inconsistency in how injury is reported in the elderly in the NTDB can bias studies examining mortality as an outcome.[43] Another limitation of the NTDB is that no follow-up data is available on patients. It is possible that long-term mortality differs for smokers and nonsmokers. Future studies should investigate the effect of smoking on 30 day and 1 year mortality following injury.

Lastly, because this study is observational, the design allows for the possibility of confounding by unmeasured factors. Considering that smokers often present with cardiovascular conditions such as acute myocardial infarction nearly 10 years earlier than nonsmokers, age is a major confounder when assessing the effects of smoking status on mortality outcomes.[23] We sought to minimize this by including patient age and interaction effects into the model.

Conclusion

Our study demonstrates that trauma patients experience a "smoker's paradox" similar to that of cardiovascular patients.[1,2,5,6,23,44] We found that there was an independent association between smoking status and mortality and complication outcomes in severely injured patients, with smoking greatly reducing the risk of death even after adjusting for potential confounders such as age. Several potential mechanisms may explain the protective effect of smoking following trauma and future studies investigating therapeutic applications of these findings should be conducted.

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Declaration of Interests

None declared.

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