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PUBLICATIONS

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PRESENTATIONS

Knott J, Longinaker NL, **Greene C**, Kasten J, Snyder F, Bryan HB, Using Medicare to Identify Opioid Use and Potential Misuse and Among Dual Eligibles- Beneficiary and Prescriber Perspectives. June 2013. Academy Health.

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Ryb G, **Greene C**, Dischinger P, Smith GS. Narcotic Poisonings Following Injury. June 2016; Congress of Epidemiology, Society for Epidemiologic Research.

Strong B, Torain J, **Greene C**, Smith G. Outcomes of Trauma Admission for Falls: Influence of Race and Age on In-hospital and Post-Discharge Mortality. April 2016; Society of Black Academic Surgeons.

Strong B, **Greene C**, Torain J, Smith GS. Trauma Recidivism and Preventable Death. April 2015; Scientific Assembly of The Society of Black Academic Surgeons.

Greene C, Strong B, Torain J, Smith GS. Trauma Recidivism by Race: Importance of Cause of Injury. April 2015; Annual Yale Bouchet Conference on Diversity and Graduate Education.

Ryb G, **Greene C**, Dischinger P, Smith GS. Post Discharge TBI Mortality. January 2015; Eastern Association for the Surgery of Trauma.

Smith GS, Abraham D, Auman K, **Greene C**, Dischinger P. Linking Trauma Registry with National Death Index: Why Are Some In-Hospital Deaths Missing? October 2014; International Collaborative Effort on Injury Statistics and Methods.

Lane WG, Krugman S, Goldstein M, **Greene C**, Dubowitz H. Evaluation of an Abusive Head Trauma Prevention Program Using a Case-Control Design. May 2013; Pediatric Academic Societies Annual Meeting.

McAninch J, **Greene C**, Sorkin JD, Lavoie MC, Smith GS. Association Between Psychological Distress & Unintentional Non-Occupational Injuries Among U.S. Adults. April 2013; Public Health Research at Maryland.

Abstract

Title of Dissertation: **Risk of drug overdose death following discharge from a trauma center for an injury**

Christina R. Greene, Doctor of Philosophy, 2019

Dissertation Directed By:

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Background: Trauma patients have a higher rate of long-term mortality due to natural and external causes, yet drug overdose (OD) death within this population has not been explored previously. Pre-existing behavioral risk factors, such as drug and alcohol use disorders (DUD/AUD), and chronic pain resulting from traumatic injury may increase trauma patient's risk of subsequent drug overdose death.

Objectives: To determine whether trauma patients are at greater risk of drug OD death than the general population and detect whether smoking status or fracture is associated with future drug OD death among surviving trauma patients.

Methods: Trauma patients between 18 and 64 years of age who were discharged alive from a Level I Trauma Center between January 1999 and October 2008 were linked to the National Death Index (N=36,288). Patients who were alive at least 30 days after

discharge without cancer were included in this study. Trauma patient risk of drug OD death was compared with the age, gender and race adjusted state population using a standardized mortality ratio (SMR) and 95% confidence intervals (CI). Cox proportional hazard regression was used to determine whether current smoking status or lower limb fracture injury were risk factors for drug overdose death factors.

Results: Trauma patients had a significantly higher drug overdose mortality rate than the state population [SMR=6.10 (95% CI 5.35-6.93)]. Cox proportional hazard modeling revealed a significant increased risk of drug overdose for current smokers [HR = 1.66 (95% CI 1.25-2.21)]. The effect of smoking was stronger in patients with no DUD/AUD and BAC< 80mg/dL [HR=2.45, 95% CI 1.67-3.57], while smoking was not associated with drug OD death in those with DUD/AUD or BAC≥ 80mg/dL on admission. Patients with lower limb fracture were not at increased risk of drug overdose death compared to those without fracture injuries.

Conclusion: Trauma patients have a higher risk of drug OD death than the general population. Smoking is a significant risk factor for drug OD following traumatic injury. Future drug overdose prevention programs should focus efforts on reducing drug overdose mortality in trauma patients, particularly those who smoke.

Risk of drug overdose death following discharge from a trauma center for an injury

by
Christina Greene

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2019

DEDICATION

To my daughter, Shannen Rose Greene, my son, Timothy Kevin Greene, and my parents, Kevin and Virginia Reagan.

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List of Abbreviations

AUD	Alcohol Use Disorder
BAC	Blood Alcohol Content
CDC	Center for Disease Control
COPD	Chronic Obstructive Pulmonary Disease
DUD	Drug Use Disorder
ICD	International Classification of Diseases
ISS	Injury Severity Score
NDI	National Death Index
OCME	Office of the Centralized Medical Examiner
OUD	Opioid Use Disorder
PDMP	Prescription Drug Monitoring Program
SES	Socioeconomic Status
SMR	Standardized Mortality Ratio
STC	Shock Trauma Center
STR	Shock Trauma Registry
SUD	Substance Use Disorder
WONDER	Wide-ranging OnLine Data for Epidemiologic Research

CHAPTER I: INTRODUCTION, AIMS, AND BACKGROUND

A. Introduction

Drug overdose deaths are considered the largest public health problem of our time. According to the Centers for Disease Control (CDC), from 1999 to 2016 the age adjusted drug overdose death rate in the United States tripled.[1] During this interval there was an average 10% increase in drug overdose deaths per year, consisting of a 3% yearly increase from 2006 to 2014, and a 18% yearly increase from 2014 to 2016.[1] Since 2011, drug overdoses have become the leading cause of injury deaths overall, surpassing motor vehicle crashes.[2] The rise in drug overdose deaths has been driven primarily by the increase in prescription opioid drugs, which were involved in 63% of drug overdose deaths in 2015.[3] From 1999 to 2010 prescription opioids were the primary driver behind the increase in the rate of opioid-related drug overdose deaths.[4] However, in later years a greater number of opioid-drug overdose deaths were primarily due to heroin or synthetic opioids, such as fentanyl.[5]

The increase in drug overdose deaths has resulted in a declaration of a nationwide public health state of emergency by the President Trump[6] as well as the allocation of $6 billion dollars of funding allocated to the treatment of drug related disorders over the next two years.[7] In an effort to respond to the opioid crisis, the Department of Health and Human Services[8] has identified five priorities aimed at reducing the burden of disease arising from the opioid epidemic:

1. Improving access to treatment/recovery
2. Promoting use of overdose reversal drugs
3. Understanding the epidemic better through public health surveillance

4. Supporting research on pain and addiction
5. Pursuing better management practices for pain

In order to address the problem of drug overdose deaths on a national level, it is imperative that we first identify and target those populations that are at greatest risk of this outcome. This, in turn, could help tailor prevention efforts aimed at reducing the risk of drug overdose in vulnerable populations.

Trauma patients may be at higher risk of drug overdose deaths after discharge from hospital. Past literature has shown that the populations at greatest risk for drug overdose death are those with substance use disorders and those experiencing chronic pain.[9-11] Chronic pain is common after trauma. If chronic pain is managed with opioids, dependency could result.[9-11] Trauma patients may also be at increased risk of opioid addiction and subsequent drug overdose death due to behavioral factors present at admission, such as pre-existing substance use disorders.[9,12-18] Past research indicates that trauma patients engage in more risk-taking behaviors and use drugs and alcohol more commonly than the general population.[19] Both the increased prevalence of pre-existing risk factors and the development of an injury leading to chronic pain may increase trauma patients' risk of addiction and subsequent overdose, [12-13,16, 20] yet no studies have examined drug overdose death in this population.

To prevent future drug overdose deaths in trauma patients, it is also important to focus on identifying the risk factors for this outcome within the trauma population. Understanding how pre-existing conditions and type of injury impact a patient's risk of drug overdose is essential to effectively target potential drug misuse among trauma patients. Previous studies that examined risk factors for opioid addiction focused

primarily on drug or alcohol use disorders, yet neglected to consider smoking as a risk factor for opioid addiction, despite similar biological mechanisms between nicotine and opioid addiction.[21] Smoking is more prevalent among trauma patients[22] and smokers are known to have increased sensitivity to pain,[23-25] poorer injury healing compared to non-smokers,[26] and increased risk of addiction to opioid pain medications following lower extremity fractures.[27-28]

Literature regarding whether type and severity of traumatic injury has any effect on opioid use is currently unclear.[12, 16, 29-31] Some studies have shown prolonged opioid use has been associated with severe injuries[29] or pelvic and lower extremity injuries.[31] Other studies have found that prolonged opioid use is associated with higher pain intensity[16] and pre-existing psychological risk factors, [12, 30] but not injury-level risk factors.

The primary objectives of this study are: 1) to compare the rate of drug overdose death in the trauma population to the general population in Maryland, 2) to determine whether smoking is associated with an increased risk of drug overdose death, and 3) to determine whether fracture injury is associated with subsequent drug overdose death among trauma patients.

Research Question

Research Question: Is the drug overdose death rate higher in survivors of traumatic injury than in the general population and can we identify risk factors for this outcome?

B. Specific Aims

Aim 1. Compare the rate of drug overdose deaths among surviving trauma patients to the Maryland general population

I will compare the rate of drug overdose deaths among trauma patients discharged alive from the University of Maryland Shock Trauma Center using a Standardized Mortality Ratio (SMR) from the period of 1999-2008, adjusting for age, race, and sex.

Hypothesis 1: Trauma patients who are discharged alive have a higher drug overdose mortality rate than that of the Maryland general population after adjusting for age, race, and sex.

Aim 2. Determine the excess risk of drug overdose death among trauma patients due to smoking status at the time of admission

I will estimate the association between being a smoker at the time of trauma admission and drug overdose death following discharge, taking into account competing causes of death.

Hypothesis: Trauma patients who are smokers have a significantly higher hazard of drug overdose death compared to non-smoking trauma patients.

Aim 3. Determine the excess risk of subsequent drug overdose death among trauma patients associated with fracture injury.

I will estimate the association between fracture injury and subsequent drug overdose death following discharge taking into account competing causes of death.

Hypothesis Aim 3: Trauma patients who sustain a fracture injury have a significantly higher hazard of drug overdose death compared to those who do not sustain a fracture at the time of trauma.

Aim 3. Exploratory Sub-aim: Determine if smoking status modifies the association between fracture injury and drug overdose death in surviving trauma patients.

I will estimate the association between fracture injury at the time of trauma admission and drug overdose death stratified by smoking status and taking into account competing causes of death using a hazards ratio (HR).

Hypothesis Sub-aim 3: Being a smoker at the time of trauma injury will modify the association of fracture injury on drug overdose death, with fracture injury being associated with a higher hazard of drug overdose death in current smokers than in others.

C. Background and Review of the Literature

To inform the study methodology, a review of the scientific literature on the association of trauma with pain, prolonged opioid use, potential opioid misuse or addiction, and drug overdose death and the risk factors associated with these outcomes was conducted. Because many drug overdose deaths are due to opioids, I primarily focused on opioid misuse or dependence as a precedent to drug overdose death, as there is no published study that has examined subsequent drug overdose death in the trauma population. First, research on the association between trauma injury admission and causes of death will be discussed. I will also discuss the potential for opioid misuse or dependence within the trauma population. Secondly, research regarding the association of pre-existing substance abuse factors, such as alcohol use, drug use, and smoking, and the

risk of pain, prolonged opioid use, and opioid misuse will be discussed. Lastly, literature regarding the association of trauma injury factors, such as type and location of injury, and opioid misuse and dependence, which could potentially lead to drug overdose death, will be reviewed.

1. Trauma Injury Admission and Drug Overdose Death

Describing the Trauma Population

Trauma is described as a primary cause of death and disability in the United States.[32] Between 2000 and 2011, there were over 20 million inpatient traumatic injury discharges in the United States, comprising 4.4% of all hospital discharges for that period of time.[32] In 2015, nearly 40% of trauma admissions experienced a lower extremity injury compared to any other injury type.[33]

Increased Risk of Death Following Trauma

Much of the research on mortality outcomes following trauma has focused on in-hospital mortality, surgical outcomes, and 30-day mortality following trauma discharge. However, there is an ever-growing body of literature investigating the long-term mortality outcomes of trauma patients. A literature review by Niven *et. al* reviewed 19 studies that investigated long-term mortality following trauma admission, finding that long-term mortality due to any cause was higher among trauma patients when compared to uninjured cohorts.[34]

When examining specific causes of death, trauma patients are at increased risk of injury death from another external cause unrelated to the initial traumatic injury.[35] Studies also show increased risk of all-intent injury[36] as well as suicide[37] among trauma

patients who survived 30 days following hospital discharge. Furthermore, the use of alcohol at the time of admission appears to modify the association between trauma admission and risk of injury or suicide death. In both Dischinger's[36] and Ryb's[37] analyses of long-term mortality due to injury and suicide causes, trauma patients who were alcohol positive at the time of injury had a greater injury and suicide mortality rate than trauma patients who were alcohol negative. Therefore, the excess mortality risk in trauma patients may not be due solely to the experience of injury but may also be influenced by pre-existing patient risk factors. However, no studies have examined drug overdose as a specific cause of death.

Trauma Patients, Chronic Pain, and the Risk of Drug Overdose Death

For any given age and comorbidity burden, trauma patients may be at higher risk for developing chronic pain syndromes than persons without trauma due to significant injuries that have prolonged recovery times. [10,30,38-39] Body region affected, number of injuries, and mechanism of injury could all potentially influence the risk of developing drug dependence,[10,30,38] particularly in patients who require orthopedic treatment.[39] The development of addiction to prescription painkillers following injury could lead to drug overdoses in trauma patients. Because trauma patients are more likely to use and abuse other substances prior to trauma admission, [16] they are at higher risk of developing an addiction to prescription painkillers which increases their risk of subsequent drug overdose.[14,15,17] However, it is unclear whether trauma patients may have a higher risk of drug overdose death due to having developed a reliance on painkillers to alleviate pain arising from a traumatic injury or due to pre-existing behavioral factors.

Studies have tried to isolate the relationship between the experience, type, and severity of trauma and the development of chronic pain or disability, yet there is limited evidence to suggest a solid relationship between trauma severity or injury type and the development of pain.[40,41] In studies that have examined the relationship between trauma and pain, most findings report that psychological factors, such as catastrophic thinking or psychological distress, are more strongly associated with the development of pain or disability following injury than the type or severity of the injury.[40-42] However, many of these studies included only a population with injuries of similar severity and type, making it difficult to compare the effect that the type of injury may have on risk of developing chronic pain following trauma.

Other studies have focused on prolonged opioid use following surgery or traumatic musculoskeletal injuries. Once again, many of these studies have found that psychological factors, such as depression, psychological distress, and substance abuse disorders are more strongly associated with prolonged opioid use following injury than the experience, type, and severity of injury itself.[28,29,40,43] It should be noted, however, that extremity fractures, particularly pelvic and lower extremity fractures, have been associated with higher pain intensity and longer opioid use compared to other injuries.[28,30,44,45] These findings lend support to the hypothesis that trauma patients may be at an increased risk of opioid dependence not only due to higher prevalence of pre-existing risk factors but also to the type of injury they experience at the time of trauma. Findings on this matter are limited, however, as no studies to date have examined this association in great detail with a large cohort of trauma patients. Most studies that examine opioid use following trauma focus on small, restrictive cohorts of patients, some

of which may not be representative of trauma populations, such as the former or active duty military members.[30, 46,47] Because of this, it is difficult to generalize these limited findings to the larger population of trauma patients.

Another limitation of many prior studies is a focus on intermediate outcomes following trauma, such as the development of pain or prolonged opioid use, rather than risk of subsequent drug overdose admission or death. One study by Baird *et. al* examined risk factors for opioid overdose among trauma patients.[48] While Baird's study reported that 42.5% of trauma patients had at least one risk factor for substance misuse and 68.2% had at least one risk factor for opioid overdose,[48] there was no follow-up to assess drug overdose admission or death following discharge for the initial trauma. As drug overdose deaths continue to rise, drug overdose should be studied as a potential adverse outcome for surviving trauma patients, similarly to other post-hospital complications.

Many studies have analyzed drug overdose death rate trends in the general population, [3,4, 49-51] yet no published research has yet explored how the rates of drug overdose death may differ in trauma patients compared to the general population. Preliminary data from University of Maryland Medical Center (UMMC) Shock Trauma Center suggests that trauma patients who had blunt injuries have a significantly higher rate of drug overdose deaths due to narcotics compared to the Maryland population.[52] However, this study did not include all types of fatal drug overdose outcomes among surviving trauma patients. Consequently, some drug overdose deaths could have been misclassified due to polysubstance use, as it can be difficult to correctly classify opioid overdose deaths due to the presence of multiple substances in toxicology reports.[53,54]

2. Pre-existing Risk Factors for Drug Overdose among the Trauma Population

Known Risk Factors for Opioid Dependence

Given the impact that the opioid epidemic has had on mortality, much of the literature has focused on pre-existing risk factors associated with opioid addiction following treatment of chronic pain as well as drug overdose death risk. Drug and alcohol abuse at the time of trauma has been associated with prolonged opioid use and the development of prescription drug use disorders. A study by Massey *et. al*[15] conducted among orthopedic trauma patients found that positive alcohol or drug toxicology at the time of admission was associated with prolonged prescription opioid use following trauma discharge. In a study conducted in two level I trauma centers, Field *et. al*[13] reported that non-medical prescription opioid (NMUPO) use 12 months following trauma discharge was more likely among patients who reported illicit drug use on admission (OR 2.62, 95% C.I. 1.70-4.04). Other studies have associated prolonged opioid use with mental health symptoms, such as depression or psychological distress.[30,40,41,43,55] Rosenbloom *et. al* [16] examined risk factors for opioid use four months after a traumatic musculoskeletal injury. While limited by small study size (n=122), Rosenbloom found that opioid use was more strongly associated with severe pain (OR=1.25, 95% C.I. 1.07-1.74) than any past or current recorded mental health or substance abuse condition.[16] The flaw in Rosenbloom's predictive model, however, is that pain was included in the model but it is in the causal pathway between psychological risk factors, such as depression, and increased reliance on powerful prescription opioids. Past literature has found that depression, psychological distress, anxiety, and pain catastrophizing are associated with higher pain intensity[40-42] therefore any model that includes pain as a predictor for opioid

use should consider the association of pre-existing psychological risk factors with pain prior to analysis.

Smoking as a Risk Factor for Opioid Dependence

Smoking is typically excluded from consideration in most studies that examine opioid substance misuse despite the similar biological mechanisms between nicotine and opioid addiction.[21] Smokers may be at increased risk of developing an addiction post-trauma due to higher propensity for risk taking behaviors, different perception of pain, and an increased predisposition to developing addiction.[21] In a cohort of motor vehicle trauma patients, smokers were found to be more likely to engage in risk-taking behaviors, such as no seat belt use and intoxicated driving.[22] Smoking has also been positively associated with depression[23,24] and more severe discomfort among chronic pain patients.[23] Because smokers are likely to perceive pain more intensely than non-smokers[24,25] they may also be at an increased risk of needing a higher dosage of medication to treat the pain, thus increasing risk of overdose death. Two cross-sectional studies have found that smoking is associated with both prescription[20] and illicit[56] opioid use disorder in chronic pain patients. Brummett *et. al*[12] investigated risk of new persistent opioid use, defined as an opioid prescription fill that occurred 90-180 days following surgery, in patients undergoing elective surgical procedures based on pre-operative patient risk factors. Tobacco use at the time of surgery was independently associated with an increased odds of persistent opioid use following surgery (OR 1.35, 95% C.I. 1.21-1.49) following surgery.[12] Young-Wolff *et. al* [57] also found that current smoking was marginally associated with increased odds of developing an opioid use disorder among females (OR=2.30, 95% C.I. 1.00-5.32, p=0.05), despite the fact that smoking status was

not associated with pain intensity in this study. Montbriand *et. al* [26] also conducted a study that examined pain and opioid use following major surgery. Smokers reported greater pain scores one month following surgery than past or never smokers ($F_{(2.\ 172)}$=5.4, p=0.005)(25). Smokers also used higher doses of opioids use one-month post-surgery, based on Morphine Milligram Equivalent dosage, compared to never smokers[26] ($F_{(2.\ 206)}$=3.1, p=0.047).. Additionally, current or past smokers experienced less of a decline in daily opioid use from one to three months following surgery compared to never smokers[26] ($F_{(2.187)}$=4.0, p=0.02). While understanding of the association between smoking and pain intensity is limited, new findings provide some evidence that smokers use opioids at a higher doses and for longer periods of time following trauma injury or surgery compared to non-smokers. Additionally, one case control study reported that smoking was associated with a five times higher odds of prescription opioid death,[58] yet information on cause or extent of the potential injury that could have led to the opioid use disorder prior to death was not available.

Mental health diagnoses and substance use disorders have been linked repeatedly to a higher risk of opioid misuse and drug overdose death.[40,43,53,59] Smokers are not included within the substance use category, despite evidence that they may be at a similar risk for opioid abuse and drug overdose following trauma. In order to identify those trauma patients who may be at high risk of drug overdose death, it is important that smoking status, in addition to mental health or substance use, be considered at the time of trauma.

3. The Role of Fracture in the risk of opioid dependence and future drug overdose among surviving trauma patients

Much of the literature regarding opioid misuse, addiction, and overdose has focused primarily on pre-injury risk factors. However, the development of iatrogenic dependence on opioids following injury should be considered given that opioid prescribing following traumatic injury is common.[16] While pre-injury risk factors have been investigated in association to pain, opioid dependence, and drug overdose risk, the literature examining the relationship between injury type and these outcomes has been comparatively sparse. A literature review by Ip *et. al*[40] found that the strongest predictors for postoperative pain were preoperative pain, anxiety, age, and type of surgery, with orthopedic surgery being associated with more intense pain and increased opioid analgesic consumption, and emergency and major surgeries with the highest analgesic consumption. Chaudhary *et. al*[29] found that chest, abdominal, extremity injuries and polytrauma (defined as having an injury in more than one location), were associated with prolonged opioid use. Holman *et. al* [31] found that surgery for certain types of orthopedic trauma, such as pelvic or acetabular trauma, was associated with longer opioid use following surgery compared to upper extremity trauma. Other studies found no association between surgery type and opioid use.[12] However, the heterogeneity of these findings may be due to study population differences, as some studies restrict to trauma surgery patients while others look at elective surgery patients.

Additionally, studies that have examined opioid use following traumatic musculoskeletal injuries have been primarily restricted to patients with fractures only.[15,30,41,42] Studies conducted by Massey,[15] Helmerhorst,[30] Vranceanu,[41] and Bot[42] did

not find an association between injury severity, fracture site, or numbers of fractures and prolonged opioid use following surgery for the traumatic injury. These findings, however, should be interpreted cautiously due to small sample sizes. The small samples within these studies make it difficult to detect any potential effect of injury type or severity. These studies also did not compare fracture injuries to non-fracture injuries as well as causes of traumatic injuries. Given that fracture patients may be prescribed opioids as treatment for pain following their injury, it is worthwhile to investigate the risk of drug overdose in trauma patients based on fracture status.

Moreover, fracture healing may not be uniform among all patients based on their pre-injury risk factors at the time of trauma admission. Being a current smoker has also been shown to delay bone healing in fracture patients,[60] which may predispose smokers to a greater degree of chronic pain following fracture. Smoking has also been associated with slower wound healing, increased risk of non-union among those patients with long-bone and lower extremity fractures,[27] and increased risk of developing long-term disability following meniscal injuries of the knee.[28] Poorer wound healing in smokers could contribute to increased likelihood of chronic pain following injury. The fact that their injuries may take longer to heal could also potentially provide a longer exposure to prescription opioid increasing the risk of non-medical prescription opioid use or eventual opioid use disorder.

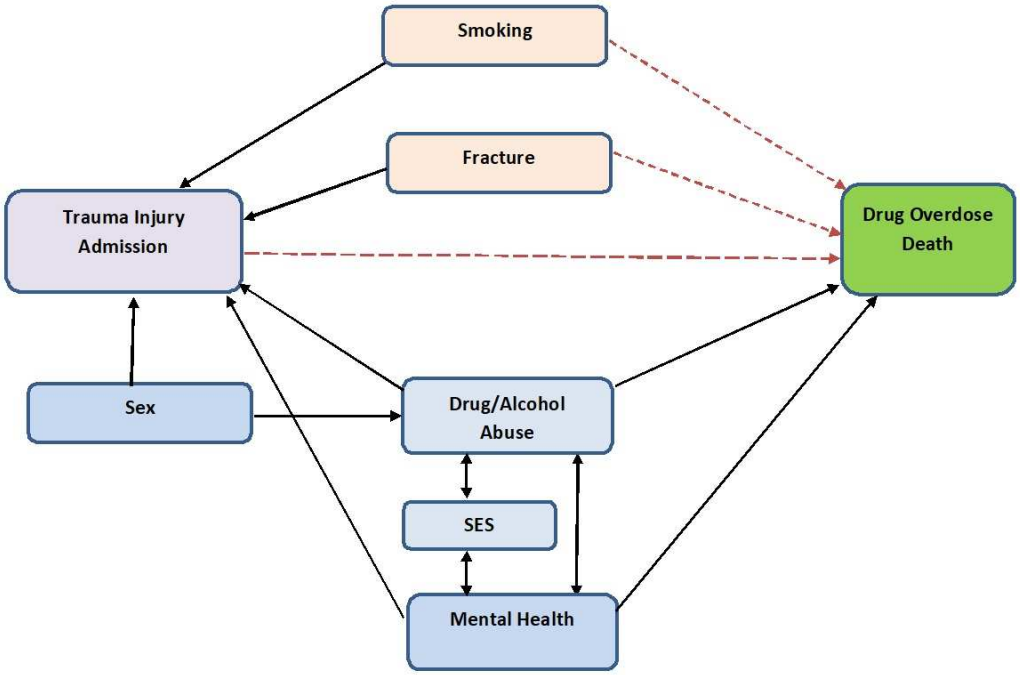
Because trauma patients may be at higher risk of drug overdose due not only to pre-injury risk factors but also to injuries sustained during trauma, it is important to investigate how fractures may impact the risk of drug overdose. Also, since smoking may possibly delay fracture healing, it is also important to understand how smoking status at

the time of admission may modify the association between fracture and drug overdose risk among surviving trauma patients.

4. Conceptual Model

Based upon the literature reviewed in the previous section, I have developed a conceptual model which details the relationships between the different variables of interest within this analysis. This conceptual model graphically represents how risk factors, such as trauma injury, patient smoking, or fracture injury, are to drug overdose death in addition to other confounding variables, such as drug or alcohol abuse. The conceptual model also details how other patient risk factors, such as sex or patient mental health, may be associated with both the risk factors and outcome of interest.

Figure 1: Conceptual Diagram of Association between Trauma Admission and Risk Factors with Future Drug Overdose Death



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CHAPTER II: STUDY DESIGN AND METHODS

A. Study Design

This study was a retrospective cohort study of adults admitted from the scene of injury to R. Adams Cowley STC from January 1, 1999 to October 31, 2008 for a penetrating or blunt injury and who were alive at the time of discharge. This study linked follow-up data on subsequent mortality post-discharge identified by linkage with death certificate data, which I had for all patients admitted to Shock Trauma Center until December 31, 2008. This study used three datasets: the R. Adams Cowley Shock Trauma Registry dataset, the National Death Index (through 2008), and CDC Wonder.

B. Data Sources

1. R Adams Cowley Shock Trauma Center Registry Maryland (STR)

To determine the rate of drug overdose deaths in the trauma population, I used data from the R. Adams Cowley Shock Trauma Center (STC) data registry (STR). The STC is Maryland's state designated primary adult resource center. The R. Adams Cowley Shock Trauma Data Registry (STR) records information on all admissions to Shock Trauma. The registry contains information on patients such as age, sex, and race, date of admission and discharge, cause of injury, the area of injuries by International Classification of Diseases 9th revision, Clinical Modification (ICD-9-CM) code, injury severity score, pre-existing conditions, previous drug, alcohol or tobacco use, length of stay, urine drug screen, and blood alcohol concentration (BAC), when obtained, on admission, approximately 90% of the time. The trauma registry also has information on the number of injuries sustained as well as surgery and complications resulting from

injury. I obtained registry information for all patient admissions from 1999-2008 who meet the inclusion criteria as defined below in "Study Population".

2. National Death Index

The STR has been linked to the National Death Index (NDI) to obtain information on all deaths occurring among STC admissions from the inception of the registry until December 31, 2008. To create the linkage to the NDI, personal identifiable information, such as social security number, name, and date of birth was sent to the National Center for Health Statistics for linkage into the NDI-Plus system. The NDI-plus includes date of death, underlying cause of death, and up to twenty contributing causes of death for patients identified as having died. Underlying cause of death and contributing causes of death were recorded using International Classification of Diseases 10th revision (ICD-10) mortality codes. Patient records were sent to the NDI to obtain information on deaths and causes of death based on patient records. Probabilistic matches were returned by the NDI. Matches that fell within the grey area of the threshold of being considered a true match were hand reviewed by an epidemiologist at the National Study Center. [61]

3. CDC Wonder Death Database: Maryland deaths from 1999 to 2008

The death rates for the statewide population were determined using CDC WONDER, a web-based data query system that delivers mortality information based on user menu response.[62] I obtained information on the mortality for different age, race, sex groups in the State of Maryland from 1999 to 2008 based on underlying causes of death as listed in the death record.

C. Study Population

Aim 1: The trauma study population consisted of the last recorded admission from the scene of the injury for trauma patients age 18-64 admitted for blunt or penetrating injury from January 1, 1999 to October 31, 2008. To be included patients must have been discharged alive and survived at least 30 days following discharge from STC. Patients must have had a valid age, race, and sex record and must have been Maryland residents at the time of admission in order to make a valid comparison to the mortality rates in the Maryland general population and adjust for age, sex, and race. Patients were excluded if mechanism of injury was due to a non-blunt or penetrating cause, such as burns, poisonings, or other external causes of injury. Patients were also excluded if they had an ICD-9-CM indicating a pre-existing condition of malignant cancer (ICD-9-CM code between 140 and 209 in the first 3 digits).[63]

Aim 2: The study population for this aim was the same as for Aim 1, except analysis for this aim included patients that were non-Maryland residents at the time of admission. I included non-Maryland residents for this aim because analysis looked at risk factors within the trauma cohort and did not compare to the Maryland general population. The study population for this aim also excluded those who did not have a recorded BAC value on admission in the registry.

Aim 3: Study population for this aim was the same as the Study Population for Aim 1, except analysis for this aim included patients that were non-Maryland residents at the time of admission. I included non-Maryland residents for this aim because analysis looked at risk factors within the trauma cohort and did not compare to the Maryland

general population. Multivariable models excluded those patients that have a missing value for Injury Severity Score (ISS) on admission.

D. Study Variables

Exposure Variables

Smoking: Current smoking was recorded as a binary variable in the STC Registry, based on patient records. While past smoking information was not available for trauma patients, there is evidence that past smoking behavior does not present as significant a risk factor for post-surgical and injury complication as current smoking.[64] This information was obtained via patient questioning by the patient's nurse or doctor at the time of trauma admission.

Presence and Type of Fracture: Fracture injury was determined based on ICD-9 code recorded for patient injury. I first identified the presence or absence of fracture injury. I then subdivided fractures based on ICD-9 codes consistent with fracture injuries in any of the following regions: head, upper extremity, chest/abdominal, spine, pelvic/acetabular, and lower limb). I collapsed the category of spine and pelvic/acetabular due to spine fractures comprising a small number of all fractures. Patients with fractures in multiple locations were counted as having a fracture in each injured body region. Fractures were also classified as open or closed based on ICD-9-CM code. Fractures of the phalanges were excluded from classification as fracture injuries. Because past studies considered lower limb fractures as more likely to result in chronic pain and prolonged opioid use than other fractures, [31] I considered this type of fracture to be at potentially higher risk of

drug overdose death than other types of fracture. Further detail on classification of fractures by region is given in the Appendix A.

Outcome Variables

Drug Overdose Death: I obtained cause of death information for all patients who were identified as having died by December 31, 2008 from the NDI. I classified patients based on "Underlying cause of death" as the determinant of the primary cause of death for patients. Deaths were classified as drug overdose deaths, non-overdose injury deaths, and death due to natural causes based on underlying cause of death in the NDI. Drug overdose deaths included patients who died and had any of the following codes listed as an underlying cause of death: accidental (X40-44), Intentional (X60-64), and undetermined (Y10-14) drug overdose poisonings. All other non-drug overdose injury deaths were considered "other external cause injury deaths" based on underlying cause of death V01-Y89, excluding drug overdose death codes (X40-44, X60-64, and Y10-Y14). All other deaths with a valid non-injury underlying cause of non-injury death were classified as "deaths due to natural causes".

Time to overdose death among patients discharged alive: I examined death status for the entire length of follow-up after date of trauma discharge, excluding person time in the first 30 days following trauma discharge, with a maximum of 10 years of follow-up time for patients admitted to STC at the beginning of 1999. Patients were censored at date of death or at the end of the follow-up period (December 31, 2008).

Independent Variables

Substance Use: Patients were considered to have indicators of substance use if they met any of the following conditions: BAC on admission above the legal limit (80mg/dL) or a recorded alcohol or drug substance use disorder based in the medical record. Pre-existing patient drug or alcohol substance use information was obtained by the patient's nurse or doctor during the trauma admission. The diagnosis was self-reported or family reported as part of medical history. BAC was obtained as part of routine testing of all admitted trauma patients and is recorded numerically. A past study of the registry confirms that valid BAC testing results are obtained for approximately 94% of patients on admission.[65]

Substance Use Disorders: Presence of an alcohol or drug use disorder was based upon pre-morbid conditions as recorded in the trauma registry. Pre-morbid conditions were obtained upon admission and are recorded for each trauma admission with an ICD-9-CM code accompanying the admission. Alcohol Use Disorder was determined based on a pre-morbid condition associated with the patient in the registry that has an ICD-9-CM code of 303 for the first three digits. Drug Use Disorder was determined based on a pre-morbid condition associated with the patient in the registry that has an ICD-9-CM code of 304 for the first three digits. These ICD-9-CM codes were acquired from the ICD-9-CM free medical coding reference online.[63]

Blood Alcohol Concentration: BAC was obtained on admission for nearly all trauma admissions. Values were recorded as negative (-999), positive, or untested. If positive, BAC is recorded as a numeric positive value, ranging from 1-500. I considered the patient to have significant alcohol use if their BAC is 80mg/dL or greater at the time of admission.

Neighborhood Median Income: Neighborhood Median Income was obtained as an estimate of socioeconomic status (SES) using zip code level data from the Census website.[66] Zip codes were based on zip code of residence as recorded in the trauma registry for each patient admission. Information on residents' median income as an indicator of neighborhood SES was determined by linkage to the US Census median income information for each zip code in the year 2000.

Other Co-morbidities: Reported co-morbidities that could be associated with overdose death were explored as potential confounders of the association of smoking and drug overdose death, as well as the association of fracture and drug overdose death. Based on past literature, this included comorbidities associated with drug overdose death, such as Chronic Obstructive Pulmonary Disease (COPD) or Liver Disease. I also explored how mental health comorbidities, such as Depression, Bipolar Disorder, Schizophrenia, and Other Mental Health disorders, were associated with both smoking and drug overdose death.

Chronic Obstructive Pulmonary Disease (COPD) was determined based on an ICD-9-CM code between 490 and 496 for the first three digits recorded in the patient's medical record. A description of all associated codes is shown in the table below. All descriptions were obtained from ICD-9-data.[63]

Table 1: ICD-9-CM codes indicating Chronic Obstructive Pulmonary Disease (COPD) and associated conditions

ICD-9-CM Code	Description
490	Bronchitis, not specified as acute or chronic
491	Chronic bronchitis

Table 1: Continued

492	Emphysema
493	Asthma
494	Bronchiectasis
495	Extrinsic allergic alveolitis
496	Chronic airway obstruction, not elsewhere classified

Liver Disease was determined based on an ICD-9-CM code between 571 and 573 for the first three digits recorded in the patient's medical record. A description of all associated codes is shown in the table below. All descriptions were obtained from ICD-9-data.[63]

Table 2: ICD-9-CM codes associated with Liver Disease

ICD-9-CM Code	Description
571	Chronic Liver Disease and Cirrhosis
572	Liver abscess and sequelae of chronic liver disease
573	Other disorders of liver

Mental Health Conditions were determined based on a pre-morbid condition associated with the patient in the registry that has an ICD-9-CM code indicative of a mental condition based on the table below. Descriptions for each ICD-9-CM code is shown below. All descriptions were obtained from ICD-9-data.[63]

Table 3: ICD-9-CM codes associated with Mental Health Conditions

ICD-9-CM Code	Description
295	Schizophrenic disorders
296	Episodic mood disorders (includes Bipolar disorders, Major Depressive disorders, and unspecified mood disorders)
297	Delusional Disorders (Paranoid state, Shared psychotic disorder)
298	Other nonorganic psychoses
300	Anxiety, dissociative, and somatoform disorders
311	Depressive disorder, not elsewhere classified

Age: Patient age was determined based on recorded age in the STR. Age will be categorized as follows: 18-24, 25-44, and 45-64.

Race: Race was categorized as Black, White, or Other/Unknown, which includes Hispanic, Asian, and American Indian/Alaska Native, Other and Unknown races, based on recorded values in the Registry.

Sex: Patient sex was obtained from the trauma registry.

Mechanism of Injury: Information regarding patient mechanism of injury admission was obtained from trauma registry records. Patient cause of admission is coded based on External Cause of Injury, ICD-9-CM code. Mechanism of injury was grouped into the following categories: Vehicular (Motor Vehicle Crash/Other Vehicle), Falls, Penetrating (Firearm/Knife), Beating/Assault, and Other/Unknown injuries. Injuries will be grouped based on the cause of admission code.

Number of Regions Injured/ Polytrauma: Polytrauma, or traumatic injury in more than one body region, will be determined based on injury severity score (ISS), a numerical

outcome aimed at describing injury severity in patients.[67] Patients were considered to have polytrauma if they had an ISS of 16 or greater, a definition that has been used in previous literature.[68,69]

E. Sample Size and Power

Aim 1: We identified 32,918 individuals included within the trauma cohort for this aim, with approximately 154,421 person years of follow-up time from 1999 to 2008. The number of person years for the Maryland Population for this period of time (1999-2008) was 34,975,095 for those between the ages of 18 to 64. Based on the number of person-years currently available from Maryland residents in the dataset and the drug overdose mortality rate in the Maryland population from 1999 to 2008 (19.0 per 100,000), we would be able to detect a Rate Ratio of 1.6 or greater with a power above 89% based on using the normal approximation of two sample rate ratio described by Magder and Shardell comparing the rate of overdose death in trauma patients to the Maryland population.[70]

Aim 2: We used proc power in SAS to determine whether there was sufficient statistical power to detect a moderate effect of smoking on the hazard ratio while taking into account other causes of death. The sample size for this aim would be 34,801 with a potential length of follow-up of 10 years. The projected drug overdose death rate for the reference population was projected to be 0.7% and 37% of the cohort were estimated to be smokers at the time of admission. Based on my current sample size in data from 1999 to 2008, the proportion in the exposed, or current smoker, group (37%), the length of our enrollment period (10 years), and the projected survival time for the reference population

(about 0.7% overdose death among non-smokers), we would be sufficiently powered to detect a hazard ratio of 1.5 or higher with 81.8% Power.

Aim 3: We used proc power in SAS to determine whether there was sufficient statistical power to detect a moderate effect of fracture on the hazard ratio. Based on the current sample size in data from 1999 to 2008 (N=36,288) , the length of our enrollment period (10 years), the projected survival time for the reference population (about 0.7% overdose death among those without fractures), and the proportion of patients who are anticipated to have a fracture injury, based on preliminary data (42%), the study would be sufficiently powered to detect a hazard ratio of 1.5 or higher with 96.5% Power.

F. Statistical Analysis

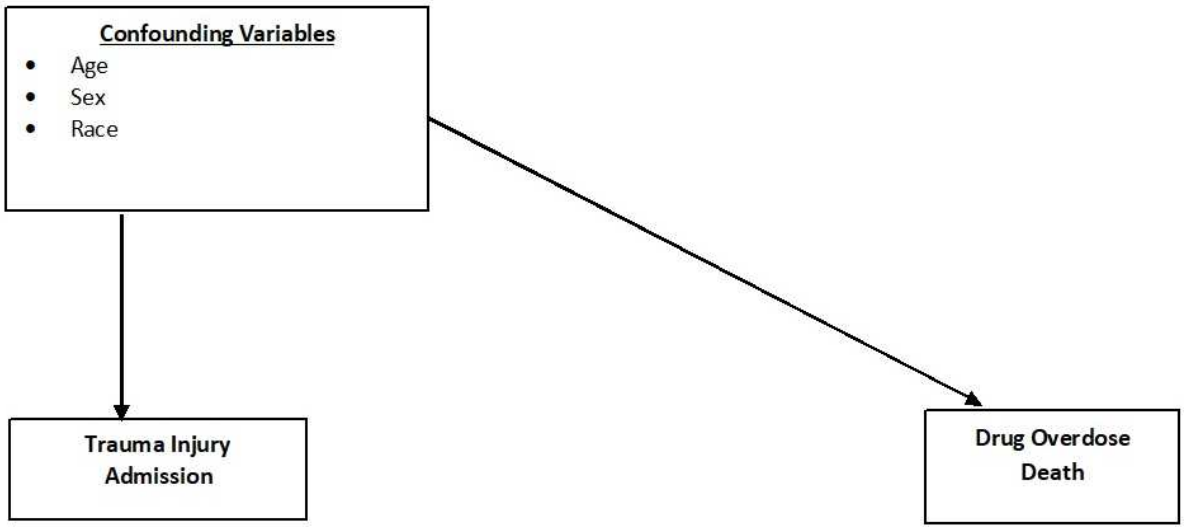
1. Analysis of Drug Overdose Deaths in Trauma Patients compared to General Population

Aim 1: I compared the rate of drug overdose deaths in trauma patients to the drug overdose death rate in the Maryland population. First, I obtained drug overdose deaths in the study population for Aim 1 that occurred within the follow-up period in my cohort for each age, race, and sex grouping. Then, I calculated the number of person years contributed by each age, sex, and race category to determine how the trauma population was distributed demographically. Using CDC Wonder, I obtained the Maryland drug overdose death rate for 1999 to 2008 for each age, sex, and race group. Following this, I computed an "expected" estimate of what the number of drug overdose deaths would be in the study trauma cohort if the mortality rates were the same as the Maryland general population for each age, sex, and race group.

Rate ratio comparisons were made using a standardized mortality ratio (SMR) through comparing the number of "observed" trauma deaths to the number of "expected" trauma deaths based on the rates in the Maryland population, adjusting for age, race, and sex distribution. Using an SMR, I compared the observed number of drug overdose deaths in trauma to the expected number of deaths, calculating the expected rate based on the person year distribution for every age, sex, and race group. A significance level of 0.05 was used for all analyses in Aim 1 based on a rate ratio that does not include 1.0 in the 95% Confidence Interval estimate. The confidence interval was calculated using the method which was previously described by Ulm.[71] To explore potential time trends, I examined the SMR over the entire time period (1999-2008) and at 3 separate time periods, 1999-2001, 2002-2004, 2005-2008. Because the Confidence Intervals SMR for drug overdose mortality were very close for all three periods and overlapped I did not test for significant differences in SMRs.

Additionally, the SMR was used to compare the ratio between trauma patients and the Maryland general population for other external injury cause and natural cause deaths, respectively. The methodology used was identical to that previously described for calculating the SMR for drug overdose deaths in trauma patients versus the general population.

Figure 2: Graphical Representation of Relationship of Trauma to Drug Overdose Death



Preliminary Univariate Analysis: Prior to starting analytics on Aims 2 and 3, I conducted a univariate analysis on variables of interest within the trauma registry. Because the outcome of interest for Aims 2 and 3 is time to overdose death after trauma discharge, follow up time was censored at the end of study follow-up period, December 31, 2008. Deaths due to drug overdoses based on ICD-10 underlying cause of death as noted in the National Death Index (NDI) were considered the event of interest in both of these analyses. Deaths due to other causes, such as natural causes or other injury causes, which occur during follow-up after patient discharge, were classified as events of competing risk. I included patients who survived 30 days past the date of trauma discharge and had a valid BAC result for the analyses conducted for Aim 2. Analyses for Aim 3 did not include the restriction for BAC testing and included patients that had an unknown BAC value based on patient registry record.

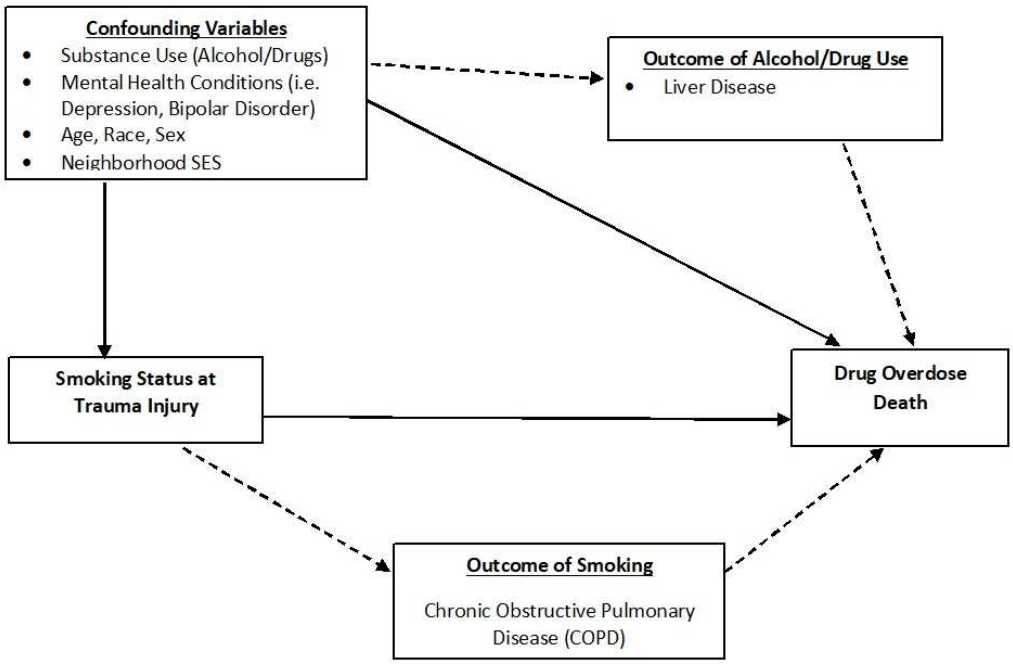
I explored the study population's distribution of smoking, diagnosed drug or alcohol use disorders, age, race, sex, ISS, area of injury, mechanism of injury as indicated

by ICD-9-CM injury cause of admission, neighborhood socioeconomic status (as defined by neighborhood median income), presence of other comorbidities (Mental Health, COPD, Liver Disease), and BAC. I also examined the distribution of injury related factors within trauma admissions such as presence of fracture injury, location of injury, presence of multiple areas injured, and, if a fracture was sustained whether it was open or closed. Drug overdose mortality overall was also explored as well as time to death and length of follow-up overall and among sub-groups of interest: smokers/non-smokers, fracture groups.

Analysis of the Risk of Drug Overdose Death associated with being a current smoker at the time of trauma injury admission

Bivariate Analysis: I conducted a bivariate analysis that examined the unadjusted association between smoking at the time of trauma admission and other independent variables, such as diagnosed substance use disorders, presence of other comorbidities, BAC, demographic variables (age, race, and sex), and neighborhood socioeconomic status, injury severity score (ISS), and cause of injury admission. Grouping of independent variables with more than two values were determined based on the findings from univariate analysis.

Figure 3: Graphical Representation of Relationship of Smoking Status to Drug Overdose Death



Exploration of Potentially Co-linear variables: Because many of the confounding variables identified may be highly associated with each other, collinearity was taken into account in analysis. To inform the exploration of collinearity among the variables I primarily relied on the conceptual model that was developed based on the review of the literature regarding this topic. Collinearity was explored between Alcohol/Alcohol Use Disorder and Drug Positivity/Drug Use Disorder. While variables were not considered to be significantly collinear based on a Variance Inflation Factor of 10 or greater, chi-squared test of association found strong correlations between Alcohol Use Disorder, BAC above the legal limit, and Drug Use Disorder ($p<0.05$). As a result, I included one variable in the multivariable model indicating the presence of BAC above the legal limit or Drug Substance Use or Alcohol or Drug Substance Use Disorder at the time of trauma admission.

Additionally, I explored the relationship between a recorded Mental Health condition at the time of trauma admission and the potential for collinearity with Alcohol/Alcohol Use Disorder, Drug Use/Drug Use Disorder, or any Substance Use or Substance Use Disorder. While variables were not strongly collinear, as defined by a Variance Inflation factor of 10 or greater, I did find that all of these variables were strongly correlated with Mental Health conditions. However, I decided to include an indicator for Mental Health Condition within the model based on the fact that Mental Health conditions usually precede substance use conditions causally. Also, research previously discussed has treated Mental Health conditions separately from substance abuse conditions, meriting this variable's inclusion as an independent predictor of the outcome.

Collinearity was also explored between other comorbidities, such as Liver Disease and Alcohol Use/Alcohol Use Disorder as well as Smoking and Chronic Obstructive Pulmonary Disease (COPD). However, I excluded both of these conditions from the model because both likely were results of Alcohol or Drug Use Disorder and Smoking, for Liver Disease and COPD, respectively. Chi-square analysis of correlation between both associations (Alcohol or Drug Use Disorder and Liver Disease, Smoking and COPD) was significant at a p-value <0.0001.

Following bivariate analyses, the multivariable model was created. Variables were included in the model if they were identified as confounders in the Figure 3 causal diagram (shown above). Figure 3 above is a graphical representation of the relationship of the primary exposure (smoking), the outcome (drug overdose death), and potential confounders as identified in the literature and conceptual model. I created a competing

risks Cox Proportional Hazards model (i.e., an extension of the Cox Proportional Hazards model to the proportional sub-distribution hazards model) which examined the time to drug overdose death based on being a smoker at the time of trauma admission. The competing risk model was determined to be of importance as we wanted to account for other potential causes of patient mortality, such as external injuries and natural causes. To account for competing risks of death among patients we used the methods previously described by Fine and Grey.[72] The model included variables that were previously determined to be potential confounders of the association between smoking and drug overdose death. The model did not include variables that are determined to be in the causal pathway of the exposure and the outcome, regardless of the statistical association observed in the preliminary bivariate analysis. While Mental Health condition was associated with substance use (BAC>80 mg/dL, Alcohol Use Disorder, or Drug Use Disorder), I felt that this variable deserved inclusion into the multivariable model based on previous research which treated it as a separate variable in analyses.

Proportionality of hazards was verified using negative log-log (1-CIF) curves. Hazards were considered proportional if the negative log-log (1-CIF) curves were parallel among different values of variables. If a variable did not meet this requirement the model was further tested by including an interaction term of this variable with time. If the value of the interaction term was statistically significant the proportionality of hazards assumption was considered to have been violated. Only the variable of age was found to have non-parallel negative log-log (1-CIF) curves. When an interaction term between age and time was added to the model, however, the term was found to be non-significant. Current smoking status was considered to be significantly associated with time to

overdose death if significant at a p-value of 0.05 or lower in the multivariable cox proportional hazards model.

Analysis of the Risk of Drug Overdose Death associated with fracture injury at the time of trauma admission

Bivariate Analysis: I conducted a bivariate analysis that examines the unadjusted association between fracture grouping (lower limb fracture, other fracture, no fracture) at the time of trauma admission and other independent variables, such as smoking status, cause of injury, ISS, BAC, demographic variables (age, race, and sex). For the bivariate analysis, I conducted a chi-square statistical analysis that compared patients who died of drug overdose, those who died of other causes, and those who did not die upon follow-up for the exposure of interest in this analysis, by region of fracture injury, and all other independent variables.

Figure 4: Graphical Representation of Association of Region of Fracture with Drug Overdose Death

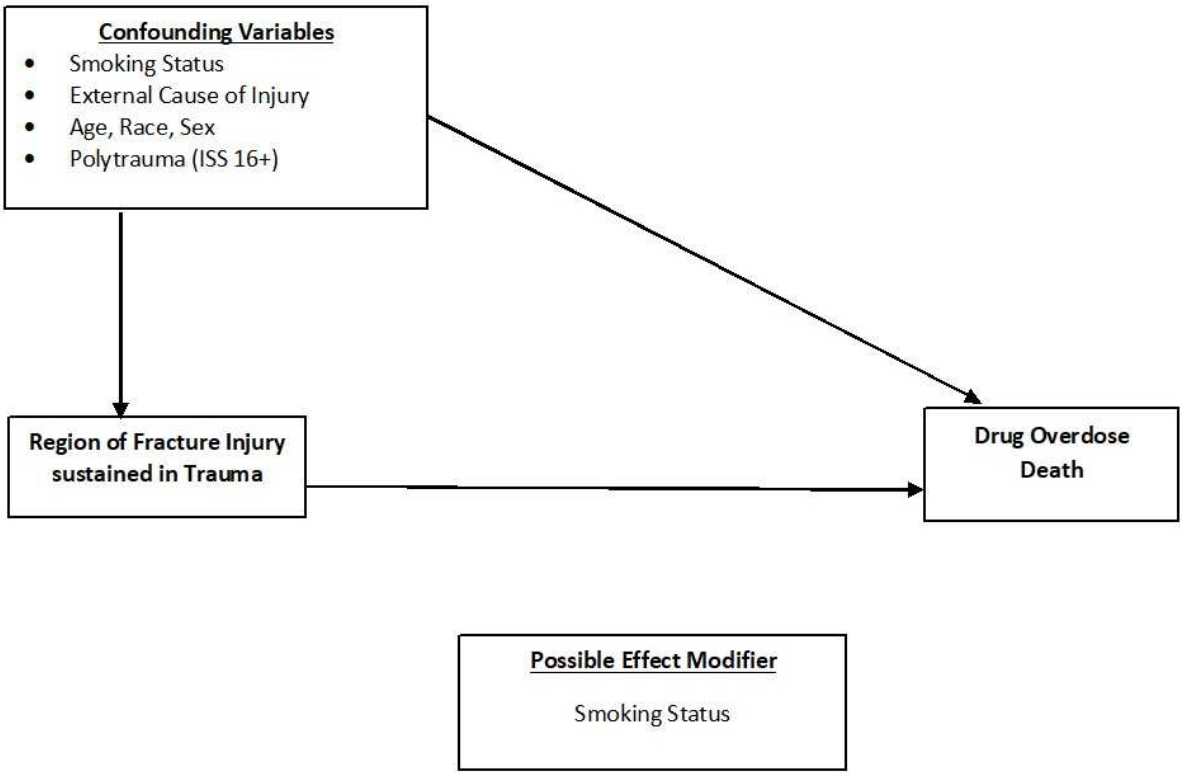


Figure 4 shown above graphically represents the causal relationship for Aim 3 in relation to the primary exposure (region of fracture), outcome (drug overdose death), confounders (as identified in the literature and/or the conceptual model), and effect modifiers, or variables that could potentially modify the effect of fracture on drug overdose death. This graphic helped further inform the creation of the multivariable model for Aim 3 and Sub-Aim 3.

Variables will be included in the model if they are identified as confounders in Figure 4 above. In Analysis for Aim 3, I created a competing risks Proportional Subdistribution Hazards model that examined the time to drug overdose death based on fracture injury during trauma. The methodology previously described by Fine and Gray[72]

was used to account for competing causes of death observed in the study cohort. The model for Aim 3 included independent variables that were previously determined to be potential confounders of the association between region of fracture and drug overdose death, based on the Figure 4 above.

Initial analysis examined the association between fracture injury as a binary variable and risk of drug overdose death. Because fracture injury was not found to be associated with drug overdose death at a binary level, patients with fractures were sub-divided into separate groupings, as the committee suggested that the association may be different based on the region of fracture (lower limb or non-lower limb). Further detail on the initial results between fracture injury at a binary level and drug overdose death hazard is provided in Appendix B.

For final analysis patients were subdivided into the following three mutually exclusive groups based on whether they sustained a lower limb fracture at the time of trauma: those with a lower limb fracture with or without other fractures, those with one or more fractures in other regions, and those with no fractures. Based on discussion with the committee, two cox multivariable regression models were created for Aim 3. One which adjusted for smoking status, age, sex, race, and external cause of injury and another that included an additional adjustment for polytrauma (ISS $\geq$ 16). It was debated as to whether ISS should be adjusted for in the multivariable model due to the fact that it could be considered in the causal pathway as it could be a potential by-product of fracture injury. As a result, both models were created and estimates of the main effect (region of fracture injury) were compared. Blood Alcohol Content was not included in the multivariable model due to the significant association between BAC and smoking in

preliminary analysis (chi-squared, $p<0.0001$). The proportionality of hazards was verified before constructing the model using negative log-log (1-CIF) curves previously described in the preceding section. Because all variables that would potentially be included in this model are not time-dependent, this assumption was verified based on comparison of variables at different values using negative log-log (1-CIF) curves for the outcome of interest. Fracture injury was considered to be significantly associated with time to overdose death if significant at a p-value of 0.05 or lower.

Sub-Analysis Aim 3: For this aim, I explored whether current smoking status at the time of trauma admission modified the association between fracture region and risk of drug overdose death. This analysis determined whether the association between fracture region and drug overdose death was stronger among smokers than among non-smokers, based on literature that reports that smokers heal more slowly from fractures compared to non-smokers.[27,60] Preliminary analyses in Aim 2 were relevant to exploring this aim. The results of the bivariate analysis for both Aims 2 and 3, as specified previously, informed the creation of the adjusted hazards model for this sub-analysis. An adjusted cox proportional hazards model was created as previously described in Aim 3 analysis, however this model included an interaction term between smoking and fracture region injury. I tested whether the effect of fracture region is stronger among smokers compared to non-smokers at the time of trauma admission based on the statistical significance of the interaction term in the model between smoking and fracture region. The interaction between smoking and other substance use was considered significant at an alpha of 0.05 or less. The results of this analysis are detailed in Appendix C, but are not included in the Chapter results.

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CHAPTER III: THE RISK OF DRUG OVERDOSE DEATH FOLLOWING SURVIVAL OF TRAUMATIC INJURY[1].

A. Introduction

Since 2011, drug overdoses have become the leading cause of injury death, surpassing motor vehicle crashes.[73] The national age-adjusted drug overdose death rate tripled between 1999 and 2016.[74] The rise in drug overdose deaths has been declared a nationwide public health emergency prompting a concerted effort by the Department of Health and Human Services to decrease rates of drug overdose deaths.[75] To support these efforts, it is essential to identify populations at high risk for drug overdose death.

Trauma patients may be at higher risk of drug overdose death due to several factors. They are more likely to have a past or current substance use disorders (SUD) at the time of admission.[76-81] Both alcohol use disorders (AUD) and other SUDs have been associated with a higher risk of opioid dependence and drug overdose death.[82-85] Development of chronic pain after a traumatic injury, which is often managed with opioids, can also result in the development of opioid dependency, a risk factor for drug overdose death.[83, 86-89] Thus, increased prevalence of pre-existing risk factors and development of chronic pain following injury may increase trauma patients' risk of opioid use disorder (OUD) and subsequent overdose,[76,79,83,89] yet no studies to date have examined drug overdose death in this population.

Baird *et. al* (2017) recently examined risk factors for non-fatal opioid overdose among trauma patients and found that nearly 70% of trauma patients had at least one risk factor for opioid overdose.[90] Zedler *et. al* (2014) also examined patient risk factors

[1] Christina R Greene, Jennifer S Albrecht, Gordon S Smith, Gabriel Ryb, Min Zhan, David Mann, Patricia C Dischinger. In Preparation for Submission.

associated with opioid overdose among veterans and found that traumatic injury was significantly associated with higher adjusted odds of experiencing a non-fatal opioid-related overdose ($p<0.0001$).[91] Neither study examined drug overdose death.

Past studies have shown that trauma patients who survive to hospital discharge are at an increased risk of all-cause,[92] natural cause,[93] injury,[92-94] and suicide[95] mortality following trauma discharge,[92] yet no current study has specifically examined drug overdose mortality following trauma. This study aims to determine whether trauma patients are at an increased risk of drug overdose death by comparing their subsequent drug overdose mortality rate to that of the general population.

B. Methods

Study Design, Data Source, and Study Population

To determine the rate of drug overdose deaths in the trauma population, we used data from the R. Adams Cowley Shock Trauma Center (STC) data registry (STR). The STC is Maryland's state designated primary adult resource center for traumatic injuries. The STR includes information on patient demographics, premorbid conditions at the time of injury, blood alcohol toxicology upon admission, mechanism and external cause of injury, and Injury Severity Score (ISS). Individuals between the ages of 18 and 64 years who were admitted to the STC from the injury scene between January 1, 1999 and October 31, 2008 were considered for inclusion. We required a blunt or penetrating injury mechanism and survival to at least 31 days following the recorded date of discharge. If a patient had more than one trauma admission to STC during this period of time only the last recorded admission was included. Patients who had a recorded premorbid condition of malignant cancer upon admission, as defined by the International

Classification of Diseases 9th revision, Clinical Modification (ICD-9-CM) code, were excluded.

Clinical records for trauma admissions were linked to the National Death Index (NDI) Plus system to determine death status of the patient by December 31, 2008. To create the linkage to the NDI, personal identifiable information, such as social security number, name, and date of birth was sent to the National Center for Health Statistics for linkage into the NDI-Plus system. The NDI-plus includes date of death, underlying cause of death, and up to twenty contributing causes of death. Underlying cause of death and contributing causes of death were recorded using the International Classification of Diseases 10th revision (ICD-10) mortality codes. Further detail on this methodology is provided elsewhere.[96]

Deaths were classified as drug overdose deaths, other injury cause deaths, and deaths due to natural causes based on underlying cause of death ICD-10 code. Drug overdose deaths were identified based on CDC definitions:[74,97,98] accidental (X40-44), intentional (X60-64), and undetermined (Y10-14) drug overdose poisonings. Other Injury deaths were determined based on underlying cause of death code between V01-Y89, excluding drug overdose codes. All other deaths with a valid cause of non-injury death were classified as natural cause deaths. Cause and intent of death is determined by the state death investigation.

Information on patient demographics, external cause of injury, Injury Severity Score (ISS), a numerical calculation that is meant to describe the overall injury severity of those with more than one injury,[99] and discharge location were abstracted from the STR. Information on SUD was based on patient record indicating the presence of a

premorbid Alcohol Use Disorder (AUD) or DUD (ICD-9-CM codes 305.XX or 304.XX) Level of Blood Alcohol Content was based on toxicology blood testing results was obtained for most patients admitted from the scene of injury on admission.

Statistical Analysis

Standardized mortality ratios (SMRs) were used to compare overdose deaths in the trauma patient cohort to those in the Maryland general population. This methodology has been used previously by Ryb *et. al* (2006) to compare suicide mortality rates in surviving trauma patients to the general population.[95] Person-time for each patient was determined by computing the time starting at 31 days following hospital discharge to death outcome or end of follow-up period, December 31, 2008. Total person time was determined for each aggregated age, sex, and race group in the study cohort. Standardized Mortality Ratios for drug overdose deaths were calculated using aggregated mortality rates for each of these specific causes of death in the Maryland population, stratified by race, age, and sex from 1999 to 2008. The death rates for the statewide population were obtained from CDC WONDER, a web-based data query system that delivers mortality information based on user menu response.[100] Within the trauma cohort, patient characteristics were compared between patients who did and did not die of drug overdose using Pearson's χ^2 statistic. Mean follow-up time was compared between four patient outcome categories (survival, drug overdose death, other injury death, and natural cause death) using a one-way ANOVA test.

To assess the incidence of drug overdose death in each year following trauma survival, we determined the number of drug overdose deaths that occurred within each year interval following the first month after trauma discharge based on patient date of

discharge. The number of person years of follow-up was determined following the first month after trauma discharge. We divided the number of drug overdose deaths within each year by the number of person time for that year to obtain an incidence rate of drug overdose deaths based on yearly person-time.

Drug overdose deaths were further explored by substances involved and intent of overdose death based on underlying cause of death. Substances were classified into the following categories based on ICD-10 mortality codes: 1) Non-Opioid Analgesics, including Antipyretics and Antirheumatics (X40, X60, Y10), 2) Anti-epileptics, including sedative-hypnotics and psychotropic medications (X41, X61, Y11), 3) Narcotics and Psychodysleptics (X42, X62, Y12), 4) Drugs acting on the Autonomic Nervous System (X43, X63, Y13), and 5) Other unspecified drugs, medicaments and biological substances (X44, X64, Y14). Further reference on drugs and medications included in these categories can be found through the World Health Organization (WHO) International Statistical Classification of Diseases and Related Health Problems 10th Edition. This study was approved by the IRB (IRB proposal #HP-00043633).

C. Results

There were 45,469 trauma patients aged 18 to 64 years who were t admitted to the STC between January 1999 and October 2008. After excluding transfers (n=7,234), those who died in hospital (n=1,506) and within 30 days after discharge (n=381), those with a cancer diagnosis on admission (n=55), unknown sex (n=5), and non-Maryland residents at the time of admission (n=3,370), the final analytic sample consisted of 32,918 trauma patients. Characteristics of the trauma patient cohort are detailed in Table 1. Most trauma patients were male (72%), white (55.6%), BAC negative (66.4%), and

had no documented past or current AUD or DUD (85.8%) at the time of admission. Over 75% of patients were under 45 years old, with over 27% between the ages of 18 and 24. The majority of patients were admitted due to a motor vehicle crash (57.1%) and over half had an ISS between 1 and 8.

Over 4% of patients in the trauma cohort (N=1,403) died during follow-up. Most of these expired due to natural causes (N=848, 60.4% of deaths). One percent of trauma patients (n=325, 23.2% of deaths) died due to non-drug overdose injury causes and 0.7% of trauma patients died due to drug overdose (n=230, 16.4% of deaths).

Patients who died of drug overdose were predominantly male (76%), white (68.7%). and between the ages of 35 and 44 (38.3%) at the time of admission (Table 4). Drug overdose decedents were more likely to have a past or current AUD or DUD noted in their health record; however, there was no significant different in the distribution of positive BAC categories between those who did and did not die of drug overdose (Table 4). Over half of those who died of drug overdose were current smokers at the time of admission (53%). The prevalence of smoking at the time of admission was nearly 16% lower in trauma patients who did not die of drug overdose (37.4%, $p<0.001$). Those who died of drug overdose death were more likely to have injuries due to beating (14.4%) or knife (12.2%) compared to those who did not die of drug overdose, as shown in Table 4 ($p<0.001$). Distribution of all demographic and patient characteristics were significantly different for age, race, sex, substance use disorder, smoking status, mechanism of injury, and place of discharge based on drug overdose death outcome (Table 4).

Table 4: Characteristics of Surviving Trauma Patients by Drug Overdose Death Status during follow-up: 1999-2008

	All (N=32,918)	Drug Overdose Deaths 230 (0.7%)*	All Other Trauma Patients 32,688 (9.3%)	p-value**
Sex, n (%)				0.23
Male	23,725 (72.1)	174 (75.7)	23,551 (72.1)	
Female	9,193(27.9)	56 (24.3)	9,175 (27.9)	
Age, n(%)				<0.001
18-24	9,024 (27.4)	36 (15.7)	8,988 (27.5)	
25-34	8,115 (24.7)	54 (23.5)	8,061 (24.7)	
35-44	7,665 (23.3)	88 (38.3)	7,577 (23.2)	
45-54	5,495 (16.7)	41 (17.8)	5,454 (16.7)	
55-64	2,619 (8.0)	11 (4.8)	2,608 (8.0)	
Race, n(%)				<0.001
White	18,302 (55.6)	158 (68.7)	18,144 (55.5)	
Black	12,086 (36.7)	68 (29.6)	12,018 (36.8)	
Other /Unknown	2,530 (7.7)	4 (1.7)	2,526 (7.7)	
Blood Alcohol Content, n(%)				0.07
BAC Negative	21,864 (66.4)	139 (60.4)	21,725 (66.7)	
Under 80mg/dL	2,182 (6.6)	21 (9.1)	2,161 (6.6)	
80-219 mg/dL	4,659 (14.2)	29 (12.6)	4,630 (14.2)	
220+ mg/dL	2,860 (8.7)	29 (12.6)	2.831 (8.7)	
Unknown	1,353 (4.1)	12 (5.2)	1,341 (4.1)	
Substance Use Disorder diagnosis, n (%)				<0.001
No Substance Use Disorder	26,752 (85.8)	158 (68.7)	28,167 (82.6)	
Alcohol Use Disorder only	1,053 (3.4)	27 (11.7)	1,086 (3.3)	
Drug Use Disorder only	1,870 (6.0)	20 (8.7)	1,894 (5.8)	
Alcohol and Drug Use Disorder	1,519 (4.9)	25 (10.9)	1,541(4.7)	
Smoking Status, n(%)				<0.001
Non-Smoker	20,562 (62.5)	108 (47.0)	20,454 (62.6)	
Smoker	12,356 (37.5)	122 (53.0)	12,234 (37.4)	
Mechanism of Injury (Unknown=3), n(%)				<0.001
Motor Vehicle Crash	18,787(57.1)	109 (47.4)	18,678 (57.1)	
Other Vehicle	642 (2.0)	3 (1.3)	639 (2.0)	
Firearm	2,373 (7.2)	12 (5.2)	2,361 (7.2)	
Fall	4,489 (13.6)	33 (14.4)	4,456 (13.6)	
Knife	2,391 (7.3)	28 (12.2)	2,363 (7.2)	
Beating	2,472 (7.5)	33 (14.4)	2,439 (7.5)	
Other*	1,761 (5.4)	12 (5.2)	1,749 (5.4)	

Table 4: Continued

	All (N=32,918)	Drug Overdose Deaths 230 (0.7%)*	All Other Trauma Patients 32,688 (9.3%)	p-value**
Injury Severity Score, n(%)				0.73
Missing/Unknown	1,122 (3.4)	7 (3.2)	1,115 (3.4)	
ISS 1-3	7,447 (22.6)	50 (21.7)	7,397 (22.6)	
ISS:4-8	10,661 (32.4)	83 (36.1)	10,578 (32.4)	
ISS: 9-15	7,281 (22.1)	51 (22.2)	7.230 (22.1)	
ISS" 16-24	3,755 (11.4)	26 (11.2)	3,729 (11.4)	
ISS: 25+	2,652 (8.1)	13 (5.7)	2,639 (8.1)	
Place of Discharge, n(%)				<0.001
Home No Services	26,466 (80.4)	166 (72.2)	26,300 (80.5)	
Home Care/Services	967 (2.9)	6 (2.6)	961 (2.9)	
Inpatient Facility	3,862 (11.7)	34 (14.8)	3,828 (11.8)	
Rehabilitation/ Psychiatric Facility	191 (0.6)	9 (3.9)	182 (0.6)	
UMMS	623 (1.9)	7 (3.0)	616 (1.9)	
Police	366 (1.1)	4 (1.7)	362 (1.1)	
Other¥	443 (1.4)	4 (1.7)	439 (1.3)	

*Other Injuries include accidental blunt injuries due to striking by object or persons, accidental blunt injuries due to machinery, accidental penetrating injuries due to machinery, accidental blunt injuries due to sports, and all other blunt or penetrating injuries not elsewhere classified.

¥Other places of discharge include Residential Facility, Shelter, Acute or Chronic Care, AMA, Other locations of discharge not otherwise classified, and Unknown place of discharge.

The aggregated annual drug overdose mortality rate for the trauma cohort was 148.9 per 100,000 (230 drug overdose deaths per 154,421.2 person-years) compared with an age, race, and sex adjusted rate of 24.4 per 100,000 in the Maryland general population for the reference period of 1999 to 2008. The expected number of drug overdose deaths using the rates within the Maryland population was 37.7, assuming an identical age, race, and sex distribution to that of trauma study population. The observed number of trauma drug overdose deaths (230) was over 6 times the expected number of drug overdoses given the drug overdose rate observed in the Maryland population (SMR=6.10, 95% C.I. 5.35-6.93, Table 5). Trauma Patients were also more likely to die

of future injury causes (SMR=2.77, 95% C.I. 2.48-3.08) and natural causes (SMR=2.75, 95% C.I. 2.57-2.94) than the Maryland reference population.

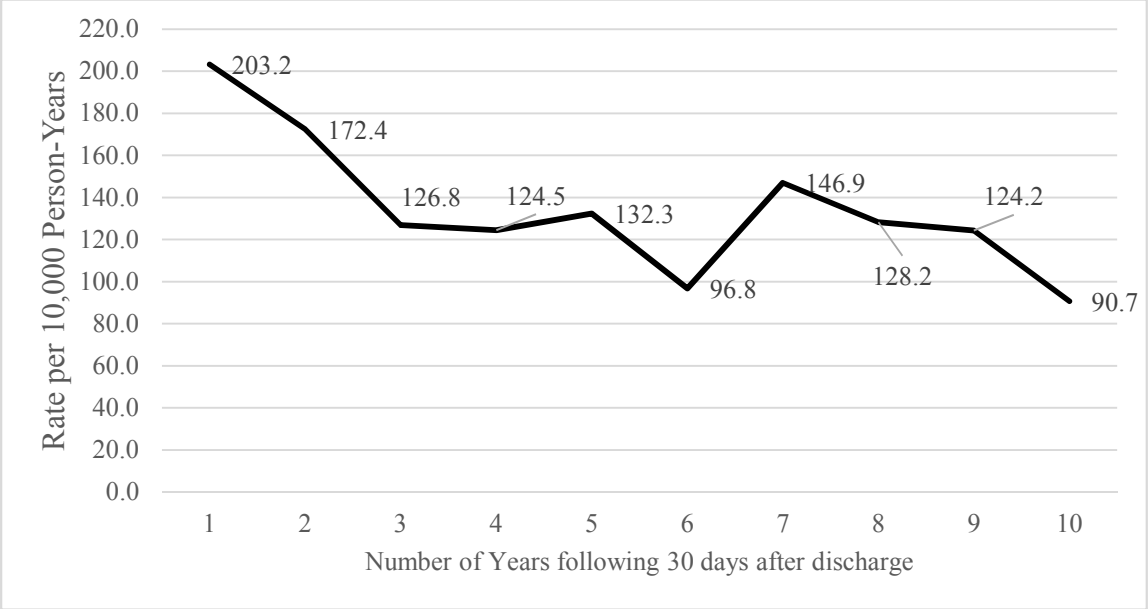
Table 5: Comparison of Observed and Expected number of Drug Overdose Deaths in Trauma Patients adjusting for Age, Race, and Sex Population Differences:1999-2008

Cause of Death	Observed Deaths	Expected* Deaths	SMR	95% C.I.
Drug Overdose	230	37.71	6.10	5.35-6.93
Other Injury Cause	325	117.50	2.77	2.48-3.08
Natural Cause	848	308.19	2.75	2.57-2.94

**Number of deaths that would be observed if the rate of drug overdose death in trauma patients was equal to the Maryland general population, adjusting for age, race, and sex distribution differences.*

As shown in Figure 5, the highest incidence rate of drug overdose deaths was observed within the first 2 years of trauma discharge. The incidence of drug overdose mortality was highest within the first year following trauma discharge, with a rate of 203.2 per 100,000 person-years. The incidence of drug overdose death remained high in the second year following trauma discharge at 172.4 per 100,000 person-years. Subsequent years following trauma discharge show a dip in the incidence of drug overdose death among trauma patients, varying between 90.7 and 146.9 per 100,000 person-years. The rate of drug overdose deaths among trauma patients remained substantially higher than the overall drug overdose death rate of the Maryland general population throughout the entirety of the follow-up period.

Figure 5: Annual Rates of Drug Overdose Death among trauma patients admitted to STC and surviving to 30 days post-discharge



Drug Overdose Deaths by Substance and Intent

Most drug overdose deaths (80.8%) were due to narcotics or psychodysleptics (Table 6). Over 12% of drug overdose deaths were due to other and unspecified drugs, which includes general and local anesthetics and other drugs as detailed in the ICD-10 World Health International Classification: 5.2% were due to anti-epileptic, sedative hypnotic or psychotropic drugs, and 1.7% were due to non-opioid analgesic drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs). The large majority of drug overdose deaths were of undetermined intent (n=201, 87%) and most of these were due to narcotics or psychodysleptics (n=171). Only 8% of drug overdose deaths (n=19) were considered unintentional and 4% were intentional or suicidal (n=10).

Table 6: Primary Substance of Abuse involved in Drug Overdose Deaths among Trauma Patients: 1999-2008

Category of Substances	ICD-10 Mortality Codes	Examples of Drugs in Category*	Number of Drug Overdose Deaths
Non-Opioid Analgesics	X40, X60, Y10	Nonsteroidal anti-inflammatory drugs (NSAID) Salicylates	4 (1.7%)
Anti-epileptics, including sedative hypnotics	X41, X61, Y11	Antidepressants Barbituates, Psychoactive drugs (e.g. Benzodiazepines)	12 (5.2%)
Narcotics and Psychodysleptics	X42, X62, Y12	Opioids Cocaine LSD Cannabis derivatives	186 (80.9%)
Other Unspecified Drugs	X44, X64, Y14	Anaesthetics Hormones Antibiotics Therapeutic gases Vaccines	28 (8.7%)

**Further examples of drugs in each category/code can be found at http://apps.who.int/classifications/icd10/browse/2008/en*

D. Discussion

After adjusting for age, race, and sex, the drug overdose mortality rate among surviving trauma patients was six times higher than that in the Maryland general population. While we did observe a higher rate of deaths due to natural and other injury causes in trauma patients compared to the Maryland population, the magnitude of effect was much smaller than that observed for drug overdoses. Past studies have confirmed a higher suicide,[95] injury,[93,94,101] and natural cause mortality rate[92,93,101] in trauma patients compared to statewide reference populations and non-trauma populations.

We found that trauma patients were at highest risk for drug overdose in the first two years following trauma discharge. These findings agree with previous studies on drug overdose death among prisoners, with previous studies[102] finding that the first year following release is the time where patients are at greatest risk. While the incidence of

drug overdose deaths among surviving trauma patients decreased from the third year following trauma discharge, the rate of drug overdose deaths remained consistently higher than that of the reference population, which averaged 24.4 per 100,000 from 1999-2008 after adjusting for age, race, sex distribution. This finding indicates that while drug overdose mortality may be greatest in the first two years following trauma, the additional risk can persist for up to 10 years after the traumatic event.

Similar to other findings for drug overdose death,[84,85] male sex, white race, and recorded DUD or AUD were associated with an increased risk of drug overdose death in trauma patients. In our study, an identified DUD/AUD was a better indicator of future drug overdose death than BAC level on admission.

Trauma patients who died of drug overdose did not differ from others in injury severity based on ISS scores. Previous studies did not find an association between higher ISS and prolonged opioid usage[103,104] so these results seem to add further strength to the conclusion that drug overdose death risk is primarily based on a patient's pre-existing condition and not injury severity.

We found that over 80% of drug overdose deaths were due to a narcotics or psychodysleptics. While we sought to investigate which specific prescription drugs were involved in these deaths, we were unable to do so reliably given the potential under-reporting of specific substances involved in drug overdose death records.[105] Citing the specific drugs involved as being the primary cause of the overdose is far more difficult to do, primarily because drugs such as heroin may metabolize more quickly and might be missed in a toxicology screen.

The strengths of this study included the completeness of the trauma patient demographic information, a large sample of trauma patients from an urban level 1 trauma center, and the use of CDC Wonder to obtain age, race, and sex specific drug overdose mortality rates for the Maryland population. Our study had several limitations, however, as we were not able to determine whether opioids were prescribed after trauma injury. First of all, we were limited in that we were only able to capture drug overdoses that resulted in fatalities. While we were unable to determine which trauma patients were prescribed opioids, other published research has reported that almost all (95%) of trauma patients receive opioids following discharge.[79] We were also unable to determine whether trauma patients sought treatment for any opioid or other substance use disorders.

Despite the limitations of our data, our findings bring attention to the excess drug overdose risk among trauma patients. The excess drug overdose mortality observed in our study should raise an alarm to those tasked with identifying and targeting overdose prevention efforts to high-risk populations. We hope that our findings will lead to future research on drug overdose outcomes in trauma patients.

Our findings also shed light on which trauma patients may be at risk of drug overdose death. Further research will be needed to fully address the risk factors for drug overdose from within the trauma population. This research could help clarify the extent to which patient demographic and injury risk factors are associated with drug overdose.

Conclusion

Trauma patients who survive the first 30 days following discharge have a significantly increased risk of drug overdose death. The excess risk of drug overdose death is much more pronounced than the excess risks associated with other injury or

natural death causes in surviving trauma patients. As a result of these findings, trauma patients should be considered a high risk population for drug overdose. Future intervention efforts should be targeted towards this population to reduce future drug overdose mortality following trauma. Prescribers should also be aware of the excess drug overdose risk among trauma patients and take extra caution in prescribing narcotics, since over 81% of drug overdose deaths in trauma patients were due to narcotics.

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CHAPTER IV: SMOKING AS A RISK FACTOR FOR DRUG OVERDOSE DEATH IN TRAUMA PATIENTS

[1].

A. Introduction

Drug overdoses are the leading cause of injury death, and since 2011 have even exceeded the number of deaths due to motor vehicle crashes.[106] In response to the sharp increase in drug overdose deaths, the Department of Health and Human Services declared a public health emergency to address the national opioid crisis.[107] Much of the initial rise in drug overdose deaths has been due to prescription opioid drugs, which have been responsible for 63% of drug overdose deaths that occurred in 2015.[108] Since 2013, however, most fatal opioid-drug overdose deaths were due to heroin or synthetic opioids, such as fentanyl, rather than other prescription drugs.[109] It is essential that we identify and target populations at increased risk of opioid use disorder (OUD) and drug overdoses through focused intervention efforts.

Trauma patients may be at higher risk of developing OUD and drug overdose death due to several reasons. First of all, trauma patients have a higher prevalence of pre-existing substance use disorders [110-115] which have been independently associated with drug overdose death.[116,117] Trauma patients also are at higher risk of chronic pain following injury which could lead to dependence on opioids potentially leading to dependence and an increased risk of drug overdose. [118-120] These risk factors, coupled with the availability of prescription opioids following trauma,[121] may place trauma

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patients at a higher risk of drug overdose death. One risk factor that may beget further investigation in its association to drug overdose death is smoking. While smoking is reported in approximately 27-38% of trauma patients,[122, 123] little is known regarding its possible role as a risk factor for drug overdose death following trauma.

Smokers may be at a higher risk of developing an opioid addiction following trauma. Smokers report higher levels of pain[124-127] and also are more likely to engage in high risk behaviors,[122] both factors association with future addiction. Smoking also commonly coexists with past or current alcohol and substance use disorders[127] and other psychological conditions,[128] such as depression.[124, 125] While a few studies have identified an association between smoking and prolonged opioid use in trauma and surgery patients,[127, 129-131,] the risk of drug overdose mortality among smokers has not been examined prospectively. One case-control study conducted among non-trauma patients [132] reported that smoking was associated with significantly higher odds of death due to prescription opioids.

The objective of this study was to determine whether current smoking at the time of trauma is independently associated with a higher risk of subsequent drug overdose death following discharge from hospital.

B. Methods

Study Design, Data Source, and Study Population

A retrospective cohort study was conducted using data from the R. Adams Cowley Shock Trauma Center (STC) data registry (STR) linked to the National Death Index (NDI). The STC is Maryland's state designated primary adult resource center. The STR includes information on patient demographics, premorbid conditions at the time of

injury, blood alcohol toxicology upon admission, mechanism and external cause of injury, and Injury Severity Score (ISS). Individuals between the ages of 18 and 64 years who were admitted to the STC from the injury scene between January 1, 1999 and October 31, 2008 were considered for inclusion. We required a blunt or penetrating injury mechanism and survival to at least 30 days following the recorded date of discharge. If a patient had more than one trauma admission to STC during this period of time, only the last recorded admission was included. Patients who had a recorded premorbid condition of malignant cancer upon admission, as defined by the International Classification of Diseases 9th revision, Clinical Modification (ICD-9-CM) code, were excluded. The study cohort was further restricted to patients who were tested for blood alcohol level on admission (95.9% of remaining sample) to adequately account for known level of alcohol use in trauma patients at the time of admission. This study was approved by the University of Maryland IRB (IRB proposal #HP-00043633).

Drug Overdose Death

Clinical records for trauma admissions were linked to the NDI Plus system to determine death status of trauma patients by December 31, 2008. To create the linkage to the NDI, personal identifiable information, such as social security number, name, and date of birth from the STR was sent to the National Center for Health Statistics for linkage into the NDI-Plus system. The NDI-plus includes date of death, underlying cause of death, and up to twenty contributing causes of death for patients identified as having died. Underlying cause of death and contributing causes of death were recorded using International Classification of Diseases 10th revision (ICD-10) mortality codes. Further detail on this methodology is provided elsewhere. [133]

Patients who were not identified as having died were censored at the end of the follow-up period (12/31/08). Deaths were classified as drug overdose deaths, other injury cause deaths, and deaths due to natural causes based on underlying cause of death ICD-10 code. Drug overdose deaths were identified based on CDC definitions[109]: accidental (X40-44), intentional (X60-64), and undetermined (Y10-14) drug overdose poisonings. Other Injury deaths were determined based on underlying cause of death code between V01-Y89, excluding drug overdose codes. All other deaths with a valid cause of non-injury death were classified as natural cause deaths. Cause and intent of death is determined by the state death investigation.

Smoking

Current smoking is recorded as a binary variable in the STC Registry, based on patient records indicating an ICD-9-CM code of 305.1X. This information is obtained via patient report by the patient's nurse or doctor at the time of trauma admission. If the patient was unable to answer the question, a proxy respondent was used.

Substance Use Disorders and Blood Alcohol Content (BAC)

Patients were considered to have "substance use" if they had a BAC $\geq$ 80mg/dL or a known ICD-9-CM diagnosis of AUD or DUD in their electronic health record. Information on known drug or alcohol use disorder was based on patient premorbid condition record as noted in the patient's electronic health record (EHR) indicating the presence of a premorbid Alcohol Use Disorder or Drug Use Disorder (ICD-9-CM codes 305.XX and 304.XX, excluding 305.1). Level of Blood Alcohol Content was based on toxicology testing results obtained for 95.9% of patients admitted from the scene of injury on admission. Because BAC above 80mg/dL, Drug Use Disorder (DUD), and

Alcohol Use Disorder (AUD) were strongly associated ($p<0.001$) with each other in exploratory analyses we decided to adjust only for one indicator of "substance use" within the adjusted multivariable model.

Mental Health Conditions

Presence of a known mental health condition was determined based on patient record indicating the presence of a premorbid known mental health condition in the patient's EHR defined by ICD-9-CM codes: Schizophrenic disorders (295.XX), episodic mood disorders (296.XX), and delusional disorders (297.XX), other nonorganic psychoses (298.XX), anxiety disorders (300.XX), and depressive disorders (311.XX).

Other Covariates

Neighborhood Socioeconomic Status (SES) was estimated using median income from the US Census for each patient residential zip code.[134] Zip codes are based on zip code of residence as recorded in the trauma registry for each patient admission. Median Income categories was categorized by quartiles for ease of interpretation.

Patient demographics, Injury Severity Score (ISS), a numerical calculation that is commonly used to describe the overall injury severity of those with more than one injury,[134] and external causes of injury were abstracted from the STR. Patient cause of injury admission is coded based on External Cause of Injury, ICD-9-CM code.

Statistical Analysis

We conducted bivariate analyses to assess the potential relationships between smoking and patient demographic characteristics, premorbid conditions, blood alcohol content (BAC), neighborhood median income, injury severity, and external cause of injury admission. We compared the distribution of current smoking status between those

who died of drug overdose, other injuries, and natural causes compared to those who did not die at the end of the follow-up period using Chi-Square Goodness of Fit. For continuous variables, such as age and neighborhood median income, we use a student's t-test for comparison of means based on smoking status. Kaplan-Meier survival curves were used to compare unadjusted rates of drug overdose death overall and stratified by sex. Drug overdose survival rates were compared based on smoking status reported upon trauma admission using the Log-rank test.

We used a Cox Proportional-hazards model to assess the relationship between smoking status and drug overdose death. Covariates were included in the adjusted model if they were identified as potential confounders. Age, sex, race, median neighborhood income, mental health condition, and substance use, were selected as potential cofounders based on a review of the literature regarding smoking and drug overdose death among trauma and orthopedic surgery populations.

Because some patients died of other causes during follow-up, we adjusted for cause-specific mortality outcomes using methods for competing risks described by Fine and Grey[136] in both the CIF curves and the proportional subdistribution hazards model. Additionally, we tested for interaction of smoking with sex and substance use, separately, within our adjusted model by adding an interaction term for each of these terms in the adjusted model. We chose to test for an interaction with sex based on previous findings that reported a difference between males in females in the association of smoking with the development of opioid use disorder (OUD).[130] Additionally, we explored the interaction between smoking and substance use to further explore how smoking may behave as a risk factor in those with and without other known drug overdose risk factors.

We considered an interaction term significant if the coefficient was associated with the outcome at a significance level of 0.05 or less using the chi-squared test statistic associated with the beta coefficient in the model. If the interaction term was significant, we reported our results as stratified by the interaction variable of interest. Findings were considered significant at a p value of <0.05 and proportionality of hazards for covariates was verified using negative log-log Kaplan-Meier survival curves for each variable.

C. Results

During the study period, 45,469 trauma patients between the ages of 18 and 64 were admitted to the STC. We excluded those not admitted from the scene (n=7,234), those who died at discharge (n=1,506) and within 30 days after discharge (n=381), those with a cancer diagnosis on admission (n=55), unknown sex (n=5), and patients who were not tested for BAC on admission (n=1,487). The final analytic sample consisted of 34,801(76.5% of initial sample) trauma patients.

Most trauma patients were male (72.3%), white (56.7%), and BAC negative (69.7%, Table 7). Over 75% of patients were under 45, with over 27% between the ages of 18 and 24. The majority of patients were admitted due to a vehicular injury (60.0%) and over half had an ISS between 1 and 8.

Compared to non-smokers, trauma patients who smoked were more likely to be Male (76.5% vs 69.8%, p<0.001) and have a known AUD (14.4% vs. 4.0%, p<0.001), a known DUD (17.9% vs. 6.1%, p<0.0001), or a known mental health condition (9.2% vs. 6.3%, p<0.0001) identified during trauma admission (Table 7). Smokers were also more likely to have a positive BAC at any level (<80mg/dL, 80-219mg/dL, 220+ mg/dL) compared to non-smokers (Table 7). Smokers were also more likely to be admitted for

Beating (9.4% vs. 6.0%) and Knife/Gunshot (15.6% vs. 12.1%, p<0.001) injuries compared to non-smokers and were less likely to have an ISS over 25 (5.5% vs. 10.0%, p<0.001), indicating less severe injury. Smokers were also more likely to be in the lowest median income quartile compared to non-smokers (29.8% vs. 24.4%, p<0.001).

Table 7: Association of Smoking with Patient Demographics, Premorbid Conditions, and Injury variables for trauma patients who survived 30 days past discharge

	All (N=34,801)	Non-Smokers 21,807 (62.7%)	Smokers 12,994 (37.3%)	p-value
Sex, n (%)				<0.001
Male	25,158 (72.3)	15,214 (69.8)	9,944 (76.5)	
Female	9,643 (27.7)	6,593 (30.2)	3,050 (23.5)	
Age, n (%)				<0.001
18-24	9,528 (27.4)	5,904 (27.1)	3,624 (27.9)	
25-34	8,597 (24.7)	5,417(24.8)	3,180 (24.5)	
35-44	8,071 (23.2)	4,850 (22.2)	3,221 (24.8)	
45-54	5,788 (16.6)	3,626 (16.6)	2,162 (16.6)	
55-64	2,817 (8.1)	2,010 (9.2)	807 (6.2)	
Age (μ ±SD)	35.0 ± 12.4	35.3 ± 12.7	34.5 ± 11.9	<0.001
Race, n (%)				<0.001
White	19,729 (56.7)	12,070 (55.4)	7,659 (58.9)	
Black	12,190 (35.0)	7,581 (34.8)	4,609 (35.5)	
Other /Unknown*	2,882 (8.3)	2,156 (9.9)	726 (5.6)	
Condition, n (%)				
Alcohol Use Disorder	2,742 (7.9)	870 (4.0)	1,872 (14.4)	<0.001
Drug Use Disorder	3,660 (10.5)	1,335(6.1)	2,325 (17.9)	<0.001
Mental Health	2,564 (7.3)	1,365 (6.3)	1,199 (9.2)	<0.001
Blood Alcohol Content, n (%)				<0.001
BAC Negative	24,266 (69.7)	16,324 (74.9)	7,942 (61.1)	
BAC <80	2,363 (6.8)	1,286 (5.9)	1,077 (8.3)	
BAC 80-219	5,057(14.5)	2,571	2,486 (19.1)	
BAC 220+	3,115 (9.0)	(11.8)	1,489 (11.5)	
		1,626 (7.5)		
BAC>80 or Substance Use Disorder, n (%)	10,287 (29.6)	4,893 (22.4)	5,394 (41.5)	<0.001
Injury Severity Score, n (%)				<0.001
ISS 1-3	7,551 (21.7)	4.575 (21.0)	2,976 (22.9)	
ISS:4-8	11,378 (32.7)	6,963 (31.9)	4,415 (34)	
ISS: 9-15	7,758 (22.3)	4,724 (21.7)	3,034 (23.4)	
ISS:, 16-24	4,082(11.7)	2,614 (12)	1,468 (11.3)	
ISS: 25+	2,885 (8.3)	2,173 (10)	712 (5.5)	
Missing/Unknown	1,147 (3.3)	758 (3.5)	389 (3.0)	

Table 7: Continued

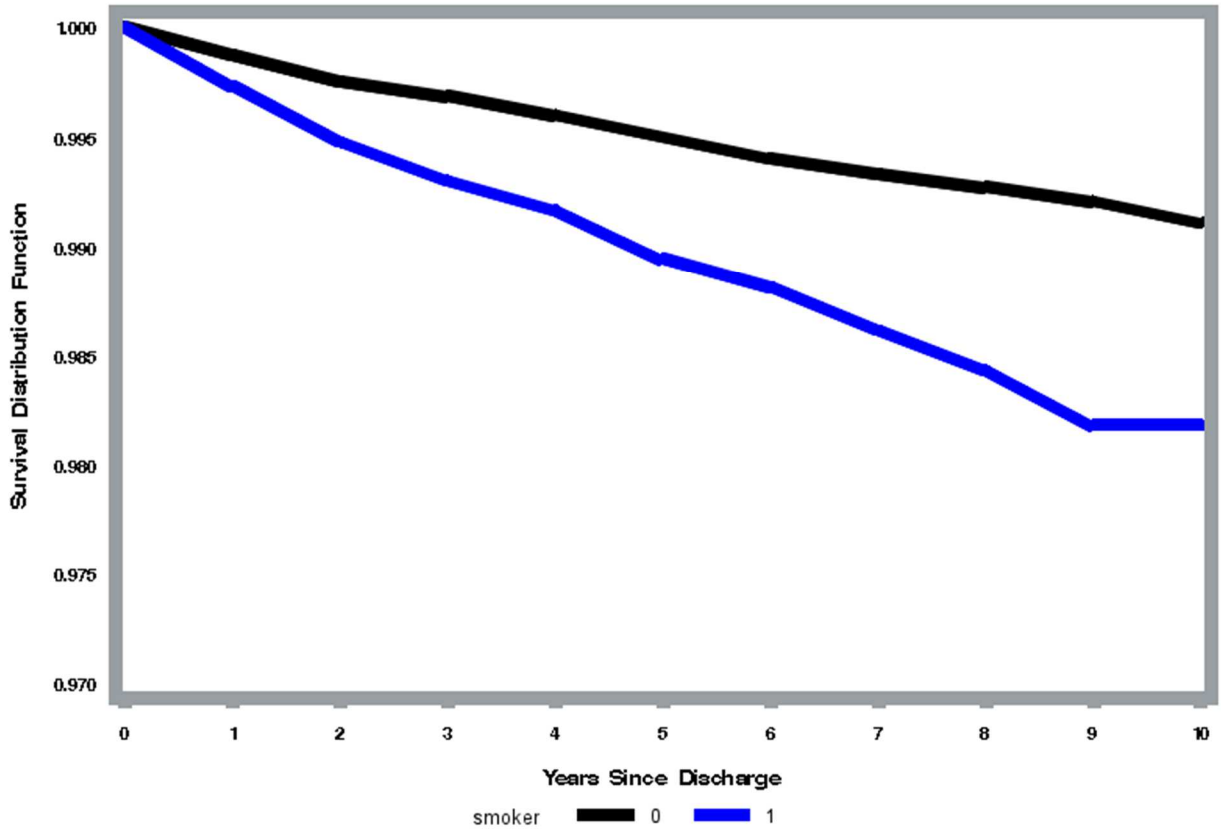
Median Neighborhood Income,				
n(%)	9,160 (26.3)	5,286 (24.4)	3,874 (29.8)	<0.001
<$41,621	7,656 (22.0)	4,783 (21.9)	2,873 (22.1)	
$41,622-$60,506	8,447 (24.3)	5,474 (25.1)	2,973 (22.9)	
$60,507-$83,610	8,365 (24.0)	5,548 (25.4)	2,817 (21.7)	
$83,611+	1,173(3.4)	716 (3.3)	457 (3.5)	
Unknown				

*Other/Unknown Race includes Hispanic/Latinos of any race, Asian, American Indian/Alaska Native, races classified as Other or Unknown

¥ Other Injuries include accidental blunt injuries due to striking by object or persons, accidental blunt injuries due to machinery, accidental penetrating injuries due to machinery, accidental blunt injuries due to sports, and all other blunt or penetrating injuries not elsewhere classified.

Patient follow-up time ranged from 31 days to 10 years, with a mean follow-up time of 4.7 years (standard deviation 2.8 years). Among the trauma patients included in the study, 4.1% (n=1,478) were identified as having died by the end of the follow-up period, 0.7% (n=230) of patients died of drug overdose. Comparing cumulative incidence of death, current smoking status was significantly associated with subsequent drug overdose (1.0% vs. 0.5%), other injury (1.0% vs. 0.9%), and natural cause mortality (3.1% vs. 2.1%) at the end of study period ($p<0.001$). Kaplan-Meier curves also showed that smokers were more likely to die from drug overdose than non-smokers ($p<0.001$, Figure 6).

Figure 6: Unadjusted Survival Rates for Subsequent Drug Overdose Death based on Current Smoking Status at Trauma Admission



The final Cox Proportional hazards model was adjusted for age, race, known mental health condition indicated by reported diagnosis, substance use (defined as alcohol use above the legal limit or known AUD/DUD), male sex, and median income quartile. The unadjusted risk of drug overdose for trauma patients who were smokers at the time of trauma was double compared non-smokers (HR 2.12: 95% C.I. 1.64-2.75). Following adjustment for potential confounders, smokers were still significantly more likely to die of a drug overdose (HR 1.66: 95% C.I. 1.25-2.21, Table 8).

Table 8: Cox Proportional Hazard Ratios for Drug Overdose Mortality by Smoking Status and other covariates

Variable	Overall Adjusted HR (95% C.I.)
Smoking (Unadjusted)	2.12 (1.64-2.75)
Smoking	1.66 (1.25-2.21)
Age	
18-24	Ref.
25-34	1.59 (1.05-2.41)
35-44	2.42 (1.65-3.56)
45-54	1.72 (1.10-2.69)
55-64	0.96 (0.48-1.95)
Race	
White	Ref.
Black	0.45 (0.33-0.62)
Other	0.20 (0.07-0.55)
Mental Health Condition	2.18 (1.52-3.12)
Substance Use *	1.58 (1.19-2.09)
Male Sex	1.24 (0.90-1.70)
Income	
Unknown	2.17 (1.14-4.13)
(<$41,621)	2.35 (1.59-3.48)
$41,622-$60,506	1.23 (0.81-1.89)
$60,507-$83,610	1.28 (0.85-1.93)
$83,611+	Ref.

*Alcohol Use Disorder or Drug Use Disorder premorbid condition or BAC >80 on admission

In our analysis of interactions between smoking and sex and substance use, we found that the interaction between smoking and substance use at the time of trauma was statistically significant, based on the chi-squared statistic associated with the interaction term (p=0.001, Table 9). The interaction between smoking status and sex, however, was not significant (p=0.16, Table 9).

Table 9: Potential Interaction of Smoking Status with Sex and Substance Use¥, Respectively

Interaction Term	Coefficient β	Standard Error SE	p-value*
Male* Smoking	-0.442	0.316	0.16
Substance Use*Smoking	-0.872	0.270	0.001

]

*Based on chi-square statistic associated with interaction term in model

¥ Alcohol Use Disorder or Drug Use Disorder premorbid condition or BAC >80 on admission

Because the interaction between substance use and smoking status was statistically significant in our exploratory analysis, we decided to stratify our adjusted model by patient substance use. Among patients with substance use, smoking status was not associated with a higher drug overdose hazard (HR=1.01, 95% C.I 0.69-1.48, Table 4). Among patients without substance use, smoking status was associated with a significant increase in the hazard of drug overdose death compared to non-smokers (HR=2.45, 95% C.I. 1.69-3.56, Table 10).

Table 10: Adjusted Cox Proportional Hazard Ratios for Drug Overdose Mortality by Smoking Status and other covariates stratified by Substance Use* on Admission

Variable	Substance Use at Trauma Admission (95% C.I.)	No Substance Use at Trauma Admission (95% C.I.)
Smoking	1.01 (0.69-1.48)	2.45 (1.69-3.56)
Age		
18-24	Ref	Ref.
25-34	2.53 (1.31-4.89)	1.12 (0.63-1.97)
35-44	3.09 (1.63-5.83)	2.11 (1.29-3.45)
45-54	2.24 (1.06-4.72)	1.49 (0.83-2.67)
55-64	2.32 (0.87-6.21)	0.50 (0.17-1.46)
Race		
White	Ref	Ref.
Black	0.47 (0.30-0.75)	0.42 (0.27-0.66)
Other	****	0.32 (0.11-0.88)
Mental Health Condition	2.37 (1.46-3.89)	1.96 (1.15-3.40)

Table 10: Continued

Male Sex	0.94 (0.59-1.49)	1.47 (0.96-2.26)
Income		
Unknown	1.46 (0.49-4.33)	2.74 (1.24-6.05)
(<$41,621)	2.53 (1.42-4.51)	1.98 (1.15-3.40)
$41,622-$60,506	1.19 (0.62-2.25)	1.21 (0.69-2.14)
$60,507-$83,610	1.11 (0.58-2.13)	1.34 (0.80-2.27)
$83,611+	Ref.	Ref.

*Alcohol Use Disorder or Drug Use Disorder premorbid condition or BAC >80 on admission

D. Discussion

Smoking status at trauma admission was significantly associated with an increased risk of drug overdose mortality even after adjusting for important confounders such as age, race, sex, mental health condition, substance use, and median neighborhood income. Previous studies have found that smoking is strongly associated with all external causes of death,[127,138] accidental deaths,[139] and suicides,[140] yet our study is the first to find an increased risk of drug overdose mortality based on current smoking status at the time of trauma. Our results build upon previous studies that found that smoking was independently and significantly associated with prolonged opioid use following musculoskeletal trauma and surgery.[127, 129, 130,

There are several ways that smoking status may be operating causally as a risk factor for drug overdose death. One possibility is that smokers are at increased risk of pain[125, 126] and therefore more likely to develop a dependence on narcotic painkillers for pain-management following a traumatic injury. Another possibility is that smokers may be healing at slower rates compared to non-smokers, a finding which has been previously observed in other studies.[141, 142] The fact that smokers may take longer to heal and perceive more intense pain may provide a pathway to development of chronic pain following traumatic injury and an increased dependence on narcotic painkillers. This

increased physiological dependence could then lead to a potential addiction resulting in a future drug overdose death.

The association between smoking status and drug overdose death differed based on whether the patient had a BAC over the legal limit or known drug or alcohol use disorder documented in EHR on admission. We observed a strong association between smoking status and drug overdose death in trauma patients who did not have a BAC above the legal limit or a known drug or alcohol use disorder. Our results indicated that trauma patients who smoke may be at higher risk of subsequent drug overdose death following injury compared to non-smokers, even if they do not have a BAC above the legal limit or any reported history of alcohol or drug use disorders. One possibility for this observation is that smokers may be more likely to become addicted to narcotic painkillers independent of any other risk factors. Nicotine alters brain chemistry and response to other neurochemicals in a way that leads to an increased risk of addiction of other substances.[143] Smoking has also been associated with impulsivity and sensation-seeking behavior,[144] a trait that has been linked to future substance abuse dependence.[145] Another possible explanation is that smoking is acting as a marker for other unreported or undiagnosed mental health conditions, [146] such as anxiety, depression, and psychological distress, all which are associated with prolonged opioid use and opioid dependence.[117, 147, 148]

Smoking status was not found to be a risk factor for subsequent drug overdose death among patients with substance use. This may be due to the fact that these trauma patients are already at a higher risk of drug overdose, as substance use is associated with prolonged opioid use,[118,149] opioid use disorder,[110, 111, 113]and drug overdose death.[150, 151] It

could also be that substance use may be in the causal pathway between smoking and drug overdose. Based on previous research, we know that smokers are more likely to develop other substance use disorders[143] as well as relapse into previous substance use.[152] In examining our data, however, the direction of the relationship between smoking and other substance use is unclear. It is possible that the smoking behavior could have preceded the use of other substances, yet it is also plausible that other the use of substances may have led to smoking. Due to the fact that all the information is collected at the same time point it is impossible to know which condition preceded the other.

To our knowledge this is the first study to investigate the link between smoking and drug overdose death in a cohort of trauma patients. Our detailed information on patient demographics, comorbidities, and BAC on admission gives us a clear portrait of trauma patients at the time of admission. Blood Alcohol testing on most patients enabled us to determine the alcohol level for the vast majority of trauma patients at the time of admission. Additionally, our linkage to data from the national death index provides accurate cause of death information.

This study also has limitations that should be considered. Because smoking was recorded in a binary manner in the registry, we were unable to assess the potential impact of the frequency and duration of smoking on future risk of drug overdose death. Additionally, comorbidities may have been incomplete as we relied on disorders recorded within the patient's chart based on patient or proxy report. Despite the fact that previous studies on trauma patients report that almost all patients are prescribed opioids at the time of discharge, [118] we did not have information on opioid prescriptions at discharge or thereafter. While we would have preferred to examine prescription opioid drug overdose

death exclusively as an outcome, we were unable to do so due to lack of specificity regarding primary substance of use in many drug overdose death records.[153] Had we chosen to study a more specific outcome, such as prescription opioid overdose death, we could have missed overdose deaths where prescription opioid were a contributing factor yet the specific substances involved were not detailed in the death record.

Despite the limitations of our data, our study quantified the impact of smoking on future drug overdose deaths. Our findings can be used to help tailor future prevention efforts, such as targeted opioid screening towards smokers, that could aim to address intermediate outcomes preceding drug overdose death, such as prolonged or nonmedical opioid use, in smokers following traumatic injury. Additionally, further monitoring of trauma patients who smoke through linkage of data coming from multiple sources (trauma patient records, patient primary care records, and patient prescription drug data) could help health care professionals curb potentially harmful opioid prescribing towards patients who smoke. Additionally, a linkage of such records would also enable other health care providers to screen for potential opioid dependence in former trauma patients at highest risk for future drug overdose death.

Conclusion

Smoking was associated with a significantly higher risk of drug overdose death among trauma patients. This effect was present among trauma patients without substance use at the time of admission, but not among patients with substance use at the time of admission. As a result of these findings, trauma patients who are smokers at the time of admission should be considered at high risk for future drug overdose. Health providers

should take a patient's smoking status into account when managing the prescribing of opioids and narcotics following trauma injury.

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CHAPTER V: THE ASSOCIATION BETWEEN FRACTURE INJURY TYPE AND SUBSEQUENT DRUG OVERDOSE AMONG TRAUMA PATIENTS[1].

A. Introduction

Drug overdose deaths have become the leading cause of injury mortality since 2011, surpassing motor vehicle crashes and firearm related deaths.[154] This increase is primarily fueled by opioids, accounting for 66% of drug overdose deaths in 2016.[154] The alarming rise in the rate of drug overdose deaths over the past 15 years has prompted a declaration of a public health state of emergency by President Trump[155] and the Department of Health and Human Services.[156] As a result, there has been a nationwide effort to reduce drug overdose deaths by identifying and targeting intervention programs to high risk populations.

Trauma injury survivors may be at increased risk of drug overdose death because they have a higher prevalence of substance use and risk taking behaviors.[157, 158] Furthermore, nearly all trauma patients are prescribed opioids upon discharge,[159] which could lead to reliance on opioids for treatment of chronic pain and increase the potential for addiction.

The type of injury sustained may also play a role in the risk of drug overdose death. There is evidence that patients with traumatic lower limb fractures may be at higher risk for prolonged opioid use because they are more likely to experience chronic pain, psychological distress, and disability following the injury.[160-162] For example, Holman *et.*

[1] Christina R Greene, Jennifer S Albrecht, Gordon S Smith, David Mann, Gabriel Ryb, Min Zhan, Erin Winstanley, Patricia C Dischinger. In Preparation for Submission.

Al (2013) found that lower extremity fractures and acetabular fractures were associated with prolonged opioid use.[163] Another study reported that 45% of patients with femoral shaft fractures continued to receive opioids 6 months post-injury, and 36% continues to used opioids 12 months after injury.[164] On the other hand, other studies by Helmerhorst (2014) and Massey (2005) found no association between lower extremity fracture site and prolonged opioid use[165-166] We must take into consideration however, that Massey's study included only 50 fracture patients with very little variation in injury severity.[165] Additionally, Helmerhorst's study may have also been underpowered as it included a total of 145 patients and relied on self-reported opioid use one to two months after orthopedic surgery.[166] Because drug overdose can be an adverse outcome of prolonged opioid use,[158, 167] we sought to investigate the association between lower limb fracture injury and risk of drug overdose in trauma patients.

B. Methods

Study Design, Data Source, and Study Population

A retrospective cohort study using data was conducted using data from the R. Adams Cowley Shock Trauma Center (STC) registry (STR) linked to the National Death Index (NDI). Information on patient demographic characteristics, premorbid conditions at the time of injury, blood alcohol toxicology upon admission, mechanism and external cause of injury, and Injury Severity Score (ISS) was recorded in the STR. The study included non-transfer patients between the ages of 18 and 64 years admitted to the STC between January 1, 1999 and October 31, 2008. Inclusion was restricted to patients with a blunt or penetrating injury mechanism and survival to at least 30 days following the recorded date of discharge. The last recorded admission was included for analysis, if a

patient had more than one trauma admission. Patients who had malignant cancer upon admission, as defined by the International Classification of Diseases 9th revision, Clinical Modification (ICD-9-CM) code, were excluded. This study was approved by the IRB (IRB proposal #HP-00043633).

Drug Overdose Death

Trauma admission clinical records were linked to the NDI Plus system to determine death status of the patient by the end of the follow-up period. Personal identifiable information, such as social security number, name, and date of birth obtained from the STR was sent to the National Center for Health Statistics for linkage into the NDI-Plus system. The information from the NDI-plus included date of death, underlying cause of death, and up to twenty contributing causes of death for patients who died during the study period. Underlying cause of death and contributing causes of death were recorded using International Classification of Diseases 10th revision (ICD-10) mortality codes. A more in-depth discussion of this methodology is provided in another study that utilized a similar cohort.[158]

Patients who did not die according to NDI records were censored at the end of the follow-up period (12/31/08). Deaths were classified based on underlying cause of death ICD-10 code as drug overdose deaths, other injury cause deaths, and deaths due to natural causes. Drug overdose deaths were identified based on CDC definitions:[154] accidental (X40-44), intentional (X60-64), and undetermined (Y10-14) drug overdose poisonings. Deaths due to non-drug external causes were determined based on underlying cause of death code between V01-Y89, excluding drug overdose codes. Other deaths with a valid

non-external cause of death were classified as natural cause deaths. Underlying cause and death intent was determined by the state death investigation.

Presence and Type of Fracture

We identified fractures based on ICD-9-CM codes consistent with fracture injuries in any of the following regions: head, upper extremity, chest/abdominal, spine, pelvic/acetabular, and lower extremity. Due to small numbers of spinal fractures, we collapsed the category of spine and pelvic/acetabular fracture. Patients with fractures in multiple locations were counted as having a fracture in each injured body region. For analysis we divided patients into three mutually exclusive groups: those with a lower limb fracture with or without other fractures, those with one or more fractures in other areas, and those with no fractures.

External Cause of Injury Admission

External cause of trauma injury was obtained from trauma registry records using External Cause of Injury, ICD-9-CM code. External causes of injuries were grouped into the following categories based on external cause of admission code: Vehicular (Motor Vehicle Crash/Other Vehicle), Falls, Penetrating (Firearm/Knife), Beating/Assault, and Other/Unknown injuries.

Other Covariates

Information on patient demographics and comorbidities, smoking status, Blood Alcohol Content (BAC), and Injury Severity Score (ISS) were abstracted from the STR. Level of Blood Alcohol Content was based on toxicology testing results obtained for most patients admitted from the scene of injury at the time of admission. Injury Severity Score (ISS), a numerical calculation that is meant to describe the overall injury severity

of those with more than one injury, [169] was also abstracted from the STR. We defined polytrauma as an ISS greater than or equal to 16, consistent with the definition used in other literature. [170,171]

Statistical Analysis

We conducted bivariate analysis to assess the association between presence and type of fracture and patient demographics, smoking status, blood alcohol content (BAC), injury severity, and external cause of injury admission. Because age was a continuous variable, we used a one way ANOVA test for comparison of mean age based on fracture region.

We used a Cox Proportional-hazards model to assess the relationship between presence and type of fracture and drug overdose deaths. Patients without fracture were considered our reference group and were compared to those with lower limb fractures and fractures in other regions. To determine whether patients with an isolated lower limb fracture differed from those with a lower limb fracture and fracture in another region, we conducted a comparative analysis that determined the difference in drug overdose mortality between both sub-groups of patients with lower limb fracture.

Because some patients died of other causes during follow-up, we adjusted for cause-specific mortality outcomes using methods for competing risks described by Fine and Grey.[172] Covariates were included in the adjusted model if they were identified as potential confounders in the literature. Confounders were identified based on a review of the literature and included age, sex, race, smoking status, and external cause of injury were selected. Our initial model did not include polytrauma as Injury Severity Score is a variable that is directly influenced the presence and severity of fracture injuries sustained.

Yet to determine the extent to which main effect estimates changed, polytrauma (ISS ≥ 16) was included in one variation of the multivariable model to potentially account for injury severity. Although BAC was associated with fracture type, we did not include it in the model due to its strong association with patient smoking status at the time of admission. Hazard ratios (HR) and 95% confidence intervals (CI) are reported. Findings were considered significant at a p-value of <0.05 and proportionality of hazards for covariates was verified using negative log-log Kaplan-Meier survival curves for each variable.

C. Results

During the study period, 45,469 trauma patients between the ages of 18 and 64 were admitted to the STC. After excluding those who were transferred (n=7,234), those who died at discharge (n=1,506) and within 30 days after discharge (n=381), and those with a cancer diagnosis on admission (n=55) or unknown sex (n=5), the final analytic sample consisted of 36,288 (79.8% of initial sample) trauma patients.

Most trauma patients included were male (72.1%), white (56.5%), and admitted due to vehicular injuries (59.6%, Table 1). Over 75% of trauma patients included were under the age of 45 and 37% were current smokers at the time of trauma admission (Table 11). The majority of trauma patients had an ISS of 8 or less (54.8%) and nearly 20% had an ISS of 16 or more.

Nearly 42% of trauma patients experienced any fracture injury: 13% of trauma patients had a lower limb fracture with or without a fracture in another region and 28.9% had one or more fractures in other regions (Table 11). Due to the large sample size, distribution of all demographic and patient characteristics differed significantly by

fracture presence and type. A higher percentage of male patients were observed in both those with lower limb (73.0%) and other (75.9%) fractures compared to those with no fracture (70.0%). Patients with a lower limb or other fracture were also two years older on average (36.4, SD=12.6; 36.4, SD=12.8) compared to patients without a fracture (34.0, SD=12.1). Patients with a lower limb fracture were admitted for vehicular injuries (76.1%) more often than those without a fracture (56.4%) or a fracture in another area (58.8%). Polytrauma, or an ISS of 16 or more, was more commonly observed in patients with lower limb fractures (36.7%) and those with other fractures (40.7%) compared to those with no fracture (5.3%).

Table 11: Association of Traumatic Fracture Injury with Patient Characteristics at Admission

	All (N=36,288)	Lower Limb Fracture 4,706 (13.0%)	All Other Fractures 10,505 (28.9%)	No Fracture 21,077 (58.1%)	p-value
Sex, n(%)					<0.001
Male	26,161 (72.1)	3,436 (73.0)	7,969 (75.9)	14,756 (70.0)	
Female	10,127(27.9)	1,270 (27.0)	2,536 (24.1)	6,321 (30.0)	
Age, n(%)					<0.001
18-24	9,931 (27.3)	1,156 (24.6)	2,551 (24.3)	6,224 (29.5)	
25-34	8,975 (24.7)	1,054 (22.4)	2,412 (23.0)	5,509 (26.1)	
35-44	8,402 (23.2)	1,159 (24.6)	2,500 (23.8)	4,743 (22.5)	
45-54	6,039 (16.6)	883 (18.8)	2,010 (19.1)	3,146 (14.9)	
55-64	2,941 (8.1)	454 (9.7)	1,032 (9.8)	1,455 (6.9)	
Age (μ±SD)	35.0 ± 12.4	36.4 ± 12.6	36.4 ± 12.8	34.0 ± 12.1	<0.001
Race, n(%)					<0.001
White	20,520 (56.5)	2,905 (61.7)	6,464 (61.5)	11.151 (52.9)	
Black	12,788 (35.2)	1,469 (31.2)	3,133 (29.8)	8,186 (38.8)	
Other /Unknown	2,980 (8.2)	332 (7.1)	908 (8.6)	1,740 (8.3)	
Current Smoker, n(%)	13,474 (37.1)	1,745 (37.1)	3,802 (36.2)	7,927 (37.6)	0.05

Table 11: Continued

Blood Alcohol Content, n(%)					<0.001
BAC Negative	24,266 (66.9)	3.236 (68.8)	6,790 (64.6)	14,240 (67.6)	
Under 80mg/dL	2,363 (6.5)	327 (7.0)	727 (6.9)	1,309 (6.2)	
80-219 mg/dL	5,057 (13.9)	677 (14.4)	1,689 (16.1)	2,691 (12.8)	
220+ mg/dL	3,115 (8.6)	353 (7.5)	1,024 (9.8)	1,738 (8.3)	
Missing/Unknown	1,487 (4.1)	113 (2.4)	275 (2.6)	1,099 (5.2)	
Mechanism of Injury, n(%)					<0.001
Vehicular					
Firearm/Knife	21,633 (59.6)	3,579 (76.1)	6,174 (58.8)	11,880 (56.4)	
Fall	4,953 (13.6)	325 (6.9)	1,047 (10.0)	3,581 (17.0)	
Beating	5,067 (14.0)	548 (11.6)	1,721 (16.4)	2,798 (13.3)	
Other*	2,628 (7.2)	50 (1.1)	1,084 (10.3)	1,494 (7.1)	
	2,007 (5.5)	204 (4.3)	479 (4.6)	1,324 (6.3)	
Injury Severity Score, n(%)					<0.001
ISS 1-3	8,118 (22.3)	2 (0.04)	104 (1.0)	8,012 (38.0)	
ISS:4-8	11,808 (32.5)	862 (18.3)	2,269 (21.6)	8,677 (41.2)	
ISS: 9-15	7,997 (22.0)	2,111 (44.9)	3,851 (36.7)	2,035 (9.7)	
ISS: 16-24	4,167 (11.5)	956 (20.3)	2,417 (23.0)	794 (3.8)	
ISS: 25+	2,948 (8.1)	773 (16.4)	1,856 (17.7)	319(1.5)	
Missing/Unknown	1,250 (3.4)	2 (0.04)	8 (0.1)	1,240 (5.9)	

*Other Injuries include accidental blunt injuries due to striking by object or persons, accidental blunt injuries due to machinery, accidental penetrating injuries due to machinery, accidental blunt injuries due to sports, and all other blunt or penetrating injuries not elsewhere classified.

Less than half (48%) of patients with a lower limb fracture had an isolated injury (Table 12). The most common fracture region that accompanied lower limb fracture was the chest (56.6%), followed by the upper limbs (49.6%). Nearly three quarters of patients in the other fracture group had a single fracture (73.1%, Table 12). Only 5.3% of this same group had fracture in three or more regions (5.3%). The most common region for fracture in this group was chest (48.7%) followed by head (36.7%) and then upper limb (32.7%). The least common region was spine and pelvis, which occurred in 14.6% of patients in this group.

Table 12: Specific Area and Number of Fractures among Trauma Injury Survivors

Variable	Patients with Lower Limb Fracture (N=4,706)	Drug Overdose Deaths (N=37)	Patients with Other Fracture (N=10,505)	Drug Overdose Deaths (N=57)
Area of Fracture, n(%)				
Head	627 (13.4)	6 (16.2)	3,854 (36.7)	29 (50.9)
Chest	1,375 (29.2)	12 (32.4)	5,117(48.7)	26 (45.6)
Upper Limb	1,205 (25.6)	7 (18.9)	3,436 (32.7)	13 (22.8)
Spine/Pelvis	730 (15.5)	6 (16.2)	1,535 (14.6)	6 (10.5)
Number of Fractured Areas, n(%)				
One	2,275 (48.3)	17 (46.0)	7,681 (73.1)	41 (71.9)
Two	1,320 (28.1)	11 (29.7)	2,270 (21.6)	15 (26.3)
Three or more	1,111 (23.6)	9 (24.3)	553 (5.3)	1 (1.8)

Patient follow-up time ranged from 31 days to 10 years, with a mean follow-up time of 4.8 years (standard deviation 2.8 years). Among the trauma patients included in the study, 4.6% (n=1,495) were identified as having died by the end of the follow-up period. Among trauma patients who died by the end of follow-up, 16.2% (n=242) died of drug overdose, 23.2% (n=348) died of other external injury causes, and 60.5% (n=905) died of natural causes. In trauma patients with a lower limb fracture, 4.1% (n=191) died by the end of follow-up with 19.4% (n=37) of these deaths due to drug overdose, 26.7% (n=51) due to other external injuries, and 53.9% (n=103) due to natural causes. In patients with other fractures, 4.8% (n=500) died by the end of follow-up with 11.4% (n=57) of deaths due to drug overdose, 26.2% (n=131) due to external injuries, and 62.4% (n=312) due to natural causes. In patients with no fracture, 3.8% (n=804) died by the end of follow-up with 18.4% (n=148) of deaths due to drug overdose, 20.6% (n=166) due to external injuries, and 60.9% (n=490) due to natural causes. Drug overdose, other external injury, and natural cause deaths were significantly different based on patient fracture group ($p<0.001$).

In unadjusted analysis, patients with lower limb fracture were not at increased risk of drug overdose death compared to those with no fractures (HR= 1.16, 95% C.I. 0.81-1.67). Our final Cox regression model was adjusted for age, race, smoking status, male sex, and cause of injury admission. Patients with lower limb fracture were not at increased risk of drug overdose death compared to those with no fracture (HR=1.27, 95% C.I. 0.88-1.83, Table 13). Patients with fractures in other regions had a lower risk of drug overdose death compared to those with no fracture (HR=0.74, 95% C.I. 0.54-1.00), but this effect was only marginally significant (p-value: 0.05). The point estimates for lower limb fracture did not differ largely between multivariable models (Table 13).

Table 13: Risk of Drug Overdose based on Lower Limb and Other Fracture among Trauma Patients

Variable	Adjusted Model 1 HR (95% C.I.)	Adjusted Model 2 HR (95% C.I.)
Fracture (Unadjusted)		
No Fracture	Ref.	Ref.
Lower Limb	1.16 (0.81-1.67)	1.16 (0.81-1.67)
Other Area	0.79 (0.58-1.07)	0.79 (0.58-1.07)
Fracture (Adjusted)		
No Fracture	Ref.	Ref.
Lower Limb	1.27 (0.88-1.83)	1.25 (0.87-1.80)
Other Area	0.74 (0.54-1.00)	0.72 (0.51-1.03)
Age		
18-24	Ref.	Ref.
25-34	1.67 (1.11-2.51)	1.67 (1.11-2.52)
35-44	2.75 (1.88-4.02)	2.75 (1.90-4.08)
45-54	1.97 (1.26-3.07)	1.97 (1.26-3.07)
55-64	1.15 (0.58-2.26)	1.15 (0.58-2.26)
Race		
White	Ref.	Ref.
Black	0.53 (0.38-0.73)	0.53 (0.38-0.73)
Other	0.19 (0.07-0.52)	0.19 (0.07-0.52)
Male Sex	1.14 (0.83-1.56)	1.14 (0.83-1.56)
ISS 16+	****	1.06 (0.73-1.53)
Smoker	1.75 (1.35-2.26)	1.75 (1.35-2.27)

Table 13: Continued

External Cause of Injury		
Vehicle-related	Ref.	Ref.
Knife/Firearm	1.90 (1.24-2.90)	1.90 (1.24-2.90)
Fall	1.15 (0.78-1.70)	1.15 (0.78-1.70)
Beating	2.75 (1.86-4.08)	2.76 (1.87-4.09)
Other	1.03 (0.56-1.88)	1.03 (0.56-1.88)

Further sensitivity analysis that examined patients with lower limb fracture only compared lower limb patients with isolated fractures to those with fractures in other regions and found no significant difference in unadjusted and adjusted risk of drug overdose death between those with and without multiple fractures (unadjusted p-value: 0.70; adjusted p-value: 0.85).

D. Discussion

Although we hypothesized that lower limb fracture might be a risk factor for future drug overdose due to the development of chronic pain,[173, 174] our study found no significant association between lower limb fracture and subsequent drug overdose death among trauma patients.

While some prior literature has reported higher opioid use among individuals with lower limb fracture, [165,166] we did not observe an association with drug overdose death. Our analysis focused on a group of traumatically injured patients, all of whom experience considerable pain following injury regardless of injury type. Thus, the effect of lower limb fracture injury on drug overdose death may not be much different than the effect of a traumatic non-fracture injury.

Another possible explanation for our findings is that drug overdose risk among trauma patients may be influenced most strongly by previously identified non-injury related risk factors, such as substance use and mental health conditions.[158, 167] Our

findings add further support to the theory that addiction and eventual drug overdose is not due to iatrogenic addiction to opioids following injury but to pre-injury risk factors that drive eventual opioid addiction and subsequent drug overdose in high-risk trauma patients.

This study has several strengths. It is the first study to examine drug overdose death among surviving trauma patients based upon fracture presence and type in a trauma cohort of substantial size. The availability of injury information in the registry enabled us to be able to correctly account for and classify fracture injuries among patients. Additionally, our reliance on the National Death Index, considered by some to be the "Gold Standard" for mortality and cause of death information, [175, 176] accounted for near complete follow-up of our trauma patients until the end of 2008.

The limitations of this study should also be considered. Because we did not have access to prescription data upon discharge we were unable to account for the dose or duration of opioids prescribed for each injury. Additionally, there could have been differences in dose and duration of opioids prescribed to patients at the time of discharge based on type of fracture. While we would have preferred to examine drug overdose death due to opioids as an outcome, we were unable to do so due to lack of specificity regarding primary substance of use in many drug overdose death records.[177] Despite the limitations of our study, our results were able to add to the literature regarding drug overdose risk based on injury severity and type.

Conclusion

In a cohort of surviving trauma patients, those with lower limb fracture were not at increased risk of drug overdose death compared to patients who sustained non-fracture injuries.

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CHAPTER VI: SUMMARY AND DISCUSSION

The research that has been presented in this dissertation was based upon a retrospective cohort of 36,288 trauma patients who survived at least 30 days post-discharge. The primary objective of this study was to determine whether trauma patients were at increased risk of drug overdose and if current smoking status or lower limb fracture was associated with increased risk of drug overdose within the surviving trauma cohort.

Results from this study suggest that trauma patients have a six fold increase in the risk of drug overdose death compared to the Maryland general population. Among trauma patients, current smoking status was associated with a significantly higher risk of drug overdose death but lower limb fracture was not. Current smoking status was not an effect modifier of the association between lower limb fracture and drug overdose death.

This chapter summarizes the key findings of this dissertation by aim, describes the strengths and limitations of the work, and discusses the implications of this research and future directions.

A. Risk of Drug Overdose Following Trauma Injury

My first hypothesis predicted that trauma patients would have a significantly higher drug overdose mortality rate than the Maryland general population. Based on my findings, trauma patients had a six-fold increase in drug overdose mortality rate compared to the Maryland general population after adjusting for age, sex, and race (SMR=6.10, 95% C.I. 5.35-6.93). While trauma patients also had a significantly higher mortality rate for other external injury causes (SMR=2.77, 95% C.I. 2.48-3.08) and natural causes (SMR=2.75, 95% C.I. 2.57-2.94), the SMRs were not as large as the SMR

for drug overdose mortality. Trauma patients were at highest risk of drug overdose in the first two years after trauma discharge, yet maintained a considerably higher drug overdose mortality rate than the Maryland general population even ten years after discharge, suggesting that increased risk of drug overdose mortality may persist up to a decade after trauma survival.

Traumatic injury has been associated with risk factors for drug overdose, such as drug or alcohol use disorders[178] and mental health conditions.[179] Traumatic injury has also been associated with higher risk of opioid use disorder[180] (OUD) and non-fatal overdose after discharge, yet this study is the first to show a positive association between traumatic injury and drug overdose mortality.[181]

Results from this study provide strong evidence that fatal drug overdoses are more common among surviving trauma patients than in the general population, making trauma patients a particularly "high risk" population for this outcome. Prevention efforts should be directed toward trauma patients prior to hospital discharge and, if feasible, after discharge as well. Improved screening for drug use or drug use disorders at the time of trauma could help identify individuals at high risk for drug overdose. As a result, these individuals could be referred to treatments centers or programs prior to being discharged.

B. Smoking Status as a Risk Factor for Drug Overdose Death

Current smoking status on admission was associated with a 67% increase in the risk of subsequent drug overdose death after adjusting for patient age, race, sex, reported mental health condition, substance use (BAC at or above 80mg/dL or known AUD/DUD), and neighborhood median income (HR=1.66, 95% C.I. 1.25-2.21). Patient substance use significantly modified the effect of smoking on future risk of drug

overdose death. Smoking was associated with a greater hazard of drug overdose death (HR 2.45, 95% C.I. 1.69-3.56) among those with no substance use yet was not associated with drug overdose death in patients with substance use (HR 1.01, 95% C.I 0.69-1.48). This difference could be due to the fact that substance use has been associated drug overdose death independently, [182, 183] and patients with substance use are at a uniformly high risk of drug overdose regardless of smoking behavior.

There are several possible explanations for the strong association between smoking status and drug overdose death. Because nicotine is associated with addiction to other substances,[184, 185] smokers may be at increased risk of developing new substance use disorders or relapsing into previous substance use.[185, 186] This may be due to the fact that smokers are more likely exhibit impulsivity,[187] which has been linked to future substance use problems.[188] Smoking status at the time of trauma may be an indicator for undiagnosed mental health conditions,[186] such as anxiety, depression, and psychological distress, all of which have been associated with opioid use disorder (OUD) and drug overdose death.[189-193, 183] A third possibility is that smoking has been associated with higher levels of pain sensitivity[194] and chronic pain,[195, 196] making this population more vulnerable to OUD and subsequent drug overdose death after traumatic injury.

C. The Association of Lower Limb Fracture Injury with Drug Overdose Death

Patients that had a lower limb fracture were not at higher risk of drug overdose death (HR=1.27, 95% C.I. 0.88-1.83). While over half of those with a lower limb fracture also had a fracture in another region, no difference in drug overdose mortality was noted between these patients and those with an isolated lower limb fracture. Patients without a lower limb fracture but with fractures in other regions had a lower risk of drug overdose

death (HR=0.74, 95% C.I. 0.54-1.00), this association was only marginally significant (p-value: 0.05).

While there are no published studies on the association between lower limb fracture and drug overdose death, prior studies have reported mixed results on the association between lower limb fracture and prolonged opioid use.[197, 189, 198, 199] The lack of association between lower limb fracture and risk of drug overdose provides further evidence that drug overdose death risk is primarily driven by patient behavioral risk factors.

Smoking as a Potential Effect Modifier of Association between Fracture and Drug Overdose

Because smokers may experience slower healing from lower limb fractures than non-smokers[200] and may also be more likely to experience pain, [194-196, 201] I hypothesized that smoking would be an effect modifier of the association between lower limb fracture and drug overdose death, with a stronger association between lower limb fracture and drug overdose death among the sub-group of smokers. However, the interaction term for smoking status and lower limb fracture was not statistically significant (p=0.27). While previous research has reported that smoking status was associated with prolonged opioid use following surgery, [201-203] this relationship does not appear to be mediated through fracture healing. The relationship between smoking and drug overdose death does not appear to be due to injury severity or type, but to differences in pre-injury risk factors between smokers and non-smokers at the time of trauma admission. Further detail and tables of these results are provided in Appendix C.

D. Strengths, Limitations, and Considerations

This study identified trauma patients as a high risk group for drug overdose death. While previous studies provided evidence that trauma patients may be at a higher risk of OUD[180] and non-fatal drug overdose, [181] this study is the first to compare the rate of drug overdose deaths in the trauma population to the general population.

The use of ICD-9 and ICD-9-CM codes in recording injuries, premorbid conditions, and external cause of admission within the trauma database allowed for clarity in classification and grouping of fracture type, patient comorbidities, and cause of admission. The ability to gather neighborhood median income at the zip code level also provided a good estimate of neighborhood socioeconomic status among trauma patients. Additionally, the use of the Fine and Gray method also allowed for adjustment of the competing risk of deaths due to other causes, such as external injury and natural cause.

The National Death Index (NDI) was a particular asset of this study as it is considered to be the gold standard[204-206] for mortality and cause of death information. Additionally, the study was adequately powered to detect moderate effect sizes due to the number of patients in the study cohort.

The limitations of this study should also be considered. There was no information on the quantity smoked among patients who were smokers at the time of admission. As a result, we were unable to examine a "dose-response" effect based on the severity of the smoking behavior. Additionally, illicit or prescription opioid drug users may have been missed due to non-valid drug urine test results at the time of admission, so we may have underestimated DUD in trauma patients at the time of admission, resulting in a reduced ability to fully account for the confounding due to substance use in our smoking effect

estimate. Pre-existing conditions for patients in the registry may also be incomplete, making it likely that patient comorbidities are not fully accounted for in analysis.

While it is likely that near all patients were prescribed opioids at the time of discharge based on previous studies,[207] we were unable to fully account for differences in prescribing patterns based on patient pre-existing or injury-level risk factors at the time of trauma. We were also unable to account for OUD, a significant drug overdose risk factor, [182] in trauma patients at the time of admission.

This study analyzed data from trauma patients admitted from January 1, 1999 and followed up until December 31, 2008 and may not reflect the current state of drug overdose in trauma patients. However, it is likely that opioid prescribing patterns were less conservative at this time, as drug overdose deaths were not the leading cause of injury death until 2011, three years after the end of this study period. Additionally, this study period ended eight years prior to the CDC Guidelines for Prescribing Opioids for Chronic Pain[208] and five years prior to the beginning of the implementation of the Maryland Prescription Drug Monitoring Program (PDMP), [209] therefore the prescribing patterns to trauma patients during this period of time may be very different from the prescription patterns toward trauma survivors today.

Maryland deaths are tested for toxicology only based on suspicion and Office of the Centralized Medical Examiner (OCME) referral due to a sudden or unexpected death in an otherwise healthy individual.[210] Because of the high chance that drug overdose deaths could be underreported in the elderly or those with a known pre-existing chronic condition, I excluded patients over the age of 65 and patients with a pre-existing condition of malignant cancer from my study. This inclusion criteria results in reduced

generalizability of our findings, as they are only reflective of adult trauma patients under the age of 65.

E. Implications of Research

Our results provided strong evidence that trauma patients are at higher risk of drug overdose death and that smoking is independently associated with this outcome. While smoking is usually considered a strong risk factor for natural cause deaths, such as cancer and heart disease, it tends to be overlooked as a risk factor for drug overdose death. However, past findings indicate that smokers are at higher risk for pain as well as prolonged opioid use following injury, [202, 194-196, 201, 211-212] which could increase risk of drug overdose death in this population. Future prevention efforts should consider smoking a risk factor for drug overdose death following traumatic injury.

These results can inform drug overdose prevention efforts in a few ways. First, these findings can inform screening for drug and drug use disorder at the time of trauma admission. Better detection of drug misuse at the time of trauma could result in referral for substance abuse treatment services prior to hospital discharge. Further prevention efforts could also aim to educate and inform families of the risk of OUD in addition to providing overdose reversal medication, such as naloxone, [213] to prevent a potentially fatal drug overdose.

Secondly, these findings can help target overdose prevention services towards smokers. Because smokers are three to five times more likely to meet criteria for abuse of nonmedical prescription opioids within the past year, [214] it is essential that we screen them for pre-existing opioid dependence at the time of trauma admission. Because

nicotine has been associated with an increased risk of developing opioid addiction, [215] patients who are smokers without any substance misuse could also be monitored and screened for future opioid abuse and dependence following discharge at primary care visits. The Chesapeake Regional Information System for our Patients (CRISP) Health Information Exchange (HIE) [216] system could also provide an ideal way to identify patients who are high risk of drug overdose death based on risk factors at the time of traumatic injury. The sharing of information recorded in the patient's health record at the time of trauma could also enable other health care professionals to monitor patient prescription opioid fill patterns through the use of the PDMP, provide future screening for OUD, and potentially prescribe alternative pain treatments for trauma patients after discharge.

Future research is needed to further understand potential risk factors for drug overdose death in surviving trauma patients. Results from these future studies could help inform future drug overdose prevention efforts aimed at an already identified high risk population.

Performing this study in other states and with more current data would provide information on generalizability and current trends. Future studies could also examine smoking as a multi-level exposure, through assessing the quantity, duration, and length of smoking in relation to future drug overdose death. To capture and account for mental health conditions more accurately in trauma patients, future studies could also assess mental health using validated tools such as the Center for Epidemiological Studies Depression scale (CES-D) [217] and Kessler scale for Psychological distress[218] to measure conditions such as depression and psychological distress, respectively. A more accurate

measure of mental health would enable us to assess the true effect of smoking independent of its association with mental health and tease out whether the association between smoking and drug overdose death is due to unmeasured mental health conditions or to the independent addictive effect of nicotine.

Finally, a study that links clinical patient electronic health records with patient prescription drug event (PDE) and medical patient claims following trauma discharge could provide insight into trauma patients' opioid prescription patterns as well as the receipt of OUD treatment services following discharge. Using both patient CRISP health records and prescription drug information recorded in the PDMP, researchers could examine trauma patient health records and future opioid prescription patterns. Additionally, these records could be further linked to state or national death records to determine future drug overdose death. Research such as this could help us identify what prescribing patterns were associated with future drug overdose death following trauma, and what patient risk factors were associated with a higher risk of prescription drug misuse and subsequent drug overdose death following trauma.

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APPENDIX A: DESCRIPTION OF ICD-9-CM FRACTURE INJURY CODES

Table 14: Region, Description, and Type of Fracture by ICD-9-CM Injury code

ICD-9-CM	Description	Region	Open/Closed
800.0-800.99	Fracture of vault of skull	Head	800.0-800.49: Closed 800.5-800.99: Open
801.0-801.99	Fracture of base of skill	Head	801.0-801.49: Closed 801.5-801.99: Open
802.0-802.9	Fracture of face bones	Head	802.0, 802.2, 802.4, 802.6, 802.8: Closed 802.1, 802.3, 802.5, 802.7, 802.9: Open
803.0-803.99	Other and Unqualified skull fractures	Head	801.0-801.49: Closed 801.5-801.99: Open
804.0-804.99	Multiple fractures involving skull or face with other	Head	801.0-801.49: Closed 801.5-801.99: Open
805	Fracture of vertebral column without mention of spinal cord injury	Chest/Abdominal	805.0, 805.2, 805.4, 805.6, 805.8: Closed 805.1, 805.3, 805.5, 805.7, 805.9: Open
806	Fracture of vertebral column with spinal cord injury	Chest/Abdominal	806.0, 806.2, 806.4, 806.6, 806.8: Closed 806.1, 806.3, 806.5, 806.7, 806.9: Open
807	Fracture of rib(s) sternum larynx and trachea	Chest/Abdominal	807.0, 807.2, 807.4, 807.6, 807.8: Closed 807.1, 807.3, 807.5, 807.7, 807.9: Open
808	Fracture of pelvis	Pelvis/Acetabular	808.0, 808.2, 808.4, 802.8: Closed 808.1, 808.3, 808.5, 808.9: Open
809	Ill-defined fractures of bones of trunk	Chest/Abdominal	809.0: Closed 809.1: Open
810	Fracture of Clavicle	Upper Limb	810.0: Closed 810.1: Open
811	Fracture of scapula	Upper Limb	811.0: Closed 811.1: Open

Table 14: Continued			
812	Fracture of humerus	Upper Limb	812.0, 812.2, 812.4: Closed 812.1, 812.3, 812.5: Open
813	Fracture of radius and ulna	Upper Limb	802.0, 802.2, 802.4, 802.8: Closed 802.1, 802.3, 802.5, 802.9: Open
814	Fracture of carpal bone(s)	Upper Limb	814.0: Closed 814.1: Open
815	Fracture of metacarpal bone(s)	Upper Limb	815.0: Closed 815.1: Open
817	Multiple fractures of hand bones	Upper Limb	817.0: Closed 817.1: Open
818	Ill-defined fractures of upper limb	Upper Limb	818.0: Closed 818.1: Open
819	Multiple fractures involving both upper limbs and upper limb with ribs and sternum	Upper Limb and Chest/Abdominal	819.0: Closed 819.1: Open
820	Fracture of neck of femur	Lower Limb	820.0, 820.2, 820.8: Closed 820.1, 820.3, 820.9: Open
821	Fracture of other and unspecified parts of femur	Lower Limb	821.0, 821.2: Closed 821.1, 821.3: Open
822	Fracture of patella	Lower Limb	822.0: Closed 822.1: Open
823	Fracture of tibia and fibula	Lower Limb	823.0, 823.2, 823.4, 823.8: Closed 823.1, 823.3, 823.9: Open
824	Fracture of ankle	Lower Limb	824.0, 824.2, 824.4, 824.6, 824.8: Closed 824.1, 824.3, 824.5, 824.7, 824.9: Open
825	Fracture of one or more tarsal or metatarsal bones	Lower Limb	825.0, 825.2: Closed 825.1, 825.3: Open

Table 14: Continued			
827	Other multiple and ill-defined fractures of lower limb	Lower Limb	827.0: Closed 827.1: Open
828	Multiple fractures involving both lower limbs with upper limb and lower limb and sternum	Lower Limb, Upper Limb	828.0: Closed 828.1: Open
829	Fracture of unspecified bones	Unspecified	829.0: Closed 829.1: Open

APPENDIX B: ADJUSTED ASSOCIATION OF BINARY FRACTURE INJURY WITH DRUG OVERDOSE DEATH

The table below describes the association between fracture injury as a binary variable and drug overdose death. These multivariable models did not take into account the region of fracture injury. The complete analytic results for Aim 3 are detailed in the results portion of Chapter V.

Table 15: Adjusted Association of Fracture with Drug Overdose Death among trauma patients who survived 30 days post admission

Variable	Adjusted Model 1	Adjusted Model 2
Fracture	0.88 (0.68-1.14)	0.87 (0.65-1.16)
Smoking Status	1.75 (1.35-2.27)	1.75 (1.35-2.27)
Age		
18-24	Ref	Ref
25-34	1.67 (1.10-2.51)	1.67 (1.10-2.51)
35-44	2.75 (1.88-4.02)	2.75 (1.88-4.02)
45-54	1.96 (1.26-3.05)	1.96 (1.26-3.05)
55-64	1.15 (0.58-2.26)	1.15 (0.58-2.25)
Race		
White	Ref.	Ref.
Black	0.53 (0.39-0.74)	0.53 (0.39-0.74)
Other	0.19 (0.07-0.52)	0.19 (0.07-0.52)
Male Sex	1.14 (0.83-1.56)	1.14 (0.83-1.56)
ISS 16+	***	1.04 (0.72-1.51)
Mechanism of Injury		
Vehicle-related	Ref.	Ref.
Penetrating	1.84 (1.21-2.80)	1.84 (1.21-2.80)
Fall	1.12 (0.76-1.65)	1.12 (0.76-1.65)
Beating	2.53 (1.73-3.72)	2.54 (1.73-3.72)
Other	1.01 (0.55-1.84)	1.01 (0.55-1.85)

APPENDIX C: RESULTS OF SUB-AIM 3 EXPLORATORY ANALYSIS

Interaction of smoking with fracture type was tested within the adjusted model shown in the Chapter V results by adding an interaction term for smoking with both patient fracture groups. This interaction term would have been considered significant if the coefficient was associated with the outcome at a significance level of 0.05 or less using the chi-squared test statistic associated with the beta coefficient in the model for either patient fracture category.

The interaction of smoking status with each fracture group was non-significant at a p-value of 0.27 for the lower limb fracture group and 0.15 for the other fracture group. While the interaction term was non-significant, we sought to explore the association between fracture type and drug overdose stratified for smoking status, adjusting for age, race, sex, and external cause of injury. Among non-smokers exclusively, patients with lower limb fracture had a significantly higher risk of drug overdose than non-smokers without fracture (HR=1.70, 95% C.I. 1.05-2.76, Table 16). Among this same stratum of non-smokers, however, patients with other non-lower limb fractures had a significantly lower risk of drug overdose compared to those without fractures (HR=0.57, 95% C.I. 0.35-0.94, Table 16). Among smokers, both patients with lower limb fractures and fractures in other areas only did not have a significantly higher risk of drug overdose risk compared to smokers with no injury.

Table 16: Risk of Drug Overdose based by Mutually Exclusive Fracture Groups stratified by Smoking Status

Variable	Non-Smokers HR (95% C.I.)	Smokers HR (95% C.I.)
Fracture		
No Fracture	Ref.	Ref.
Lower Limb	**1.70 (1.05-2.76)**	0.92 (0.52-1.63)
Other Fracture	**0.57 (0.35-0.94)**	0.88 (0.60-1.31)

Table 16: Continued

Age		
18-24	Ref.	Ref.
25-34	1.32 (0.77-2.28)	2.28 (1.21-4.32)
35-44	1.81 (1.07-3.07)	4.39 (2.46-7.85)
45-54	1.20 (0.63-2.31)	3.41 (1.80-6.48)
55-64	0.69 (0.26-1.84)	2.16 (0.83-5.59)
Race		
White	Ref.	Ref.
Black	0.55 (0.34-0.88)	0.50 (0.32-0.79)
Other	0.24 (0.07-0.76)	0.13 (0.02-0.93)
Male Sex	1.36 (0.83-2.20)	0.96 (0.64-1.45)
External Cause of Injury		
Vehicle-related	Ref.	Ref.
Knife/Firearm	2.20 (1.16-4.16)	1.68 (0.95-2.96)
Fall	1.29 (0.72-2.33)	1.02 (0.61-1.71)
Beating	4.35 (2.50-7.59)	1.90 (1.11-3.24)
Other	1.37 (0.62-3.06)	0.74 (0.29-1.87)

To determine whether there was any real association with smoking and fracture type, patients were grouped into six different categories based on a combination of fracture type and smoking status. The six groups were: non-smokers without fracture, non-smokers with lower limb fracture, non-smokers with other fractures, smokers without fracture, smokers with lower limb fracture, and smokers with other fracture. The results are shown in Table 17.

Table 17: Risk of Drug Overdose among Other Fracture Group by Region Fractured and Smoking Status

Variable	Hazard Ratio 95% C.I.
Fracture and Smoking Status	
Non-Smoker, No Fx	Ref.
Non-Smoker, Lower Limb Fx	1.53 (0.95-2.46)
Non-Smoker, Other Fx	**0.57 (0.35-0.93)**
Smoker, No Fx	**1.67 (1.20-2.33)**
Smoker, Lower Limb Fx	1.69 (0.96-2.98)
Smoker, Other Fx	1.50 (0.99-2.25)

Table 17: Continued	
Age	
18-24	Ref.
25-34	1.67 (1.11-2.51)
35-44	2.74 (1.87-4.00)
45-54	1.96 (1.26-3.06)
55-64	1.15 (0.58-2.26)
Race	
White	Ref.
Black	0.53 (0.38-0.73)
Other	0.19 (0.07-0.52)
Male Sex	1.15 (0.84-1.57)
Mechanism of Injury	
Vehicle-related	Ref.
Knife/Firearm	1.92 (1.25-2.93)
Fall	1.16 (0.79-1.71)
Beating	2.73 (1.84-4.05)
Other	1.03 (0.56-1.88)

Compared to non-smokers without fracture, non-smokers with lower limb fracture were not at a significantly increased risk of drug overdose death (HR=1.53, 95% C.I. 0.95-2.46). Non-smokers with one or more non-lower limb fracture were at a significantly lower risk of drug overdose death risk than non-smokers without fractures (HR=0.57, 95% C.I. 0.35-0.93). Smokers without fracture were at a significantly higher risk of drug overdose death than non-smokers without fracture (HR=1.67, 95% C.I. 1.20-2.33). While smokers with lower limb fracture were at an increased risk of drug overdose death compared to non-smokers without fracture, this association was not significant (HR=1.69: 95% C.I. 0.96-2.98). Smokers with non-lower limb fractures were at a marginally significant higher risk of drug overdose death compared to non-smokers without a fracture (HR=1.50, 95% C.I. 0.99-2.25, p-value=0.054).

APPENDIX D: ADDITIONAL SENSITIVITY ANALYSES

Sensitivity analyses were run specific to the results of Aim 2. I examined the effect of differing lengths of follow-up time and different definitions of substance dependence on effect estimates of smoking. First, I reran analyses including those who were discharged alive yet died within the first 30 days following trauma discharge. An additional 10 drug overdose deaths were observed in the first 30 days following trauma discharge (N total=240). As shown in Table 18, the risk of drug overdose death associated with smoking remained the same whether we included or excluded those who died in the first 30 days after discharge.

Table 18: Adjusted Hazard of Drug Overdose Death Including Deaths that occurred in the First 30 Days Following Discharge

Variable	Adjusted HR excluding deaths in first 30 days (95% C.I.)	Adjusted HR including deaths in first 30 days (95% C.I.)
Smoking (Unadjusted)	2.12 (1.64-2.75)	2.13 (1.65-2.74)
Smoking	1.66 (1.25-2.21)	1.66 (1.26-2.20)
Age		
18-24	Ref.	Ref.
25-34	1.59 (1.05-2.41)	1.64 (1.09-2.48)
35-44	2.42 (1.65-3.56)	2.55(1.74-3.73)
45-54	1.72 (1.10-2.69)	1.78 (1.14-2.78)
55-64	0.96 (0.48-1.95)	0.95 (0.47-1.93)
Race		
White	Ref.	Ref.
Black	0.45 (0.33-0.62)	0.47 (0.35-0.64)
Other	0.20 (0.07-0.55)	0.20 (0.07-0.53)
Mental Health Condition	2.18 (1.52-3.12)	2.28 (1.61-3.23)
Substance Use *	1.58 (1.19-2.09)	1.53 (1.16-2.02)
Male Sex	1.24 (0.90-1.70)	1.22 (0.89-1.66)

Table 18: Continued

Income		
Unknown	2.17 (1.14-4.13)	2.29 (1.23-4.27)
(<$41,621)	2.35 (1.59-3.48)	2.39 (1.63-3.50)
$41,622-$60,506	1.23 (0.81-1.89)	1.23 (0.80-1.87)
$60,507-$83,610	1.28 (0.85-1.93)	1.27 (0.85-1.91)
$83,611+	Ref.	Ref.

Next, we examined the monthly adjusted hazard of drug overdose death, limiting to the first year following discharge from trauma. For this analysis, we chose to include deaths which occurred within the first 30 days following discharge to determine if inclusion of these deaths would make the estimates of effect higher. As shown in Table 19, smoking was significantly associated with an increased risk of drug overdose death within the first year in both unadjusted (HR 2.16: 95% C.I. 1.36-3.43) and adjusted (HR 1.81: 95% C.I. 1.08-3.02) estimates.

Table 19: Adjusted Hazard of Drug Overdose Death within the First Year following Trauma Discharge

Variable	Adjusted HR per month (95% C.I.)
Smoking (Unadjusted)	2.16 (1.36-3.43)
Smoking	1.81 (1.08-3.02)
Age	
18-24	Ref.
25-34	3.54 (1.61-7.80)
35-44	2.50 (1.10-5.68)
45-54	3.02 (1.28-7.12)
55-64	1.70 (0.50-5.75)
Race	
White	Ref.
Black	0.69 (0.42-1.15)
Other	0.17 (0.02-1.25)
Mental Health Condition	1.93 (0.98-3.81)
Substance Use *	1.38 (0.83-2.30)
Male Sex	0.75 (0.44-1.27)

Table 19: Continued	
Income	
Unknown	2.76 (0.87-8.75)
(<$41,621)	2.56 (1.27-5.17)
$41,622-$60,506	1.51 (0.70-3.27)
$60,507-$83,610	1.35 (0.62-2.93)
$83,611+	Ref.

Next we sought to examine whether the estimates of effect were strongest in the first five years following hospital discharge. For this analysis we once again restricted to include only follow-up time from 31 days after patient discharge. We only included those drug overdose deaths that occurred within 5 years following the 31st day after patient discharge and censored patient follow-up at this time.

As is shown in Table 20, the adjusted smoking hazard ratio within the first five years was identical to that reported in Table 18. The only difference between the estimates for the entire follow-up period and the first five years was a slightly wider confidence interval as the number of deaths was lower (N=188 vs. N=230).

Table 20: Risk of Drug Overdose Death within the First Five Years Following Trauma excluding the first 30 days after discharge

Variable	**Adjusted HR per year (95% C.I.)**
Smoking (Unadjusted)	2.08 (1.56-2.77)
Smoking	1.66 (1.22-2.27)
Age	
18-24	Ref.
25-34	1.79 (1.11-2.89)
35-44	2.62 (1.68-4.09)
45-54	2.15 (1.30-3.54)
55-64	1.29 (0.62-2.67)
Race	
White	Ref.
Black	0.48 (0.34-0.68)
Other	0.24 (0.09-0.66)
Mental Health Condition	2.27 (1.53-3.36)
Substance Use *	1.43 (1.05-1.95)

Table 20: Continued	
Male Sex	1.33 (0.93-1.90)
Income	
Unknown	2.47 (1.25-4.88)
(<$41,621)	2.36 (1.53-3.65)
$41,622-$60,506	1.26 (0.78-2.02)
$60,507-$83,610	1.29 (0.82-2.03)
$83,611+	Ref.

Based on the results presented, it appears that the association between smoking and risk of future drug overdose was consistent. Smoking was associated with an 81% higher hazard of drug overdose death within the first year. When restricted to the first five years, the hazard of drug overdose death based on smoking status at the time of admission was no different than during the entire analysis period.

To examine the impact of our substance use definition on effect estimates of smoking, we defined "substance use" as only a known alcohol or drug use disorder as reported in patient record. Because we relied on patient report of drug or alcohol use disorder and not blood alcohol content, we did not exclude patients who were not tested for BAC at the time of admission.

Using the previous definition of "substance use", which included a BAC of 80mg/dL, the hazard ratio for substance use was 1.58 (95 C.I.: 1.19-2.09, Table 18). However, when we restricted the definition of substance use to only those with a known drug or alcohol use disorder as noted in the patient record the association to drug overdose was stronger (HR 1.82: 95% C.I. 1.35-2.45, Table 21). The main effect of smoking was also not as strong as in previous estimates yet remained significant (HR 1.51: 95% C.I. 1.14-1.99, Table 21). The interaction term between smoking and known substance use disorder was statistically significant (p-value= 0.01).

Similar to previous findings in Aim 2, smoking was not associated with drug overdose death in the cohort of trauma patients with known alcohol or drug use disorders using the new more restrictive definition (HR 0.88: 95% C.I. 0.55-1.42, Table 21). However, smoking was associated with drug overdose death in the cohort without any known drug or alcohol use disorder (HR 1.84: 95% C.I. 1.35-2.52, Table 21).

Table 21: Adjusted Hazard of Drug Overdose Death based on Smoking Status and Known Substance Use Disorder

Variable	Adjusted Overall HR (95% C.I.)	Adjusted HR in those with SUD (95% C.I.)	Adjusted HR in those without SUD (95% C.I.)
Smoking	1.51 (1.14-1.99)	0.88 (0.55-1.42)	1.84 (1.35-2.52)
Age			
18-24	Ref.	Ref.	Ref.
25-34	1.59 (1.05-2.39)	2.43 (1.04-5.70)	1.39 (0.86-2.23)
35-44	2.49 (1.71-3.63)	3.51 (1.57-7.83)	2.28 (1.48-3.53)
45-54	1.72 (1.11-2.68)	2.26 (0.89-5.77)	1.64 (0.99-2.73)
55-64	1.02 (0.52-2.00)	1.94 (0.49-7.63)	0.86 (0.39-1.90)
Race			
White	Ref.	Ref.	Ref.
Black	0.48 (0.36-0.65)	0.71 (0.42-1.23)	0.40 (0.28-0.59)
Other	0.20 (0.07-0.53)	*****	0.22 (0.08-0.61)
Known Substance Abuse Disorder	Ref. 1.84 (1.35-2.52)	*****	******
Mental Health Condition	2.08 (1.46-2.95)	2.96 (1.72-5.07)	1.59 (0.98-2.59)
Male Sex	1.26 (0.92-1.71)	0.80 (0.46-1.38)	1.47 (1.02-2.14)
Income			
Unknown	2.34 (1.25-4.37)	1.55 (0.43-5.58)	2.62 (1.28-5.37)
(<$41,621)	2.47 (1.66-3.61)	1.80 (0.88-3.70)	2.67 (1.68-4.24)
$41,622-$60,506	1.29 (0.85-1.97)	1.28 (0.59-2.77)	1.26 (0.76-2.10)
$60,507-$83,610	1.30 (0.87-1.96)	1.07 (0.48-2.39)	1.36 (0.85-2.18)
$83,611+	Ref.	Ref.	Ref.

*****Not Applicable

Based on these results, a reported drug or alcohol use disorder at the time of admission is a better indicator of future drug overdose death risk than a BAC above the legal limit. While a BAC above the legal limit at the time of admission may indicate

some additional risk of drug overdose death following trauma, a reported drug or alcohol use disorder appeared to be a much stronger indicator of future drug overdose death risk following trauma. Similar to the results observed previously, smoking was significantly associated with drug overdose death in trauma patients that did not have a known drug or alcohol use disorder, however, smoking was not associated with drug overdose death in those with a known drug or alcohol use disorder.

To determine how drug testing results could have impacted the association of smoking with future risk of drug overdose death, we ran another analysis that took into account drug testing results at the time of admission. Slightly less than half were tested at the time of admission (N=18,532) and there were 124 drug overdose deaths among those who were tested for drugs on admission. When restricted to only those who were tested for drugs on admission, smoking was strongly associated with drug overdose death in a cohort of only those tested for drugs on admission (HR 1.94: 95% C.I. 1.33-2.83, Table 22).

We also examined the association of positive drug toxicology with drug overdose death among those who were tested for drugs on admission. Positive drug urine toxicology was defined as a positive drug urine test result for any of the following substances: Cocaine, Opiates, Marijuana, Barbituates, Benzodiazepines, or Amphetamines. Drug toxicology was strongly associated with drug overdose death (HR 2.78:95% C.I. 1.78-4.34, Table 22).

Table 22: Adjusted Hazard of Drug Overdose Death based on Smoking Status and Positive Drug Toxicology on Admission

Variable	Adjusted Overall HR (95% C.I.)
Smoking	1.94 (1.33-2.83)
Age	
18-24	Ref.
25-34	1.85 (0.98-3.49)
35-44	3.37 (1.90-5.99)
45-54	2.42 (1.27-4.61)
55-64	1.33 (0.48-3.71)
Race	
White	Ref.
Black	0.46 (0.29-0.73)
Other	0.37 (0.11-1.18)
Positive Drug Toxicology	2.78 (1.78-4.34)
Mental Health Condition	2.41 (1.52-3.82)
Male Sex	1.13 (0.74-1.72)
Income	
Unknown	1.98 (0.81-4.85)
(<$41,621)	2.31 (1.32-4.02)
$41,622-$60,506	1.13 (0.62-2.05)
$60,507-$83,610	1.32 (0.76-2.32)
$83,611+	Ref.

To determine whether drug testing status modified the effect of smoking we choose to examine the interaction between smoking and drug testing status. For this analysis, trauma patients were divided into three categories based on drug testing status, drug tested positive, drug tested negative, and not tested for all drugs. The interaction between smoking status and drug urine testing results was examined. While the interaction of smoking was not significant among those who had a positive drug urine test ($p=0.10$), the interaction of smoking was significant among those who were not tested for drugs at the time of admission ($p=0.03$).

Smoking was associated with an increased risk of drug overdose death among both those who had positive and negative drug toxicology test results on admission

(Positive Drug HR 1.68: 95% C.I. 1.11-2.54; Negative Drug HR 3.27: 95% C.I. 1.47-7.26, Table 23). However, smoking was not associated with drug overdose death among those who were not tested for drugs at the time of admission (Unknown Drug HR 1.32: 95% C.I. 0.91-1.92, Table 23).

Table 23: Adjusted Hazard of Drug Overdose Death based on Smoking Status and Drug Urine Test Results on Admission

Variable	Positive Drug HR (95% C.I.)	Negative Drug HR (95% C.I.)	Unknown Drug HR (95% C.I.)
Smoking	1.68 (1.11-2.54)	3.27 (1.47-7.26)	1.32 (0.91-1.92)
Age			
18-24	Ref.	Ref.	Ref.
25-34	1.40 (0.69-2.86)	5.12 (1.11-23.57)	1.41 (0.82-2.44)
35-44	2.76 (1.47-5.18)	7.75 (1.80-33.44)	1.91 (1.14-3.21)
45-54	2.51 (1.26-5.01)	2.23 (0.38-13.16)	1.36 (0.73-2.54)
55-64	1.82 (0.64-5.16)	---------	0.95 (0.38-2.37)
Race			
White	Ref.	Ref.	Ref.
Black	0.44 (0.27-0.74)	0.55 (0.20-1.51)	0.48 (0.32-0.72)
Other	0.39 (0.10-1.63)	0.32 (0.04-2.52)	0.09 (0.01-0.67)
Mental Health Condition	1.97 (1.13-3.42)	4.13 (1.83-9.33)	1.64 (0.92-2.91)
Male Sex	1.11 (0.68-1.81)	1.14 (0.49-2.63)	1.31 (0.83-2.07)
Income			
Unknown	1.94 (0.73-5.18)	2.17 (0.25-18.70)	2.61 (1.09-6.23)
(<$41,621)	2.22 (1.20-4.11)	2.68 (0.75-9.63)	2.44 (1.41 -4.20)
$41,622-$60,506	1.01 (0.51-1.99)	1.62 (0.46-5.80)	1.43 (0.79-2.60)
$60,507-$83,610	1.08 (0.56-2.07)	2.34 (0.75-7.31)	1.24 (0.69-2.25)
$83,611+	Ref.	Ref.	Ref.

The association of smoking with drug overdose death appeared to be consistent in the first year following discharge as well as up to five years after the 31st day following the date of discharge. The effect of smoking was modified by the presence of a known drug or alcohol abuse disorder at the time of admission, consisted with the results reported previously in this dissertation. Smoking was strongly associated with drug overdose death among both those who tested positive or negative for drugs on admission.

However, among those who were not tested for drugs, smoking was not associated with drug overdose death.

The lack of association observed among those who were not tested for drugs leads us to believe that the process of drug testing on admission selected for a group of patients who may be affected differently by patient risk factors, such as smoking, compared to those who were not tested. The decision to test a trauma patient for drugs at the time of admission was based on suspicion; it is unclear exactly what factors may have contributed to testing and not testing patients for drugs on admission. While this difference demands further investigation, we cannot determine which patient factors at the time of admission may have contributed to drug testing results based on the limitations of the data. However, based on our results, we can conclude that smoking at the time of admission was associated with drug overdose death in a subset of the trauma population. Additional information on prescription drug usage after trauma is needed to further understand the contributing factors that lead to future drug overdose death based on patient behavioral risk factors at the time of admission.

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