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# Complications associated with blood alcohol concentration following injury

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ABSTRACT

Alcohol increases the risk of injuring oneself and others. However, following an injury there appears to be a benefit to alcohol in mediating the body's response to a traumatic injury and reducing mortality. The physiological mechanism underlying this reported association is poorly understood. One approach to explaining the pathways by which alcohol affects acute mortality following a traumatic injury is to identify differential prevalence of medical complications associated with increased mortality. The goal of this study was to evaluate the association between blood alcohol concentration and complications subsequent to a traumatic injury that are associated with increased in-hospital mortality. This study involved a retrospective analysis of traumatic injuries occurring between 2000 and 2009 as reported by all level I and II trauma units in the state of Illinois. The study includes all patients with blood alcohol toxicological examination levels ranging from zero to 500 mg/dL and meeting additional inclusion criteria ($n$ = 84,974). A reduction in complications of cardiac and renal function by 23.5% and 30.0%, respectively, was attributable to blood alcohol concentration. In addition, blood alcohol concentration was associated with fewer cases of pneumothorax and convulsions. However, blood alcohol concentration continued to be positively associated with aspiration pneumonitis and acute pancreatitis in the final models. The net impact of alcohol following an injury is protective, largely attributable to a reduction in complications relating to cardiac and renal function. This study helps to explain the observed protective effect from blood alcohol concentrations in reducing in-hospital mortality after an injury, as reported in many studies.



## Introduction

Alcohol increases an individual's risk of injuring oneself and others through various mechanisms (Cherpitel et al., 2003; Cherpitel, Tam, Midanik, Caetano, & Greenfield, 1995; WHO, 2007). However, following an injury there appears to be a benefit to alcohol in mediating the body's response to a traumatic injury and reducing overall in-hospital mortality (Blondell, Looney, Krieg, & Spain, 2002; Friedman, 2012; Kraus, Morgenstern, Fife, Conroy, & Nourjah, 1989; O'Phelan, McArthur, Chang, Green, & Hovda, 2008; Salim et al., 2009; Tien et al., 2006; Ward, Flynn, Miller, & Blaisdell, 1982; Yaghoubian, Kaji, Putnam, De Virgilio, & De Virgilio, 2009). In a recent study, blood alcohol concentration was analyzed as a continuous variable, and it was strongly associated with a substantial, near-linear inverse relationship between in-hospital mortality and blood alcohol concentration, with up to a 50% reduction in mortality (Friedman, 2012).

The physiological mechanisms underlying this epidemiologic finding are unclear, since most studies have been conducted using animal models, and findings in humans have been contradictory, most likely due to differences in inclusion criteria and the outcome measures considered. One study evaluating traumatically injured, intoxicated patients showed an increase in the need for infusion of blood products (Fabbri et al., 2002), while another a decrease (Zeckey et al., 2011), and still another found no difference (Tien et al., 2006). One study demonstrated an absence of significant differences in markers of immunosuppression following injury among alcohol-intoxicated patients (Fabbri et al., 2002), and two others found no significant difference in the occurrence of infection (Fabbri et al., 2002; von Heymann et al., 2002). Other researchers have reported an adverse immunoresponse following hemorrhagic shock (Molina et al., 2004; Phelan, Stahls, Hunt, Bagby, & Molina, 2002), and an increase in infection and other medical complications among burn patients with elevated BACs (Choudhry & Chaudry, 2006; Griffin, Poe, Cross, Rue, & McGwin, 2009; Kelley & Lynch, 1992). Some studies have reported neuroprotective effects

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of alcohol through action on the Nmethyl-Daspartate (NMDA) complex. Inhibition of NMDA receptors reduces intracellular calcium accumulation and hyperglycolysis, which is associated with reduced lesion size in the brain (Kelly, Lee, Pinanong, & Hovda, 1997; Türeci et al., 2004), and this relationship may be modified by the presence of caffeine (Piriyawat, Labiche, Burgin, Aronowski, & Grotta, 2003; Strong, Grotta, & Aronowski, 2000). An improved understanding of the physiological mechanisms underlying this reported association between alcohol and acute mortality would allow for an intervention following an injury that targets these protective mechanisms, thereby mimicking alcohol's beneficial effects.

One approach to explaining the pathways by which alcohol affects acute mortality following a traumatic injury is to identify differential prevalence of medical complications that occur following an injury and are associated with an increase in acute mortality (Khuri et al., 2005; Silber et al., 2005; Zhan & Miller, 2003), and determine the physiological influence that alcohol has on these complications. There have been several studies that have identified a short list of medical complications subsequent to an injury (not comorbidities) that are associated with in-hospital mortality (Healey, Shackford, Osler, Rogers, & Burns, 2002; Ingraham et al., 2010; Osler, Glance, & Hosmer, 2012). In a recent study by Osler and colleagues (Osler et al., 2012), 64% of post-traumatic deaths were attributable to a finite list of post-injury complications. Evaluating these complications would not exclusively explain all deaths, but it would serve as a starting point for evaluating the biomechanism behind the relationship between alcohol and reduced in-hospital mortality. In this study, medical complications associated with increased in-hospital mortality are assessed in relation to blood alcohol concentrations.

## Materials and methods

### *Data source*

This study entailed a retrospective analysis of traumatic injuries occurring between 2000 and 2009 as reported to the State of Illinois Trauma Registry, which includes all level I and II trauma centers. All reliability and cleaning operations were previously performed on the Illinois Trauma Registry (ITR), and the registry was found to meet the highest quality control criteria as assessed by the North American Association of Central Cancer Registries (Friedman & Forst, 2007).

### *Inclusion criteria*

The analysis included all patients with a reported blood alcohol toxicological examination, with levels ranging from zero to 500 mg/dL ($n = 131{,}182$). An analysis of missing data indicated that the data for patients without reported blood alcohol concentrations were missing at random (MAR) within strata (Allison, 2002; Friedman, 2012). Blood alcohol concentration (BAC) is measured at the time of admission to the trauma unit. Patients with a BAC greater than 500 mg/dL were excluded from the analysis; although a BAC above 500 mg/dL is physiologically possible, it is rare and there was concern that the reported concentration levels may be incorrect. The number excluded with a BAC greater than 500 mg/dL was very small as a proportion of all the patients included in the analysis (0.2% of total cases with BAC). In a previous study, when the patients with BAC levels greater than 500 mg/dL were included, the parameter estimates remained unchanged (Friedman, 2012).

Based on a previous analysis and other studies (Friedman, 2012; Glance et al., 2009; Ingraham et al., 2010; Osler et al., 2012), the following patients were also excluded from this analysis: patients under the age of 16 years, patients 65 years and older with isolated hip fractures, and patients suffering exclusively from late effects (ICD-9905–909.9), superficial injuries (910–924.9), foreign bodies (930–939), and burns (940–949). Patients under the age of 16 were excluded because so few have a positive BAC and they are disproportionately less likely to be screened for BAC (Friedman, 2012). Furthermore, in the previous study (Friedman, 2012), the relationship between BAC and mortality did not differ substantially between the models including and excluding patients under the age of 16 years. Patients 65 years and older with isolated hip fractures were also excluded because they are known to have a very high mortality and incidence of medical complications. In addition, each hospital differs in whether they include hip fractures in their trauma registry data. There was concern that they may obscure the relationship between BAC and complications, or simply introduce error into the models. The exclusion of this group of patients is consistent with three recent studies relating to medical complications following an injury (Glance et al., 2009; Ingraham et al., 2010; Osler et al., 2012). Patients whose injuries were exclusively late effects (ICD-9 905–909.9), superficial injuries (910–924.9), or foreign bodies (930–939) were also excluded. Most studies relating to traumatic injuries exclude these patients since they inflate the denominator and have no overall impact on most associations evaluated using trauma data. Finally, burns were also excluded for two reasons: 1) in the previous analysis (Friedman, 2012), burn injuries were the only subgroup of injuries in which BAC was not significantly associated with in-hospital mortality (a different ongoing analysis is looking at burns separately), and 2) the exclusion of this group of patients is consistent with three recent studies relating to medical complications following an injury (Glance et al., 2009; Ingraham et al., 2010; Osler et al., 2012).

### *Complications*

Each patient in the trauma registry has up to 25 ICD-9 diagnosis codes listed in his or her record and these were used to evaluate medical complications. Since some facilities only report the primary traumatic event, one of the tools used to identify facilities that report complications occurring during hospitalization is to look for at least one trauma case with a diagnosis of pneumonia (Huseynova, Xiong, Ray, Ahmed, & Nathens, 2009; Ingraham et al., 2010). Only participating facilities in Illinois reporting at least one case of pneumonia through ICD-9 diagnosis codes were included in the analysis. ICD-9 diagnoses were evaluated as potential candidates for this analysis as long as a minimum of 10 deaths was associated with the specific diagnosis. To augment the internal list of diagnoses, lists of complications reported in the literature were also included (Agency for Healthcare Research and Quality, 2008; Dimick, Pronovost, Cowan, Pamela, & Lipsett, 2003; Glance, Dick, Meredith, & Mukamel, 2011; Healey et al., 2002; Ingraham et al., 2010; Osler et al., 2012). The latter process added diagnoses with fewer than 10 deaths. Cardiac arrest (427.5) was not included since this is often a default diagnosis when the actual cause is unknown and technically all fatalities can receive this diagnosis (Osler et al., 2012).

### *In-hospital mortality*

Case fatality rates are calculated based on reported deaths during hospitalization. Deaths occurring prior to arrival at the trauma center (i.e., persons who died at the scene of injury) and those occurring during the initial assessment within the emergency room were not used to calculate the in-hospital mortality. The latter

group includes two types of patients: 1) no vitals on admission, achieves measured BP during resuscitation, but then subsequently dies prior to formal intake, and 2) dies in the emergency department with no measurable vital signs on admission or during resuscitation.

### *Statistical analysis*

All statistical analyses were conducted using SAS software (v.9.2; SAS Institute Inc., Cary, NC). The Mantel test for trend was used for crude assessment of dose–response. Multivariable logistic regression models were developed to evaluate the relationship between specified complications and BAC. Only complications that were significantly associated with BAC after adjustment are reported. In addition, the subsets of complications relating to cardiac and renal function were combined into two groups. BAC was a continuous variable in all the logistic regression models. Previous work showed that the relationship between mortality and BAC persists when the data are stratified by severity, nature, and mechanism of injury (Friedman, 2012). Therefore, the current study restricted its focus to specific complications without presenting models stratified by specific independent variables. Odds ratios for the adjusted models are presented, including the 95 percent confidence intervals. The statistics was used as a diagnostic measure to assess model fit. No evidence of multi-collinearity among the independent variables was indicated.

Statistical evaluation of covariates, as well as *a priori* knowledge, was used to determine inclusion of covariates in the final models. The final multivariable logistic regression models included the following variables: BAC (continuous), age (continuous), gender (dichotomous), race/ethnicity (categorical; white was the reference category; Hispanic, black and other as categorical variables), penetrating injuries (dichotomous), injury severity using the Trauma Mortality Prediction Model (TMPM) (Glance et al., 2009), and the Elixhauser algorithm to control for comorbidities (Elixhauser, Steiner, Harris, & Coffey, 1998). All odds ratios are presented as the odds of diagnosis of a trauma complication for every change in BAC of 100 mg/dL units.

In addition, to make the adjusted odds ratios more meaningful, attributable fractions were calculated. The attributable fraction provides an estimate of the proportion of cases presenting with complications attributable to blood alcohol concentration. However, the attributable fractions for continuous variables are difficult to interpret. Therefore, BAC was dichotomized (any value greater than 0 mg/dL) to determine the average attributable fractions associated with a positive BAC. Methods described by Greenland & Drescher and Eide & Gefeller were used to calculate the attributable fraction (Eide & Gefeller, 1995; Greenland & Drescher, 1993; Rückinger, von Kries, & Toschke, 2009).

Human subjects approval was given by the University of Illinois at Chicago Institutional Review Board. The protocol approval number was 2012–0116.

## Results

Of 131,182 patients in the Illinois Trauma Registry with measured blood alcohol concentrations, 84,974 patients met the inclusion criteria. Among the patients, 13.4% ($n = 11{,}370$) developed at least one complication. The overall mortality rate was 3.2% ($n = 2708$ deaths), but was substantially higher among those that developed complications compared to those who did not (10.3% vs. 2.1%). Among those that died, 43.2% had at least one complication. The demographic characteristics of patients with and without medical complications did not differ substantially (Table 1). Not surprisingly, a greater proportion of patients with complications had pre-existing comorbidities, were more likely to suffer serious injuries and have longer hospitalizations (Table 1).

Table 2 presents the list of complications used in the analysis and proportions by major blood alcohol concentration categories. In a narrow assessment of only those complications with five or more deaths, blood alcohol concentration was associated with a decline in complications relating to cardiac function, renal function, acute post-hemorrhagic anemia, obstructive hydrocephalus, cerebral occlusion and hemorrhage, coma, pneumothorax, convulsions, and severe sepsis (Table 2). The proportion of patients diagnosed with aspiration pneumonitis and acute pancreatitis actually increased as BAC increased. BAC was both positively and negatively associated with specific disorders of fluid, electrolyte, and acid-base balance (Table 2).

Overall, BAC was associated with a reduced risk of developing any complication (a diagnosis for any complication listed in Table 2; adjusted OR = 0.97 per 100 mg/dL; CI 95%: 0.94, 0.99; $p = 0.006$), and BAC was associated with a fewer number of complications overall (adjusted linear regression model; $p = 0.002$). After controlling for important covariates and stratifying the main outcome variable (all complications), BAC was strongly associated with a cohesive subset of complications, in particular complications relating to cardiac and renal function (Table 3). Acute post-hemorrhagic anemia, obstructive hydrocephalus, cerebral occlusion and hemorrhage, coma, and severe sepsis did not remain

**Table 1**
Demographics characteristics and measures of injury severity by blood alcohol concentration and presence of complications among injured patients treated in level I and II trauma units in Illinois: 2000–2009.

| | Patients without complications ($N = 73{,}604$) | Patients with complications ($N = 11{,}370$) | BAC below level of detection ($N = 43{,}910$) | BAC under 100 mg/dl ($N = 13{,}065$) | BAC 100–199 mg/dl ($N = 11{,}280$) | BAC 200–299 mg/dl ($N = 11{,}682$) | BAC 300 mg/dl and above ($N = 5037$) |
|---|---|---|---|---|---|---|---|
| Demographic characteristics | | | | | | | |
| Male | 54341 (73.8%) | 8373 (73.6%) | 29566 (67.3%) | 10081 (77.2%) | 9193 (81.5%) | 9657 (82.7%) | 4217 (83.7%) |
| Black | 17572 (23.9%) | 2830 (24.9%) | 9368 (21.3%) | 4458 (34.1%) | 3011 (26.7%) | 2481 (21.2%) | 1084 (21.5%) |
| Hispanic | 11771 (16.0%) | 1629 (14.3%) | 6124 (13.9%) | 1694 (13.0%) | 2030 (18.0%) | 2520 (21.6%) | 1032 (20.5%) |
| Mean age | 38.0 (sd = 16.6) | 42.4 (sd = 18.7) | 40.6 (sd = 18.9) | 35.7 (sd = 15.4) | 34.5 (sd = 13.8) | 36.7 (sd = 13.7) | 41.6 (sd = 12.4) |
| Measures of injury severity | | | | | | | |
| Mean length of stay in days (sd) | 3.8 (sd = 10.8) | 9.9 (sd = 9.9) | 4.8 (sd = 11.5) | 4.6 (sd = 12.7) | 4.5 (sd = 12.3) | 4.0 (sd = 10.0) | 4.1 (sd = 13.6) |
| In-hospital fatalities | 1537 (2.1%) | 1171 (10.3%) | 1637 (3.7%) | 405 (3.1%) | 319 (2.8%) | 268 (2.3%) | 79 (1.6%) |
| Penetrating injury | 10,136 (13.8%) | 1910 (16.8%) | 5290 (12.0%) | 2720 (20.8%) | 2171 (19.2%) | 1476 (12.6%) | 389 (7.7%) |
| Injury severity score ≥16 | 10,749 (14.6%) | 3970 (34.9%) | 8111 (18.5%) | 2354 (18.0%) | 1881 (16.7%) | 1760 (15.1%) | 613 (12.2%) |
| Mean TMPM severity score | 0.05 (sd = 0.10) | 0.11 (sd = 0.16) | 0.06 (sd = 0.11) | 0.07 (sd = 0.12) | 0.06 (sd = 0.11) | 0.06 (sd = 0.10) | 0.05 (sd = 0.09) |
| Comorbidities based on Elixhauser Index | 4898 (6.7%) | 4601 (40.5%) | 5505 (12.5%) | 1161 (8.9%) | 1088 (9.6%) | 1155 (9.9%) | 590 (11.7%) |

**Table 2**
Complications following an injury associated with in-hospital mortality by blood alcohol concentration levels.

| Medical complication by ICD-9 Categories | ICD-9 diagnosis code | Total cases with diagnosis | Case fatality rate (%) | BAC below level of detection ($N = 43,910$) | BAC under 100 mg/dl ($N = 13,065$) | BAC 100–199 mg/dl ($N = 11,280$) | BAC 200–299 mg/dl ($N = 11,682$) | BAC 300 mg/dl and above ($N = 5037$) | Mantel test for trend $p$-value |
|---|---|---|---|---|---|---|---|---|---|
| Blood disorders | | | | | | | | | |
| Acute posthemorrhagic anemia | 285.1 | 1364 | 8.7% | 788 (1.79%) | 168 (1.29%) | 185 (1.64%) | 151 (1.29%) | 72 (1.43%) | 0.001 |
| Defibrination syndrome | 286.6 | 43 | 53.5% | 24 (0.05%) | 8 (0.06%) | 6 (0.05%) | 2 (0.02%) | 3 (0.06%) | 0.356 |
| Acquired coagulation factor deficiency | 286.7 | 6 | 16.7% | 3 (0.01%) | 1 (0.01%) | 1 (0.01%) | 1 (0.01%) | 0 (0.00%) | 0.898 |
| Other coagulation defects NOS | 286.9 | 143 | 35.0% | 74 (0.17%) | 20 (0.15%) | 15 (0.13%) | 20 (0.17%) | 14 (0.28%) | 0.402 |
| Cerebrovascular disorders | | | | | | | | | |
| Subarachnoid hemorrhage | 430 | 56 | 16.1% | 28 (0.06%) | 9 (0.07%) | 7 (0.06%) | 9 (0.08%) | 3 (0.06%) | 0.827 |
| Intracerebral hemorrhage | 431 | 60 | 31.7% | 43 (0.10%) | 8 (0.06%) | 4 (0.04%) | 3 (0.03%) | 2 (0.04%) | 0.002 |
| Subdural hemorrhage and unspecified intracranial hemorrhage | 432.1, 432.9 | 70 | 17.1% | 32 (0.07%) | 9 (0.07%) | 12 (0.11%) | 9 (0.08%) | 8 (0.16%) | 0.118 |
| Cerebral embolism with cerebral infarction | 434.11 | 14 | 35.7% | 10 (0.02%) | 1 (0.01%) | 2 (0.02%) | 1 (0.01%) | 0 (0.00%) | 0.157 |
| Cerebral artery occlusion, unspecified with cerebral infarction | 434.91 | 77 | 41.6% | 53 (0.12%) | 7 (0.05%) | 9 (0.08%) | 7 (0.06%) | 1 (0.02%) | 0.005 |
| Iatrogenic cerebrovascular infarction or hemorrhage, postoperative stroke | 997.02 | 1 | 0.0% | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.01%) | 0 (0.00%) | 0.142 |
| Disorders of cardiac function | | | | | | | | | |
| Acute myocardial infarction NOS or Coronary occlusion NOS during initial episode of care | 410.9 | 31 | 16.1% | 23 (0.05%) | 6 (0.05%) | 2 (0.02%) | 0 (0.00%) | 0 (0.00%) | 0.002 |
| Acute myocardial infarction of anterior wall, during initial episode of care | 410.11 | 3 | 0.0% | 2 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.01%) | 0 (0.00%) | 0.928 |
| Acute myocardial infarction of inferior wall, during initial episode of care | 410.41 | 4 | 25.0% | 2 (0.00%) | 1 (0.01%) | 0 (0.00%) | 1 (0.01%) | 0 (0.00%) | 0.917 |
| Subendocardial infarction, nontransmural infarction during initial episode of care | 410.71 | 37 | 27.0% | 27 (0.06%) | 1 (0.01%) | 4 (0.04%) | 5 (0.04%) | 0 (0.00%) | 0.052 |
| Unspecified disease of pericardium | 423.9 | 73 | 16.4% | 44 (0.10%) | 8 (0.06%) | 7 (0.06%) | 11 (0.09%) | 3 (0.06%) | 0.326 |
| Aortic valve disorders including incompetence, insufficiency, regurgitation, stenosis | 424.1 | 48 | 6.3% | 35 (0.08%) | 5 (0.04%) | 5 (0.04%) | 3 (0.03%) | 0 (0.00%) | 0.003 |
| Other primary cardiomyopathies | 425.4 | 75 | 8.0% | 46 (0.10%) | 11 (0.08%) | 10 (0.09%) | 6 (0.05%) | 2 (0.04%) | 0.042 |
| Paroxysmal ventricular tachycardia | 427.1 | 90 | 21.1% | 59 (0.13%) | 15 (0.11%) | 9 (0.08%) | 5 (0.04%) | 2 (0.04%) | 0.001 |
| Atrial fibrillation and flutter | 427.31, 427.32 | 500 | 13.8% | 342 (0.78%) | 48 (0.37%) | 39 (0.35%) | 48 (0.41%) | 23 (0.46%) | 0.001 |
| Heart failure | 428 | 323 | 22.9% | 234 (0.53%) | 29 (0.22%) | 28 (0.25%) | 21 (0.18%) | 11 (0.22%) | 0.001 |
| Ventricular fibrillation | 427.41 | 35 | 68.6% | 27 (0.06%) | 2 (0.02%) | 4 (0.04%) | 2 (0.02%) | 0 (0.00%) | 0.006 |
| Cardiac dysrhythmias including coronary sinus, ectopic, and nodal | 427.89 | 514 | 8.8% | 287 (0.65%) | 76 (0.58%) | 63 (0.56%) | 63 (0.54%) | 25 (0.50%) | 0.050 |
| Cardiomegaly including cardiac dilatation, cardiac hypertrophy, ventricular dilatation | 429.3 | 77 | 3.9% | 46 (0.10%) | 12 (0.09%) | 7 (0.06%) | 8 (0.07%) | 4 (0.08%) | 0.158 |
| Cardiac complications | 997.1 | 25 | 32.0% | 16 (0.04%) | 2 (0.02%) | 6 (0.05%) | 1 (0.01%) | 0 (0.00%) | 0.139 |
| Other disorders of circulatory system | | | | | | | | | |
| Abdominal aneurysm without mention of rupture | 441.4 | 43 | 7.0% | 32 (0.07%) | 3 (0.02%) | 4 (0.04%) | 4 (0.03%) | 0 (0.00%) | 0.008 |
| Arterial embolism and thrombosis of lower extremity | 444.22 | 23 | 4.3% | 14 (0.03%) | 4 (0.03%) | 2 (0.02%) | 2 (0.02%) | 1 (0.02%) | 0.296 |
| Iatrogenic hypotension | 458.29 | 0 | 0.0% | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | ~ |
| Other specified hypotension | 458.8 | 24 | 33.3% | 17 (0.04%) | 1 (0.01%) | 2 (0.02%) | 3 (0.03%) | 1 (0.02%) | 0.235 |
| Hypotension, unspecified | 458.9 | 476 | 26.5% | 240 (0.55%) | 78 (0.60%) | 60 (0.53%) | 67 (0.57%) | 31 (0.62%) | 0.618 |
| Disorders of digestive system | | | | | | | | | |
| Acute and unspecified vascular insufficiency of intestine | 557.0, 557.9 | 24 | 12.5% | 14 (0.03%) | 3 (0.02%) | 3 (0.03%) | 4 (0.03%) | 0 (0.00%) | 0.47 |
| Intestinal obstruction inc mural thickening causing obstruction | 560.89 | 0 | 0.0% | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0.416 |
| Unspecified intestinal obstruction | 560.9 | 1 | 100.0% | 1 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | ~ |
| Unspecified peritonitis | 567.9 | 109 | 1.8% | 53 (0.12%) | 32 (0.24%) | 17 (0.15%) | 5 (0.04%) | 2 (0.04%) | 0.045 |
| Perforation of intestine | 569.83 | 13 | 7.7% | 7 (0.02%) | 3 (0.02%) | 2 (0.02%) | 1 (0.01%) | 0 (0.00%) | 0.411 |
| Acute and subacute necrosis of liver | 570 | 22 | 45.5% | 12 (0.03%) | 5 (0.04%) | 3 (0.03%) | 2 (0.02%) | 0 (0.00%) | 0.291 |
| Hepatic coma inc. hepatic encephalopathy, hepatocerebral intoxication, portal-systemic encephalopathy | 572.2 | 20 | 20.0% | 9 (0.02%) | 1 (0.01%) | 2 (0.02%) | 2 (0.02%) | 6 (0.12%) | 0.021 |
| Hepatorenal syndrome | 572.4 | 3 | 66.7% | 1 (0.00%) | 1 (0.01%) | 0 (0.00%) | 1 (0.01%) | 0 (0.00%) | 0.727 |
| Acute pancreatitis | 577.0 | 160 | 4.4% | 59 (0.13%) | 22 (0.17%) | 21 (0.19%) | 30 (0.26%) | 28 (0.56%) | 0.001 |
| Gastrointestinal hemorrhage | 578 | 83 | 15.7% | 53 (0.12%) | 8 (0.06%) | 8 (0.07%) | 13 (0.11%) | 1 (0.02%) | 0.07 |
| Disorders of genitourinary system | | | | | | | | | |
| Hypertensive chronic kidney disease | 403.91 | 57 | 12.3% | 48 (0.11%) | 7 (0.05%) | 2 (0.02%) | 0 (0.00%) | 0 (0.00%) | 0.001 |
| Acute renal failure with lesion of tubular necrosis | 584.5 | 67 | 34.3% | 45 (0.10%) | 8 (0.06%) | 7 (0.06%) | 7 (0.06%) | 0 (0.00%) | 0.008 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Acute renal failure, unspecified | 584.9 | 259 | 25.5% | 183 (0.42%) | 35 (0.27%) | 22 (0.20%) | 13 (0.11%) | 6 (0.12%) | 0.001 |
| Renal failure, unspecified | 586 | 17 | 35.3% | 11 (0.03%) | 3 (0.02%) | 1 (0.01%) | 2 (0.02%) | 0 (0.00%) | 0.186 |
| Unspecified disorder of kidney inc. renal disease NOS and salt-losing nephritis or syndrome | 593.9 | 154 | 6.5% | 108 (0.25%) | 17 (0.13%) | 12 (0.11%) | 9 (0.08%) | 8 (0.16%) | 0.001 |
| Urinary tract infection, site not specified | 599.0 | 569 | 3.9% | 361 (0.82%) | 91 (0.70%) | 52 (0.46%) | 51 (0.44%) | 14 (0.28%) | 0.001 |
| Disorders of mineral metabolism and fluid, electrolyte, and acid-base balance | | | | | | | | | |
| Disorders of mineral metabolism | 275 | 394 | 6.6% | 210 (0.48%) | 35 (0.27%) | 52 (0.46%) | 58 (0.50%) | 39 (0.77%) | 0.066 |
| Hyperosmolality and/or hypernatremia Hyposmolality and/or hyponatremia | 276.0, 276.1 | 671 | 10.6% | 354 (0.81%) | 88 (0.67%) | 91 (0.81%) | 89 (0.76%) | 49 (0.97%) | 0.64 |
| Acidosis | 276.2 | 931 | 14.0% | 351 (0.80%) | 115 (0.88%) | 185 (1.64%) | 188 (1.61%) | 92 (1.83%) | 0.001 |
| Alkalosis | 276.3 | 385 | 5.2% | 300 (0.68%) | 33 (0.25%) | 25 (0.22%) | 14 (0.12%) | 13 (0.26%) | 0.001 |
| Mixed acid-base balance disorder | 276.4 | 38 | 26.3% | 17 (0.04%) | 3 (0.02%) | 2 (0.02%) | 8 (0.07%) | 8 (0.16%) | 0.006 |
| Hyperpotassemia | 276.7 | 104 | 16.3% | 67 (0.15%) | 14 (0.11%) | 10 (0.09%) | 9 (0.08%) | 4 (0.08%) | 0.011 |
| Electrolyte and fluid disorders not elsewhere classified | 276.9 | 83 | 8.4% | 51 (0.12%) | 13 (0.10%) | 4 (0.04%) | 9 (0.08%) | 6 (0.12%) | 0.163 |
| Disorders of pulmonary function | | | | | | | | | |
| Iatrogenic pulmonary embolism and infarction | 415.11 | 10 | 10.0% | 7 (0.02%) | 1 (0.01%) | 2 (0.02%) | 0 (0.00%) | 0 (0.00%) | 0.171 |
| Other pulmonary embolism and infarction | 415.19 | 74 | 5.4% | 50 (0.11%) | 6 (0.05%) | 11 (0.10%) | 7 (0.06%) | 0 (0.00%) | 0.008 |
| Obstructive chronic bronchitis with acute exacerbation | 491.21 | 11 | 0.0% | 6 (0.01%) | 2 (0.02%) | 0 (0.00%) | 3 (0.03%) | 0 (0.00%) | 0.862 |
| Aspiration pneumonitis due to solids and liquids | 507 | 382 | 13.9% | 194 (0.44%) | 42 (0.32%) | 54 (0.48%) | 65 (0.56%) | 27 (0.54%) | 0.081 |
| Empyema | 510 | 32 | 15.6% | 9 (0.02%) | 8 (0.06%) | 10 (0.09%) | 5 (0.04%) | 0 (0.00%) | 0.237 |
| Pneumothorax | 512 | 160 | 11.9% | 94 (0.21%) | 25 (0.19%) | 23 (0.20%) | 15 (0.13%) | 3 (0.06%) | 0.010 |
| Pulmonary insufficiency | 518.4 | 23 | 30.4% | 9 (0.02%) | 5 (0.04%) | 5 (0.04%) | 4 (0.03%) | 0 (0.00%) | 0.701 |
| Pulmonary insufficiency following trauma and surgery | 518.5 | 1001 | 17.9% | 508 (1.16%) | 168 (1.29%) | 141 (1.25%) | 139 (1.19%) | 45 (0.89%) | 0.58 |
| Acute respiratory failure | 518.81 | 792 | 13.3% | 419 (0.95%) | 93 (0.71%) | 109 (0.97%) | 124 (1.06%) | 47 (0.93%) | 0.506 |
| Other pulmonary insufficiency inc. acute respiratory distress and acute respiratory insufficiency | 518.82 | 323 | 15.5% | 169 (0.38%) | 48 (0.37%) | 41 (0.36%) | 38 (0.33%) | 27 (0.54%) | 0.774 |
| Acute and chronic respiratory failure | 518.84 | 12 | 0.0% | 7 (0.02%) | 1 (0.01%) | 1 (0.01%) | 2 (0.02%) | 1 (0.02%) | 0.969 |
| Respiratory complications | 997.3 | 56 | 0.0% | 32 (0.07%) | 7 (0.05%) | 7 (0.06%) | 7 (0.06%) | 3 (0.06%) | 0.552 |
| Disorders of the central nervous system | | | | | | | | | |
| Obstructive hydrocephalus | 331.4 | 86 | 22.1% | 56 (0.13%) | 10 (0.08%) | 8 (0.07%) | 7 (0.06%) | 5 (0.10%) | 0.041 |
| Grand mal status | 345.3 | 32 | 12.5% | 19 (0.04%) | 8 (0.06%) | 2 (0.02%) | 2 (0.02%) | 1 (0.02%) | 0.101 |
| Anoxic brain damage | 348.1 | 183 | 56.3% | 106 (0.24%) | 26 (0.20%) | 22 (0.20%) | 22 (0.19%) | 7 (0.14%) | 0.075 |
| Encephalopathy, unspecified | 348.3 | 34 | 2.9% | 20 (0.05%) | 3 (0.02%) | 5 (0.04%) | 5 (0.04%) | 1 (0.02%) | 0.571 |
| Compression of brain | 348.4 | 97 | 61.9% | 50 (0.11%) | 11 (0.08%) | 16 (0.14%) | 18 (0.15%) | 2 (0.04%) | 0.918 |
| Cerebral edema | 348.5 | 415 | 44.1% | 231 (0.53%) | 58 (0.44%) | 55 (0.49%) | 55 (0.47%) | 16 (0.32%) | 0.082 |
| Other conditions of brain including calcification, posttraumatic calcifications have been described in the capsule surrounding both chronic subdural and epidural hematomas | 348.8 | 413 | 31.2% | 207 (0.47%) | 63 (0.48%) | 68 (0.60%) | 51 (0.44%) | 24 (0.48%) | 0.805 |
| Other convulsions NEC | 780.39 | 629 | 4.1% | 440 (1.00%) | 48 (0.37%) | 48 (0.43%) | 52 (0.45%) | 41 (0.81%) | 0.001 |
| Infection | | | | | | | | | |
| Clostridium difficile, pseudomembranous colitis | 8.45 | 79 | 10.1% | 43 (0.10%) | 10 (0.08%) | 4 (0.04%) | 14 (0.12%) | 8 (0.16%) | 0.517 |
| Septicemia | 38 | 193 | 23.8% | 109 (0.25%) | 23 (0.18%) | 26 (0.23%) | 26 (0.22%) | 9 (0.18%) | 0.344 |
| All pneumonia | 480–487 | 932 | 9.0% | 490 (1.12%) | 162 (1.24%) | 105 (0.93%) | 135 (1.16%) | 40 (0.79%) | 0.139 |
| Pneumonia, organism unspecified | 486 | 524 | 8.8% | 261 (0.59%) | 104 (0.80%) | 61 (0.54%) | 80 (0.68%) | 18 (0.36%) | 0.463 |
| Infective myositis | 728.0 | 1 | 0.0% | 1 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0.416 |
| Severe sepsis | 995.91–995.93 | 133 | 26.3% | 85 (0.19%) | 19 (0.15%) | 12 (0.11%) | 10 (0.09%) | 7 (0.14%) | 0.007 |
| Post surgery infection | 998.5 | 17 | 11.8% | 8 (0.02%) | 4 (0.03%) | 2 (0.02%) | 3 (0.03%) | 0 (0.00%) | 0.829 |
| Surgical complications | | | | | | | | | |
| Postoperative shock | 998.0 | 5 | 0.0% | 2 (0.00%) | 0 (0.00%) | 0 (0.00%) | 1 (0.01%) | 2 (0.04%) | 0.054 |
| Hemorrhage or hematoma or seroma complicating a procedure | 998.1 | 77 | 9.1% | 46 (0.10%) | 14 (0.11%) | 9 (0.08%) | 3 (0.03%) | 5 (0.10%) | 0.065 |
| Accidental puncture or laceration during a procedure | 998.2 | 29 | 10.3% | 14 (0.03%) | 4 (0.03%) | 6 (0.05%) | 3 (0.03%) | 2 (0.04%) | 0.777 |
| Disruption of operation wound | 998.3 | 46 | 8.7% | 20 (0.05%) | 7 (0.05%) | 11 (0.10%) | 6 (0.05%) | 2 (0.04%) | 0.513 |
| Symptoms, signs and Ill-defined conditions | | | | | | | | | |
| Cardiogenic shock | 785.51 | 19 | 57.9% | 14 (0.03%) | 2 (0.02%) | 2 (0.02%) | 0 (0.00%) | 1 (0.02%) | 0.072 |
| Shock, other | 785.59 | 19 | 21.1% | 10 (0.02%) | 2 (0.02%) | 1 (0.01%) | 5 (0.04%) | 1 (0.02%) | 0.638 |
| Apnea | 786.03 | 7 | 14.3% | 5 (0.01%) | 0 (0.00%) | 1 (0.01%) | 1 (0.01%) | 0 (0.00%) | 0.476 |
| Tachypnea | 786.06 | 13 | 7.7% | 7 (0.02%) | 2 (0.02%) | 1 (0.01%) | 3 (0.03%) | 0 (0.00%) | 0.85 |
| Other symptoms involving respiratory system and other chest symptoms | 786.09 | 92 | 2.2% | 43 (0.10%) | 18 (0.14%) | 12 (0.11%) | 18 (0.15%) | 1 (0.02%) | 0.895 |
| Bacteremia | 790.7 | 103 | 4.9% | 57 (0.13%) | 9 (0.07%) | 13 (0.12%) | 20 (0.17%) | 4 (0.08%) | 0.945 |

(*continued on next page*)

**Table 2** (*continued*)

| Medical complication by ICD-9 Categories | ICD-9 diagnosis code | Total cases with diagnosis | Case fatality rate (%) | BAC below level of detection ($N = 43{,}910$) | BAC under 100 mg/dl ($N = 13{,}065$) | BAC 100–199 mg/dl ($N = 11{,}280$) | BAC 200–299 mg/dl ($N = 11{,}682$) | BAC 300 mg/dl and above ($N = 5037$) | Mantel test for trend *p*-value |
|---|---|---|---|---|---|---|---|---|---|
| Abnormal coagulation profile | 790.92 | 35 | 2.9% | 21 (0.05%) | 3 (0.02%) | 5 (0.04%) | 6 (0.05%) | 0 (0.00%) | 0.41 |
| Coma and transient alteration of awareness | 780.01, 780.02 | 234 | 13.2% | 116 (0.26%) | 22 (0.17%) | 39 (0.35%) | 43 (0.37%) | 14 (0.28%) | 0.082 |
| Adult failure to thrive | 783.7 | 5 | 0.0% | 3 (0.01%) | 1 (0.01%) | 0 (0.00%) | 1 (0.01%) | 0 (0.00%) | 0.648 |
| Gangrene | 785.4 | 25 | 0.0% | 17 (0.04%) | 2 (0.02%) | 2 (0.02%) | 1 (0.01%) | 3 (0.06%) | 0.384 |
| Shock, unspecified | 785.50 | 16 | 31.3% | 10 (0.02%) | 2 (0.02%) | 2 (0.02%) | 2 (0.02%) | 0 (0.00%) | 0.332 |
| Ascites, fluid in peritoneal cavity | 789.5 | 64 | 9.4% | 27 (0.06%) | 13 (0.10%) | 8 (0.07%) | 10 (0.09%) | 6 (0.12%) | 0.165 |
| Asphyxia | 799.0 | 84 | 15.5% | 42 (0.10%) | 22 (0.17%) | 6 (0.05%) | 14 (0.12%) | 0 (0.00%) | 0.253 |
| Other | | | | | | | | | |
| Embolism, posttraumatic wound infection, traumatic shock, Volkmann's ischemic contracture, traumatic subcutaneous emphysema | 958–958.2<br>958.3–958.5<br>958.6–959 | 1987 | 14.6% | 979 (2.23%) | 376 (2.88%) | 296 (2.62%) | 237 (2.03%) | 99 (1.97%) | 0.401 |
| Secondary and recurrent hemorrhage | 958.2 | 88 | 33.0% | 48 (0.11%) | 14 (0.11%) | 13 (0.12%) | 10 (0.09%) | 3 (0.06%) | 0.328 |
| Traumatic anuria inc. crush syndrome and renal failure following crushing | 958.5 | 10 | 50.0% | 7 (0.02%) | 3 (0.02%) | 0 (0.00%) | 0 (0.00%) | 0 (0.00%) | 0.064 |
| Diabetes insipidus | 253.5 | 37 | 56.8% | 18 (0.04%) | 8 (0.06%) | 7 (0.06%) | 4 (0.03%) | 0 (0.00%) | 0.488 |
| Acute osteomyelitis, periostitis without mention of ostemyelitis, other infection of bone | 730.0, 730.2, 730.3, 730.8, 730.9 | 18 | 5.6% | 14 (0.03%) | 2 (0.02%) | 0 (0.00%) | 2 (0.02%) | 0 (0.00%) | 0.044 |

significantly associated with BAC in the multivariable models. However, BAC continued to be positively associated with aspiration pneumonitis and acute pancreatitis in the adjusted models.

BAC was protective for the development of cardiac and renal complications, attributed to an average reduction in cardiac and renal cases by 23.5% and 30.0%, respectively (Table 3). BAC was also protective against developing convulsions and pneumothorax. The four groups of complications for which alcohol appears to be protective were seen in 3064 unique patients – more than a fourth of all patients with complications. In contrast, BAC was associated with 28.6% of the cases of acute pancreatitis ($n = 160$), but this complication was associated with only 7 deaths (Table 3).

Among those that did develop complications following a traumatic injury, BAC was also associated with reduced in-hospital mortality ($n = 11{,}370$; adjusted OR = 0.87 per 100 mg/dL; CI 95%: 0.81, 0.92; $p < 0.0001$), controlling for age, gender, race/ethnicity, penetrating injury, injury severity (TMPM), and comorbidities.

## Discussion

This study follows a previous analysis that found a strong inverse association between in-hospital mortality following a traumatic injury and BAC (Friedman, 2012). The current analysis shows distinct constellations of medical complications inversely associated with measured blood alcohol concentrations, dominated by the cardiovascular system and kidneys. Furthermore, among patients that did develop complications, patients with elevated BAC were less likely to die.

It is important to remember that within the context of this study population we are observing the acute effects of alcohol on the body, which may be modified to a degree by adaptive physiological mechanisms from subacute and chronic exposure. In this study, alcohol was associated with a reduced risk of complications in cardiac function including infarction, fibrillation, other severe arrhythmias, and heart failure. Alcohol impacts the cardiovascular system in various ways including increasing release of catecholamines (Child, Kovick, Levisman, & Pearce, 1979; Eisenhofer, Lambie, & Johnson, 1983; Kelbaek et al., 1987; Newsome, 1988), increasing muscle sympathetic nerve activity (Spaak et al., 2008; van de Borne, Mark, Montano, Mion, & Somers, 1997), increasing vasodilation through smooth muscle relaxation (Tawakol, Omland, & Craeger, 2004), increasing cardiac output (Gould, Reddy, Becker, Oh, & Kim, 1978; Kelbaek et al., 1988; Spaak et al., 2008; van de Borne et al., 1997), antithrombotic effects (Rubin & Rand, 1994), and potentiating the effects of many other drugs, including those commonly used in the treatment of injured patients (Weathermon & Crabb, 1999). Some of these effects may also be biphasic in nature – the physiological response to ethanol changes over time as it is metabolized (Bau, Bau, Naujorks, & Rosito, 2005; Malhotra, Mehta, Mathur, & Khandelwal, 1985). Based on physiological studies on the biomechanism of alcohol, alcohol's acute sympathoexcitatory (Randin et al., 1995; Wallin, 1983) and pressor effects "keep the blood pumping." Furthermore, renal failure is caused by an array of factors, but pre-renal causes include heart failure and reduced cardiac output, which explains, to a degree, the clear protective effect of BAC against developing complications associated with renal function (Waikar & Bonventre, 2012).

Some studies have reported neuroprotective effects of alcohol through action on the NMDA complex and catecholamines (Kelly et al., 1997; Türeci et al., 2004; Ward et al., 1982), in part, by inhibiting NMDA receptors, which causes a reduction in intracellular calcium accumulation and hyperglycolysis, which is associated with reduced lesion size in the brain (Kelly et al., 1997). In the crude analysis, this study did identify a decrease in complications associated with the central nervous system – in particular the risk of

**Table 3**
Multivariable logistic regression analysis of risk of developing complications associated increased in-hospital mortality with attributable fraction among injured patients treated in level I and II trauma units in Illinois: 2000–2009.

| Medical complication | Total cases | CFR | Adjusted odds ratio per 100 mg/dl of alcohol (CI 95%) | *p*-value | Average attributable fraction |
|---|---|---|---|---|---|
| Protective relationship | | | | | |
| Cardiac function complications group[a] | 1490 | 14.4% | 0.91 (0.86, 0.96) | 0.0003 | −23.5% |
| Renal function complications group[b] | 1057 | 11.5% | 0.76 (0.71, 0.81) | <0.0001 | −30.0% |
| Other convulsions NEC | 629 | 4.1% | 0.85 (0.78, 0.92) | <0.0001 | −35.4% |
| Pneumothorax | 160 | 11.9% | 0.81 (0.69, 0.95) | 0.0104 | −13.7% |
| Adverse relationship | | | | | |
| Acute pancreatitis | 160 | 4.4% | 1.44 (1.29, 1.61) | <0.0001 | +28.6% |
| Aspiration pneumonitis due to solids and liquids | 382 | 13.9% | 1.12 (1.03, 1.22) | 0.0065 | +1.7% |

Bonferroni correction for 11 models tested − $p = 0.0009$.
[a] Cardiac complications include the following ICD-9 diagnosis codes: 410 (all), 424.1, 425.4, 427.1, 427.31, 427.32, 427.41, 427.89, 428, 997.1.
[b] Renal complications include the following ICD-9 diagnosis codes: 403.2, 584.5, 584.9, 586, 593.9, 599.0.

cerebral hemorrhage, occlusion, and embolism − but these complications were not significantly associated with BAC after adjusting for key covariates. However, an analysis exclusive to traumatic brain injury patients may identify specific complications not identified in this larger dataset of patients suffering a wide array of injuries. In this study, BAC was associated with reduced odds of developing convulsions, which can be related to a reduced risk of intracranial hemorrhage, as observed in the crude analysis (Herman, 2002), but it may also be related to alcohol's anticonvulsant properties by inhibiting the excitatory activity of the NMDA receptor (Gonzales & Jaworski, 1997).

Because of the complex and varied effects of alcohol on the human body, there were some complications positively associated with BAC, in particular acute pancreatitis. However, this relationship does not appear to be the result of injury to the pancreas, since the proportion of pancreatic injuries does not differ substantially by BAC level. However, alcohol is directly associated with pancreatitis and therefore the observed association may not be related to the injury, but rather directly related to alcohol consumption (Yadav & Lowenfels, 2013).

Categories of 100 mg/dL units of change in BAC were used for descriptive purposes only. This was chosen so that the reader can view changes in proportions of characteristics across different levels of BAC (Tables 1and 2). In the multivariable models, we did not categorize BAC, but kept it as a continuous variable so that we could assess the relationship without obscuring any potential non-linear relationship. The descriptive results were not presented in categories of 80 mg/dL units because this is an arbitrary legal limit for drivers of motor vehicles. Numerous studies show physiological, cognitive, and behavioral responses to ethanol at levels well below 80 mg/dL, and in fact, the legal limit varies dramatically by country and age of the driver. Furthermore, these legal limits only apply to persons driving motor vehicles. The current study includes patients injured from all mechanisms, not just motor vehicle crashes. There is no general legal limit in most countries outside of motor vehicle laws. Therefore, for the primary analyses we kept the BAC variable as a continuous variable rather than categorizing BAC into legalistic (and arbitrary) defined categories such as below and above 80 mg/dL.

Since BAC is a continuous variable in all the multivariable models, the parameter estimates are measuring the change in odds of a specific complication per unit change in BAC. To make the findings more meaningful, the final odds ratios are presented per 100 mg/dL units of change. A common problem with odds ratios is that they often do not describe true risk accurately. One example of the limitation of odds ratios is seen when the independent variable is not dichotomous. In this study, the odds ratio for the relationship between BAC and cardiac function complications per 1 mg/dL unit change in BAC is 0.99, but is 0.91 per 100 mg/dL (as presented in Table 3), or 0.62 per 500 mg/dL units (CI 95%: 0.58, 0.65). The initial parameter estimates represent the change in odds per 1 mg/dL of BAC, but these parameter estimates are converted so that it represents a change of 100 mg/dL. A 1 mg/dL change is not clinically meaningful and may lead the reader to draw incorrect conclusions regarding the possible effect size across the continuum of BAC.

### *Limitations*

A major concern prior to undertaking the analysis was in regard to underreporting of complications, which varies substantially between coders and institutions and may be correlated with the outcome of the patient (Mann, Guice, Cassidy, Wright, & Koury, 2006; Osler et al., 2012; Phillips, Clark, Nathens, Shiloach, & Freel, 2008). Two basic design elements were undertaken to minimize the effect from underreporting. First, only facilities in Illinois reporting at least one case of pneumonia through ICD-9 diagnosis codes were included in the analysis. Previous studies have shown that this is a useful mechanism for identifying facilities with more rigorous reporting practices (Huseynova et al., 2009; Ingraham et al., 2010). Second, the final list of complications used in this analysis was based on both an internal review of cases and was augmented by lists of complications previously reported in the literature (Agency for Healthcare Research and Quality, 2008; Dimick et al., 2003; Glance et al., 2011; Healey et al., 2002; Ingraham et al., 2010; Osler et al., 2012). There is a large degree of overlap between the internal list and those reported in the literature and these complications are generally pronounced, severe, and life threatening. It is likely that these complications will be more likely to be reported than rarer and less life-threatening complications (Osler et al., 2012).

Among those with complications, BAC appears to continue to be protective in a dose-dependent manner (Table 4). This indicates that alcohol may not only reduce the occurrence of certain medical complications, but when complications do occur, alcohol may also decrease their severity. However, the dataset we used for this analysis does not provide information on the severity of the

**Table 4**
Case fatality rates by BAC levels among patients with and without reported medical complications among injured patients treated in level I and II trauma units in Illinois: 2000–2009.

| | BAC below level of detection | BAC under 100 mg/dl | BAC 100–199 mg/dl | BAC 200–299 mg/dl | BAC 300 mg/dl and above |
|---|---|---|---|---|---|
| Patients without complications ($N = 73{,}604$) | 2.48% | 2.11% | 1.73% | 1.49% | 0.92% |
| Patients with complications ($N = 11{,}370$) | 11.25% | 10.09% | 10.17% | 8.17% | 6.31% |

complications. For example, the trauma registry only tells us if there was acute post-hemorrhagic anemia or myocardial infarction, but does not provide data on biomarkers or ECG abnormalities that could be used to determine severity.

Furthermore, many injured persons die prior to developing the complications identified in this study. This study only informs us about the subset of patients who typically die later in the course of treatment. However, previous work has shown that alcohol's protective effects appear to be immediate and sustained (Friedman, 2012); therefore, this study likely only explains a portion of alcohol's protective effect on the body following an injury. In the current analysis, the inverse dose-dependent relationship between alcohol and mortality persisted in the subgroup of patients that did not have reported medical complications (Table 4). This indicates that a reduction in complications is not the only pathway in which BAC is associated with reduced in-hospital mortality. There are probably other mechanisms that ICD-9 codes cannot capture adequately, and this is the next set of studies planned to assess the relationship between alcohol and in-hospital mortality following a trauma.

Another potential limitation is that the trauma registry does not capture the time during the course of treatment that a complication develops. This prevents an analysis of estimated BAC at the time of onset of the documented complications. Furthermore, the choice to use the quantitative measure of blood alcohol concentration in mg/dL provides the benefit of not restricting the analysis to arbitrary or legal cut-offs of intoxication (e.g., 80 mg/dL), but ignores the role of physiological adaptation to alcohol and treats all patients as equal at any given BAC value. Individuals with similar quantitative measures of BAC may present with clear signs of intoxication, normal neuropsychiatric steady state, or even ethanol withdrawal. However, the registry does not capture clinical measures of intoxication that would help assess levels of physiological response.

Duration and frequency of alcohol intake among the patients in this study is not known. It is possible that the findings are modified by the effects of chronic alcohol intake or are directly the result of chronic dependence/abuse. In addition, this study does not distinguish between the physiological effects of ethanol and its metabolites. Most complications have been shown to occur later in the course of treatment (Ingraham et al., 2010; Osler et al., 2012), after the point of time we would expect the vast majority of ethanol in the body to have been metabolized, which makes it difficult to assess the biomechanism involved in reducing complications and death following injury.

If patients with BAC levels above zero were more likely to die prior to hospitalization or be over-triaged to facilities with specialized trauma teams, then the findings would likely be biased. However, there is no conclusive evidence that intoxicated individuals are more likely to die prior to hospitalization. The most comprehensive prospective study to date, which looked at pre-hospital, and in-hospital mortality did not show that persons with elevated BAC were more likely to die in the field (Jurkovich et al., 1993). There are some conflicting findings contradicting Jurkovich's study, but they are based on studies that exclusively look at deaths and not the rate of deaths across all reported accidents/injuries (Demetriades et al., 2004), or only a small fraction of patients are tested for BAC and those without a BAC measurement are included in the comparison group (Stübig et al., 2012).

In addition, research clearly shows that patients transported directly to trauma units with advanced care, bypassing closer hospitals without specialized care, are more likely to survive their injuries (Härtl et al., 2006; MacKenzie et al., 2006). Acute and chronic alcohol use is associated with physiological changes that may result in the over-triage of these patients to hospitals with specialized trauma units, in particular the misdiagnosis of traumatic brain injuries through the use of the Glasgow Coma Scale. The ICD-9 codes, which are based on final diagnoses at the time of discharge, allow us to evaluate our model based on anatomic and mechanistic triage criteria that are not influenced by pre-hospital physiological triage assessments — the physiologic effects of alcohol would be unrelated to triaging these patients. Therefore, the severity measure (TMPM) used in this analysis would also help control for this. However, if an important bias exists, the subset of injured patients suffering no traumatic brain injuries would be biased because of the initial misdiagnosis of a traumatic brain injury, but the previous work showed that the association between BAC and mortality persisted in models that included 1) only TBIs, 2) only patients without head injuries, and 3) only patients meeting anatomic and mechanistic triage criteria (Friedman, 2012).

## Conclusions

Overall, it appears that alcohol is protective following an injury (Blondell et al., 2002; Friedman, 2012; Kraus et al., 1989; O'Phelan et al., 2008; Salim et al., 2009; Tien et al., 2006; Ward et al., 1982; Yaghoubian et al., 2009). This study identified several pathways in which the association between BAC and in-hospital mortality can be explained. Although the odds ratios do not appear to diverge dramatically from unity — in part, because BAC is a continuous variable, the effect size is large when the odds ratios are converted into attributable fractions, which are far more meaningful for assessing the clinical importance of the findings. Furthermore, in a study by Osler and colleagues (Osler et al., 2012), corresponding complications relating to pneumothorax, convulsions, and cardiac and renal function accounted for almost 20% of all deaths following traumatic injuries. In fact, the proportion and mortality rate of patients with complications in this study were comparable to a recently published study that used very similar inclusion criteria involving a different dataset (11% had at least one complication; of those that died, 45.6% had at least one complication) (Ingraham et al., 2010).

This study begins to help explain the observed protective effect of blood alcohol in reducing in-hospital mortality after an injury, as reported in so many studies. The fact that we see clear and explicable reductions in traumatic complications associated with alcohol concentration raises two fundamental questions. First, despite the rather rapid metabolism of alcohol, the benefit is sustained long after there should be only trace levels of alcohol in the body. Therefore, there is a question of whether the benefit associated with alcohol would be further enhanced if BAC levels or drugs that mimic ethanol's beneficial effect were sustained through the course of hospitalization or whether the multiphasic physiologic effect of alcohol is an important key to explaining this relationship (implicating its metabolites or compensatory physiological responses). Second, is mortality to a large degree influenced by the initial physiological response that immediately follows an injury? The latter hypothesis is not entirely unsupported in the scientific literature: interventions within a short initial window of time following ischemic stroke and acute myocardial infarction have been shown to be associated with an improved prognosis at discharge and afterward (Anderson et al., 2007; ISIS-4 Collaborative Group, 1995; Jauch et al., 2013; Scirica et al., 2006). Further analysis of the potential benefits of alcohol and its metabolites following an injury is warranted.

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## References


Agency for Healthcare Research and Quality. (2008). *Patient safety indicators: technical specifications, version 3.2 (revised March 2008)*. Rockville, MD: Department of Health and Human Services.

Allison, P. D. (2002). *Missing data*. Thousand Oaks, CA: Sage Publications.

Anderson, J. L., Adams, C. D., Antman, E. M., Bridges, C. R., Califf, R. M., Casey, D. E., Jr., et al. (2007). ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST elevation myocardial infarction. *Journal of the American College of Cardiology, 50*, e1–e157.

Bau, P. F., Bau, C. H., Naujorks, A. A., & Rosito, G. A. (2005). Early and late effects of alcohol ingestion on blood pressure and endothelial function. *Alcohol (Fayetteville, N.Y.), 37*, 53–58.

Blondell, R. D., Looney, S. W., Krieg, C. L., & Spain, D. A. (2002). A comparison of alcohol-positive and alcohol-negative trauma patients. *Journal of Studies on Alcohol, 63*, 380–383.

Cherpitel, C. J., Bond, J., Ye, Y., Borges, G., MacDonald, S., & Giesbrecht, N. (2003). A cross-national meta-analysis of alcohol and injury: data from the Emergency Room Collaborative Alcohol Analysis Project (ERCAAP). *Addiction (Abingdon, England), 98*, 1277–1286.

Cherpitel, C. J., Tam, T., Midanik, L., Caetano, R., & Greenfield, T. (1995). Alcohol and non-fatal injury in the U.S. general population: a risk function analysis. *Accident; Analysis and Prevention, 27*, 651–661.

Child, J. S., Kovick, R. B., Levisman, J. A., & Pearce, M. L. (1979). Cardiac effects of acute ethanol ingestion unmasked by autonomic blockade. *Circulation, 59*, 120–125.

Choudhry, M. A., & Chaudry, I. H. (2006). Alcohol intoxication and postburn complications. *Frontiers in Bioscience, 11*, 998–1005.

Demetriades, D., Gkiokas, G., Velmahos, G. C., Brown, C., Murray, J., & Noguchi, T. (2004). Alcohol and illicit drugs in traumatic deaths: prevalence and association with type and severity of injuries. *Journal of the American College of Surgeons, 199*, 687–692.

Dimick, J. B., Pronovost, P. J., Cowan, J. A., Pamela, A., & Lipsett, P. A. (2003). Complications and costs after high-risk surgery: where should we focus quality improvement initiatives? *Journal of the American College of Surgeons, 196*, 671–678.

Eide, G. E., & Gefeller, O. (1995). Sequential and average attributable fractions as aids in the selection of preventive strategies. *Journal of Clinical Epidemiology, 48*, 645–655.

Eisenhofer, G., Lambie, D. G., & Johnson, R. H. (1983). Effects of ethanol on plasma catecholamines and norepinephrine clearance. *Clinical Pharmacology and Therapeutics, 34*, 143–147.

Elixhauser, A., Steiner, C., Harris, D. R., & Coffey, R. M. (1998). Comorbidity measures for use with administrative data. *Medical Care, 36*, 8–27.

Fabbri, A., Marchesini, G., Morselli-Labate, A. M., Rossi, F., Cicognani, A., Dente, M., et al. (2002). Positive blood alcohol concentration and road accidents. A prospective study in an Italian emergency department. *Emergency Medicine Journal, 19*, 210–214.

Friedman, L. S. (2012). Dose-response relationship between in-hospital mortality and alcohol following acute injury. *Alcohol (Fayetteville, N.Y.), 46*, 769–775.

Friedman, L. S., & Forst, L. (2007). Occupational injury surveillance of traumatic injuries in Illinois, using the Illinois trauma registry: 1995–2003. *Journal of Occupational and Environmental Medicine, 49*, 401–410.

Glance, L. G., Dick, A. W., Meredith, J. W., & Mukamel, D. B. (2011). Variation in hospital complication rates and failure-to-rescue for trauma patients. *Annals of Surgery, 253*, 811–816.

Glance, L. G., Osler, T. M., Mukamel, D. B., Meredith, W., Wagner, J., & Dick, A. W. (2009). TMPM-ICD9: a trauma mortality prediction model based on ICD-9-CM codes. *Annals of Surgery, 249*, 1032–1039.

Gonzales, R. A., & Jaworski, J. N. (1997). Alcohol and glutamate. *Alcohol Health and Research World, 21*, 120–127.

Gould, L., Reddy, C. V., Becker, W., Oh, K. C., & Kim, S. G. (1978). Electrophysiologic properties of alcohol in man. *Journal of Electrocardiology, 11*, 219–226.

Greenland, S., & Drescher, K. (1993). Maximum likelihood estimation of the attributable fraction from logistic models. *Biometrics, 49*, 865–872.

Griffin, R., Poe, A. M., Cross, J. M., Rue, L. W., 3rd, & McGwin, G., Jr. (2009). The association between blood alcohol level and infectious complications among burn patients. *Journal of Burn Care & Research, 30*, 395–399.

Härtl, R., Gerber, L. M., Iacono, L., Ni, Q., Lyons, K., & Ghajar, J. (2006). Direct transport within an organized state trauma system reduces mortality in patients with severe traumatic brain injury. *The Journal of Trauma, 60*, 1250–1256.

Healey, M. A., Shackford, S. R., Osler, T. M., Rogers, F. B., & Burns, E. (2002). Complications in surgical patients. *Archives of Surgery, 137*, 611–617.

Herman, S. T. (2002). Epilepsy after brain insult: targeting epileptogenesis. *Neurology, 59*(9 Suppl. 5), S21–S26.

Huseynova, K., Xiong, W., Ray, J. G., Ahmed, N., & Nathens, A. B. (2009). Venous thromboembolism as a marker of quality of care in trauma. *Journal of the American College of Surgeons, 208*, 547–552.

Ingraham, A. M., Xiong, W., Hemmila, M. R., Shafi, S., Goble, S., Neal, M. L., et al. (2010). The attributable mortality and length of stay of trauma-related complications: a matched cohort study. *Annals of Surgery, 252*, 358–362.

ISIS-4 Collaborative Group. (1995). ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet, 345*, 669–685.

Jauch, E. C., Saver, J. L., Adams, H. P., Jr., Bruno, A., Connors, J. J., Demaerschalk, B. M., et al. (2013). Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke; A Journal of Cerebral Circulation, 44*, 870–947.

Jurkovich, G. J., Rivara, F. P., Gurney, J. G., Fligner, C., Ries, R., Mueller, B. A., et al. (1993). The effect of acute alcohol intoxication and chronic alcohol abuse on outcome from trauma. *The Journal of the American Medical Association, 270*, 51–56.

Kelbaek, H., Fløistrup, S., Gjørup, T., Christensen, N. J., Hartling, O. J., & Godtfredsen, J. (1988). Central and peripheral haemodynamic changes after alcohol ingestion. *Alcohol and Alcoholism, 23*, 211–216.

Kelbaek, H., Gjørup, T., Hartline, O. J., Marving, J., Christensen, N. J., & Godtfredsen, J. (1987). Left ventricular function during alcohol intoxication and autonomic nervous blockade. *The American Journal of Cardiology, 59*, 685–688.

Kelley, D., & Lynch, J. B. (1992). Burns in alcohol and drug users result in longer treatment times with more complications. *The Journal of Burn Care & Rehabilitation, 13*, 218–220.

Kelly, D. F., Lee, S. M., Pinanong, P. A., & Hovda, D. A. (1997). Paradoxical effects of acute ethanolism in experimental brain injury. *Journal of Neurosurgery, 86*, 876–882.

Khuri, S. F., Henderson, W. G., DePalma, R. G., Mosca, C., Healey, N. A., Kumbhani, D. J., et al. (2005). Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Annals of Surgery, 242*, 326–341.

Kraus, J. F., Morgenstern, H., Fife, D., Conroy, C., & Nourjah, P. (1989). Blood alcohol tests, prevalence of involvement, and outcomes following brain injury. *American Journal of Public Health, 79*, 294–299.

MacKenzie, E. J., Rivara, F. P., Jurkovich, G. J., Nathens, A. B., Frey, K. P., Egleston, B. L., et al. (2006). A national evaluation of the effect of trauma-center care on mortality. *The New England Journal of Medicine, 354*, 366–378.

Malhotra, H., Mehta, S. R., Mathur, D., & Khandelwal, P. D. (1985). Pressor effects of alcohol in normotensive and hypertensive subjects. *Lancet, 2*, 584–586.

Mann, N. C., Guice, K., Cassidy, L., Wright, D., & Koury, J. (2006). Are statewide trauma registries comparable? Reaching for a national trauma dataset. *Academic Emergency Medicine, 13*, 946–953.

Molina, P. E., Zambell, K. L., Norenberg, K., Eason, J., Phelan, H., Zhang, P., et al. (2004). Consequences of alcohol-induced early dysregulation of responses to trauma/hemorrhage. *Alcohol (Fayetteville, N.Y.), 33*, 217–227.

Newsome, H. H., Jr. (1988). Ethanol modulation of plasma norepinephrine response to trauma and hemorrhage. *The Journal of Trauma, 28*, 1–9.

O'Phelan, K., McArthur, D. L., Chang, C. W., Green, D., & Hovda, D. A. (2008). The impact of substance abuse on mortality in patients with severe traumatic brain injury. *The Journal of Trauma, 65*, 674–677.

Osler, T., Glance, L. G., & Hosmer, D. W. (2012). Complication-associated mortality following trauma: a population-based observational study. *Archives of Surgery, 147*, 152–158.

Phelan, H., Stahls, P., Hunt, J., Bagby, G. J., & Molina, P. E. (2002). Impact of alcohol intoxication on hemodynamic, metabolic, and cytokine responses to hemorrhagic shock. *The Journal of Trauma, 52*, 675–682.

Phillips, B., Clark, D. E., Nathens, A. B., Shiloach, M., & Freel, A. C. (2008). Comparison of injury patient information from hospitals with records in both the national trauma data bank and the nationwide inpatient sample. *The Journal of Trauma, 64*, 768–779.

Piriyawat, P., Labiche, L. A., Burgin, W. S., Aronowski, J. A., & Grotta, J. C. (2003). Pilot dose-escalation study of caffeine plus ethanol (caffeinol) in acute ischemic stroke. *Stroke; A Journal of Cerebral Circulation, 34*, 1242–1245.

Randin, D., Vollenweider, P., Tappy, L., Jéquier, E., Nicod, P., & Scherrer, U. (1995). Suppression of alcohol-induced hypertension by dexamethasone. *The New England Journal of Medicine, 332*, 1733–1737.

Rubin, R., & Rand, M. L. (1994). Alcohol and platelet function. *Alcoholism: Clinical and Experimental Research, 18*, 105–110.

Rückinger, S., von Kries, R., & Toschke, A. M. (2009). An illustration of and programs estimating attributable fractions in large scale surveys considering multiple risk factors. *BMC Medical Research Methodology, 9*, 7.

Salim, A., Ley, E. J., Cryer, H. G., Margulies, D. R., Ramicone, E., & Tillou, A. (2009). Positive serum ethanol level and mortality in moderate to severe traumatic brain injury. *Archives of Surgery, 144*, 865–871.

Scirica, B. M., Sabatine, M. S., Morrow, D. A., Gibson, C. M., Murphy, S. A., Wiviott, S. D., et al. (2006). The role of clopidogrel in early and sustained arterial patency after fibrinolysis for ST-segment elevation myocardial infarction: the ECG CLARITY-TIMI 28 Study. *Journal of the American College of Cardiology, 48*, 37–42.

Silber, J. H., Rosenbaum, P. R., Trudeau, M. E., Chen, W., Zhang, X., Kelz, R. R., et al. (2005). Changes in prognosis after the first postoperative complication. *Medical Care, 43*, 122–131.

Spaak, J., Merlocco, A. C., Soleas, G. J., Tomlinson, G., Morris, B. L., Picton, P., et al. (2008). Dose-related effects of red wine and alcohol on hemodynamics, sympathetic nerve activity, and arterial diameter. *American Journal of Physiology. Heart and Circulatory Physiology, 294*, H605–H612.

Strong, R., Grotta, J. C., & Aronowski, J. (2000). Combination of low dose ethanol and caffeine protects brain from damage produced by focal ischemia in rats. *Neuropharmacology, 39*, 515–522.

Stübig, T., Petri, M., Zeckey, C., Brand, S., Müller, C., Otte, D., et al. (2012). Alcohol intoxication in road traffic accidents leads to higher impact speed difference,

higher ISS and MAIS, and higher preclinical mortality. *Alcohol (Fayetteville, N.Y.), 46*, 681–686.
Tawakol, A., Omland, T., & Creager, M. A. (2004). Direct effect of ethanol on human vascular function. *American Journal of Physiology. Heart and Circulatory Physiology, 286*, H2468–H2473.
Tien, H. C., Tremblay, L. N., Rizoli, S. B., Gelberg, J., Chughtai, T., Tikuisis, P., et al. (2006). Association between alcohol and mortality in patients with severe traumatic head injury. *Archives of Surgery, 141*, 1185–1191.
Türeci, E., Dashti, R., Tanriverdi, T., Sanus, G. Z., Oz, B., & Uzan, M. (2004). Acute ethanol intoxication in a model of traumatic brain injury: the protective role of moderate doses demonstrated by immunoreactivity of synaptophysin in hippocampal neurons. *Neurological Research, 26*, 108–112.
van de Borne, P., Mark, A. L., Montano, N., Mion, D., & Somers, V. K. (1997). Effects of alcohol on sympathetic activity, hemodynamics, and chemoreflex sensitivity. *Hypertension, 29*, 1278–1283.
von Heymann, C., Langenkamp, J., Dubisz, N., von Dossow, V., Schaffartzik, W., Kern, H., et al. (2002). Posttraumatic immune modulation in chronic alcoholics is associated with multiple organ dysfunction syndrome. *The Journal of Trauma, 52*, 95–103.
Waikar, S. S., & Bonventre, J. V. (2012). Acute kidney injury. In D. L. Longo, A. S. Fauci, D. L. Kasper, S. L. Hauser, J. L. Jameson, & J. Loscalzo (Eds.), *Harrison's principles of internal medicine* (18th ed.). (pp. 2293–2308) New York: McGraw Hill.
Wallin, G. (1983). Intraneural recording and autonomic function in man. In R. Bannister (Ed.), *Autonomic failure* (pp. 36–51). London, UK: Oxford University Press.
Ward, R. E., Flynn, T. C., Miller, P. W., & Blaisdell, W. F. (1982). Effects of ethanol ingestion on the severity and outcome of trauma. *American Journal of Surgery, 144*, 153–157.
Weathermon, R., & Crabb, D. W. (1999). Alcohol and medication interactions. *Alcohol Research & Health, 23*, 40–54.
World Health Organization (WHO). (2007). *WHO collaborative study on alcohol and injuries: final report*. Geneva: World Health Organization [WHO].
Yadav, D., & Lowenfels, A. B. (2013). The epidemiology of pancreatitis and pancreatic cancer. *Gastroenterology, 144*, 1252–1261.
Yaghoubian, A., Kaji, A., Putnam, B., De Virgilio, N., & De Virgilio, C. (2009). Elevated blood alcohol level may be protective of trauma patient mortality. *The American Surgeon, 75*, 950–953.
Zeckey, C., Dannecker, S., Hildebrand, F., Mommsen, P., Scherer, R., Probst, C., et al. (2011). Alcohol and multiple trauma: is there an influence on the outcome? *Alcohol (Fayetteville, N.Y.), 45*, 245–251.
Zhan, C., & Miller, M. R. (2003). Excess length of stay, charges, and mortality attributable to medical injuries during hospitalization. *The Journal of the American Medical Association, 290*, 1868–1874.