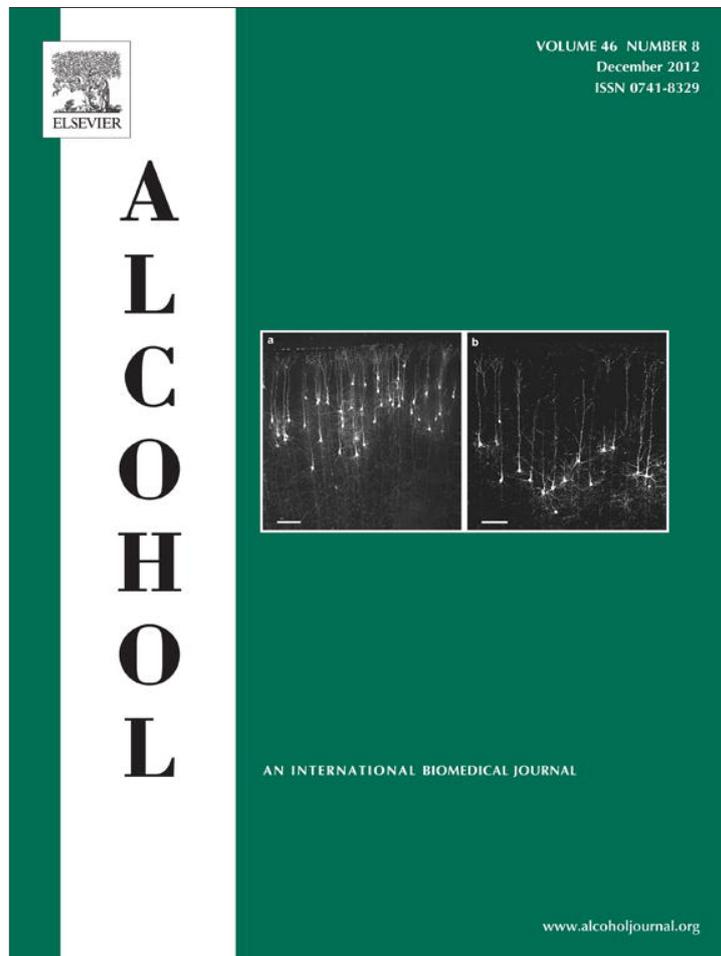


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Dose–response relationship between in-hospital mortality and alcohol following acute injury

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ABSTRACT

Although the relationship between alcohol and injury incidence is well researched, there continues to be dispute about the relationship between alcohol and mortality following an injury. Findings from past studies have varied primarily because of methodological issues and have failed to characterize the dose–response relationship. The main objective of this study was to evaluate the dose response relationship of in-hospital mortality and blood alcohol concentration (BAC). This study was a retrospective analysis of traumatic injuries occurring between 1995 and 2009 as reported by all level 1 and 2 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 ($N = 190,612$). The Illinois trauma registry includes all patients sustaining traumatic injuries and admitted to a trauma center for ≥ 12 h. A total of 6733 patients meeting the inclusion criteria died following admission. Patients that were dead on arrival and those that died during the initial assessment within the emergency room were excluded. In the adjusted multivariable model, a decrease in in-hospital mortality was strongly associated with an increase in blood alcohol concentration (adjusted OR = 0.83 per 100 mg/dl units change in BAC; CI 95%: 0.80, 0.85; $p < 0.001$). The direction of the dose response relationship was consistent across the stratified models, with the exception of patients suffering burns. The largest reduction of in-hospital case fatality rates by blood alcohol concentration was observed among patients suffering penetrating or severe injuries (Injury Severity Score ≥ 16). In the clinical setting, it is important to understand not only how to recognize intoxicated patients, but also how alcohol may affect the course of treatment. The consistency of the findings across the multivariable models indicates that blood alcohol concentration is strongly associated with lower in-hospital mortality among those that survive long enough to receive treatment in specialized trauma units.

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Introduction

Alcohol intoxicated individuals are at an increased risk of injury (Cherpitel et al., 2003; Cherpitel, Tam, Midanik, Caetano, & Greenfield, 1995; WHO, 2008). Alcohol increases an individual's risk of injury as a result of impaired judgment, motor coordination, alertness, and reaction time (WHO, 2008). Within hospitals, the number of trauma patients with elevated blood alcohol concentration (BAC) ranges widely by region, population characteristics and time. Among general emergency room patients, the proportion of injuries involving alcohol ranges from 10 to 20%, (WHO, 2008) but has been reported to exceed 50% in facilities with specialized

trauma units (Lowenfels & Miller, 1984; Rivara, Koepsell, Jurkovich, Gurney, & Soderberg, 1993; WHO, 2008).

Although the relationship between alcohol and injury incidence is well researched, particularly among injuries caused by motor vehicle crashes, there continues to be dispute about the relationship between alcohol and mortality following an injury. There have been numerous studies that have evaluated the relationship between blood alcohol concentration and in-hospital mortality. Some have shown an increase in mortality, (Fabbri et al., 2001; Pories et al., 1992; Waller et al., 1986) others a decrease (Blondell, Looney, Krieg, & Spain, 2002; 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) and still some which have shown no significant relationship (Huth, Maier, Simonowitz, & Herman, 1983; Jurkovich et al., 1993; Madan, Yu, & Beech, 1999; Shandro et al., 2009; Shih et al., 2003; Zeckey

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et al., 2011). It is important to understand the true relationship between BAC and in-hospital mortality in order to identify the physiological factors underlying the relationship so that emergency physicians can provide the most appropriate treatment to the injured patient.

Past studies have been restricted to specific injury types (in particular traumatic brain injury), specific causes of injury (e.g. motor vehicle crashes), localized in individual hospitals without specialized trauma units, and small sample sizes with few deaths (<1000 patients and/or <100 fatalities). Nearly all the past studies have used the definition of “intoxication” based on legal precedent rather than on physiological rationale. These studies have considered “unintoxicated” patients as persons with a BAC below 50–100 mg/dl (as a reference, the legal BAC in the U.S. is generally 80 mg/dl). But research clearly shows that physiological changes occur even at levels below 50 mg/dl, although these effects vary with frequency of exposure to alcohol (McKim, 1991; Mitchell, 1985; Ogden & Moskowitz, 2004). Most have restricted their analyses to dichotomous categories for blood alcohol concentration (negative vs. positive; not intoxicated vs. intoxicated), which have prevented an analysis of the dose–response relationship. Two studies restricted to specific injury types have used two levels of positive BAC in addition to a reference group, but both studies had very few fatalities within their defined BAC groups, making the confidence limits unstable (Pories et al., 1992; Tien et al., 2006). All the variations in study inclusion criteria, facility type, classification of BAC and sample size issues may explain the different outcomes reported in the literature. In addition, no study has looked at the spectrum of BAC across multiple dosage levels to better elucidate the dose response relationship between alcohol and in-hospital mortality.

Studies are needed that include a large sample size and broad representation of the population with a sufficient number of in-hospital fatalities that allow to control for multiple confounders; this is critical to evaluating the effect of alcohol on in-hospital mortality, as well as investigating the relationship within subgroups. The objective of this study was to evaluate the dose–response relationship of BAC and in-hospital mortality using a large population based state trauma registry, and to assess this relationship within subgroups of patients previously reported in the literature in order to describe how the relationship between BAC and mortality is influenced by severity and type of injury.

Materials and methods

This study was a retrospective analysis of traumatic injuries occurring between 1995 and 2009 as reported to the State of Illinois trauma registry. The Illinois Department of Public Health provided us with complete trauma registry dataset. All of the State's level I and II trauma centers ($N = 62$) are required to report all patients (1) sustaining traumatic injuries (ICD-9-CM external injury codes E800-995) and admitted to a trauma center for ≥ 12 h, (2) transferred to a level I or II trauma center or (3) dead-on-arrival or died in the emergency department. Trained personnel enters data into a standardized electronic form at each respective trauma center from medical records upon discharge of a patient. 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 ($N = 190,612$). Blood alcohol concentration (BAC) is measured at the time of admission to the trauma unit. Patients with BAC greater than 500 mg/dl were excluded from the analysis ($N = 371$). Although BAC above 500 mg/dl is physiologically possible, it is rare and there was concern that the reported concentration levels may be incorrect.

Primary outcome variable

The outcome of interest for this study was in-hospital mortality of patients treated in the level I and II trauma centers. 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 admit but achieves measure BP during resuscitation but then subsequently dies prior to formal intake, and (2) dies in ED who has no vitals on admit and never achieves measure BP/vital during resuscitation.

Covariates

In this study, the distribution of traumatically injured patients by BAC and patterns of traumatic injuries by severity of injury are described. ICD-9 NCODES were used to assess body region and type of injury based on the Barell classification matrix (Barell et al., 2002). The study includes various measures of injury severity including the injury severity scores indicating serious injuries ($ISS \geq 16$). The injury severity score is based on the Abbreviated Injury Scale (Baker, O'Neill, Haddon, & Long, 1974). ISS scores are calculated at the time of discharge and are based on all NCODES for injuries identified during the course of hospitalization.

Statistical analysis

All statistical analyses were conducted using SAS software (v.9.2; SAS Institute Inc., Cary, NC). A multivariable logistic regression model was developed to evaluate the relationship between BAC and in-hospital mortality, and the final model was selected using the maximum likelihood statistical method (similar to manual stepwise model building). BAC was a continuous variable in all the models. Odds ratios for both the unadjusted and adjusted models are presented, including the 95 percent confidence intervals. The c -statistic, a measure of predictive model accuracy, is also presented as one of the diagnostic measures used to assess model fit. The final multivariable logistic regression models included the following variables: BAC (continuous), age (continuous), gender (dichotomous), race/ethnicity (categorical; white was the reference category), number of hospitalization days (Length of Stay; continuous), treatment in an intensive care units (dichotomous), use of mechanical ventilation (dichotomous), need for surgical intervention (dichotomous), penetrating injuries (dichotomous), injury severity scores indicating serious injuries ($ISS \geq 16$; dichotomous), the Charlson Comorbidity Index (Charlson, Pompei, Ales, & MacKenzie, 1987) and complications associated with increased mortality in trauma patients (continuous; cumulative frequency of distinct diagnostic codes). The trauma complications included in the analysis were general complications with ICD-9-CM codes of 958–959, poisoning during the course of medical treatment, acute posthemorrhagic anemia, cerebral edema/anoxia/encephalopathy, hypotensive shock, pulmonary insufficiency as a result of trauma, acute respiratory failure, and septicemia. Each patient in the trauma registry has up to 25 ICD-9 diagnosis codes listed in their record and these were used to calculate the Charlson Comorbidity Index and evaluate trauma complications. No evidence of multicollinearity

among the independent variables was indicated (Tolerance values ranged from 0.65 to 0.97, averaging 0.85).

Because past studies have used various inclusion criteria or focused on specific injury types, a variety of stratified multivariable models were evaluated to look at the relationship between BAC and in-hospital mortality among patients suffering light/moderate injuries (ISS < 16), serious injuries (ISS ≥ 16), burns, type 1 and 2 traumatic brain injuries, (Barell et al., 2002) internal injuries to the torso, spinal cord injuries, blunt injuries only, and penetrating injuries. In addition, to further evaluate potential selection bias, stratified models of injuries excluding traumatic brain injuries, patients who met the anatomic triage criteria, patients who met the mechanism of injury triage criteria, and only inpatients (LOS ≥ 24 h) were analyzed. Patients meeting the physiological triage criteria (blood pressure, respiratory rate or Glasgow Coma Scale) were not analyzed because these can change between the pre-hospital setting where the triage decision is made and the point of hospital admission—the point in which the data are collected and reported in the registry. A two-sided *p*-value less than 0.05 was considered statistically significant. All odds ratios are presented as the odds of dying during hospitalization for every 100 mg/dl units change in BAC. The dose response curves (Figs. 2 and 3) provide the change in predicted in-hospital case fatality rates per individual unit of BAC based on the unadjusted and stratified logistic regression models. Among those who died, proportional ratios (proportion in patients with no measureable BAC divided by persons testing positive for BAC) were calculated to determine differences in medical complications. Only proportional ratios greater than 2.0 are provided.

Missing data analysis

There were a total of 466,869 (71%) patients missing toxicological exams for blood alcohol concentration. The patients missing toxicological findings on BAC were disproportionately under the age of 16 and over 65 years of age (52%) compared to only 10.8% among those with reported BAC levels. In addition, patients with missing toxicological exams for BAC disproportionately suffered injuries from falls (50.0%), compared to only 13.6% among persons with toxicological exams. A comparison of persons missing toxicological exams for blood alcohol concentration and those with no detectable BAC were nearly identical across all demographic, cause of injury and place of injury measures. The in-hospital fatality rate was also nearly identical (missing BAC, 4.4% CFR; BAC equal to zero, 4.3% CFR) as well as the number of severe injuries (ISS ≥ 16; missing BAC, 19.5%; BAC equal to zero, 21.6%). In order to address the issue of missing BAC data, three alternative multivariable models were developed. An analysis of missing data indicated the data were missing at random (MAR) within strata (Allison, 2002).

In the first alternative model, only patients from hospitals (*N* = 8) that tested and reported BAC results for 70% or more their patients were analyzed. This high reporting rate is in contrast to the overall reporting rate of approximately 30%. Toxicological examination policies vary by hospital as do the reporting of these results in medical records. These hospitals include three of the large urban Chicago trauma centers and five suburban/rural facilities. The second model, included only patients between the ages of 16 and 65 years to account for differences in missingness between age strata.

The third alternative model using Rubin's multiple imputation method (Allison, 2002) to impute missing BAC (SAS 9.1; Proc MI and MIANALYZE) was developed based on the assumption that persons without toxicological examinations may have positive BACs. Rubin's multiple imputation method derives a final regression model from the average of twenty random imputation models utilizing distributions via Markov chains. The condition of missing

at random was confirmed prior to imputation. The regression coefficients were used to calculate estimated missing BAC. All the variables included in the multivariable logistic regression models were included in the imputation model and were all statistically significant.

IRB approval was made the University of Illinois at Chicago Internal Review Board. Protocol approval number # 2008-0060. No funding was solicited or received for this study.

Assessment of potential selection bias

To describe the case capture and potential selection bias in the trauma registry, the Illinois hospital discharge database (1999–2009) was evaluated. The Illinois hospital discharge database includes all patients treated for more than 23 h in any Illinois hospital (i.e. inpatients only) for any medical reason. The hospital discharge database includes patients found in the trauma registry, as well as those treated in hospitals without trauma units. The Illinois Hospital Association compiles, manages and ensures quality control of the database. The hospital discharge database includes detailed variables on patient demographic characteristics, reason for hospitalization, diagnoses, medical procedures, and type of specialists. To assess the case capture rate of the trauma registry, the proportion of acutely injured patients admitted and the total number of traumatic injury deaths that occur in hospitals with and without specialized trauma care are analyzed in the hospital discharge database. Because BAC toxicological screening is not available in the hospital discharge database, a proxy measure for pre-hospital alcohol consumption based on ICD-9-CM codes identifying alcohol dependency, diseases associated with ethanol abuse, and alcohol rehabilitation/detoxification was used to identify potential BAC positive patients (NCODES: 291, 303, 305.0, 357.5, 425.5, 535.3, 571.0–3, 790.3, 980; VCODES: 11.3, 70.4, 79.1; ECODES: 860.0; PCODES: 94.62, 94.63, 94.68, 94.69). The hospital discharge data were used to validate the case capture rate of the trauma registry and were not used in the primary analysis.

Results

Table 1 presents measures of severity of injury by BAC. The lowest proportion of penetrating injuries was observed among those with the highest BAC. The proportion of patients suffering severe injuries (ISS ≥ 16) was also lower in the highest BAC groups. In contrast, the mean Glasgow Coma Scale and the proportion of patients treated in an intensive care unit or requiring mechanical ventilation were relatively consistent across all groups. The most common types of injuries across all BAC categories were fractures, internal injuries, and open wounds. Table 1 shows the distribution of injuries by major body part and type of injury.

In-hospital fatalities

There were a total of 6733 in-hospital fatalities in this study (BAC below level of detection, *N* = 4002 (4.2%); under 100 mg/dl, *N* = 1028 (3.3%); 100–199 mg/dl, *N* = 832 (3.1%); 200–299 mg/dl, *N* = 669 (2.6%); and 300–500 mg/dl, *N* = 202 (1.9%)). Among those that died following admission to the hospital, mean length of stay had a curvilinear relationship with increasing BAC as follows (mean LOS): BAC below level of detection, 4.63 days; under 100 mg/dl, 3.81 days; 100–199 mg/dl, 3.17 days; 200–299 mg/dl, 4.54 days; and 300–500 mg/dl, 5.18 days. Fig. 1 shows the survival curves by BAC. The overall shapes of the survival curves are similar across all BAC groups. Most patients died during the first 24–48 h, and then the mortality rate steadied off during the remainder of the first 31 days of hospitalization. Among those who died, patients with zero BAC

Table 1
Injury severity measures and types of injuries in relation to blood alcohol concentration among injured patients treated in level I and II trauma units in Illinois: 1995–2009.

	BAC below level of detection (N = 95,901)	BAC under 100 mg/dl (N = 30,935)	BAC 100–199 mg/dl (N = 26,855)	BAC 200–299 mg/dl (N = 26,194)	BAC 300 mg/dl and above (N = 10,727)
Measures of injury severity					
Mean length of stay in days (sd)	5.1 (10.5)	4.7 (10.1)	4.6 (10.4)	4.1 (9.3)	4.1 (11.1)
Mean Glasgow Coma Scale (sd)	13.9 (3.0)	13.9 (3.0)	13.7 (3.3)	13.5 (3.3)	13.4 (3.2)
In-hospital fatalities	4002 (4.2%)	1028 (3.3%)	832 (3.1%)	669 (2.6%)	202 (1.9%)
Penetrating injury	13,507 (14.1%)	7080 (22.9%)	5351 (19.9%)	3606 (13.8%)	992 (9.2%)
ISS 16 and higher	18,835 (19.6%)	5739 (18.6%)	4898 (18.2%)	4255 (16.2%)	1485 (13.8%)
Required surgical intervention	29,068 (30.3%)	10,026 (32.4%)	9020 (33.6%)	7320 (27.9%)	2123 (19.8%)
Treated in an intensive care unit	28,080 (29.3%)	8724 (28.2%)	7472 (27.8%)	7113 (27.2%)	2875 (26.8%)
Required mechanical ventilation	10,422 (10.9%)	3282 (10.6%)	3066 (11.4%)	3018 (11.5%)	1157 (10.8%)
Fracture					
Skull (cranial)	7636 (8.0%)	2410 (7.8%)	2364 (8.8%)	2201 (8.4%)	763 (7.1%)
Other head and face (facial)	8322 (8.7%)	3299 (10.7%)	3327 (12.4%)	3401 (13.0%)	1267 (11.8%)
Vertebral column injury	10,550 (11.0%)	2868 (9.3%)	2330 (8.7%)	1927 (7.4%)	579 (5.4%)
Torso	16,566 (17.3%)	4568 (14.8%)	3572 (13.3%)	3046 (11.6%)	902 (8.4%)
Upper extremities	14,430 (15.0%)	4061 (13.1%)	3512 (13.1%)	2671 (10.2%)	711 (6.6%)
Lower extremities	15,402 (16.1%)	4745 (15.3%)	4143 (15.4%)	3529 (13.5%)	1010 (9.4%)
Internal injury					
Traumatic brain injury	28,603 (29.8%)	9570 (30.9%)	8023 (29.9%)	9016 (34.4%)	4213 (39.3%)
Spinal cord injury	650 (0.7%)	184 (0.6%)	167 (0.6%)	143 (0.5%)	48 (0.4%)
Torso	19,569 (20.4%)	6659 (21.5%)	5329 (19.8%)	4179 (16.0%)	1011 (9.4%)
Open wound					
Other head and face	23,511 (24.5%)	8759 (28.3%)	9050 (33.7%)	9803 (37.4%)	4241 (39.5%)
Torso	5068 (5.3%)	2745 (8.9%)	2248 (8.4%)	1608 (6.1%)	474 (4.4%)
Upper extremities	8058 (8.4%)	3093 (10.0%)	2930 (10.9%)	2377 (9.1%)	636 (5.9%)
Lower extremities	6503 (6.8%)	2529 (8.2%)	1898 (7.1%)	1401 (5.3%)	332 (3.1%)

were disproportionately more likely to suffer from the following medical complications as compared to cases (proportional ratios given): all ischemic heart disease (9.2), acute myocardial infarction (10.4), aortic aneurism (6.2), atrial fibrillation (2.3), paroxysmal ventricular tachycardia (2.0), and alkalosis (2.4). Similar differences were observed among patients that survived. The proportion of patients diagnosed with infectious diseases during hospitalization was slightly higher among patients with zero BAC (BAC below level of detection, 4.1%; under 100 mg/dl, 3.3%; 100–199 mg/dl, 3.8%; 200–299 mg/dl, 3.5%; and 300–500 mg/dl, 3.0%).

Multivariable models

In the primary multivariable model (Table 2), the odds of dying during hospitalization decreased in a dose dependent manner with increasing BAC. The adjusted odds ratio was relatively consistent across (1) the primary adjusted model, (2) the model including only patients from facilities with reporting rates for BAC above 70% of the patients entered into the trauma registry, (3) the truncated model which only included patients 16–75 years of age, and (4) the model with imputed values for patients with missing BAC. Among those suffering burns, positive BAC was not associated with a significant change in mortality. There was no statistical evidence that the relationship between in-hospital mortality and BAC was non-linear in any of the models.

Case capture and selection bias

Based on the analysis of the hospital discharge dataset, 61.8% of persons suffering traumatic injuries are admitted to hospitals with trauma units. However, 75.6% of serious injuries (ISS \geq 16) are admitted to hospitals with trauma units in Illinois, and therefore captured in the trauma registry. A large proportion of the deaths (70.5%) occurring following admission to a hospital for a traumatic injury occur in hospitals with trauma units, but the proportion of deaths is much higher among the seriously injured (ISS \geq 16; 86.9% of all deaths). Based on data from the trauma registry, the specificity and positive predictive values of the proxy measure for BAC based

on diagnostic and procedure codes were 99% and 95% respectively, although the sensitivity was low (18%; i.e. misses most of the true positive BAC cases). In the hospital discharge dataset, the dichotomous proxy measure for identifying positive BAC was strongly associated with lower in-hospital mortality (adjusted OR = 0.62; CI 95%: 0.59, 0.65; $p < 0.001$). The same proxy measure in patients from the trauma registry showed an adjusted odds ratio of 0.41 (CI 95%: 0.35, 0.49; $p < 0.001$). The direction of the relationship between BAC and in-hospital mortality was the same as observed in the primary model based only on patients from the trauma registry.

Discussion

The primary finding from this retrospective analysis of a registry including all patients treated for traumatic injuries in level 1 and 2 trauma units in Illinois between 1995 and 2009 is a substantial inverse relationship between in-hospital mortality and blood alcohol concentration. The large database allowed for a comprehensive stratification of the data to look at subgroups, and to describe the dose–response relationship between BAC and in-hospital mortality. Across all the multivariable models, increasing levels of BAC were strongly associated with lower in-hospital case fatality rates, with the exception of persons suffering burns. Fig. 3 demonstrates a substantial reduction of in-hospital case fatality rates by BAC in particular among patients suffering penetrating and or severe injuries (ISS \geq 16). The most important finding within the missing data analysis was that among the eight hospitals with BAC results for 70% or more of all their patients, the dose–response curve was nearly identical to the general crude and multivariable models, further confirming that absent BAC values were missing at random (though not missing completely at random-MCAR) (Allison, 2002).

The large sample used for this analysis allowed for the simultaneous analysis of subgroups, but may have potentially lead to identifying statistically significant associations that were not clinically important. In-hospital mortality in Illinois trauma units is rather low (2–4%), therefore small absolute differences between groups can result in large relative differences. However, when the

Table 2

Multivariable logistic regression analysis of in-hospital risk of death by blood alcohol concentration among injured patients treated in level I and II trauma units in Illinois: 1995–2009.

Model	N	Unadjusted odds ratio per 100 mg/dl (CI 95%)	p-value	Adjusted odds ratio per 100 mg/dl (CI 95%)*	p-value	c-statistic ^g
Primary analysis						
Main model	190,612	0.82 (0.80, 0.84)	<0.001	0.83 (0.80, 0.85)	<0.001	0.905
Missing data analysis						
^a Only hospitals with 70%+ BAC reporting rate	33,991	0.85 (0.80, 0.91)	<0.001	0.83 (0.77, 0.90)	<0.001	0.918
Only patients 16–65 yrs	169,473	0.89 (0.87, 0.92)	<0.001	0.86 (0.83, 0.89)	<0.001	0.905
^b Multiple imputation model	657,481	0.90 (0.88, 0.92)	<0.001	0.78 (0.76, 0.80)	<0.001	0.839
Stratified models^c						
Injury severity score						
ISS 1–15 (minor and moderate injuries)	155,400	0.79 (0.75, 0.83)	<0.001	0.75 (0.71, 0.80)	<0.001	0.816
ISS 16 and higher (severe injuries)	35,212	0.88 (0.86, 0.91)	<0.001	0.86 (0.83, 0.89)	<0.001	0.856
Injury/ies included						
Burns	3330	1.04 (0.86, 1.26)	0.682	1.02 (0.82, 1.27)	0.857	0.874
Traumatic brain injuries (Type 1 and 2) ^d	70,778	0.80 (0.77, 0.82)	<0.001	0.83 (0.80, 0.86)	<0.001	0.927
All injuries excluding traumatic brain injuries	118,266	0.80 (0.77, 0.84)	<0.001	0.82 (0.78, 0.86)	<0.001	0.849
Spinal cord injuries	3674	0.75 (0.65, 0.86)	<0.001	0.80 (0.68, 0.93)	0.005	0.869
Internal injuries in torso	36,747	0.91 (0.88, 0.95)	<0.001	0.88 (0.84, 0.93)	<0.001	0.876
Penetrating injuries	30,536	0.74 (0.70, 0.79)	<0.001	0.73 (0.67, 0.79)	<0.001	0.909
Blunt injuries only	160,076	0.84 (0.81, 0.86)	<0.001	0.86 (0.83, 0.88)	<0.001	0.906
Met anatomic triage criteria ^e	99,935	0.81 (0.78, 0.83)	<0.001	0.79 (0.77, 0.82)	<0.001	0.906
Met mechanism of injury triage criteria ^f	105,705	0.90 (0.87, 0.93)	<0.001	0.90 (0.86, 0.94)	<0.001	0.910
Inpatient only (LOS ≥ 24 h)	161,062	0.81 (0.79, 0.83)	<0.001	0.81 (0.79, 0.84)	<0.001	0.926

* Adjusted models include the following covariates: age, gender, race/ethnicity, length of stay, treatment in an intensive care units, use of mechanical ventilation, penetrating injuries, injury severity score, need for a surgical intervention, Charlson Comorbidity Index and trauma complications.

^a Truncated model—only includes data from hospitals in which 70% or more of all patients had a reported BAC level.

^b Adjusted model used multiple imputation method (20 iterations) to impute missing blood alcohol levels for all patients missing reported toxicological findings.

^c Stratified models restricted to patients within identified strata.

^d Barell et al., 2002.

^e Anatomic triage criteria include penetrating injuries to head, neck, torso and extremities proximal to elbow and knee, flail chest, two or more proximal long-bone fractures, crushed/deglomed/mangled extremity, amputation proximal to wrist/ankle, paralysis, pelvic fractures, and open or depressed skull fracture.

^f Mechanism of injury triage criteria included falls from one level or more (including intentional), motor vehicle crashes, pedestrian/cyclist crash with motor vehicle, and all motorcycle accidents.

^g c-Statistic is a measure of predictive model accuracy, values <0.7 indicate poor predictive fit; 0.7–0.8, acceptable; 0.8–0.9, excellent; 0.9+, outstanding.

odds ratios were converted into predicted probabilities, the reduction in case fatality rates was substantial—up to 50% decline (Figs. 1–3).

An important next step is to test the relationship in a controlled setting and conduct more physiological studies to identify the biomechanism behind this phenomenon. There have been only a few studies evaluating the physiological mechanisms related to alcohol and injury in human subjects—the majority involves animal studies, but the studies often contradict one another because of different inclusion criteria. Some studies evaluating traumatically injured intoxicated patients have shown an increase in the use of blood products, (Fabri et al., 2001) while others a decrease, (Zeckey et al., 2011) and some no difference (Tien et al., 2006). One study demonstrated an absence of significant differences in markers of

immunosuppression following injury, (Zeckey et al., 2011) and two others found no significant difference in the occurrence of infection (von Heymann et al., 2002; Zeckey et al., 2011). While other researchers have reported adverse immunoresponse following hemorrhagic shock, (Molina, Zambell, & Norenberg, 2004; Phelan, Stahls, Hunt, Bagby, & Molina, 2002) and an increase in infection and other medical complications among burn patients (Choudhry & Chaudry, 2006; Griffin, Poe, Cross, Rue, & McGwin, 2009; Kelley & Lynch, 1992). Some studies have reported neuroprotective effects of alcohol through action on the NMDA complex and catecholamines, (Kelly, Lee, Pinanong, & Hovda, 1997; Türeci et al., 2004; Ward et al., 1982) and this relationship may be modified by the

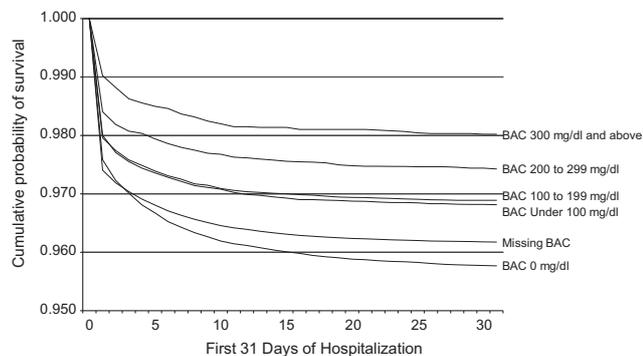


Fig. 1. Cumulative probability of survival during first 31 days of hospitalization by blood alcohol concentration levels.

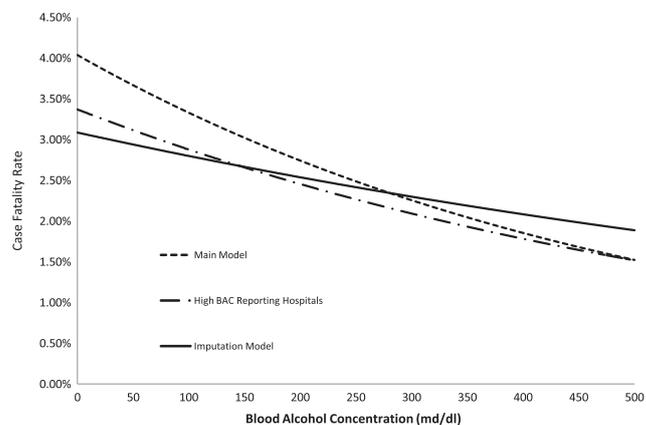


Fig. 2. Dose–response relationship between predicted in-hospital case fatality rate and blood alcohol concentration (mg/dl), comparison of models.

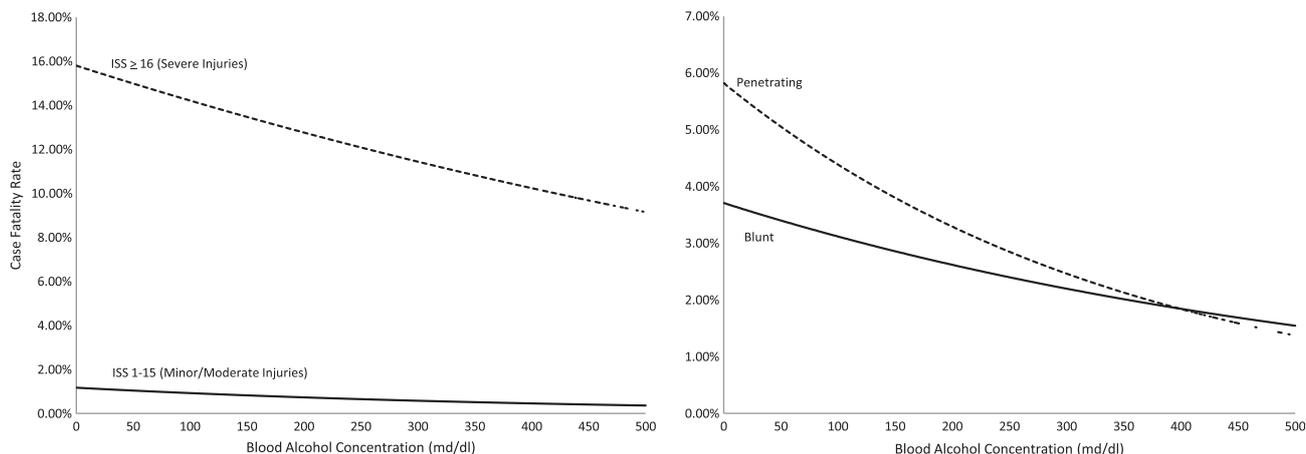


Fig. 3. Dose–response relationship between predicted in-hospital case fatality rate and blood alcohol concentration (mg/dl), stratified models.

presence of caffeine (Piriyawat, Labiche, Burgin, Aronowski, & Grotta, 2003; Strong, Grotta, & Aronowski, 2000). Inhibition of NMDA receptors reduces intracellular calcium accumulation and hyperglycolysis, which is associated with reduced lesion size in the brain (Kelly et al., 1997). In our study, cases were disproportionately less likely to have cardiac complications, and slightly lower proportion of infections.

A selection bias represents the greatest potential limitation to this study if the following occur (1) persons with elevated BAC are more likely to die in the pre-hospital setting, (2) persons with elevated BAC are more likely to be triaged to hospitals with specialized trauma units because of confounding of the pre-hospital triage assessment, and (3) persons with a negative BAC are disproportionately under-triaged to facilities without specialized trauma care.

The findings from this study do not tell us about overall mortality, pre-hospital mortality or deaths occurring among patients undertriaged to lower level trauma units or general emergency rooms. Therefore, injuries occurring in rural areas and individuals who die in the pre-hospital setting may not be included in this dataset. If persons with elevated BAC are more likely to die during the pre-hospital phase, then our findings may be biased. However, 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).

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 (Hartl, Gerber, & Iacono, 2006; MacKenzie, Rivara, & Jurkovich, 2006). Acute and chronic alcohol use is associated with physiological changes that may result in the overtriage 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 physiologic triage assessments. The analysis shows that among persons with confirmed serious brain injuries using discharge diagnoses the inverse relationship between BAC and mortality persists. 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 this subgroup shows the same pattern between BAC and mortality.

Finally, if patients who did not consume alcohol prior to injury are disproportionately under-triaged to facilities without specialized trauma care then their deaths would be missed in the trauma registry. However, this would primarily affect the subgroup of patients suffering traumatic brain injuries as discussed above. Our analysis of all patients admitted to hospitals for acute injuries in Illinois shows that most injuries resulting in hospitalization and deaths following admission are treated in facilities with trauma units, especially for the most serious injuries. The findings from the stratified models looking at serious injuries ($ISS \geq 16$) and inpatients only (hospital discharge database only includes inpatients) continue to show an inverse relationship between BAC and in-hospital mortality. Furthermore, among those patients triaged to trauma units based on anatomic and mechanistic triage criteria (CDC, 2009)—the physiological effects of alcohol would be unrelated to triaging these patients—the stratified models evaluating these subgroups continued to validate the primary model. Lastly the proxy measure based on diagnosis and medical procedure codes, which had a low sensitivity but high positive predictive value of positive BAC levels, continued to show an inverse relationship between BAC and in-hospital mortality in the universe of inpatients in all Illinois hospitals as well as those within the subset treated in trauma units.

Approximately 70% of the total patients in the registry did not have reported toxicological results for BAC. However, in the subset of hospitals with high BAC reporting rates, the relationship between in-hospital mortality and BAC was nearly identical to that observed in the main model. In addition, the demographic characteristics and type of injuries among this subset of patients were nearly identical to the overall sample. Furthermore, among those missing BAC results, the majority were patients that would generally fall under the radar—the elderly suffering orthopedic injuries from falls and injured minors. Both age groups would have disproportionately fewer individuals testing positive for elevated BAC (Peck, Gebers, Voas, & Romano, 2008), and the relationship between BAC and in-hospital mortality persisted in the stratified model which excluded these two age groups (16–65 yr stratified model). Furthermore, the survival curve of those missing BAC findings is most similar to the zero BAC group (Fig. 1), as was the overall CFR, the proportion of severe injuries ($ISS \geq 16$) and certain demographic variables. For the second alternative model, multiple imputation methodology was used to impute missing BAC values. This approach has been used widely in many prominent governmental and private studies, including some that have evaluated BAC, (Barnard & Meng, 1999; Subramanian & Utter, 2003) and the

dose response curve using imputed values approximated the main model.

Conclusion

In the clinical setting, it is important to understand not only how to recognize intoxicated patients but also how alcohol may affect the course of treatment. The strength of the association, the observed dose–response relationship, and the consistency of the findings across the various multivariable models indicate that blood alcohol concentration is associated with a reduction in in-hospital mortality among those that survive long enough to receive treatment in specialized trauma units. The reduction in in-hospital mortality is not uniform but does vary across subgroups, in particular for patients suffering burns (absence of association) and penetrating injuries (strongest association). The substantial reduction in case fatality rates in those with elevated BAC indicates that if the biomechanism was better understood, it would be feasible to consider treating patients with alternative prophylactic treatments upon admission to help mirror the potential benefits of alcohol.

References

- Allison, P. D. (2002). *Missing data*. Thousand Oaks, CA: Sage Publications.
- Baker, S. P., O'Neill, B., Haddon, W., Jr., & Long, W. B. (1974). The injury severity score, a method for describing patients with multiple injuries and evaluating emergency care. *Journal of Trauma*, 14, 187–196.
- Barell, V., Aharonson-Daniel, L., Fingerhut, L. A., Mackenzie, E. J., Ziv, A., Boyko, V., et al. (2002). An introduction to the Barell body region by nature of injury diagnosis matrix. *Injury Prevention*, 8, 91–96.
- Barnard, J., & Meng, X. L. (1999). Applications of multiple imputation in medical studies: from AIDS to NHANES. *Statistical Methods in Medical Research*, 8, 17–36.
- 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(3), 380–383.
- Centers for Disease Control and Prevention. (2009). Guidelines for field triage of injured patients. Recommendations of the national expert panel on field triage. *Morbidity and Mortality Weekly Report*, 58(RR-1), 1–35.
- Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies, development and validation. *Journal of Chronic Diseases*, 40(5), 373–383.
- 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*, 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.
- Choudhry, M. A., & Chaudry, I. H. (2006). Alcohol intoxication and postburn complications. *Frontiers in Bioscience*, 11, 998–1005.
- Fabbri, A., Marchesini, G., Morselli-Labate, A. M., Rossi, F., Cicognani, A., Dente, M., et al. (2001). Blood alcohol concentration and management of road trauma patients in the emergency department. *Journal of Trauma*, 50(3), 521–528.
- 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(4), 401–410.
- Griffin, R., Poe, A. M., Cross, J. M., Rue, L. W., & McGwin, G. (2009). The association between blood alcohol level and infectious complications among burn patients. *Journal of Burn Care & Research*, 30(3), 395–399.
- Hartl, R., Gerber, L. M., & Iacono, L. (2006). Direct transport within an organized state trauma system reduces mortality in patients with severe traumatic brain injury. *Journal of Trauma*, 60, 1250–1256.
- 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. *Journal of Trauma*, 52, 95–103.
- Huth, J. F., Maier, R. V., Simonowitz, D. A., & Herman, C. M. (1983). Effect of acute ethanolism on the hospital course and outcome of injured automobile drivers. *Journal of Trauma*, 23(6), 494–498.
- 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. *Journal of the American Medical Association*, 270(1), 51–56.
- Kelley, D., & Lynch, J. B. (1992). Burns in alcohol and drug users result in longer treatment times with more complications. *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.
- 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(3), 294–299.
- Lowenfels, A. B., & Miller, T. T. (1984). Alcohol and trauma. *Annals of Emergency Medicine*, 13, 1056–1060.
- MacKenzie, E. J., Rivara, F. P., & Jurkovich, G. J. (2006). A national evaluation of the effect of trauma center care on mortality. *New England Journal of Medicine*, 354, 366–378.
- Madan, A. K., Yu, K., & Beech, D. J. (1999). Alcohol and drug use in victims of life-threatening trauma. *Journal of Trauma*, 47(3), 568–571.
- McKim, W. A. (1991). *Drugs and behavior* (2nd ed.). New Jersey: Prentice Hall, Inc.
- Mitchell, M. C. (1985). Alcohol induced impairment of central nervous system function: behavioral skills involved in driving. *Journal of Studies on Alcohol*, 10(Suppl), 109–119.
- Molina, P. E., Zambell, K. L., & Norenberg, K. (2004). Consequences of alcohol-induced early dysregulation of responses to traumatic hemorrhage. *Alcohol*, 33, 217–227.
- Ogden, E. J., & Moskowitz, H. (2004). Effects of alcohol and other drugs on driver performance. *Traffic Injury Prevention*, 5(3), 185–198.
- 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. *Journal of Trauma*, 65(3), 674–677.
- Peck, R. C., Gebers, M. A., Voas, R. B., & Romano, E. (2008). The relationship between blood alcohol concentration (BAC), age, and crash risk. *Journal of Safety Research*, 39, 311–319.
- 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. *Journal of Trauma*, 52, 675–682.
- 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*, 34, 1242–1245.
- Pories, S. E., Gamelli, R. L., Vacek, P., Goodwin, G., Shinozaki, T., & Harris, F. (1992). Intoxication and injury. *Journal of Trauma*, 32(1), 60–64.
- Rivara, F. P., Koepsell, T. D., Jurkovich, G. J., Gurney, J. G., & Soderberg, R. (1993). The effects of alcohol abuse on readmission for trauma. *Journal of the American Medical Association*, 270, 1962–1964.
- 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(9), 865–871.
- Shandro, J. R., Rivara, F. P., Wang, J., Jurkovich, G. J., Nathens, A. B., & MacKenzie, E. J. (2009). Alcohol and risk of mortality in patients with traumatic brain injury. *Journal of Trauma*, 66(6), 1584–1590.
- Shih, H. C., Hu, S. C., Yang, C. C., Ko, T. J., Wu, J. K., & Lee, C. H. (2003). Alcohol intoxication increases morbidity in drivers involved in motor vehicle accidents. *American Journal of Emergency Medicine*, 21(2), 91–94.
- 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.
- Subramanian, R., & Utter, D. (2003). *Multiple imputation of missing blood alcohol concentration (BAC) values in FARS*. Washington, DC: National Highway Traffic Safety Administration. Available at: <http://www.fcs.gov/03papers/Subramanian.pdf>.
- 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(12), 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.
- Waller, P. F., Stewart, J. R., Hansen, A. R., Stutts, J. C., Popkin, C. L., & Rodgman, E. A. (1986). The potentiating effects of alcohol on driver injury. *Journal of the American Medical Association*, 256(11), 1461–1466.
- 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.
- World Health Organisation (WHO). (2008). *WHO collaborative study on alcohol and injury: Final report*. Geneva: World Health Organization (WHO).
- Yaghoubian, A., Kaji, A., Putnam, B., De Virgilio, N., & De Virgilio, C. (2009). Elevated blood alcohol level may be protective of trauma patient mortality. *American Surgeon*, 75(10), 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*, 45(3), 245–251.