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Letter to the Editor: Ding Q, Wang Z, Shen M, Su Z, and Shen L. Acute Alcohol Exposure and Risk of Mortality of Patients with Traumatic Brain Injury: A Systematic Review and Meta-analysis

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Ding et al. performed a systematic review and meta-analysis to examine the association of blood alcohol concentration (BAC) with mortality in patients with traumatic brain injury (TBI). The authors identified eighteen observational studies for meta-analysis and reported no association between BAC and death in patients with TBI. Lower levels of BAC (1–100 mg/dL) were associated with greater odds of death than higher levels of BAC, implying a protective effect in higher BAC groups.

The authors did not discuss several limitations of observational studies that rely on BAC as the exposure and trauma death as the outcome. Methodological issues remain a major impediment to reliably examining outcomes in TBI patients with elevated BAC. We aim to highlight some of these limitations for consideration by the authors and readers of this journal when interpreting results in this field.

BAC is not systematically assessed at trauma centers. Missing data are common with proportions of missing data as high as 50%. For example, in one of the larger studies included in the meta-analysis (Shandro et al., 2009), 45% (693/1529) of patients were missing BAC. The authors accounted for this by using multiple imputation but, with such high proportions of missing data, this can lead to biased estimates. (Roudsari et al., 2008) Furthermore, BAC is not missing at random. Blood alcohol assessment is related to patient and injury-related characteristics such as age and TBI severity. (Lustenberger et al., 2011,

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Kraus et al., 1989) Characteristics that are associated with certain BAC groups introduces selection bias.

The authors comment in the introduction that alcohol increases the susceptibility to TBI. This is an important consideration in the analysis of the data. In TBI, alcohol use commonly precedes the injury and can have both a *direct* effect on death and an *indirect* effect on death through the TBI it preceded. Separating BAC's *direct* effect on death versus its *indirect* effects via other injury mediators (severity and mechanism) cannot be fully evaluated with traditional statistical methods that do not account for the temporality in the pathway between alcohol use, TBI, and death. Injury mechanism and severity measures are common covariables in adjusted models, but they are in the causal pathway and introduce an overadjustment bias.(VanderWeele, 2009) In a recently published study, we initially observed a protective association between BAC and death in a cohort of 1,084 patients with isolated TBI.(Albrecht et al., 2017) Further analyses suggested that this association was misleading, produced by the inclusion of patients with penetrating TBI (95% sustaining gunshot wounds). Stratifying by penetrating TBI changed the results. More of the penetrating TBI patients had critical or untreatable AIS scores, yet they also were more likely to have an undetectable BAC. The presence of bias and inclusion of variables that may be in the causal pathway in regression models are problems common to the studies in the meta-analysis. Mediation analysis, a method adopted from social sciences, allows for evaluation of simultaneous regression pathways on an outcome and is an alternative analysis method that can better inform the direct and indirect effects from BAC on trauma death (Figure 1) (Valeri and Vanderweele, 2013).

BAC is captured as a static laboratory value. The BAC level at time of blood draw may not reflect the peak value nor the consumption pattern of the individual. Variability in alcohol metabolism, consumption, and time to trauma onset makes it almost impossible to make comparisons between individuals or determine whether BAC is increasing or decreasing at admission. Therefore, a single measurement of BAC is not reliable for categorization of alcohol exposure and poses a major risk for misclassification bias.

Furthermore, some studies in the meta-analysis excluded patients that died prior to arrival or upon arrival to trauma centers. Nearly half of trauma deaths occur prehospitalization or near the time of admission(Clark et al., 2012) and sampling bias may occur. In one study of over 46,000 trauma patients, BAC values were captured in 96% of the full cohort. However, in the group of patients who died after arrival to the trauma center, only 69% had BAC assessed.(Afshar et al., 2015) The majority of missing BAC occurred in patients who did not have any laboratory data collected because they were pronounced dead soon after arrival. After postmortem alcohol levels from the medical examiner were retrieved, the proportion of alcohol testing in dead patients improved to 92.0%, and the proportion with elevated BAC increased. Inclusion of all trauma deaths could change the proportion of deaths in the alcohol group and likely alter outcomes.

Selection bias, overadjustment bias, misclassification bias, and sampling bias may have contributed to the observed protective association in the higher BAC groups in the meta-analysis. Randomized controlled trials are not feasible in this setting to remove these biases

so we should remain cautious in our interpretation of observational studies. We know 1 in 10 deaths in working-age adults are attributable to excessive alcohol consumption with a large contribution from trauma.(Stahre et al., 2014) Statements that alcohol is beneficial in patients with traumatic brain injury should not be made without more convincing evidence. More comprehensive assessment of blood alcohol and rigorous methods are needed to better inform outcomes in trauma deaths.

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Figure 1. Mediated Model with Traumatic Brain Injury as Mediator in Patients with Alcohol Exposure

A mediation model with exposure-mediator interactions for examining the relationship between alcohol exposure, traumatic brain injury, and in-hospital death. The filled circle represents an interaction term consisting of the variables connected to it without arrow heads, in this case blood alcohol concentration and traumatic brain injury. $\beta_1\gamma_1$ = Indirect effect; β_2 = direct effect; β_3 = exposure-mediator interaction; γ_0 = intercept.