Published in final edited form as:

Alcohol Clin Exp Res. 2018 October ; 42(10): 2064–2065. doi:10.1111/acer.13853.

Optimal cut-points for phosphatidylethanol vary by clinical setting: Response to Nguyen et al. (2017) letter to the editor

DR. Majid Afshar, MD, MSCR^{1,2,3}, Ellen L. Burnham, MD⁴, Cara Joyce, PhD³, Elizabeth J. Kovacs, PhD⁵, and Erin M. Lowery, MD, MSCE^{1,2}

¹Burn and Shock Trauma Research Institute, Stritch School of Medicine, Loyola University Health Sciences Campus, Maywood, IL

²Alcohol Research Program, Stritch School of Medicine, Loyola University Health Sciences Campus, Maywood, IL

³Department of Public Health Sciences, Stritch School of Medicine, Loyola University Chicago Health Sciences Campus, Maywood, IL

⁴Division of Pulmonary Sciences and Critical Care Medicine, Department of Medicine, University of Colorado School of Medicine, Aurora, CO

⁵Department of Surgery, University of Colorado School of Medicine, Aurora, CO

In the letter by Nguyen et al. 2018, the authors raise several concerns in measuring PEth in critically ill patients, most notably that our calculated cut-points are higher than previously described that may in part be attributable to lower red cell volume in critically ill patients. We appreciate their comments and acknowledge substantial variability in the pathway of PEth synthesis and degradation, especially in more severely ill patients. However, we also believe substantial selection bias exists in the literature regarding PEth cut-point levels, and that additional consideration should be given to the phenotype of alcohol use among patients in various clinical settings.

We acknowledge that PEth results can vary substantially between populations. First, the authors make a case that our derived cut-point levels may be skewed, comparing our study to Stewart et al. 2014 that identified 80 ng/mL as a cut-point for harmful alcohol use compared to our 250 ng/mL cut-point.(Stewart et al. 2014) We would like to highlight several major differences between our study and that of Stewart et al 2014. First, the patients in the Stewart et al. study were recruited from an outpatient setting and inpatient liver service and were therefore less severely ill than the group of intensive care unit (ICU) patients we examined. The majority of our critically ill patients with alcohol misuse were severe misuse which is consistent with prior studies including a multicenter national study of over 1,000 critically ill patients where 23% scored above the screening threshold for an alcohol use disorder. (Reisinger et al. 2015) The Stewart et al. 2014 study also used a different approach and classified patients with 4 drinks daily for their analysis. The study methods did not include

rigorous statistical methods to identify the optimal cut-point to maximize accuracy and minimize error, whereas we applied Youden's J statistic to determine the cut-point of 250 ng/mL.(Youden 1950) The variability in clinical setting also applies to the Swedish recommendations that are used in outpatient/community settings, as well as the Schrock et al. 2017 study that used lower thresholds for alcohol consumption with moderate, non-misuse drinking pattern in their reference standard.(Hoiseth et al. 2008, Schrock et al. 2017)

With regard to patient phenotype and comorbidities, Nguyen et al. 2018 make the assumption that hematocrit (Hct) decreases with severity of disease. We acknowledge that considerable variability exists in the phenotype of critically ill patients that may influence their complete blood count indices. For example, burn and trauma patients can present with hemoconcentration from flame injuries or volume loss.(Burnham 2006, Dokter et al. 2014) Moreover, many alcohol misusers are also current smokers, and heavy smoking contributes to higher levels of Hct.(S et al. 2014) A major advantage to PEth is it has previously been shown to have similar test characteristics regardless of age, sex, and comorbidities, which we demonstrated as well.(Walther et al. 2015, Wurst et al. 2015)

More importantly, we had access to complete blood counts measured within the first 24 hours of admission in enrolled participants; Hct values were available in 98.4% (N=120). We also compared Hct values between cohorts (ICU, alcohol detoxification, and healthy volunteers) and stratified by sex. We did not identify significant differences in Hct, and their ranges were within accepted reference intervals cited by Nguyen et al. 2018 for healthy individuals. In males, the median values with interquartile range between ICU cohort, alcohol detox cohort, healthy volunteer cohort were 41.3% (IQR 35.4%-44.8%), 44.5% (IQR 42.3%-46.6%), and 44.6% (41.9%-46.2%), respectively (p-value = 0.09). In females, the median values with interquartile ranges between ICU cohort, alcohol detox cohort, and healthy volunteer cohort were 38.3% (IQR 31.5% – 45.5%), 41.2 (IQR 39.3%-42.1%), and 42.2% (IQR 40.8%-42.8%), respectively (p-value = 0.66). Our ICU cohort demonstrated a non-significantly lower Hct that remained within the natural variation of 10–15% described by Nguyen et al. 2018. These observations suggest that the red cell volume in the critically ill cohort likely did not have an effect on PEth levels, and our PEth levels remain valid in this cohort.

Furthermore, we would like to highlight the relevance of patient characteristics and clinical settings when evaluating PEth and making comparisons across studies. ICU patients have been characterized as having more severe alcohol misuse, and a greater proportion have alcohol use disorders than other patient cohorts. This is a contributing factor for inconsistent benefit in the use of Screening, Brief Intervention, and Referral to Treatment (SBIRT) inpatient programs that use the AUDIT.(Moyer 2013) While SBIRT has good quality evidence of effectiveness in outpatient settings, where alcohol misuse is less severe and brief intervention may have more efficacy, clinical equipoise remains in hospitalized settings where alcohol misuse tends to be more severe.(Makdissi and Stewart 2013) Ultimately, we believe our higher cut-point is not a limitation in the performance of the assay and Hct, but a reflection of the more severe alcohol phenotype that occurs in the ICU setting. Therefore, more research in this setting is needed and differences we observed compared to other patient settings were likely due to consumption patterns among this cohort.

FUNDING INFORMATION AND CONFLICT OF INTEREST

This research was supported by the National Institute of General Medical Sciences R01GM115257 (EJK), and the National Institute of Alcoholism and Alcohol Abuse, R24AA019661 (EB), K23AA024503 (MA), K23AA022126 (EML).

No conflicts of interest to disclose amongst the authors.

REFERENCES

- Burnham EL and Moss MM. 2006 Alcohol abuse in the critically ill patient. *Lancet* 368:2231–2242. [PubMed: 17189035]
- Dokter J, Meijs J, Oen IM, van Baar ME, van der Vlies CH, Boxma H. 2014 External validation of the revised Baux score for the prediction of mortality in patients with acute burn injury. *J Trauma Acute Care Surg* 76:840–845. [PubMed: 24553558]
- Hoiseth G, Bernard JP, Stephanson N, Normann PT, Christophersen AS, Morland J, Helander A. 2008 Comparison between the urinary alcohol markers EtG, EtS, and GTOL/5-HIAA in a controlled drinking experiment. *Alcohol Alcohol* 43:187–191. [PubMed: 18230699]
- Makdissi R, Stewart SH. 2013 Care for hospitalized patients with unhealthy alcohol use: a narrative review. *Addict Sci Clin Pract* 8:11. [PubMed: 23738519]
- Moyer VA. 2013 Screening and behavioral counseling interventions in primary care to reduce alcohol misuse: U.S. preventive services task force recommendation statement. *Annals of Internal Medicine* 159:210–218. [PubMed: 23698791]
- Reisinger MW, Moss M, Clark BJ, National Heart L, Blood Institute Acute Respiratory Distress Syndrome Network I. 2015 Brief Versus Full Alcohol Use Disorders Identification Test in National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network Clinical Trials. *Crit Care Med* 43:e382–385. [PubMed: 26136102]
- S AL, Lakshmanan A, P GK, A S. 2014 Effect of intensity of cigarette smoking on haematological and lipid parameters. *J Clin Diagn Res* 8:BC11–13.
- Schrock A, Wurst FM, Thon N, Weinmann W. 2017 Assessing phosphatidylethanol (PEth) levels reflecting different drinking habits in comparison to the alcohol use disorders identification test - C (AUDIT-C). *Drug Alcohol Depend* 178:80–86. [PubMed: 28645063]
- Stewart SH, Koch DG, Willner IR, Anton RF, Reuben A. 2014 Validation of blood phosphatidylethanol as an alcohol consumption biomarker in patients with chronic liver disease. *Alcoholism, clinical and experimental research* 38:1706–1711.
- Walther L, de Bejczy A, Löf E, Hansson T, Andersson A, Guterstam J, Hammarberg A, Asanovska G, Franck J, Söderpalm B, Isaksson A 2015 Phosphatidylethanol is Superior to Carbohydrate-Deficient Transferrin and gamma-Glutamyltransferase as an Alcohol Marker and is a Reliable Estimate of Alcohol Consumption Level. *Alcohol Clin Exp Res* 39:2200–2208. [PubMed: 26503066]
- Wurst FM, Thon N, Yegles M, Schruck A, Preuss UW, Weinmann W. 2015 Ethanol Metabolites: Their Role in the Assessment of Alcohol Intake. *Alcohol Clin Exp Res*.
- Youden WJ. 1950 Index for rating diagnostic tests. *Cancer* 3:32–35. [PubMed: 15405679]