(BMI) was normal in the patients admitted with acute liver injury due to therapeutic doses (ALITD) and was not different from that of patients admitted with acetaminophen overdose: 21.9 versus 22 kg/m^2, P = 0.5. Therefore, the prevalence of metabolic syndrome was a rare event. Moreover, previous studies have not identified any relationship between BMI and the outcome or pattern of intoxication.[1] Obesity was not found to have any impact on acetaminophen toxicity in the study by Radosevich et al.[2]

In relation to drug–drug interactions, none of the published clinical studies evaluating acetaminophen toxicity has found drug intake to be an aggravating factor. The median age in our study was 35 years, making chronic drug intake a rare event, which was therefore not assessed. Interestingly, a review concluded that the use of drugs concurrent with a paracetamol overdose should not be considered a risk factor of hepatotoxicity.[3]

Our study acknowledged that fasting can be a precipitating factor, although it was not powered to address its impact on outcome. Nevertheless, the patients who had fasted before admission had the same 30-day survival as the others, 95.3% versus 95.7%, P = 0.9; and fasting was not associated with disease severity (P = 0.2). Thus, fasting seems to be more a precipitating factor of ALITD than a driver of outcome, compared to excessive alcohol consumption.

Vojjala et al. also question the presence of cirrhosis in our patients with ALITD. We disagree that cirrhosis was a confounding factor because we excluded the 7 patients with cirrhosis. In addition, when looking at the evolution of patients with ALITD, a factor V and a prothrombin rate parallel to those of patients with overdose would not have been observed if cirrhosis were present. Although we cannot exclude the presence of fibrosis, extensive fibrosis can be excluded based on the biological kinetics.

Finally, the authors' interpretation of ALITD in multivariate analysis is questionable. In fact, ALITD and excessive drinking are closely connected. Thus, in a multivariate analysis of overall patients, this close relationship results in nonsignificance, especially because alcohol is an aggravating factor in overdose.

In summary, we agree that additional data will help further understand acetaminophen toxicity, either from therapeutic doses or from overdose. Conversely, we believe that these future results can only be obtained from an evidence-based approach that can help drive expert opinion.

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REFERENCES

1) Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Hynan LS, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005;42:1364-1372.
2) Radosevich JJ, Patanwala AE, Erstad BL. Hepatotoxicity in obese versus nonobese patients with acetaminophen poisoning who are treated with intravenous N-acetylcysteine. Am J Ther 2016;23:e714-e719.
3) Kalsi SS, Wood DM, Waring WS, Dargan PI. Does cytochrome P450 liver isoenzyme induction increase the risk of liver toxicity after paracetamol overdose? Open Access Emerg Med 2011;3:69-76.

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Potential conflict of interest: Nothing to report.

Letter to the Editor: Serum Albumin in COVID-19: A Good Example in Which Analytical and Clinical Performance of a Laboratory Test Are Strictly Intertwined

TO THE EDITOR:

We read with interest the paper by Hundt et al. describing the behavior of common liver tests in Coronavirus disease 2019 (COVID-19) and their association with poor outcomes.[1] Among the presented data, we were surprised to see that serum albumin (ALB) concentrations during hospitalization did not significantly predict patient death at the multivariate

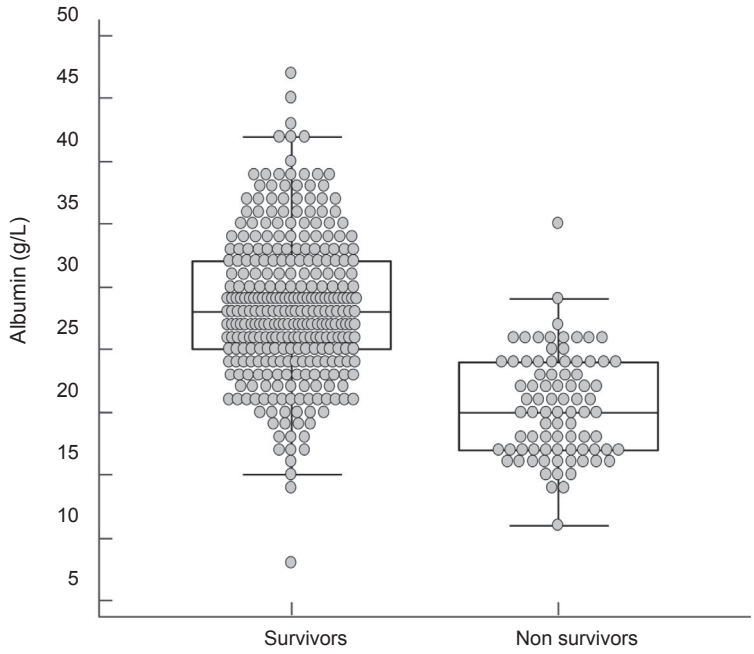

FIG. 1. Box and whisker plots showing the distribution of results of serum ALB in a cohort of 390 patients with COVID-19, according to death during hospitalization (nonsurvivors) versus hospital discharge after clinical recovery (survivors). Adapted from Aloisio et al.[2]

analysis (MA), even if 86.6% of patients showed ALB values < 35 g/L (i.e., the lower reference limit). In a similar COVID-19 population enrolled in our national reference center for infectious diseases, we recently analyzed a group of common biochemistry tests, including ALB, as major predictor of COVID-19 severity.[2] Although the patient rate showing an ALB < 35 g/L was quite similar (89%) to that of Hundt et al.'s study, at MA, low ALB concentrations remained significantly associated (P = 0.003) with higher odds of death, ALB values ≤ 18 g/L giving a positive likelihood ratio of 12.2 for predicting in-hospital death. In terms of absolute ALB levels in the respective populations, it is somewhat difficult to compare our results with those of Hundt et al., however, as the authors do not mention the methodology used to determine ALB in their hospital network. It is known that immunoturbidimetric assays for ALB determination, such as the one in use at our institution, are specific for the ALB measurement, contrary to nonspecific colorimetric methods, which are in use in most US health-care institutions, also reacting with proteins other than ALB.[3] The well-known lack of specificity of the latter methods, especially at low ALB and high globulin (including "acute phase reactants") concentrations (i.e., the typical COVID-19 situation) may have influenced Hundt et al.'s results. Figure 1 depicts ALB distribution in our patients with COVID-19, showing that even survivors displayed a median (interquartile range) of 28 g/L (25-32), which is quite lower than patients with severe COVID-19 enrolled by Hundt et al. Therefore, we cannot exclude that the inability of ALB to predict death in the Hundt et al. study was due to spuriously higher ALB values measured with nonspecific methods in the evaluated patients with COVID-19. The accuracy of ALB methods may become critical in COVID-19 cases, in which ALB is decreased but acute-phase proteins are increased; thus, use of immunological assays should be preferred in this condition.[4]

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REFERENCES

1) Hundt MA, Deng Y, Ciarleglio MM, Nathanson MH, Lim JK. Abnormal liver tests in COVID-19: a retrospective observational cohort study of 1,827 patients in a major U.S. hospital network. Hepatology 2020;70:1169-1176.

2) Aloisio E, Chibireva M, Serafini L, Pasqualetti S, Falvella FS, Dolci A, et al. A comprehensive appraisal of laboratory biochemistry tests as major predictors of COVID-19 severity. Arch Pathol Lab Med 2020;144:1457-1464.
3) Bachmann LM, Yu M, Boyd JC, Bruns DE, Miller WG. State of harmonization of 24 serum albumin measurement procedures and implications for medical decisions. Clin Chem 2017;63:770-779.
4) Aloisio E, Serafini L, Chibireva M, Dolci A, Panteghini M. Hypoalbuminemia and elevated D-dimer in COVID-19 patients: a call for result harmonization. Clin Chem Lab Med 2020;58: e255-e256.

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Letter to the Editor: Is Balloon-Occluded Retrograde Transvenous Obliteration Superior to Endoscopic Cyanoacrylate in Gastric Varices?

TO THE EDITOR:

We read with interest the study by Luo et al. comparing cyanoacrylate (CA) injection with balloon-occluded retrograde transvenous obliteration (BRTO) for the prevention of rebleed from gastric varices (GVs).[1] However, several issues need to be addressed.

Although GV size has consistently been shown to be a significant risk factor for bleeding,[2] the authors have not described the size and morphology of the GVs. Patients in the BRTO arm only underwent preprocedural contrast-enhanced CT (CECT) to delineate the shunt and variceal anatomy (Supporting Fig. S1A). Performance of similar imaging in the CA arm would have helped determine if the shunt and variceal anatomy were comparable between the two groups. Further, the use of probing to ascertain the obturation of GVs is a crude method; the use of endoscopic ultrasound (EUS) or endoscopic Doppler would have been a more objective technique.[3]

The authors have concluded that "BRTO is more effective than cyanoacrylate injection in preventing rebleeding from GVs." However, the hazard ratio of BRTO for GV rebleeding was 0.014 with a 95% CI of 0-9.979. Indeed, BRTO was not associated with a reduced risk of rebleed from GVs on univariate or multivariate analysis (Supporting Table S3). Therefore, we feel that such a conclusion is not statistically prudent.

Although the role of beta-blockers in the secondary prophylaxis of GV bleed is not clear, their role in the secondary prophylaxis of esophageal variceal bleed is unequivocally established.[4] Esophageal varices were the second most common source of rebleeding in the cohort. We wonder if beta-blockers were instituted in these patients who had esophageal variceal bleed on follow-up and, if not, what the rationale for not doing so was. Indeed, compared with CA, BRTO may be associated with a higher risk of rise in portal pressures[5] and may particularly benefit from the addition of beta-blockers.

Finally, the guidelines on primary and secondary prophylaxis of esophageal varices are mainly based on survival benefits.[4] Although this study was not powered for survival analysis, there was no difference in survival between the two groups. Further trials are needed to confirm the superiority of BRTO and study the role of beta-blockers in the prophylaxis of GV bleed.

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REFERENCES

1) Luo X, Xiang T, Wu J, Wang X, Zhu Y, Xi X, et al. Endoscopic cyanoacrylate injection vs BRTO for prevention of gastric variceal bleeding: a randomized controlled trial. HEPATOLOGY 2021;74:2074-2084.