Reply to hep-21-0216 'acute liver injury due to therapeutic doses of acetaminophen - confounders must be ruled out!'

Alexandre Louvet, Philippe Mathurin

Letter to the Editor: Acute Liver Injury Due to Therapeutic Doses of Acetaminophen—Confounders Must Be Ruled Out!

TO THE EDITOR:

We read the study by Louvet et al.[1] describing risk factors and outcomes associated with acute liver injury due to therapeutic doses of acetaminophen (ALITD) with great interest. They conclude that ALITD is associated with severe liver injury and occurs in patients with excess alcohol consumption or fasting. This makes us ponder the mechanisms behind ALITD to prospectively modify host risk factors associated with therapeutic misadventure of acetaminophen. However, certain issues warrant further clarification.

First, it is of paramount importance to rule out underlying chronic liver disease. Patients with cirrhosis have low acetaminophen clearance,[2] which may predispose these patients to ALITD. Approximately 60% patients with acute liver failure may have ascites and features of portal hypertension,[3] and absence of features of decompensation may be insufficient in ruling out cirrhosis. Apart from cirrhosis, patients with NASH have up-regulated cytochrome P450 2E1 (CYP2E1)[4] and reduced intrahepatic glutathione,[5] predisposing them to acetaminophen-induced liver injury. It would be of interest to know how many patients had NASH and whether metabolic risk factors were associated with an increased risk of developing ALITD.

Second, the duration of alcohol intake is as important as the amount of alcohol consumed. Patients with chronic alcohol abuse may have significant hepatic fibrosis, which may predispose them to ALITD. Third, an important aspect of acetaminophen toxicity is formation of N-acetyl-p-benzoquinone imine through CYP2E1, and it is pertinent to know whether patients with ALITD were on any drugs that compete with hepatic glucuronidation or induce CYP2E1 that can lead to increased acetaminophen toxicity. Last, the researchers conclude that ALITD is associated with severe disease in comparison to acetaminophen overdose. However, on multivariate analysis, ALITD was neither associated with increased mortality nor presence of at least one of the King's College Hospital criteria. Although more patients in ALITD were fasting, its effect was also not adjusted for in multivariate analysis.

In conclusion, the study provides new insight about ALITD; however, clinicians should also pay heed to presence of metabolic risk factors, fatty liver, and concurrent drug use while prescribing acetaminophen.

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Potential conflict of interest: Nothing to report.

REPLY:

We disagree with the conclusion of Vojjala et al., which states that clinicians should pay attention to metabolic risk factors, fatty liver, and concurrent drug use.

The authors questioned the presence of NAFLD in our study. However, the median body mass index

(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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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