Response to Rathi et al.

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We would like to thank Rathi et al. (1) for their interest in our study. I hope the response to their comments will be informative to the authors and the readership of the journal.

As Rathi et al. noted, less than a third of the patients admitted to hospital were tested for lipase levels in our study (2). Lipase testing was at the discretion of the clinical team, and as such, the indication for testing could not be verified using chart review as was discussed in our article (2). What prompts clinicians to check lipase usually is gastrointestinal abnormalities (based on symptoms, imaging, or biochemical findings). The presenting gastrointestinal symptoms were comparable between patients with normal and elevated lipase, suggesting that the symptoms at presentation probably did not prompt the lipase testing in our series. We agree that lipase testing could have been part of a comprehensive assessment of admitted patients who were doing poorly after coronavirus disease of 2019 (COVID-19) diagnosis. In fact, we provided 3 vignettes at the beginning of our article where we shared our initial observation of elevated lipase in severe COVID-19 cases, which prompted us to conduct our study to test the association of elevated lipase and COVID-19 clinical course (2). In response to the comment by Rathi et al. on the possible selection bias toward worse clinical course in our study population who underwent lipase testing, we reanalyzed our data and found that both the intensive care unit admission (42.5% vs 38.5%, P = 0.6) and intubation rates (33% vs 25%, P = 0.15) were comparable in patients who were tested for lipase compared with those who did not undergo lipase testing, respectively. Therefore, among admitted patients, lipase testing was not significantly biased toward cases who did poorly clinically.

We classified our cases who were tested for lipase both based on the commonly used lipase level cut off >3 upper limit of normal (ULN) and tertials of lipase. Although the former is based on the clinical definition of elevated lipase in the setting of pancreatic inflammation, the latter provides statistical categorization of our cases based on their lipase distribution; both approaches (Tables 1 and 2) confirmed the association between elevated lipase and the poor outcomes in our series (2).

Rathi et al. argue against lipase checking in light of what they describe as low prevalence of pancreatic involvement and infrequent hyperamylasemia based on 2 series: one from China and another from the United States. The series from China by Wang et al. (3) was rather a small study. However, in 52 patients with COVID-19, the authors found that 9 (~17%) patients had evidence of elevated lipase or amylase, among which 5 patients (~10%) had elevated lipase. Although association with clinical outcomes was not tested in that study, patients with elevated amylase/lipase had indeed more severe illness on admission and biochemical abnormalities. The study by McNabb-Baltar et al. (4) was a retrospective collection of data from patients who were hospitalized for COVID-19 across 6 different hospitals (2 tertiary and 4 community hospitals) in Massachusetts, and therefore, the clinical indications for lipase testing is likely more heterogeneous compared with our single center study. Having a smaller sample size, only 2 of their patients had hyperlipasemia exceeding 3 times the ULN, which limits their power to correlate hyperlipasemia with the clinical outcomes. Compared with this mainly community-based study population, our study was conducted at a tertiary referral center for COVID-19 in Chicago and was likely enriched in patients with more complex clinical course who needed admission to the hospital. This has enabled us to have a higher statistical power for testing the association between hyperlipasemia and the disease outcome among the hospitalized COVID-19 patients.

Liu et al. (5) described high expression of angiotensin converting enzyme 2 (ACE2) in the pancreatic tissue as the possible link between infection with COVID-19 and the elevated pancreatic enzymes. In 67 COVID-19 patients with at least 1 sign of respiratory distress who were admitted to the hospital, they found 11 patients (16.41%) with elevated levels of both amylase and lipase. This is consistent with our finding that 16.8% of hospitalized COVID-19 patients who were tested for lipase had >3 ULN levels of this enzyme. Both studies support the association of elevated lipase with clinical severity of COVID-19. We did not have data on pancreas involvement given the lack of imaging in most cases. Liu et al. (5) found 45% (5/11) of COVID-19 cases with elevated levels of pancreatic enzymes showed imaging alterations in their pancreas.

Although the current literature mechanistically and clinically support that pancreatic injury in the setting of COVID-19 is possible (5–9), our study specifically focused on the lipase elevation and not pancreatitis per se as a prognostic factor for COVID-19 infection. Lipase elevation in COVID-19 could be due to pancreatic involvement or as part of a systemic decompensation/multiorgan dysfunction or both. Although there are no data to support lipase testing in all COVID-19 patients, especially those with mild symptoms who account for most COVID-19 cases, our data suggest that lipase elevation in hospitalized COVID-19 patients could be associated with severe COVID-19 clinical course.

Therefore, we stand by our findings and conclusions and hope that this additional analysis of our data within the context of the existing literature will bring clarity to this topic. We are against unnecessary testing. Nevertheless, although we wait for large prospective studies to systematically test prognostic value of lipase and other biomarkers in COVID-19 patients, clinicians might consider paying closer attention to hospitalized COVID-19 patients with elevated lipase for better prognostication and allocation of resources.

CONFLICTS OF INTEREST
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