Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

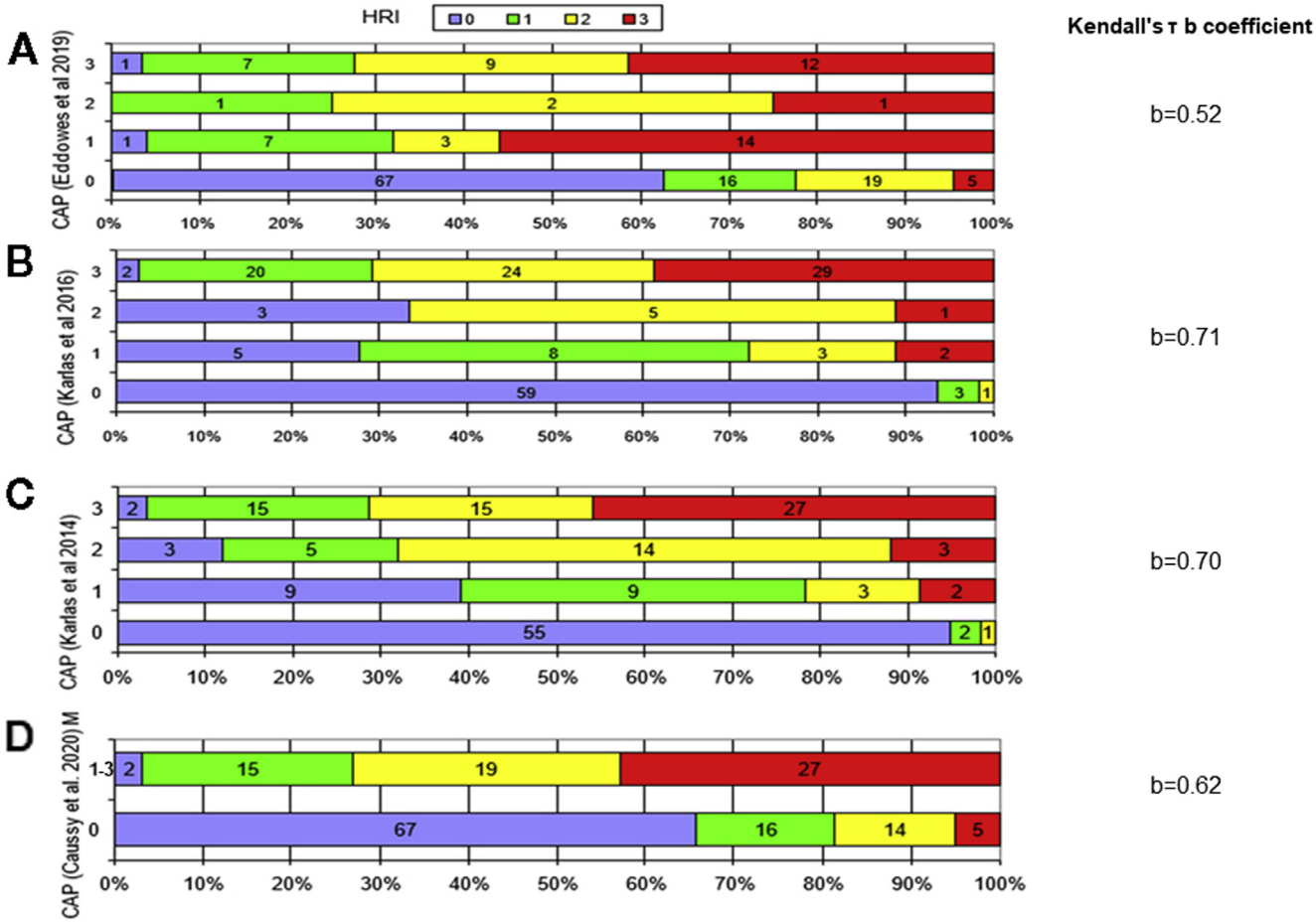

Figure 1. Discrepancies between HRI and CAP-based liver steatosis grading. Comparison between classification of liver steatosis according to HRI classification[6] and CAP thresholds proposed by Eddowes et al[3] (*A*), Karlas et al[5] (*B*), Karlas et al[4] (*C*), and Caussy et al[1] for the M probe (*D*). The interrater reliability presented as Kendall's τ b coefficient.

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Conflicts of interest
The authors disclose no conflicts.

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Liver Injury in Liver Transplant Patients With COVID-19: A Histopathologic Analysis

Dear Editor:

I read with interest the results reported by Kaltschmidt and colleagues.[1] They undoubtedly carry significant implications toward liver transplant (LT) patients infected with COVID-19.

The study investigated patterns of liver injury and recovery in 60 patients who died of COVID-19 pneumonia between March and June 2020. Thirteen patients who died of non-COVID-19 fatal pneumonia served as the control. COVID-19 patients more frequently exhibited platelet microaggregates in the microvasculature of the liver (70% vs 30%; $P = .032$). This is expected because severe COVID-19 entails a hyperinflammatory, hypercoagulable state with significantly higher rates of thromboembolism.[2] More COVID-19 patients also experienced sinusoidal dilation exceeding 75% ($P = .024$). Portal dilation was also more frequently observed ($P = .002$). SARS-CoV-2 was detected in 25% of all COVID-19 patient liver samples. Furthermore, more COVID-19 patients had higher-grade hepatic steatosis, with approximately 40% of cases at grade 2/3. The microvesicular variant was more preponderant in this cohort. Because COVID-19 patients exhibited greater extent of liver damage, there were greater activation of intrahepatic stem cell niche, and more regenerative clusters of hepatocytes in intrahepatic bile ductules. This led to aberrant regeneration efforts.

Such results proffer us an alternative view of the long-term consequences of LT patients with COVID-19. These patients were found to experience more severe disease. A US multicenter observational study showed that 72.3% (n = 81) of patients were hospitalized, and 37.0% (n = 30) were admitted to the intensive care unit; 23.2% (n = 26) were given mechanical ventilation.[3] Such results corroborated with those from a Spanish nationwide study: 86.5% (n = 96) were hospitalized[4] and 31.5% (n = 35) met the criteria for severe COVID-19, defined as needing mechanical ventilation, admission to intensive care unit, and/or death in the study. A significant proportion of such patients also suffered from acute liver injury (defined as alanine transferase level >2–5 times the upper reference limit; 34.6%).[3] Severe COVID-19 and liver injury in LT patients were significantly correlated. Rates of intensive care unit admission and mechanical ventilation were substantially higher in LT patients with liver injury (57.1% vs 22.6%, $P = .002$; 53.6% vs 29.6%; $P < .001$).[3] Therefore, LT patients with COVID-19 have higher risk of liver injury and exhibiting the histopathologic findings shown in this study.

The findings point toward higher potential of irreversible liver injury in severe disease. Hepatic steatosis is more serious in COVID-19 patients, both in degree and prevalence. With hypertension and diabetes mellitus being 2 significant risk factors of hepatic steatosis,[5] both frequently arising in LT patients with COVID-19 (57.7%, n = 64; 47.7%, n = 53),[4] they may experience even more serious steatosis. Higher-grade steatosis is independently correlated with gallstone disease,[6] and more frequently leads to liver fibrosis.[7] More severe fibrosis leads to worse survival outcomes.[8] Extensive thromboembolism in the microvasculature can lead to prolonged ischemia. With higher prevalence of metabolic syndrome in LT patients with COVID-19, hepatovascular health is further compromised by higher risk of atherosclerosis.

Some argue that upon clinical resolution of COVID-19, liver transaminases decrease dramatically from their peak levels in LT patients (alanine aminotransferase: 40.3 vs 29.8 IU/L, $P = .06$; aspartate aminotransferase: 44.9 vs 29.0 IU/L, $P = .005$). This is indicative of clinical improvement.[3] Any liver changes during COVID-19 are also thought to be transient. This belief is fortified by the fact that only 2.7% (n = 3) of LT patients with COVID-19 developed graft dysfunction.[4] However, even after clinical resolution, transaminase levels were still higher than baseline (alanine aminotransferase, 29.8 vs 23.0 IU/L; aspartate aminotransferase, 29.0 vs 19.0 IU/L).[3] One may dismiss this as incidental, or attributable to an alternative source. However, given the histopathologic results of this study, it is more likely that irreversible liver damage has occurred.

This brings us to the issues of reinfection and retransplantation. Currently, there is no literature on LT patient outcomes on COVID-19 reinfection. Because LT patients undergo immunosuppression, it is highly likely that reinfection occurs, especially when clinical follow-up requires more frequent visits to high-risk clinical settings. Whether reinfection leads to more significant and sustained liver injury, culminating in graft failure, remains unknown. Even without reinfection, graft efficacy may be severely compromised, because LT patients with COVID-19 experience greater degree of injury. Whether this translates to greater need for retransplantation in the long-term, and if yes, whether bridging therapy (for certain etiologies, such as hepatocellular carcinoma) is preferred over transplantation amid organ scarcity under the COVID-19 era, remain significant in clinical practice.

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