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.

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Reply to: "Progressive cholangiopathy in COVID-19 patients: Other possible diagnoses than ketamine-induced cholangiopathy should be considered"

Intravenous ketamine is a risk factor for jaundice in COVID-19 patients

To the Editor:

In their reply to our initial report[1] Deltenre, Moreno and Trepo[2] postulated that vasculobiliary injuries could have contributed to our cases of COVID-19 cholangiopathies, which is, undeniably, a possibility. However, critical care vasculobiliary injuries are associated with haemodynamic instabilities and hepatic ischemia. In our series, the maximum serum lactate level remained below 2.5 mmol/L in 3 out of 5 patients, which rules out shock and tissue (including hepatic) hypoperfusion. In another series of 12 patients with COVID-19 cholangiopathy, 2 (16.7%) patients never received vasopressors.[3] Therefore, we think that vasculobiliary injuries are not the only causes of COVID-19 cholangiopathies, and that multiple hits, including drug injury, and maybe SARS-CoV-2 toxicity, could account for the syndrome. At the time of writing, 24 patients with COVID-19 cholangiopathy have been reported in the literature. The common point was mechanical ventilation. Maintenance sedation with ketamine was reported in 10 (41.7%) patients.[1,4,5] Otherwise, the maintenance sedation protocol was unmentioned.

We investigated, after our initial observations, the relationship between hospital consumption of ketamine and maximum total serum bilirubin level of patients who underwent mechanical ventilation for COVID-19 in 15 adult hospitals of the Assistance Publique — Hôpitaux de Paris (AP—HP). Health data and drug consumptions were collected from the AP—HP health— (NB, MD) and central pharmacy— (VS, MT) datawarehouses. Sedative drug consumption, including ketamine, midazolam, and propofol, were estimated by hospital and by COVID-19 patient, and categorized as >median ("higher") and ≤median ("lower") drug consumptions. The sample comprised 2,258 (mean [SD] age 60 [13]; 73% men) patients. Their characteristics, overall, and by ketamine consumption are presented in Table S1. Patients in the lower ketamine group were older (p = 0.043), and were more severe, in terms of comorbidities (p <0.001) and initial serum C-reactive protein level (p = 0.045). Sex, maximum serum creatinine level, and mortality were similar between the lower and higher ketamine patient group. The mean (SD) maximum total serum bilirubin level was 19 (24) and 17 (20) μmol/L in the higher and lower ketamine groups, respectively (p = 0.016). Other surrogates of the intensive care effort, including higher consumptions of midazolam (p = 0.025) and of propofol (p = 0.62), were not associated with higher levels of total serum bilirubin (Fig. 1). Therefore, ketamine was associated with jaundice in this cohort. Whether ketamine-associated jaundice contributed, or not, to organ failure is unknown and should be investigated. The guidelines for maintenance sedation of patients with acute respiratory distress syndrome (ARDS), regardless of COVID-19, include ketamine as a second-line agent. We think that clinicians should refrain from using ketamine to sedate patients with ARDS, including those with COVID-19. If cornered into such a prescription, ketamine should only be used short-term, and bilirubin should be closely monitored.

Keywords: Ketamine; Cholestasis; Intrahepatic; Cholangiopathy; Cholangitis; COVID-19; Chemical and Drug Induced Liver Injury.
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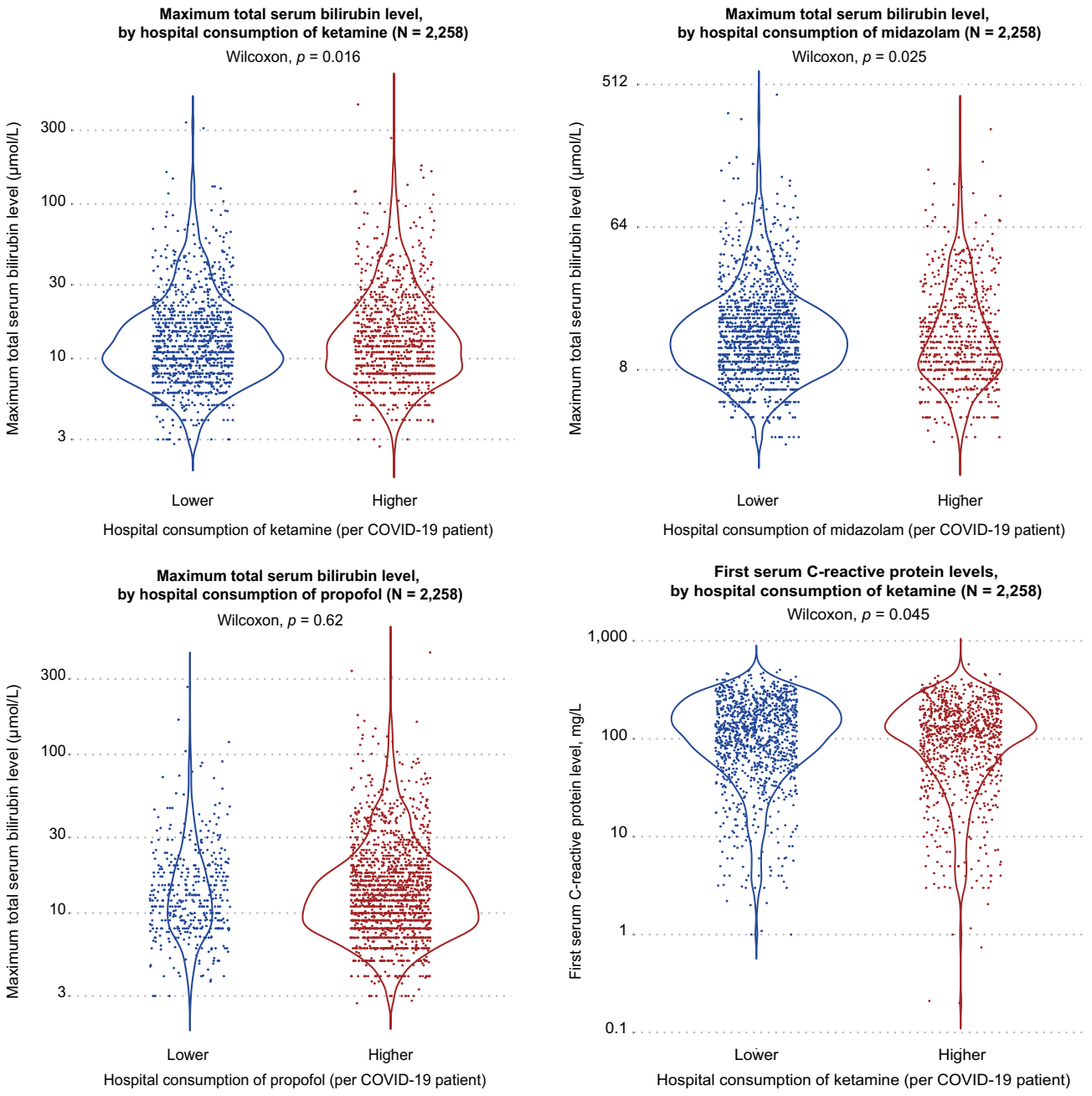

Fig. 1. Distribution of maximum total serum bilirubin level by hospital consumption of ketamine, midazolam, propofol, and first serum C-reactive protein measurement. Data are for COVID-19 patients treated with mechanical ventilation between February 6, 2020 and April 20, 2021 in 15 adult hospitals of the Assistance Publique - Hôpitaux de Paris (AP-HP). Data were extracted from the heath datawarehouses of the AP-HP. Hospital consumption of sedative drugs corresponded to the ratio of total drug consumption to the number of COVID-19 patients who underwent mechanical ventilation in each hospital. (This figure appears in color on the web.)

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.06.024.

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Non-selective beta blockers and mortality in decompensated cirrhosis: Is cirrhotic cardiomyopathy the missing link?

To the Editor:

We read with interest the article by Alvarado-Tapias *et al.*[1] which provides valuable information about the impact of non-selective beta blockers (NSBBs) on hemodynamics in patients with decompensated cirrhosis. The study eloquently showed that patients with decompensated cirrhosis and greater decline in cardiac output (CO) while on NSBBs (CO <5 L/min *vs.* CO ≥5 L/min) had worse survival. In Table S5, the authors demonstrate that patients with more remarkable decline in CO on NSBBs (<5L/min) had impaired global longitudinal strain (GLS) compared to those with higher CO on NSBBs (absolute GLS value 18%±2 *vs.* 21%±2) and they hypothesize that this detrimental response to NSBBs may reflect reduction in the cardiac compensatory reserve relating to a latent cardiomyopathy, suggested by these borderline normal strain values. This hypothesis will benefit from data that classify the patients in this important study according to their cirrhotic cardiomyopathy (CCM) status based on the new diagnostic echocardiographic criteria of CCM (Fig. 1),[2] which are congruent with the European and American guidelines for assessment of left ventricular systolic and diastolic function. If patients who meet the diagnostic criteria for CCM, in this study, are found to be at increased risk for the detrimental effect of NSBBs, this will be an invaluable information for clinical practice and provide mechanistic insight into the pathophysiology of CCM as being distinct from other cardiomyopathies.

Beta blockers, as anti-remodeling agents, have been the core of guideline-directed medical standard of care for various

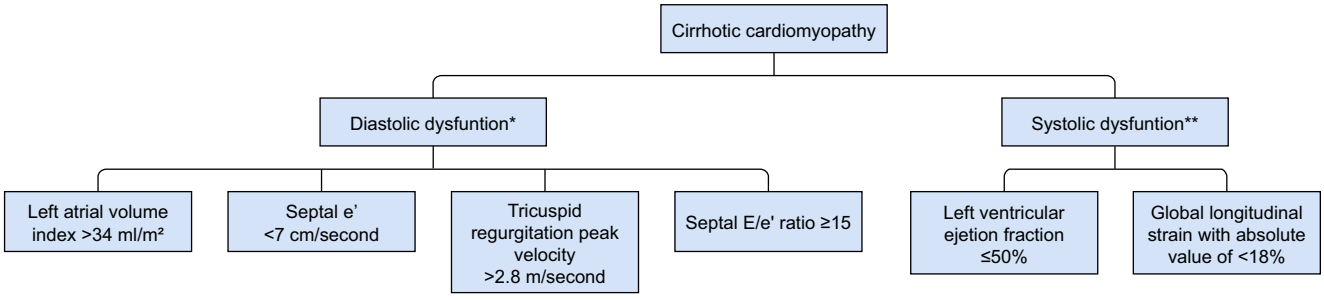

Fig. 1. The new diagnostic criteria for cirrhotic cardiomyopathy by the Cirrhotic Cardiomyopathy Consortium 2020. *If 2 criteria are present, this indicates diastolic dysfunction for which the grade is indeterminate and requires additional testing. If 3 criteria are present, that confirms diastolic dysfunction for which the grade can be determined based on E/A ratio (E/A ≥2 represents grade III, E/A 0.9-1.9 represents grade II). **Either criterion is sufficient to make the diagnosis of systolic dysfunction. A, late diastolic transmitral flow velocity; E, early diastolic transmitral flow velocity; e', early diastolic mitral annular velocity.

Keywords: end stage liver disease; heart disease; outcomes in cirrhosis.
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