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.

JOURNAL OF HEPATOLOGY

COVID-19 can mimic acute cholecystitis and is associated with the presence of viral RNA in the gallbladder wall

COVID-19 is caused by SARS-CoV-2, and typically manifests with systemic symptoms like fever and myalgia as well as respiratory symptoms including dry cough, dyspnoea and anosmia.[1] Reports suggest that lineage B β-coronaviruses that are highly pathogenic to humans such as the SARS-CoV (2002) and SARS-CoV-2 (2019) can affect the liver and induce acute hepatitis.[1,2] Herein, we report the cases of 2 patients who developed COVID-19 presenting as an acute acalculous cholecystitis.

The first case was an 84-year-old female patient who presented to our emergency department with symptoms and signs of urinary tract infection and fever (38.5°C) for 24 hours. Sepsis due to pyelonephritis was the initial diagnosis after a pathological urinalysis and positive urine culture. Blood tests revealed a slight cytolysis. Ceftriaxone was initiated alongside supportive care. On day 3, a right upper quadrant pain emerged, and on day 5, a positive Murphy sign was detected along with an increase in C-reactive protein, reaching 249.3 mg/l (Table S1). Ultrasonography revealed increased thickening of the gallbladder wall as well as peri-vesicular fluid. A thoraco-abdominal CT scan ruled out gallbladder perforation and showed a normal pulmonary parenchyma (Fig. 1A). Metronidazole was added to the treatment and the patient underwent a laparoscopic cholecystectomy on day 8.

After extubation, the patient developed respiratory symptoms evolving into acute respiratory distress syndrome. Nasopharyngeal swabs confirmed the presence of SARS-CoV-2 RNA. The patient was transferred to the intensive care unit and passed away at postoperative day 5 from multiorgan failure. Histological analysis of the gallbladder did not demonstrate any inflammation but quantitative reverse transcriptase PCR (qRT-PCR) revealed the presence of SARS-CoV-2 in all 3 sampled regions of the gallbladder wall (Fig. 1B–C).

The second case concerned an 83-year-old man on dialysis for end-stage renal disease with type 2 diabetes, arterial hypertension and moderate aortic stenosis who was admitted with fever (38.3°C). No abdominal or respiratory symptoms were identified upon admission, and chest x-ray was normal. On day 5, the patient developed right upper quadrant pain with a positive Murphy sign, degradation of his inflammatory markers (C-reactive protein 209.9 mg/l, white blood cell count 19.5 G/L [Table S2]) and an increase in hepatic enzymes. Abdominal ultrasonography revealed a 4 mm thickening of the gallbladder wall, presence of peri-vesicular liquid, absence of gallstones and a radiologic Murphy sign. Conservative management with ceftriaxone and metronidazole therapy was initiated and led to a slow recovery. On day 6, the patient presented respiratory symptoms and a SARS-CoV-2 infection was confirmed.

SARS coronaviruses have a tropism to the lungs but also to the liver.[1] Indeed, the intracellular entry of the virus occurs through interaction with the angiotensin-converting enzyme 2 receptor (ACE2) which is present in several tissues, including lungs and liver.[1] In SARS-CoV autopsies, liver tissue exhibited different patterns of hepatocyte injuries, and viral RNA was found inside hepatocytes.[3] Both SARS-CoV and SARS-CoV-2 are characterized by cytolysis with mild transaminase elevations.[4,5] Moreover, ACE2 levels are higher in bile duct cells and Xu *et al.* suggested that liver injury induced by highly pathogenic SARS coronaviruses may be due to a direct harm to bile duct cells.[5] COVID-19-related acalculous cholecystitis has been described in 2 case reports and was managed with surgery or gallbladder percutaneous drainage.[6,7] Ying *et al.* performed RT-PCR of the bile after percutaneous drainage of the gallbladder in a patient with sludge and acute cholecystitis but did not detect SARS-CoV-2.[8] Gallbladder epithelial cells are very similar to bile duct cells, express ACE2 and could be a target for SARS-CoV-2.[9] RT-PCR of the formaldehyde fixed gallbladder of the first patient did not detect SARS-CoV-2 RNA with appropriate positive and negative controls (data not shown) but qRT-PCR testing confirmed the presence of the virus, indicating that SARS-CoV-2 was specifically present in the gallbladder. However, the significance of this finding to COVID-19 pathogenesis remains to be determined.

COVID-19 can present uniquely with digestive symptoms, without any respiratory manifestations, a longer time from onset to admission, and a worse prognosis.[10] The 2 cases presented herein exhibited an evolving clinical picture of acalculous cholecystitis with radiological pattern of progressive wall thickening, perivesicular fluid and a positive radiological and clinical Murphy sign. Digestive symptoms preceded the classic respiratory manifestation of COVID-19. Hepatic COVID-19 manifestation in those patients might explain both the clinical picture that was induced by hepatitis and the radiological pattern of cholecystitis.

SARS-CoV-2 infection can mimic acalculous acute cholecystitis; viral RNA detection in the gallbladder indicates direct vesicular involvement, while the exact pathogenesis remains to be elucidated. Differential diagnosis can be challenging in this case and rapid testing for SARS-CoV-2, and potentially conservative management might make a difference to patient outcomes.

Financial support

The authors received no financial support to produce this manuscript.

Conflict of interest

The authors have no conflict of interest to disclose.

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

Authors' contributions

ABa, KG, AP and SP collected the clinical data, ABo and TM processed and analysed the specimen, ABa, ABo and TM contributed to data analysis, ABa, KG, JM, CT and SP drafted the manuscript,

Keywords: Coronavirus; Covid-19; SARS; 2019-SARS-CoV2; Cholecystitis.
Received 15 July 2020; received in revised form 7 August 2020; accepted 16 August 2020; available online 2 September 2020
https://doi.org/10.1016/j.jhep.2020.08.020

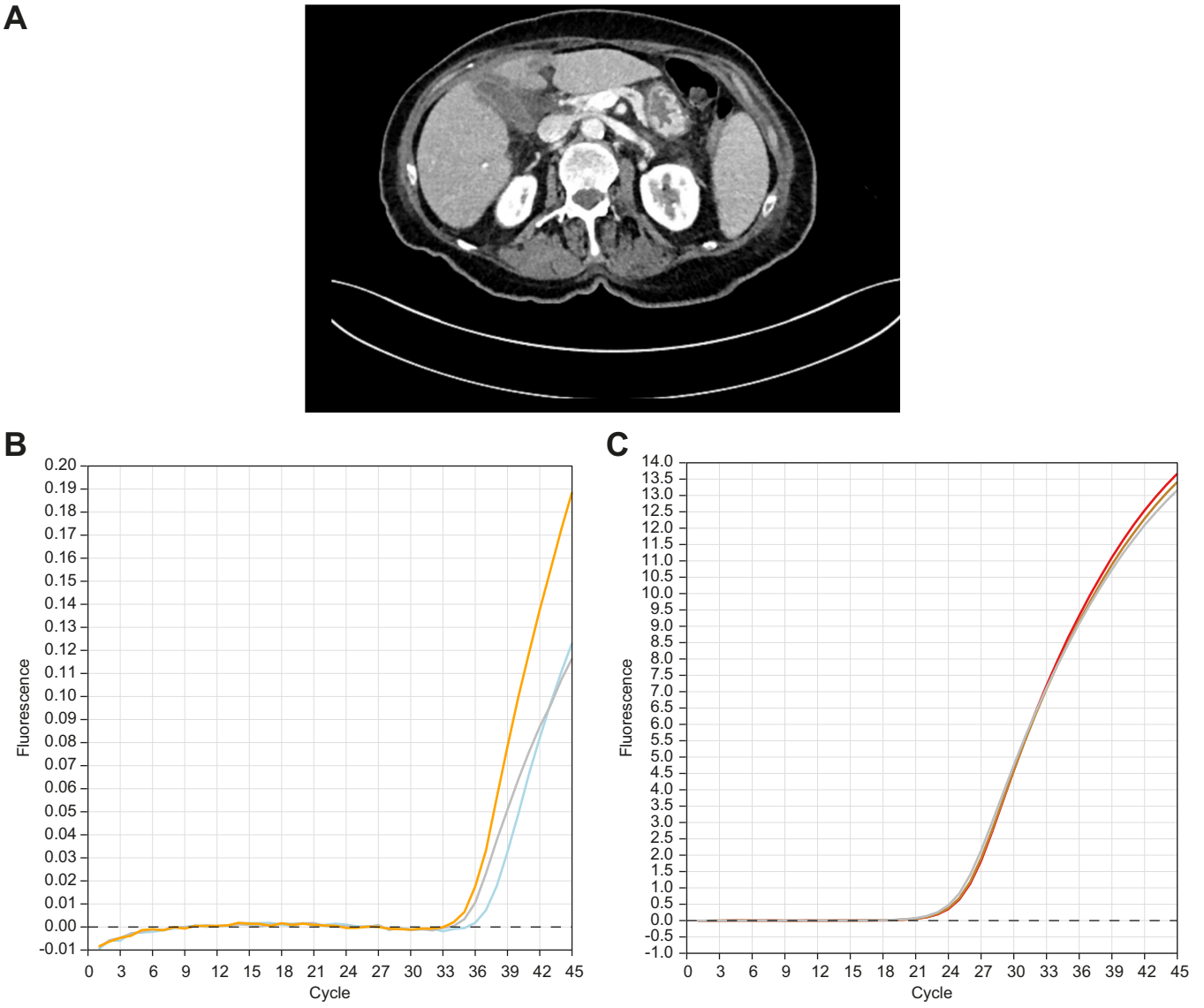

Fig. 1. Radiological findings and SARS-CoV2 qRT-PCR of the gallbladder of patient one. (A) Abdominal CT scan of the first patient showed signs of cholecystitis with peri-cholecystic fluid. qRT-PCR was performed on a gallbladder specimen to assess the presence of SARS-CoV-2. Standard protocols were used with the following primers: forward ACAGGTACGTTAATAGTTAATAGCGT reverse ATATTGCAGCAGTACGCACACA and a fluorescently labelled probe FAM-ACACTAGCCATCCTTACTGCGCTTCG-BBQ (complete protocol in supplementals) (B) The 3 samples from the gallbladder: A1 (blue), A2 (grey) and A3 (orange) were all positive for the presence of SARS-CoV-2 (experiment repeated 3 times with 2different extractions of RNA). (C) The RNA control was consistently positive (B1 [red], B2 [brown], B3 [grey]). (This figure appears in color on the web.)

ABa, KG, JM, AP, ABo, TM, CT, SP contributed to its critical revision, ABa, KG, JM, AP, ABo, TM, CT, SP approved the final version.

Ethics

For the first patient, consent for case publication was obtained from the patient's family and care representant as patient was deceased. For the second case, consent was directly obtained from the patient himself. All data, including radiology images were anonymized.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.08.020.

References

Author names in bold designate shared co-first authorship

[1] Gavriatopoulou M, Korompoki E, Fotiou D, Ntanasis-Stathopoulos I, Psaltopoulou T, Kastritis E, et al. Organ-specific manifestations of COVID-19 infection. Clin Exp Med 2020. https://doi.org/10.1007/s10238-020-00648-x.
[2] Weiss SR, Leibowitz JL. Coronavirus pathogenesis. Adv Virus Res 2011;81:85–164.
[3] Guo Y, Korteweg C, McNutt MA, Gu J. Pathogenetic mechanisms of severe acute respiratory syndrome. Virus Res 2008;133:4–12.
[4] Wu K-L, Lu S-N, Changchien C-S, Chiu K-W, Kuo C-H, Chuah S-K, et al. Sequential changes of serum aminotransferase levels in patients with severe acute respiratory syndrome. Am J Trop Med Hyg 2004;71:125–128.

[5] Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int 2020;40:998–1004.
[6] Singh R, Domenico C, Rao SD, Urgo K, Prenner SB, Wald JW, et al. Novel coronavirus disease 2019 in a patient on durable left ventricular assist device support. J Card Fail 2020;26:438–439.
[7] **Bruni A**, **Garofalo E**, Zuccalà V, Currò G, Torti C, Navarra G, et al. Histopathological findings in a COVID-19 patient affected by ischemic gangrenous cholecystitis. World J Emerg Surg 2020;15:43.
[8] Ying M, Lu B, Pan J, Lu G, Zhou S, Wang D, et al. COVID-19 with acute cholecystitis: a case report. BMC Infect Dis 2020;20:437.
[9] Zong H, Yin B, Zhou H, Cai D, Ma B, Xiang Y. Loss of angiotensin-converting enzyme 2 promotes growth of gallbladder cancer. Tumour Biol 2015;36:5171–5177.
[10] Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol 2020;115:766–773.

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The impact of COVID-19 on the clinical outcome of patients with cirrhosis deserves more attention and research

To the Editor:
We read with interest the paper "High rates of 30-day mortality in patients with cirrhosis and COVID-19" by Iavarone *et al.* in *Journal of Hepatology*.[1] In the article, the authors report that COVID-19 is associated with elevated 30-day mortality in cirrhotic patients. After carefully reading, we wish to put forth the following suggestions.

First, there were 4 predictor variables (MELD, delta-MELD, CLIF-OF, and moderate/severe respiratory failure) with 17 fatal outcome events in the multivariate Cox model. The rule of thumb is that logistic and Cox models should be used with a minimum of 10 events per predictor variable (EPV). Previous results showed increasing bias and variability, unreliable confidence interval coverage, and problems with model convergence as EPV declined below 10 and especially below 5.[2,3] Therefore, a larger sample size is needed to validate the results of this study. Second, it might be reasonable to use logistic regression, with the outcome being a dichotomous status (alive or dead) since the relative granularity of time is low (a short-term follow-up: 30 days). Third, the authors report that patients with cirrhosis had increased MELD and CLIF-OF scores at COVID-19 diagnosis. However, most patients (80%) with COVID-19 in the cohort received thromboprophylaxis, which would affect the results of prothrombin time (PT) and international normalized ratio (INR). Prolonged PT and high INR levels would result in higher MELD, Child-Pugh and CLIF-OF scores. Finial, previous studies found that ACE2 internalization by SARS-CoV-2 would potentially result in the loss of ACE2 activity at the cell surface and voids a key pathway of angiotensin (Ang)-II metabolism and Ang-(1-7) generation.[4,5] Experimentally, Ang-(1–7) inhibits liver fibrogenesis and exerts natriuretic and portal hypotensive effects.[6] The reduction in ACE2 by SARS-CoV-2-induced internalization would be predicted to aggravate liver fibrosis and portal hypertension, and exacerbate disease severity, especially in the long-term. Therefore, the impact of COVID-19 on the long-term liver-related outcomes in patients with cirrhosis deserves attention.

Received 13 June 2020; accepted 15 June 2020; available online 20 June 2020
https://doi.org/10.1016/j.jhep.2020.06.024

Financial support
The authors received no financial support to produce this manuscript.

Conflict of interest
All authors: nothing to declare.
Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
Study concept and design: Feng Gao, Zhi-Ming Huang; Drafting of the manuscript: Feng Gao; Study supervision: Zhi-Ming Huang. All authors contributed to the manuscript for important intellectual contents and approved the submission.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.06.024.

References
[1] Iavarone M, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. J Hepatol 2020;73:1063–1071.