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## LETTER TO THE EDITOR

### COVID-19-related cholecystitis



To the Editor:

Zhai and colleagues report on a patient with acute obstructive suppurative cholangitis and an atypical presentation of Covid-19 [1]. Even though cholangitis was clearly unrelated to SARS-CoV-2 infection in their case, Covid-19 could be an under-recognized cause of cholecystitis and cholangitis.

A 90-year-old Caucasian man presented with fever and pain in the right upper abdominal quadrant. He was a close contact of a Covid-19 patient and reported a single gallbladder stone that was incidentally discovered on an abdominal ultrasonography 15 years before this presentation. There was no episode of biliary colic, cholecystitis or cholangitis in his previous history. The patient also had diabetes, hypertension, and essential tremor.

On admission, temperature was 38.2°C and all other vital signs were within normal limits. Physical examination revealed a tender abdomen with a positive Murphy's sign and no rebound tenderness and was otherwise normal. Laboratory investigations showed leukocytosis, increased aminotransferases and C-reactive protein, and normal gas exchange. All other blood tests were unremarkable, however a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay of a nasopharyngeal swab returned positive for SARS-CoV-2 RNA. A computed tomography showed multifocal, peripheral ground-glass opacities of both lungs and an enlarged gallbladder with thickened wall containing a 2 × 2 cm stone and peri-vesicular fluid. The findings were consistent with Covid-19 pneumonia and acute cholecystitis. The patient was treated with antibiotics, an ultrasound-guided percutaneous transhepatic gallbladder drainage was performed, and approximately 600 mL of green bile were drained on day 3rd. A RT-PCR assay for SARS-CoV-2 RNA in bile fluid was not done. The subsequent course was uneventful, abdominal pain and fever subsided, laboratory tests returned to within the normal range, the patient never reported shortness of breath, and gas exchange remained normal. The drainage was removed and he was discharged on day 26th with a negative nasopharyngeal swab for SARS-CoV-2 RNA. At follow-up 1, 3 and 6 months after presentation

the patient was doing well with no relapse of Covid-19 or cholecystitis.

The overall findings strongly suggest that this older patient had SARS-CoV-2 acute cholecystitis. Cholecystitis has been previously described in only two other Covid-19 cases aged more than 80 years [2]. The two patients presented with acute acalculous cholecystitis and developed pneumonia and respiratory failure later on day 5th and 6th of hospital stay, respectively. Cholecystectomy was performed in the 84-year-old patient, RT-PCR assay revealed the presence of SARS-CoV-2 in the gallbladder wall, and the outcome was ultimately poor. The second patient, an 83-year-old man, did not require surgery and was managed conservatively with a favorable outcome. There are few other reports of SARS-CoV-2 cholecystitis in younger patients [3–6].

The gallbladder stone incidentally found more than 15 years earlier could be a confounder in our case. An important finding is that the patient remained asymptomatic thereafter and had cholecystitis only and for the first time when he developed Covid-19. Furthermore, repeated laboratory and imaging studies failed to show any abnormalities suggesting liver injury, an underlying cholecystitis, or biliary obstruction during the follow-up. These points make it unlikely that the patient had cholecystitis independent of SARS-CoV-2.

Many and different mechanisms are involved in the pathogenesis of cholecystitis in Covid-19 patients. First, angiotensin-converting enzyme 2 (ACE2) i.e. the major binding receptor for SARS-CoV-2 is broadly expressed in human tissues including in the liver, gallbladder, and bile ducts [7,8]. This suggests the potential of SARS-CoV-2 to localize in and directly harm the gallbladder and the biliary ducts. Accordingly, SARS-CoV-2 infection of the gallbladder has been consistently demonstrated [2]. Furthermore, SARS-CoV-2 causes systemic endothelitis, hypercoagulability, antiphospholipid antibodies, and thrombotic microangiopathy that altogether may mechanistically contribute to the occurrence of cholecystitis [9–13]. Covid-19 patients with respiratory failure could be at higher risk because of hypoxia.

SARS-CoV-2 may directly or indirectly cause cholecystitis in older Covid-19 patients. Understanding the association of SARS-CoV-2 with cholecystitis is important.

## Conflict of interests

We declare no conflict of interests.

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