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.

2 Xu Y, Gu J. Cardiac and muscle injury might partially contribute to elevated aminotransferases in COVID-19 patients. *Clin Gastroenterol Hepatol* 2020; published online May 11. DOI:10.1016/j.cgh.2020.04.042.
3 Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. *Lancet Gastroenterol Hepatol* 2020; **5:** 529–30.
4 Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med* 2020; **382:** 1787–99.
5 Cai J, Xu J, Lin D, et al. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin Infect Dis* 2020; published online Feb 28. DOI:10.1093/cid/ciaa198.
6 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395:** 497–506.

We read with interest the systematic review and meta-analysis by Ren Mao and colleagues[1] that aimed to quantify the effect of COVID-19 on the digestive system. The study concluded that digestive symptoms and liver injury are common among patients with COVID-19 and that patients with severe disease have a higher risk of developing gastrointestinal symptoms and liver injury than do patients with non-severe COVID-19. However, we would like to highlight a couple of potential limitations to the method.

First, although the authors used a rigorous and comprehensive search strategy and selection process for identification of relevant articles, they do not appear to have assessed whether some patients had been included in more than one study. This finding is a common pitfall during the current global health emergency, possibly because of the rush to communicate clinical findings. The possibility of reporting the same patients in multiple reports has raised concerns,[2] because it could compromise the internal validity of meta-analyses aiming to summarise the body of evidence, and could result in substantial underestimation or overestimation of the results. This consideration is particularly important during major public health emergencies, in which there is an imperative need for reliable information to manage patients and to allow proper allocation of health-care resources in a cost-effective manner.

Our second concern regards the analysis that aimed to determine whether severe COVID-19 is associated with gastrointestinal symptoms and liver injury—namely, the definition of severity. There is a substantial heterogeneity in the definitions used for severe COVID-19, such as those from WHO interim guidelines for COVID-19,[3] the community-acquired pneumonia guidelines from the American Thoracic Society,[4] or the Chinese novel coronavirus pneumonia prevention and control programme.[5] Additionally, some primary studies have used their own definitions for severity, whereas others do not provide their definition. We think that a sensitivity analysis including only studies with similar severity definitions might be appropriate.

We declare no competing interests.

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1 Mao R, Qiu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5:** 667–78.
2 Bauchner H, Golub RM, Zylke J. Editorial concern—possible reporting of the same patients with COVID-19 in different reports. *JAMA* 2020; **323:** 1256.
3 WHO. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance, 13 March 2020. https://apps.who.int/iris/handle/10665/331446 (accessed June 8, 2020).
4 Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019; **200:** e45–67.
5 National Health Commission of the People's Republic of China. Diagnosis and treatment protocol for COVID-19. http://en.nhc.gov.cn/2020-03/29/c_78469.htm (accessed June 15, 2020).

Authors' reply

We thank Yongxing Xu and colleagues and Francisco J Barrera and colleagues for their comments on our meta-analysis about gastrointestinal and liver involvement in patients with COVID-19.[1]

We agree with Xu and colleagues that when assessing the prevalence of liver injury, a subgroup analysis based on the severity of COVID-19 is more valuable than is a pooled analysis. As shown in figure 6 in our study,[1] there was a higher risk of increased alanine aminotransferase (odds ratio [OR] 1·89; 95% CI 1·30–2·76; p=0·0009) in patients with severe COVID-19 than in patients with non-severe disease. Similarly, the OR for increased aspartate aminotransferase in patients with severe COVID-19 was 3·08 (95% CI 2·14–4·42; p<0·00001) compared with the group with non-severe COVID-19.[1]

We concur that abnormal liver function tests do not always equate to liver injury, and that the incidence of liver injury might be overestimated in patients with COVID-19 in the currently published literature as our understanding of COVID-19 is evolving rapidly and SARS-CoV-2 has been shown to induce myocardial injury.[2] Of the 12 studies included in our meta-analysis of liver injury, only two gave a clear definition for liver injury. Thus, we adopted a loose definition based on abnormal liver function tests. For this reason, we used the terms "abnormal liver function" and "abnormal liver chemistry" in our study.[1] Additionally, we analysed other liver injury indices such as bilirubin and albumin, which are rarely influenced by myocardial injury and muscle injury.

Barrera and colleagues raise the concern that some patients might have been included in multiple studies included in our analysis. We agree that a few patients might have been included in more than one study, which has been documented during the pandemic.[3] Avoidance of this limitation would have required us to obtain individual patient data to

ensure that patients were not included in more than one publication. This process was difficult to do during the unprecedented outbreak of COVID-19. In our study, our literature search was restricted to articles published in English only, partly to try to avoid inclusion of data from patients who had been reported both in English and in Chinese, or other languages. In another meta-analysis, Sultan and colleagues[4] used a hierarchical model of data extraction to minimise double counting of patients across similar institutions with coinciding dates of study inclusion, and their findings were similar to ours.

We agree that there is heterogeneity in the definitions used for severe COVID-19. In our meta-analysis, disease severity was defined per study; in some cases, patients with pulse oxygen saturation of less than 90%, in need of intensive care unit care, or with acute respiratory distress syndrome were also classified as having severe disease.[1] In subgroup analyses by COVID-19 severity, there was no substantial heterogeneity for gastrointestinal symptoms (I^2=0–24% except for loss of appetite [I^2=64%, indicating modest heterogeneity]) or liver chemistry (I^2=0–10%). Subgroup analyses including only those studies with similar severity definitions were not done because only a few studies used the same definitions.

See Online for appendix

We declare no competing interests.

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1 Mao R, Qiu Y, He J, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5:** 667–78.
2 Jaffe AS, Cleland JGF, Katus HA. Myocardial injury in severe COVID-19 infection. *Eur Heart J* 2020; **41:** 2080–82.
3 Bauchner H, Golub RM, Zylke J. Editorial concern—possible reporting of the same patients with COVID-19 in different reports. *JAMA* 2020; **323:** 1256.
4 Sultan S, Altayar O, Siddique SM, et al. AGA Institute rapid review of the gastrointestinal and liver manifestations of COVID-19, meta-analysis of international data, and recommendations for the consultative management of patients with COVID-19. *Gastroenterology* 2020; published online May 11. https://doi.org/10.1053/j.gastro.2020.05.001.

Preoperative oral antibiotics in colon surgery

We read with great interest the Article by Eloy Espin Basany and colleagues reporting the results of the ORALEV trial, which examined the use of preoperative oral antibiotics in colon surgery.[1] The authors concluded that oral prophylaxis with ciprofloxacin and metronidazole the day before colon surgery should be routinely adopted. However, a statistically significant effect on infectious complications might not be enough to support their conclusion. To come to a change in antibiotic policy, a systematic approach is warranted that comprises more than the effect of prophylaxis on infectious complications alone (appendix).

From the data presented by Espin Basany and colleagues,[1] we calculate that the number needed to treat to prevent one surgical-site infection (primary endpoint) is approximately 16 (95% CI 9–58), which appears low. However, most of the infections were superficial. When focusing on more severe complications—eg, deeper infections and organ space infections—the difference is small (16 of 269 patients in the control group *vs* seven of 267 patients in the preoperative antibiotics group) and not statistically significant. Antibiotic prophylaxis did not have any effect on the need for an intervention (drainage or re-operation) or duration of hospital stay. Furthermore, microbiological data to support or oppose the findings were not provided. Hence, it remains unclear to what extent the proposed prophylaxis prevents (serious) infectious complications.

The benefit of any preventive treatment must be weighed against the side-effects across the entire exposed population. Both antibiotics used in the ORALEV trial have side-effects. The safety profile of quinolones has fallen into disrepute because of the association with vascular complications. Although in the context of 1-day preoperative prophylaxis, the effect on the microbiome will be low compared with prolonged therapy, even a single dose has an impact.[2]

Even if the benefits of preoperative antibiotics outweighed the risks at the individual patient level, there is a third aspect that should be given thought. Today's guidelines have responsibilities towards future generations as well, and should safeguard the long-term efficacy of antibiotics. Even though the prophylaxis proposed in the ORALEV study is given only for 24 h, the associated antimicrobial consumption is considerable, since colon surgery is a high frequency procedure worldwide.[3] Quinolones should be prescribed with caution because of concerns about development of antibiotic resistance. Decreased susceptibility to quinolones arises mainly by single-step mutations, as reflected by increasing resistance rates globally.[4] Balancing the interests of patients with the—often opposed—interest of (near) future generations, is a substantial bioethical dilemma, but should be considered part of our professional duty.[5] As such, we believe that Espin Basany and colleagues' statement—that oral prophylaxis the day before colon surgery should be routine practice worldwide—appears premature.

We declare no competing interests.

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