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.

3. Vege SS, et al. Gastroenterology 2015;148:819–822.
4. Tanaka M, et al. Pancreatology 2017;17:738–753.
5. Harris RP. Ann Intern Med 2015;162:787–789.

Conflicts of interest
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Drug-induced Liver Injury With Ritonavir-Boosted Nirmatrelvir: Evidence From Coronavirus Disease 2019 Emergency Use Authorization Adverse Event Reporting System

Dear Editors:

Little is known about the risks of drug-induced liver injury potentially associated with the use of molnupiravir or ritonavir-boosted nirmatrelvir in a real-world setting until the recently reported work by Wong et al.[1] In their study, they analyzed retrospectively the data from 13,041 molnupiravir users and 4408 ritonavir-boosted nirmatrelvir users vs 165,592 molnupiravir and nirmatrelvir nonusers in Hong Kong, China between January 1, 2022 and March 31, 2022 and concluded subsequently that both molnupiravir and ritonavir-boosted nirmatrelvir were not associated with a significantly higher risk of drug-induced liver injury as compared with nonusers. Of note, only data from the first quarter of 2022 were collected, and the sample size of ritonavir-boosted nirmatrelvir users was much smaller than that of molnupiravir users in their study. Moreover, as acknowledged,[1] their study shared limitations similar to other retrospective studies. Further studies using real-world data are warranted, particularly for ritonavir-boosted nirmatrelvir.

We therefore explored whether there is a safety signal of drug-induced liver injury associated with ritonavir-boosted nirmatrelvir using data from the US Food and Drug Administration Adverse Event Reporting System for coronavirus disease 2019 (COVID-19) Emergency Use Authorization (EUA) products.[2] This reporting system updates weekly adverse event reports submitted to the US Food and Drug Administration for medications used under the EUA for severe acute respiratory syndrome coronavirus 2 infection. A total of 25,551 adverse event reports of ritonavir-boosted nirmatrelvir was submitted to the COVID-19 EUA Adverse Event Reporting System between January 1, 2022 and January 13, 2023. Among these adverse event reports, only 0.023% (6/25,551) of ritonavir-boosted nirmatrelvir users were documented to have drug-induced liver injury, which is much lower than that reported by Wong et al.[1] The median age of the 6 patients identified was 66.0 years (interquartile range, 46.5–68.8), and 4 cases involved female patients. All 6 cases with drug-induced liver injury relating to ritonavir-boosted nirmatrelvir were recorded to have serious outcomes, but none was documented to have died, which is in agreement with the observations of Wong et al.[1]

To assess quantitatively putative associations of ritonavir-boosted nirmatrelvir with drug-induced liver injury using these pharmacovigilance data, a case–noncase (disproportionality) analysis were performed through the Bayesian neural network method,[3] which was considered to be a significant pharmacovigilance signal if the lower limit of the 95% credible interval of the information component (IC_{025}), the most robust risk measure in disproportionality analyses,[4] was greater than 0. Based on the disproportionality analysis, no significant pharmacovigilance signal of drug-induced liver injury was observed for ritonavir-boosted nirmatrelvir (IC_{025} = −0.80) (Supplementary Figure 1) as compared with other drugs used under the EUA for COVID-19, suggesting a lack of any association of ritonavir-boosted nirmatrelvir with drug-induced liver injury. Sensitivity analyses by restricting the data to those reported by healthcare professionals only showed very similar results with an IC_{025} of −0.88 (Supplementary Figure 1), ensuring no potential associations between ritonavir-boosted nirmatrelvir and drug-induced liver injury existed.

To the best of our knowledge, this is the first disproportionality analysis of drug-induced liver injury with ritonavir-boosted nirmatrelvir using large-scale and timely pharmacovigilance data, showing consistent observations with those by Wong et al.[1] Together with a previous randomized control trial[5] and the retrospective cohort study by Wong et al,[1] our disproportionality analysis using real-world pharmacovigilance data strongly support the lack of a meaningful safety signal of drug-induced liver injury with ritonavir-boosted nirmatrelvir, recommending the use of ritonavir-boosted nirmatrelvir in clinical practice without fear of adverse events in terms of drug-induced liver injury.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at https://doi.org/10.1053/j.gastro.2023.02.008.

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References

1. Wong GL-H, et al. Gastroenterology 2023;164:151–153.
2. U.S. FDA. https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard.
3. Bate A, et al. Eur J Clin Pharmacol 1998;54:315–321.
4. Almenoff JS, et al. Clin Pharmacol Ther 2007;82:157–166.
5. Hammond J, et al. N Engl J Med 2022;386:1397–1408.

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Reply. We wish to thank Dr Li and Dr Yu for their interest in our report.[1] Dr Li and Dr Yu provided us with elegant and robust data from the coronavirus disease 2019 (COVID-19) emergency use authorization Adverse Event Reporting System and consolidated the real-world safety data of ritonavir-boosted nirmatrelvir.[2] This very first disproportionality analysis of drug-induced liver injury (DILI) with ritonavir-boosted nirmatrelvir using this large-scale and timely pharmacovigilance data verified the favorable liver safety profile and the very low risk of DILI with ritonavir-boosted nirmatrelvir as observed by us.[1] Notably, under-reporting of DILI, especially the very mild and asymptomatic cases, is possible in such a reporting system; this and our approaches are complementary to each other and more illustrative of the whole picture.

COVID-19 itself often leads to abnormal liver function tests (hepatocellular, cholestatic, or mixed), independent of antiviral therapies for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[3,4] Concomitant liver diseases, namely, chronic hepatitis B, usually do not increase the risk of COVID-19–related mortality unless patients have decompensated cirrhosis.[5] We would advise clinicians to watch out for hepatitis B reactivation during systemic steroid use in moderate to severe COVID-19.[6]

Dr Li and Dr Yu have remarkably contributed to the reassuring safety profile of this potent oral antiviral agent for SARS-CoV-2, which has proven to save lives and decrease hospitalizations.[7] Together with our recent report showing a very low incidence (≤1%) of viral rebound, which is not linked to higher mortality, after ritonavir-boosted nirmatrelvir,[8] we strongly recommend prescribing ritonavir-boosted nirmatrelvir to suitable patients with COVID-19 in the early phase of the infection.

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References

1. Wong GL-H, et al. Gastroenterology 2023;164:151–153.
2. Li G-F, Yu G. Gastroenterology 2023;165:305–306.
3. Wong GL-H, et al. Lancet Gastroenterol Hepatol 2020;5:776–787.
4. Bhat M. Gastroenterology 2022;163:335.
5. Yip TC-F, et al. Hepatology 2021;74:1750–1765.
6. Yip TC-F, et al. Hepatol Int 2022;16:257–268.
7. Yip TC-F, et al. Clin Infect Dis 2023;76:e26–e33.
8. Wong GL-H, et al. JAMA Netw Open 2022;5:e2245086.

*GL-H Wong and VW-K Hui contributed equally to this work.

Conflicts of interest
These authors disclose the following: Grace Lai-Hung Wong has served as an advisory committee member for Gilead Sciences and Janssen, and as a speaker for Abbott, Abbvie, Ascletis, Bristol-Myers Squibb, Echosens, Gilead Sciences, Janssen, and Roche. She has also received a research grant from Gilead Sciences. Terry Cheuk-Fung Yip has served as an advisory committee member and a speaker for Gilead Sciences. The remaining author discloses no conflicts.

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Correction

Zhang X, Soutto M, Chen Z, et al. Induction of Fibroblast Growth Factor Receptor 4 by *Helicobacter pylori* via Signal Transducer and Activator of Transcription 3 With a Feedforward Activation Loop Involving Steroid Receptor Coactivator Signaling in Gastric Cancer. Gastroenterology 2022;163:620–636.e9.

In the above article, "SRC" was incorrectly spelled out as "steroid receptor coactivator" in the article title, abstract, abbreviation list, and text. The correct definition is "SRC proto-oncogene non-receptor tyrosine kinase." The article has been corrected online.