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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Dear editor:

We read with interest a recent paper reported by Birabaharan M et al. [1]. The authors reported a male veteran reporting rebound symptoms who was found to be hypoxic with pulmonary emboli after Nirmatrelvir/Ritonavir treatment for COVID-19. Nirmatrelvir/Ritonavir, also called Paxlovid, is an oral antiviral drug that reduces the risk of hospitalization or death for mild-to-moderate COVID-19 patients who are at risk of progression to severe disease [2]. Based on their findings, they highlighted the need to evaluate known complications of SARS-CoV-2 including venous thromboembolism in patients reporting recurring symptoms.

We commend the authors for performing a case report of acute pulmonary emboli because it is a rare rebound phenomenon after Nirmatrelvir/Ritonavir treatment for COVID-19. However, we have several concerns. First, it is unclear the levels of D-dimer and chest CT angiography before the treatment of Nirmatrelvir/Ritonavir. On day 1 of symptoms, the patient developed a cough, on day 2 of symptoms the patient found to have tachycardia. These are the symptoms of pulmonary emboli, although his COVID-19 on nasal quantitative reverse transcriptase polymerase chain reaction (RT-PCR) was positive. Hence, it is unclear whether the pulmonary emboli occurred before or after the treatment of Nirmatrelvir/Ritonavir. Both COVID-19 infection and pulmonary emboli can present with dyspnoea, tachypnoea, hypoxaemia and an elevated D-dimer. Identifying pulmonary emboli in patients with COVID-19 is challenging. Some studies showed that COVID-19 infection results prothrombotic state that may increase the risk of venous thromboembolism [3]. In addition, it is unclear the result of nasal SARS-CoV-2 RT-PCR on day 3–7 of symptoms, although the pulmonary emboli occurred with rebound symptoms after Nm/R administration. Hence, acute pulmonary emboli in this patient may be a symptom caused by COVID-19 rebound not caused by Nirmatrelvir/Ritonavir treatment.

Second, this patient had previously received four doses of the Pfizer-BioNTech SARS-CoV-2 vaccine, with the last dose 54 days prior to presentation. Was the pulmonary embolism related to the COVID-19 vaccine? COVID-19 vaccine-induced pulmonary embolism is a rare complication. One study reported one patient occurred a submassive saddle pulmonary embolism two days after receiving the second dose of the Pfizer COVID-19 vaccine [4]. Another study presented a case of a young male patient who developed severe thrombocytopenia and pulmonary embolism 12 days after the first dose of the vaccine [5]. Although use of adenovirus vector vaccines has an increased risk for pulmonary emboli. Studies have demonstrated that there is no association between the mRNA COVID-19 vaccination and pulmonary embolism. Hence, pulmonary embolism related to the COVID-19 vaccine in this patient is less likely. However, further studies should to be done to identify the association between the pulmonary embolism and mRNA COVID-19 vaccine.

Thirdly, as the authors reported that the symptoms of pulmonary embolism occurred after the treatment of Nirmatrelvir/Ritonavir. Is it a possibility that pulmonary embolism is a rare adverse event of Nirmatrelvir/Ritonavir? Although, there is no study on the relationship of pulmonary embolism and Nirmatrelvir/Ritonavir. As a new drug for COVID-19 infection treatment, a comprehensive side effect profile of Nirmatrelvir/Ritonavir is yet to be appreciated. Consider that there is no evidence to suggest Nirmatrelvir/Ritonavir use is related to pulmonary embolism events, further study should to be done to identify the relationship of pulmonary embolism and Nirmatrelvir/Ritonavir.

One meta-analysis showed that there is no significant difference of rebound in Nirmatrelvir/Ritonavir group and control group [6]. The rebound phenomenon has reached the attention of major medical journals may be attributable to more people being treated with Nirmatrelvir/Ritonavir. In conclusion, we could not denote the pulmonary emboli as the rebound phenomenon for COVID-19 in this patient. However, we provide concern about the possibility of COVID-19 infection-induced pulmonary embolism.

Funding

This work was supported by Science and Technology Fund of Guizhou Health Commission (No.gzwjk2021-024), and the cultivate project 2021 for National Natural Science Foundation of China, Affiliated Hospital of Guizhou Medical University (No.gyfyysfc-2021-14).

CRediT authorship contribution statement

Qian Zheng: Writing – original draft, Funding acquisition. Pengfei Ma: Data curation. Zhanhui Feng: Writing – review & editing.

Declaration of Competing Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

[1] Birabaharan M, Martin TCS. Acute pulmonary emboli following rebound phenomenon after Nirmatrelvir/Ritonavir treatment for COVID-19. Am J Emerg Med. 2022. https://doi.org/10.1016/j.ajem.2022.08.012.
[2] Hammond J, Leister-Tobbe H, Gardner A, Almeu P, Bao W, Wisemanadle W, et al. Oral Nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. N Engl J Med. 2022; 386(15):1397–408. https://doi.org/10.1056/NEJMoa2118542.
[3] Greenan-Barrett J, Perera A. COVID-19 and pulmonary emboli: a case series and literature review. Clin Pract Cases Emerg Med. 2020;4(3):299–303. https://doi.org/10.5811/cpcem.2020.7.48174.

Qian Zheng and Pengfei Ma are the co-first authors.
[4] Borisoff BD, Bohn KD, Sager J, Gracious BL. Unprovoked submassive saddle pulmonary embolism in an adult male after Pfizer COVID-19 vaccination. Cureus. 2022;14(8):e27717. https://doi.org/10.7759/cureus.27717.

[5] Ihnatko M, Truchla I, Ihnatkova I, Prohaszka Z, Lazurova I. Case report: a case of COVID vaccine-induced thrombotic thrombocytopenia manifested as pulmonary embolism and hemorrhagia. A first reported case from Slovakia. Front Med (Lausanne). 2021;8:789972. https://doi.org/10.3389/fmed.2021.789972.

[6] Zheng Q, Ma P, Wang M, Cheng Y, Zhou M, Ye L, et al. Efficacy and safety of Paxlovid for COVID-19: a meta-analysis. J Infect. 2022. https://doi.org/10.1016/j.jinf.2022.09.027.

Qian Zheng
Department of Neurology, Affiliated Hospital of Guizhou Medical University, Guiyang, China

Pengfei Ma
Department of Neurology, Affiliated Hospital of Guizhou Medical University, Guiyang, China

Zhanhui Feng*
Department of Neurology, Affiliated Hospital of Guizhou Medical University, Guiyang, China
*Corresponding author.
E-mail address: h9450203@126.com

12 September 2022