
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.

CHEST

*Editor's Note: Authors are invited to respond to Correspondence that cites their previously published work. Those responses appear after the related letter. In cases where there is no response, the author of the original article declined to respond or did not reply to our invitation.*

# A Study Revealed That a High Percentage of Patients With Severe COVID-19 With Viral RNAaemia Had Significantly Worse Outcomes, and This Is the First Report About the Risk Factors of Viral RNAaemia in Patients With COVID-19

## We Are Not Sure!

Li et al[1] conclude that their study published in *CHEST* (April 2021) revealed that a high percentage of patients with severe COVID-19 complicated with viral RNAaemia had significantly worse outcomes. According to their knowledge, there are no reports about the risk factors of viral RNAaemia in patients with severe COVID-19.[1] In fact, in a recent study, blood samples were collected.[2] The molecular testing indicated increased viral loads.[2] This increased viral RNAaemia was strongly correlated with the level of disseminated intravascular coagulation (DIC) as well the D-dimer levels and thus correlated with severity level.[2] Clearly the study from Li et al[1] is not the first to show a relationship between RNAaemia and level of severity.[2] Regarding pathophysiology, whether the virus itself is responsible for this direct damage is unclear in the study by Dumache et al.[2] Increased levels of RNAaemia inducing increase in DIC and D-dimers could induce more damage to various organs.[2] In another recent study, detection of viral subgenomic RNA correlated poorly with shedding of infectious virus.[3] These RNAs are produced only in actively infected cells and are not packaged into virions.[3] Subgenomic RNAs were still detected when virus cultures turned negative.[3] This could indicate that active replication continues in severely ill COVID-19 after seroconversion.[3] Possibly, infectious virions are produced but are directly neutralized by antibodies.[3] Conversely, the half-life of viral subgenomic RNAs is unknown in COVID-19 and may still be detected once replication has stopped.[3] In other words, in their evaluation, the level of RNAaemia is not related to severity, because less than 5% of this RNAaemia is able to be infective.[3] A very important issue raised by a new study was that digital polymerase chain reaction (PCR) more sensitive than quantitative PCR for the detection of SARS-CoV-2 RNAaemia in the plasma of the patients.[4] Unfortunately, in the study of Li et al,[1] they did used quantitative PCR and not digital PCR.[1] In addition, prolonged shedding of SARS-CoV-2 furthermore occurs regardless of disease severity or development of virus-neutralizing antibodies.[5] RNA viruses are capable of long-term persistence, possibly through poorly understood RNA structure-mediated effects on innate and adaptive host immune responses.[5] The assumption that resolution of COVID-19 and the appearance of anti-SARS-CoV-2 IgG antibodies represents virus clearance and protection from reinfection, implicit, for example, in the susceptible-infected-recovered model used for epidemic prediction, should be rigorously reevaluated.[5]

*Patrick M. Honore, MD, PhD*
*Sebastien Redant, MD*
*Thierry Preseau, MD*
*Keitiane Kaefer, MD*
*Leonel Barreto Gutierrez, MD*
*Rachid Attou, MD*
*Andrea Gallerani, MD*
*David De Bels, MD*
*Brussels, Belgium*

**AFFILIATIONS:** From the ICU Department (P. M. Honore, S. Redant, K. Kaefer, L. Barreto Gutierrez, R. Attou, A. Gallerani, and D. De Bels) and the ED Department (T. Preseau), Centre Hospitalier Universitaire Brugmann, ULB University.

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**CORRESPONDENCE TO:** Patrick M Honore, MD, PhD; email: Patrick.Honore@CHU-Brugmann.be



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## Response

**To the Editor:**

In the battle against COVID-19, scientists all over the world are doing their best to fight. From January 24, 2020, when the SARS-CoV-2 cases were first reported,[1] to today (February 16, 2021), more than 100,000 related articles have been published. These scientific discoveries have enabled us to better understand our enemies.

In the research article published in *CHEST*,[2] we enrolled the first 192 patients with severe COVID-19 from the Lotus study (Lopinavir Trial for Suppression of SARS-Cov-2, Chinese Clinical Trial Register number, ChiCTR2000029308), which was conducted from January 18, 2020, through February 3, 2020. Longitudinal samples including plasma, oropharyngeal swabs, and anal swabs were collected, and viral RNA was detected with reverse transcription polymerase chain reaction (PCR). Risk factors of patients complicated with viral RNAaemia were analyzed, and its association with clinical prognosis was assessed. With the spread of the epidemic, new cases have emerged worldwide, and increased amounts of evidence suggested that viral RNAaemia was associated with worse outcomes of patients with COVID-19,[3] but the risk factors for RNAaemia are not clear.

Viral RNAaemia, which might result from live virus particles in the blood and debris of virus-infected cells, does not equal viremia. Although it has been proved that viral RNA of SARS-CoV-2 could be detected in the blood of patients with COVID-19, no success at isolating live virus particles has been reported. In vitro study showed that SARS-CoV-2 could infect capillary organoids and produce progeny virus,[4] but whether it was the case in vivo remained uncertain. Isolation of live virions from blood was influenced by a series of factors, such as the presence of neutralizing antibodies and viral load.[5] Furthermore, viral RNA, as a potent trigger of immune response, might also be involved in the pathogenesis of COVID-19. Therefore, no live virion successful isolation does not mean no harm.[3]

Future basic research work is needed to understand the causes of viral RNAaemia and its role in disease pathogenesis. We agree that droplet digital PCR has higher sensitivity than quantitative PCR, and it could detect samples with low levels of nucleic acids. However, it still could not distinguish viral RNAaemia from viremia.

*Hui Li, MD*
*Jiuyang Xu, MD*
*Bin Cao, MD*
*Beijing, China*

**AFFILIATIONS:** From the Department of Pulmonary and Critical Care Medicine (H. Li and B. Cao), Center of Respiratory Medicine, National Clinical Research Center for Respiratory Diseases, China-Japan Friendship Hospital; the Department of Respiratory Medicine (H. Li and B. Cao), Capital Medical University; the Institute of Respiratory Medicine (H. Li and B. Cao), Chinese Academy of Medical Science; the Tsinghua University School of Medicine (J. Xu); and the Tsinghua University–Peking University Joint Center for Life Sciences (B. Cao).

**CORRESPONDENCE TO:** Bin Cao, MD; email: caobin_ben@163.com



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## Chronologic Bias, Confounding by Indication, and COVID-19 Care

**To the Editor:**

The authors of "Use of Ivermectin Is Associated With Lower Mortality in Hospitalized Patients With Coronavirus Disease 2019"[1] in *CHEST* (January 2021)