Dear Editor,

The SARS-CoV-2 infection can lead to severe acute respiratory distress syndrome (ARDS) with prolonged mechanical ventilation (MV). Patients with coronavirus disease 2019 (COVID-19) associated ARDS usually met the diagnosis criteria for sepsis-associated immunosuppression as acquired infections, primarily bacterial and fungal co-infections [1], are frequently encountered. Such secondary infections are associated with late mortality. *Herpesviridae* reactivation is common in non-immunocompromised patients with prolonged MV and could be responsible for increased mortality and longer duration of MV in ICU [2, 3]. Although the diagnosis of *Herpesviridae* pulmonary infection is challenging and not consensual in critically ill patients, therapeutic strategies are available to reduce morbidity and mortality [4]. As viral co-infections in these patients remain poorly investigated, we aimed to describe *Herpesviridae* pulmonary reactivations in patients with COVID-19 ARDS.

**Methods**

We reviewed all virology results for patients admitted to Rennes University Hospital (Rennes, France) for COVID-19 ARDS between March 3, 2020, and April 15, 2020. SARS-CoV-2 infection was confirmed by polymerase chain reaction (PCR). Patients mechanically ventilated longer than 7 days and who had negative PCR for herpes simplex virus (HSV) and cytomegalovirus (CMV) were included in the analysis. Herpes simplex virus and cytomegalovirus replication were measured by quantitative real-time PCR on tracheal aspirates twice a week for each patient. *Herpesviridae* reactivation was defined as two consecutive positive HSV or CMV PCR on tracheal aspirates. The Mann-Whitney rank sum test was used to compare non-parametric continuous variables, and qualitative data were compared using Fisher’s exact test. Statistical significance was defined as *P* < .05. PRISM version 8 (GraphPad Software, San Diego, CA, USA) was used to perform statistical analyses.

**Results**

A total of 38 patients were included. Table 1 shows the demographic, clinical, and biological characteristics of the included patients. The mean age was 59 years (interquartile range (IQR), 54–71), and 27 (71%) were male. Of these 38 patients, 18 (47%) presented at least one viral pulmonary reactivation. Nine patients had HSV reactivation alone, 2 presented CMV reactivation alone, and 7 had co-reactivation. Herpesviridae infection was diagnosed at a median of 9 days (IQR, 5–14). The median number of positive samples was 3 (IQR, 2–5).

Patients with *Herpesviridae* reactivation had significantly longer duration of MV compared with patients without *Herpesviridae* reactivation. Table 2 shows outcomes of patients according to *Herpesviridae* reactivation status.

**Discussion**

Our findings suggest that *Herpesviridae* reactivations are frequent in patients with COVID-19 ARDS, with higher rates than those described in previous studies performed in critically ill patients [2, 3]. This result was expected since severe forms of COVID-19 ARDS are associated...
Table 1 ARDS COVID patient’s characteristics at ICU admission

| Demographic characteristics | All patients (n = 38) | No Herpesviridae reactivation (n = 20) | Herpesviridae reactivation (n = 18) | P value |
|-----------------------------|-----------------------|----------------------------------------|-----------------------------------|---------|
| Age, years                  | 59 (54–71)            | 64 (55–72)                             | 0.07                              |         |
| Sex                         |                       |                                        |                                   |         |
| Men                         | 27 (71)               | 12 (67)                                | > 0.99                            |         |
| Women                       | 11 (29)               | 6 (33)                                 |                                   |         |
| BMI                         | 24 (24–31)            | 26.9 (24–29)                           | 0.78                              |         |
| Current smoking             | 2 (5)                 | 1 (5)                                  | 0.94                              |         |
| Coexisting conditions       |                       |                                        |                                   |         |
| Any                         | 19 (50)               | 9 (50)                                 | > 0.99                            |         |
| Diabetes                    | 15 (40.5)             | 8 (44)                                 | 0.55                              |         |
| Cancer                      | 3 (8)                 | 1 (5)                                  | > 0.99                            |         |
| Clinical and biological baseline characteristics | | | | |
| White blood cell count (10^9/L) | 10.1 (3.4–13)         | 11.2 (7.3–13.2)                        | 0.07                              |         |
| Lymphocyte count (10^9/L)   | 0.74 (0.59–1.04)      | 0.83 (0.7–1.23)                        | 0.29                              |         |
| Ratio of PaO₂ to FiO₂       | 106 (95–170)          | 116 (90–147)                           | 0.15                              |         |
| SAPS II score on day 1     | 42 (31–58)            | 42 (33–55)                             | 0.65                              |         |
| SOFA score on day 1        | 3 (2–7)               | 3 (2–7)                                | 0.81                              |         |

Data are presented as median (IQR: interquartiles), n (%). P values comparing the Herpesviridae reactivation and no Herpesviridae reactivation groups are tested by the Mann-Whitney (continuous variables) or Fisher’s exact test (categorical variables).

Abbreviations: BMI body mass index, ICU intensive care unit, PaO₂ arterial oxygen tension, FiO₂ fraction of inspired oxygen, SAPS II Simplified Acute Physiology Score, SOFA Sequential Organ Failure Assessment.

Table 2 Treatments and clinical course of COVID-19 patients according to Herpesviridae status

| Treatments and clinical course | All patients (n = 38) | No Herpesviridae reactivation (n = 20) | Herpesviridae reactivation (n = 18) | P value |
|-------------------------------|-----------------------|----------------------------------------|-----------------------------------|---------|
| Antibiotics                   | 38 (100)              | 18 (100)                               | 0.99                              |         |
| Antiviral                     | 32 (84)               | 16 (89)                                | 0.66                              |         |
| Steroids                      | 12 (32)               | 8 (44)                                 | 0.16                              |         |
| ECMO                          | 3 (8)                 | 2 (11)                                 | 0.49                              |         |
| Duration of NMB infusion      | 6 (3–11)              | 6 (3–11)                               | 0.73                              |         |
| Renal replacement therapy     | 9 (24)                | 4 (22)                                 | 0.99                              |         |
| Prone positioning ventilation | 21 (55)               | 11 (52)                                | 0.24                              |         |
| Duration of mechanical ventilation | 18 (13–25)           | 23 (18–39)                             | 0.0001                            |         |
| Ventilator-free days at day 28 | 8 (0–15)              | 2 (0–3)                                | 0.0008                            |         |
| Ratio of PaO₂ to FiO₂ on day 7 | 193 (135–248)         | 178 (135–195)                          | 0.04                              |         |
| Ratio of PaO₂ to FiO₂ on day 14 | 216 (174–308)         | 186 (114–233)                          | 0.01                              |         |
| SOFA score on day 7           | 7 (5–11)              | 10 (6–11)                              | 0.19                              |         |
| SOFA score on day 14          | 7 (2–10)              | 7 (2–10)                               | 0.39                              |         |
| Bacterial VAP                 | 9 (24)                | 6 (33)                                 | 0.18                              |         |
| ICU length of stay            | 23 (16–34)            | 29 (24–47)                             | 0.0001                            |         |
| Death in ICU                  | 4 (10.5)              | 2 (11)                                 | 0.99                              |         |

Data are presented as median (IQR: interquartiles), n (%). P values comparing the Herpesviridae reactivation and no Herpesviridae reactivation groups are tested by the Mann-Whitney (continuous variables) or Fisher’s exact test (categorical variables).

Abbreviations: ECMO extracorporeal membrane oxygenation, NMB neuromuscular blockade, PaO₂ arterial oxygen tension, FiO₂ fraction of inspired oxygen, SOFA Sequential Organ Failure Assessment, VAP ventilator-associated pneumonia, ICU intensive care unit.
with biological and clinical markers of acquired immunosuppression such as lymphopenia [1]. This state of immunodeficiency probably plays a role in the occurrence of viral reactivations.

Among the most frequent risk factors for CMV and HSV reactivation in the ICU patients, sepsis and prolonged MV have been described in several studies [5, 6]. COVID-19 patients develop typical clinical and biological manifestations of septic shock [1]. There is no clear evidence that Herpesviridae reactivations induce difficulties to wean patients from MV nor increase the length of stay in COVID-19 patients, and our sample size did not allow us to perform a multivariate analysis. Larger studies are needed to explore such association. However, previous observational studies [5, 6] showed that Herpesviridae detection in the lower respiratory tract is associated with poorer outcomes.

Finally, our results suggest that SARS-CoV-2 infection could be a risk factor for Herpesviridae reactivation. Rapid identification of these co-infections seems warranted as it may impact the prognosis of infected patients. However, the direct consequences and the usefulness of antiviral treatments for these Herpesviridae infections remain factors that deserve to be investigated.

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Authors’ contributions
PLB, KP, PS, JMT, and FR took care of the patients, performed the literature review, and wrote the first draft of the article. CP performed the diagnostic tests and raised the critical comments on the article. The authors read and approved the final manuscript.

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Availability of data and materials
The datasets from this study are available from the corresponding author on request.

Ethics approval and consent to participate
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Consent for publication
Not applicable

Competing interests
The authors report no conflict of interest related to this work.

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