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.

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Letter to the Editor

Herpesviridae systemic reactivation in patients with COVID-19-associated ARDS

Sir,

The clinical spectrum of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection can lead to acute respiratory distress syndrome (ARDS), associated with immune dysfunction and prolonged duration of mechanical ventilation (MV) [1], both of which are responsible for the acquisition of secondary infection [2]. Along these lines, ARDS and prolonged MV are recognized risk factors for *Herpesviridae* systemic reactivation (HSR), which may affect the outcome of critically ill patients [3,4]. However, the burden of these infectious events in patients with severe coronavirus disease 2019 (COVID-19) remains poorly explored. As such, we investigated the clinical features of HSR in patients with COVID-19-associated ARDS.

All consecutive ARDS patients with COVID-10 confirmed by polymerase chain reaction (PCR) admitted to the medical intensive care unit (ICU) of Rennes University Hospital between 12th March 2020 and 16th April 2021 were reviewed. Patients monitored at least weekly for herpes simplex virus (HSV) and cytomegalovirus (CMV) systemic replication by quantitative real-time polymerase chain reaction (RT-PCR) were analysed retrospectively.

HSR was considered when viral DNA was detected by PCR (lower limits of detection were 119 IU/mL for CMV with Altona RealStar CMV assay and 165 copies/mL for HSV-1 with Altona RealStar HSV assay). Respiratory samples for bacterial, fungal and viral (CMV, HSV and SARS-CoV-2 RT-PCR) examinations were collected at least weekly. Ventilator-associated pneumonia (VAP) was defined in accordance with international guidelines [5].

Mann–Whitney U-test was used to compare quantitative data, and Chi-squared test or Fisher's exact test, as appropriate, was used to compare qualitative data. All statistical analyses were two-sided, and $P<0.05$ was considered to indicate statistical significance. Analyses were performed using R Version 4.0.4. The institutional ethical review board approved the study (N 20-56).

One hundred and twenty-two patients with COVID-19-associated ARDS were included in this study. Demographic and clinical features are listed in Table I. The majority of patients were male, and the median age was 66 years. HSR was observed in 33 patients (27%), 27 patients experienced HSV viraemia (21.9%), 13 patients experienced CMV viraemia (10.7%), and seven patients had co-reactivation. Viraemia occurred at a median of 12 days following ICU admission (interquartile range 9–22). As shown in Table I, among patients experiencing HSR, a high proportion also presented *Herpesviridae* respiratory reactivation, while such viral respiratory reactivation was observed less often in patients without HSR (87.9% vs 23.6%; $P<0.001$) (Table I). Patients with HSR were lymphopenic and had positive respiratory RT-PCRs for SARS-CoV-2 for longer durations. As shown in Table I, when analysing clinical courses, patients with HSR had a prolonged duration of MV and longer ICU stay. Finally, higher rates of VAP were observed among these patients.

In this single-centre study, 27% of patients admitted to the ICU for COVID-19-associated ARDS developed HSR. This viral reactivation appeared to be associated with prolonged duration of MV and longer ICU stay, which is consistent with previous studies [3,4]. We previously showed that respiratory CMV and HSV reactivations are often observed in critically ill COVID-19 patients [6]. Moreover, patients with sepsis, even immunocompetent patients, are recognized as being at risk for viral reactivation [7] that may be promoted by sepsis-induced immunosuppression [8]. Although associated with immune defects (i.e. prolonged lymphopenia and positive respiratory SARS-CoV-2 RT-PCR), there is no clear evidence that viral reactivation has a direct impact on patient outcomes in the ICU. Viral reactivation could also be considered as a marker for disease severity [7]. Furthermore, the pathophysiology of systemic reactivation is debated. The lungs are known to be a major site of *Herpesviridae* latency. As a high proportion of patients developing systemic reactivation also experienced previous (or concomitant) respiratory reactivation in this study, it can be hypothesized that respiratory reactivation is the first step before systemic dissemination, which may be favoured by immunosuppressive mechanisms in patients with sustained SARS-CoV-2 infection.

Finally, these results suggest that HSR is common in patients with ARDS-associated COVID-19 and may influence the clinical course of these critical patients. Direct clinical consequences of systemic *Herpesviridae* reactivation and treatment of such infections remain to be investigated.

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Table I
Characteristics of patients with severe coronavirus disease 2019 according to systemic *Herpesviridae* reactivation

	All patients N=122	No viral reactivation N=89	Viral reactivation N=33	*P*-value
Demographic characteristics				
Age (years)	66 (57–73)	64 (55–72)	71 (61–73)	0.044
Male sex	83 (68)	56 (62.9)	27 (81.8)	0.08
Co-existing conditions				
Obesity	48 (39.3)	44 (49.4)	4 (12.1)	<0.001
Hypertension	61 (50)	39 (44.8)	22 (66.7)	0.042
Diabetes	28 (22.9)	17 (19.1)	11 (33.3)	0.16
Previous immunosuppression	27 (22.1)	20 (22.5)	7 (21.2)	>0.99
Clinical and biological baseline features				
Lymphocyte count (10^9/L)	0.53 (0.39–0.83)	0.55 (0.39–0.79)	0.56 (0.38–0.81)	0.9
CRP (mg/L)	120 (78–167)	116 (76–166)	150 (90–258)	0.2
Ratio of PaO_2 to FiO_2 (mmHg)	102 (84–137)	106 (83–139)	100 (86–134)	0.71
SAPS II on day 1	32 (24–41)	32 (23–40)	33 (27–41)	0.36
SOFA score on day 1	4 (3–7)	4 (3–7)	5 (3–7)	0.92
Clinical courses and ICU management				
Corticosteroid use	114 (93.4)	85 (95.5)	29 (87.9)	0.27
ECMO	7 (5.7)	3 (3.4)	4 (12.1)	0.16
Duration of lymphopenia (days)	8 (5–13)	7 (4–10)	14 (9–23)	0.001
Duration of positive respiratory SARS-CoV-2 RT-PCR (days)	19 (13–27)	16 (11–24)	24 (18–31)	0.013
Ventilated patients with positive respiratory SARS-CoV-2 PCR				
Day 5 (120 patients tested)	99 (81.1)	66/87 (75.7)	33/33 (100)	<0.001
Day 10 (84 patients tested)	65 (77.4)	35/53 (66)	30/32 (93.7)	0.003
Day 15 (58 patients tested)	44 (76)	22/34 (64.7)	22/24 (91.7)	0.02
Day 20 (45 patients tested)	31 (68.9)	15/25 (60)	16/20 (80)	0.2
VAP	26 (21.3)	14 (15.7)	12 (36.4)	0.03
Herpesviridae respiratory reactivation	50 (41)	21 (23.6)	29 (87.9)	<0.001
Duration of mechanical ventilation (days)	13 (8–23)	12 (7–20)	18 (11–31)	0.018
Length of ICU stay (days)	16 (10–28)	13 (10–24)	23 (15–33)	0.005
Day 28 mortality	9 (7.4)	8 (9)	1 (3)	0.44

CRP, C-reactive protein; PaO_2, arterial oxygen tension; FiO_2, fraction of inspired oxygen; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; PCR, polymerase chain reaction; VAP, ventilator-associated pneumonia.
Obesity was defined as body mass index >30 kg/m^2; lymphopenia was defined as lymphocyte count <1.10^9/L; and previous immunosuppression was defined as immunosuppressive treatments including corticosteroids >0.5 mg/kg/day prednisone-equivalent within 30 days prior to inclusion, severe neutropenia <0.5 G/L of neutrophils, human immunodeficiency virus seropositivity, or bone marrow or solid organ transplantation.
Data are presented as median (interquartile range) and *N* (%). *P*-values comparing patients were tested using Mann–Whitney *U*-test (continuous variables), and Chi-squared or Fisher's exact tests (categorical variables).

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Conflict of interest statement
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Ethical approval
The institutional ethical review board approved the study (N 20-56).

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

Author contributions
FR, CL, AM, AG and JMT took care of the patients, performed the literature review and wrote the first draft of the article. CP and VT performed diagnostic tests and raised critical comments on the article.

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