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Cytomegalovirus blood reactivation in COVID-19 critically ill patients: risk factors and impact on mortality

Ilenia Gatto¹, Emanuela Biagioni¹, Irene Coloretti¹, Carlotta Farinelli¹, Camilla Avoni¹, Valeria Caciagli¹, Stefano Busani¹, Mario Sarti⁵, Monica Pecorari⁵, William Gennari⁶, Giovanni Guaraldi², Erica Franceschini², Marianna Meschiari², Cristina Mussini², Roberto Tonelli³, Enrico Clini³, Andrea Cossarizza⁴ and Massimo Girardis^{1,7*}  on behalf of the Modena COVID-19 Working Group

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Abstract

Purpose: Cytomegalovirus (CMV) reactivation in immunocompetent critically ill patients is common and relates to a worsening outcome. In this large observational study, we evaluated the incidence and the risk factors associated with CMV reactivation and its effects on mortality in a large cohort of patients affected by coronavirus disease 2019 (COVID-19) admitted to the intensive care unit (ICU).

Methods: Consecutive patients with confirmed SARS-CoV-2 infection and acute respiratory distress syndrome admitted to three ICUs from February 2020 to July 2021 were included. The patients were screened at ICU admission and once or twice per week for quantitative CMV-DNAemia in the blood. The risk factors associated with CMV blood reactivation and its association with mortality were estimated by adjusted Cox proportional hazards regression models.

Results: CMV blood reactivation was observed in 88 patients (20.4%) of the 431 patients studied. Simplified Acute Physiology Score (SAPS) II score (HR 1031, 95% CI 1010–1053, $p=0.006$), platelet count (HR 0.0996, 95% CI 0.993–0.999, $p=0.004$), invasive mechanical ventilation (HR 2611, 95% CI 1223–5571, $p=0.013$) and secondary bacterial infection (HR 5041; 95% CI 2852–8911, $p<0.0001$) during ICU stay were related to CMV reactivation. Hospital mortality was higher in patients with (67.0%) than in patients without (24.5%) CMV reactivation but the adjusted analysis did not confirm this association (HR 1141, 95% CI 0.757–1721, $p=0.528$).

Conclusion: The severity of illness and the occurrence of secondary bacterial infections were associated with an increased risk of CMV blood reactivation, which, however, does not seem to influence the outcome of COVID-19 ICU patients independently.

Keywords: COVID-19, Cytomegalovirus reactivation, Mechanical ventilation, Sepsis

*Correspondence: girardis.massimo@unimo.it

⁷ Intensive Care Department, University Hospital of Modena, L.go del Pozzo 71, 41125 Modena, Italy

Full author information is available at the end of the article

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Introduction

In critically ill patients, the reactivation of Cytomegalovirus (CMV) and other Herpesviridae has been reported with a rate ranging between 20 and 70%, and it is associated with increased risk of secondary infections and mortality [1–4]. Although the risk factors remain to be defined, profound dysfunction of the immune response

is the key mechanism leading to viral reactivation in previous immunocompetent patients with critical illness [5]. In this context, the immunosuppression induced by SARS-CoV-2 direct pathogenic effects, the unregulated host response and the use of drugs to modulate such response (e.g., steroids and immunomodulators) make critically ill patients affected by coronavirus disease 2019 (COVID-19) at high risk for viral reactivation [6–9]. A recent large observational study indicated that the Herpes simplex 1 virus reactivated in around a quarter of COVID-19 patients requiring mechanical ventilation and impacted secondary infections and mortality [10]. Unfortunately, in this population, very little data are available on CMV reactivation which is one of the most pathogenic viruses and seems to be closely related to worse outcomes in other intensive care unit (ICU) populations [11, 12]. As from animal model and in vivo studies, CMV reactivation may have significant clinical effects by direct organ damage, down-regulation of the immune response and boosting a hyper-inflammatory response that may further aggravate the ongoing inflammatory processes in sepsis, in acute respiratory distress syndrome and, perhaps, in COVID-19 disease [13–17]. However, the lack of survival benefits from prophylactic or pre-emptive anti-CMV strategies generated extensive discussion on the role of CMV reactivation that is often considered only a marker of clinical complexity not requiring specific treatment in immunocompetent critically ill patients [18–20].

This large observational study aimed to evaluate the incidence and the risk factors associated with CMV reactivation and its effects on mortality risk in a large cohort of COVID-19 patients admitted to ICU for severe respiratory failure.

Methods

In this observational study using prospectively collected data, we included all the patients admitted to the three COVID-19 ICUs of the University Hospital of Modena with laboratory-confirmed SARS-CoV-2 infection and moderate to severe acute distress respiratory syndrome (ARDS) from February 22nd, 2020, to July 21st 2021 [21]. Patients with age < 18 years, ICU length of stay (LOS) < 24 h, limitation of care or do not resuscitate order were excluded from the study. The Institutional Ethics Committee of Area Vasta Emilia Nord (EC AVEN) approved the study (approval number 396/2020/OSS/AOUMO—CoV-2 MO-Study). Due to the observational nature, written informed consent was not required.

Treatment protocol

All the patients received standard ICU and supportive care as recommended by the World Health Organization (WHO) guidelines [22] and specific therapies according

Take-home message

In critically ill patients affected by coronavirus disease 2019 (COVID-19), the Cytomegalovirus (CMV) blood reactivation is frequent, and its risk depends on the severity of illness and the development of secondary bacterial infections. CMV reactivation is associated with prolonged hospital stay and higher mortality, but its role in worsening patient outcomes and the appropriate strategy for its management remain to be clarified

to national [23] and local protocol for COVID-19 treatment, including dexamethasone, low-molecular weight heparin for prophylaxis of deep vein thrombosis according to individual bodyweight and renal function. In addition, the local protocol allowed the use of steroids (methylprednisolone 2 mg/kg/day) to prevent the onset of pulmonary fibrosis in patients who maintained a PaO₂/FiO₂ ratio < 150 mmHg for at least 7 days of mechanical ventilation [24]. Since March 2020, the local management protocol has included Tocilizumab (TOCI) option in patients with moderate or severe ARDS and the need for mechanical ventilation (non-invasive or invasive). From the end of March 2020, all patients who received TOCI or a high dose of steroids received standard prophylaxis with Acyclovir. The standard supportive management in ICU did not significantly change during the study period.

Data collection

Patients' demographics, Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score II (SAPS II) and standard laboratory including coagulation and inflammatory variables were collected at ICU admission. In addition, the need for invasive mechanical ventilation, therapy with steroids, tocilizumab (also before ICU admission) and ganciclovir, the CMV blood reactivation and the occurrence of new bacterial infections were collected during ICU stay.

As for the ICU protocol, patients were screened at ICU admission and twice (in invasive mechanically ventilated patients) or once per week for bacterial colonization in the rectum, respiratory (if tracheal intubation) and urinary tract, respiratory (if tracheal intubation) and serum Galactomannan, serum Beta-d-glucan and quantitative CMV-DNAemia in the blood (see protocol in the supplementary material). The CMV reactivation was set for a DNAemia > 62 UI/ml in the whole blood, the detection threshold of the method used (Abbott, Real-Time CMV). In patients with CMV blood reactivation, in case of suspected CMV-related pneumonia, ganciclovir was initiated after detection of CMV-DNA in the broncho-alveolar lavage. The clinical suspicion of CMV pneumonia was based on the following elements: new worsening of pulmonary gas exchange, modification of

chest X-ray or computed tomography compatible with new interstitial pneumonia, CMV blood reactivation and no other causes of pneumonia/worsening of pulmonary gas exchange. Ganciclovir dosage was set based on renal function and continued for at least 10 days. Secondary infections were defined according to international guidelines [25, 26] and divided into hospital-acquired pneumonia (HAP), including also ventilator-associated pneumonia and bloodstream infection (BSI). Probable invasive pulmonary Aspergillosis was defined according to definitions from the recent consensus document [27]. According to the WHO International Standard for Human CMV, all microbiological samples were analyzed in the local Microbiology and Virology laboratory [28].

Data analysis

The risk factors associated with CMV blood reactivation within 60 days after ICU admission were estimated by Cox proportional hazards regression model adjusted for covariates with p value < 0.1 at unadjusted analysis. Similarly, we used a Cox proportional hazards regression model including variables with p value < 0.1 at unadjusted analysis to evaluate the independent association of CMV blood reactivation with mortality censored at day 60. An additional sensitivity analysis with the same procedure described above was performed only in the population with CMV-related pneumonia treated with ganciclovir to evaluate the independent association of CMV pneumonia with mortality censored at day 60. To further evaluate the association of CMV blood reactivation with mortality censored at day 60, we performed a secondary analysis by matching patients with and without CMV blood reactivation (1:1) using a propensity score estimated by multivariable logistic-regression model that included as covariates the risk factors for developing CMV reactivation; the nearest-neighbor method was applied to propensity-score matching analysis.

Non-parametric and χ^2 tests were used as appropriate for the comparisons of demographic and baseline values, outcomes in patients with and without CMV blood reactivation, and survivors and no-survivors. All results were expressed as median (range) for continuous variables and as frequency (percentage) for categorical variables. All tests were two-tailed with a p value < 0.05 considered significant. SPSS version 22.0 package (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis.

Results

In the study period, 493 patients were admitted to the three ICUs, and 431 patients met the study's inclusion criteria. Blood CMV reactivation was observed in 88 patients (20.4%) with a median onset of 17 days (IQR

5–26) after ICU admission. Interestingly, blood CMV reactivation was observed upon ICU admission in 19 out of 88 patients (21.6%). Thirty patients out of 88 (34.1%) received ganciclovir because of clinical signs of CMV-related pneumonia, and CMV-DNA detected in the broncho-alveolar lavage.

Patients with CMV reactivation showed older age ($p < 0.001$), higher SAPS II scores ($p < 0.001$), lower platelet count ($p < 0.001$) and higher procalcitonin ($p = 0.019$) than patients without CMV reactivation at ICU admission (Table 1). A larger proportion of patients with CMV reactivation received steroids (i.e., dexamethasone, methylprednisolone or both) ($p = 0.005$), required invasive mechanical ventilation ($p < 0.001$), and developed secondary bacterial infections and probable invasive pulmonary Aspergillosis during ICU stay (Table 1). The hospital mortality was larger ($p < 0.001$) in patients with CMV reactivation than without reactivation. Among patients with CMV reactivation, patients with CMV-related pneumonia and treated with ganciclovir showed higher ($p = 0.063$) mortality (24/30; 80%) than patients without signs of CMV-related clinical pneumonia (35/58; 30%) (Table 2).

Adjusted analysis by Cox regression model showed that factors related to risk of CMV reactivation within 60 days after ICU admission were SAPS II and platelet count at ICU admission and need of invasive mechanical ventilation and occurrence of secondary bacterial during ICU stay (Fig. 1). Interestingly, CMV reactivation during ICU stay occurred later (median 9, IQR 1–15 days) than the occurrence of bacterial infection in 43 patients (64.1%), at the same time (± 48 h) in 7 patients (10.4%) and earlier (median 11, IQR 9–15 days) in 17 patients (25.4%) (Fig. 1S1).

Unadjusted analysis indicated that CMV reactivation, together with many other variables, was related to an increased mortality risk at day 60. However, the adjusted analysis did not confirm the relationship between CMV reactivation and mortality at day 60 (Table 3). Similarly, the sensitivity analysis performed in patients only in patients with CMV-related pneumonia and treated with ganciclovir did not show any independent relationship between CMV pneumonia and mortality at day 60 (HR 1248; 95% CI 0.732–2129; $p = 0.415$). The secondary analysis on the 168 patients with and without CMV reactivation matched (1:1) for the individual propensity to develop CMV blood reactivation also indicated no association between CMV blood reactivation and mortality at day 60 (HR 1105; CI 0.738–1640; $p = 0.638$) (Table 1 and 2 S1). The fifty (56.8%) patients with CMV blood maximal viral load > 500 IU showed similar characteristics, treatments

Table 1 Demographics, severity scores and laboratory results at ICU admission in all the patients and in patients with or without cytomegalovirus (CMV) blood reactivation

	All patients (n = 431)	No CMV reactivation (n = 343)	CMV reactivation (n = 88)	p value
Age (years; median, IQR)	65 (56–72)	63 (54–72)	69 (64–75)	<0.001
Sex, male (n, %)	323 (74.9)	248 (72.3)	75 (85.2)	0.013
Hypertension (n, %)	222 (51.7)	174 (50.9)	48 (55.7)	0.408
Diabetes (n, %)	96 (22.4)	71 (20.8)	25 (28.4)	0.128
Immunosuppression ^a (n, %)	68 (15.9)	47 (13.7)	21 (23.9)	0.021
BMI (kg/m ² ; median, IQR)	29 (26–33)	29 (26–33)	29 (26–33)	0.738
SAPSII (median, IQR)	35 (30–40)	34 (28–39)	37 (34–44)	<0.001
D-dimer (ng/ml; median, IQR)	1470 (820–2840)	1400 (820–2660)	1805 (855–4760)	0.166
LDH (U/L; median, IQR)	808 (632–1086)	786 (633–1081)	874 (623–1148)	0.260
Lymphocyte count (10 ⁹ /L; median, IQR)	0.65 (0.46–0.91)	0.66 (0.47–0.90)	0.61 (0.41–0.96)	0.307
Platelet count (10 ⁹ /L; median, IQR)	219 (169–286)	227 (182–291)	186 (140–247)	<0.001
C-reactive protein (mg/dl; median, IQR)	7.2 (2.1–17.6)	7.5 (2.6–17.5)	6.2 (1.2–18.4)	0.408
Procalcitonin (ng/ml; median, IQR)	0.20 (0.10–0.60)	0.2 (0.1–0.5)	0.3 (0.11–1.15)	0.019
PaO ₂ /FiO ₂ (mmHg; median, IQR)	104 (83–138)	104 (84–140)	106 (83–135)	0.870

BMI body mass index; SOFA simplified organ failure assessment; SAPSII Simplified Acute Physiology Score II; LDH lactate dehydrogenase

^a Including active hematological malignancies, neoplastic diseases, AIDS, transplants

Table 2 Treatments provided and infections during ICU stay, intensive care and hospital mortality in all the patients and in patients with or without cytomegalovirus blood reactivation

	All patients (n = 431)	No CMV reactivation (n = 343)	CMV reactivation (n = 88)	p value
Invasive mechanical ventilation (n, %)	276 (64)	197 (57.4)	79 (89.8)	<0.001
Steroids (n, %)	393 (91.4)	306 (89.5)	87 (98.9)	0.005
Tocilizumab (n, %)	356 (82.6)	283 (82.5)	73 (83)	0.921
Acyclovir prophylaxis (n, %)	318 (73.8)	246 (71.7)	72 (81.8)	0.055
Ganciclovir treatment (n, %)	30 (6.9)		30 (34.1)	<0.001
Onset Time of CMV reactivation (days; median, IQR)	17 (5–26)		17 (5–26)	
New bacterial infections (n, %)	157 (37.3)	90 (26.9)	67 (77)	<0.001
HAP (n, %)	133 (32.7)	75 (23.4)	58 (67.4)	<0.001
HAP Bacterial species (n, %)	119 (89.5)	64 (89.3)	55 (94.8)	0.344
<i>S. aureus</i>	38 (28.6)	24 (32)	14 (24.1)	
<i>Pseudomonas aeruginosa</i>	34 (25.6)	16 (21.3)	18 (31)	
<i>Klebsiella spp</i>	24 (18)	14 (18.7)	10 (17.2)	
<i>Other enterobacterales</i>	15 (11.3)	6 (8)	9 (15.5)	
<i>Other</i>	8 (6)	4 (5.3)	4 (6.9)	
<i>Not identified</i>	14 (10.5)	11 (14.7)	3 (5.2)	
Multidrug resistant ^a	56 (47.1)	29 (45.3)	27 (49.1)	0.681
BSI (n, %)	65 (16)	32 (10)	33 (38.4)	<0.001
Onset time of new bacterial infection (days; median, IQR)	8 (3–14)	5 (1–9)	12 (6–17)	<0.001
Probable Invasive Pulmonary Aspergillosis (n, %)	74 (17.1)	45 (13.1)	29 (33)	<0.001
ICU LOS (days; median, IQR)	7 (4–16)	6 (3–11)	31 (12–49)	<0.001
Hospital LOS (days; median, IQR)	23 (15–37)	21 (13–31)	40 (25–57)	<0.001
ICU Mortality (n, %)	111 (25.8)	65 (19)	46 (52.3)	<0.001
Hospital mortality (n, %)	143 (33.2)	84 (24.5)	59 (67)	<0.001

CMV cytomegalovirus; HAP hospital-acquired pneumonia; BSI bloodstream infection; ICU intensive care unit; LOS length of stay; Other enterobacterales: *E. coli*, *Serratia M*, *Proteus M*

^a Multidrug resistant according to Magiorakos AP et al. Clin Microbiol Infect. 2012 Mar;18(3):268–81

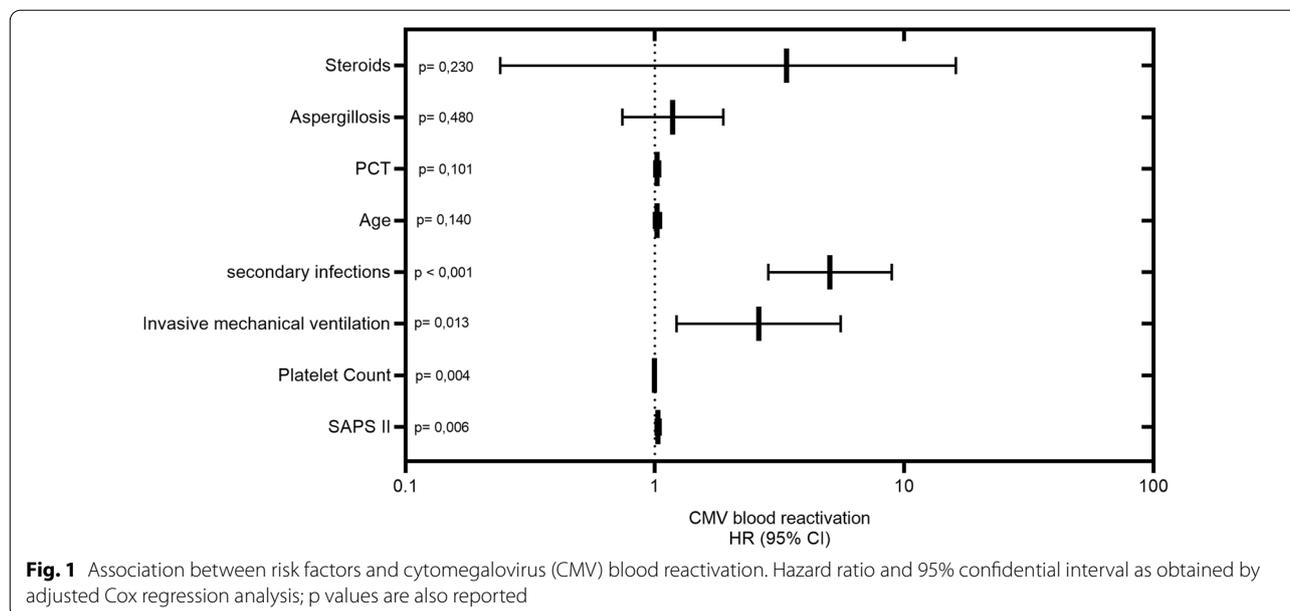


Table 3 Unadjusted and adjusted analysis for mortality censored at day 60

	Survived (n = 288)	Not survived (n = 143)	Unadjusted HR (95% CI) p value	Adjusted HR (95% CI) p value
Age (years; median, IQR)	63 (53–71)	69 (62–75)	1.043 (1.025–1.061); $p < 0.001$	1.01 (0.989–1.031); $p = 0.359$
SAPSII (median, IQR)	33 (28–38)	37 (34–44)	1.042 (1.029–1.055); $p < 0.001$	1.022 (1.004–1.041); $p = 0.017$
LDH (U/L; median, IQR)	773 (620–1050)	909 (671–1245)	1.001 (1–1.001); $p < 0.001$	1 (1–1.001); $p = 0.212$
platelet count ($10^9/L$; median, IQR)	233 (188–297)	188 (139–248)	0.994 (0.992–0.996); $p < 0.001$	0.996 (0.994–0.998); $p = 0.001$
PaO ₂ /FiO ₂ (mmHg; median, IQR)	109 (86–143)	99 (81–129)	0.994 (0.990–0.999); $p = 0.01$	0.998 (0.994–1.002) $p = 0.354$
Invasive mechanical ventilation (n, %)	140 (48.6)	136 (95.1)	14.904 (6.56–33.84); $p < 0.001$	9.02 (3.58–22.87); $p < 0.001$
New bacterial infection (n, %)	58 (20.1)	99 (69.2)	4.638 (3.174–6.777); $p < 0.001$	2.571 (1.665–3.972); $p < 0.001$
Probable Invasive Pulmonary Aspergillosis (n, %)	38 (13.2)	36 (25.2)	2.041 (1.389–3.001); $p < 0.001$	1.023 (0.675–1.54); $p = 0.916$
CMV reactivation (n, %)	29 (10.1)	59 (41.3)	2.53 (1.771–3.613); $p < 0.001$	1.141 (0.757–1.721); $p = 0.528$

Only factors with $p < 0.1$ at unadjusted analysis are reported

SAPSII Simplified Acute Physiology Score II; LDH lactate dehydrogenase; CMV cytomegalovirus

(but Ganciclovir therapy) and mortality than 38 patients with maximal viral load < 500 IU (Table 3S1).

Discussion

This large cohort observational study showed that CMV blood reactivation occurs in about 20% of COVID-19 patients admitted to ICU for respiratory failure, and 30% of these patients received anti-CMV treatment for suspected CMV pneumonia. High severity scores at ICU admission, the requirement of invasive mechanical ventilation and the development of secondary bacterial infections during ICU stay increase the risk of CMV blood reactivation. Furthermore, COVID-19 patients with

CMV blood reactivation showed increased mortality compared to patients without reactivation, but the CMV blood reactivation and the occurrence of CMV-related pneumonia did not seem to increase the risk of mortality at day 60 independently. To our knowledge, this is the most extensive study published so far on the occurrence, risk factors and impact of CMV reactivation in ICU patients with respiratory failure caused by SARS-CoV-2. The data provided should be considered high quality because it originated from a prospective clinical protocol used from the beginning of the COVID-19 surge.

As in our cohort, the previous small studies reported a CMV reactivation in about a quarter of COVID-19

critical patients, with about 50–60% of these patients showing at least one Herpesviridae reactivation [6, 8, 29]. In COVID-19 patients with a high rate of pre-existing immune defect, Epstein–Barr virus (EBV) was the Herpesviridae with the most frequent reactivation [29]. Unfortunately, our protocol did not include surveillance of EBV reactivation and then, only a few patients were screened for it. Similarly, we are not able to provide robust data on HSV-1 reactivation because very early during the first wave 2020, we introduced acyclovir prophylaxis in all the ICU patients after two cases of fatal liver failure related to HSV-1 and the high incidence of HSV-1 reactivation observed (published elsewhere) [9, 30]. Consequently, we withhold the protocol for systematic surveillance of HSV-1 that was evaluated only in patients with high clinical suspicion of infection.

In immunocompetent no-COVID-19 critically ill patients, numerous risk factors have been associated with the risk of CMV reactivation with a relationship for sepsis and mechanical ventilation. Although in our cohort many demographic characteristics, admission parameters and treatments were related to CMV reactivation in the crude analysis, as in no-COVID-19 patients, the adjusted analysis indicated that only invasive mechanical ventilation and the occurrence of new bacterial infection, that in critically ill patients frequently causes sepsis, increased the risk of CMV reactivation during ICU stay. The association observed between low platelets count and CMV reactivation may be explained by the pathobiology of SARS-CoV-2 infection that comprises persistent viral replication/viremia, uncontrolled inflammation, immune system impairment, and progressive involvement the endothelium with severe disturbances of coagulation processes leading to multiple thrombotic events [31]. Therefore, as for bacterial sepsis, the reduction of platelets indicates the degree of the hemostasis and the immune-inflammatory response impairment [32].

Interestingly, the incidence of CMV reactivation in COVID-19 appears to be lower than that reported in no-COVID-19 immunocompetent critically ill patients with sepsis, in whom it ranges between 30 and 60% depending on the time of screening, specimen and methods used [11, 33]. Several factors may theoretically explain this difference, but the severity scores of COVID-19 patients and the impact of SARS-CoV-2 infections on the immune response are usually less severe in the first 15 days than those in patients with sepsis from bacterial infections admitted to ICU [34]. These aspects, combined with younger age, fewer pre-existing comorbidities and the shorter duration of ICU stay, may justify the reduced occurrence of CMV reactivation in COVID-19 patients compared to the septic ICU population [13].

Therapy with steroids has been suggested as a potential risk for CMV reactivation in ICU patients with a low grade of certainty [35]. In our cohort, steroid therapy was administered more frequently in patients with CMV reactivation, but the adjusted analysis did not confirm this association. On the contrary, a relationship between CMV reactivation and the occurrence of new bacterial infections, the most hospital/ventilator acquired pneumonia, came out in our patients. The association between CMV and bacterial infections and their causal effect have been long debated in non-COVID-19 ICU patients [13, 33]. On one side, it is well known that sepsis profoundly deranges the immune mechanisms controlling viral reactivation with increased levels of IL-10, lymphopenia and reduced activity of T cells, natural killer and Th1 T cells [36–38]. On the other side, CMV reactivation may further induce immune suppression by complex mechanisms involving TNF- α , interleukin1- β and cellular mediated response [5] with consequent augmented risk for secondary infections. Similar to previous reports in COVID-19 and non-COVID-19 patients [8, 13], the CMV reactivation occurred in median 2 weeks after ICU admission and, noteworthy, only in a quarter of the patients occurred before secondary bacterial infection. Therefore, we believe reasonable to suppose that in COVID-19 patients, the development of secondary bacterial infections increases the risk of CMV reactivation rather than the opposite. CMV reactivation in immunocompetent ICU patients has also been indicated as a risk factor for invasive pulmonary Aspergillosis [39]. In fact, our patients with CMV reactivation also showed an increased (+20%) incidence of invasive pulmonary Aspergillosis compared to patients without CMV reactivation. Nevertheless, the adjusted analysis did not show a significant association, and, in addition, probable invasive pulmonary Aspergillosis was diagnosed at least 1 week before CMV reactivation in most of our patients.

The negative impact of CMV reactivation on the outcome of immunocompetent critically ill patients has been reported from several observational studies from at least 30 years. A recent meta-analysis reported 2.5-fold increase in ICU mortality (10 studies, $n=970$ patients), prolonged duration of mechanical ventilation (7 studies, $n=683$ patients; mean difference 6.6 days 95% CI 3.1–10.1) and increased length of ICU stay (9 studies, $n=973$ patients; mean difference 8.2 days 95% CI 6.1–10.2) associated with CMV reactivation [33]. Nevertheless, the true effect of CMV in the critically ill patient is still objective of large debate without a definitive answer. As described in the introduction, several animal and in-vivo studies described the putative mechanisms for direct and indirect pathogenicity of CMV in the ICU population, but numerous recent

interventional trials failed to demonstrate any survival improvement by anti-CMV-specific therapeutic strategies. A specific potential role of CMV reactivation in worsening COVID-19 disease has been theorized due to its capacity to reinforce and perpetuate hyper-inflammatory response and induce immune suppression with persisting SARS-CoV-2 viremia and secondary infections [17]. Our COVID-19 cohort detected increased mortality at ICU and hospital discharge, but the adjusted analysis did not confirm this association. Similar results were also observed in the sub-group of patients treated with ganciclovir because of suspected CMV-related pneumonia. Therefore, as hypostatized in the critically ill non-COVID-19 population, the CMV reactivation might be considered just a marker of disease severity rather than a factor capable of modifying outcomes in COVID-19 ICU patients. The lack of specific serial measurements related to CMV pathogenicity (e.g., IL-1Beta, IL-6, TNF-alfa) and the difficulties in diagnosing CMV pneumonia in patients with COVID-19 severe interstitial pneumonia limit any further consideration on the potential effects of CMV reactivation in these patients.

Beyond the limitations reported above, our study has other limitations. First, the study included patients admitted to 3 ICUs by the same hospital with potential limitations in generalization to other settings. Second, as in many other observational studies [33], we included all the ICU admitted patients and not only the CMV-seropositive population because seropositivity was not systematically evaluated. Third, the clinical protocol did not include systematic analysis of the respiratory sample for CMV reactivation, which was deserved only to patients with high suspicion of CMV pneumonia. This can underestimate the actual number of CMV reactivation. However, due to the uncertain significance of CMV detection in the respiratory tract, the CMV viremia is commonly used in high-quality interventional trials [18]. Last, our data did not indicate an association between CMV reactivation and the use of immune-suppressive therapies. However, the large number of patients treated with steroids (91%) and tocilizumab (84%) may have limited the sensitivity of our analysis.

Conclusions

In COVID-19 critically ill patients, the CMV blood reactivation is frequent and depends on the severity of illness and the occurrence of secondary bacterial infections but not on steroids and cytokine blocking agents. The patients with CMV reactivation showed prolonged hospital stay and higher mortality than patients without

reactivation. Nevertheless, the lack of independent association between CMV reactivation and mortality leaves open the question of its role and the appropriate strategy for its monitoring and management.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s00134-022-06716-y>.

Author details

¹ Anesthesia and Intensive Care Medicine, Policlinico di Modena, University of Modena and Reggio Emilia, Modena, Italy. ² Infectious Diseases Unit, Policlinico di Modena, University of Modena and Reggio Emilia, Modena, Italy. ³ Respiratory Diseases Unit, Policlinico di Modena, University of Modena and Reggio Emilia, Modena, Italy. ⁴ Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Modena, Italy. ⁵ Microbiology and Virology Unit, Azienda Ospedaliero-Universitaria Policlinico, 41124 Modena, Italy. ⁶ Virology and Molecular Microbiology Unit, Policlinico di Modena, University of Modena and Reggio Emilia, Modena, Italy. ⁷ Intensive Care Department, University Hospital of Modena, L.go del Pozzo 71, 41125 Modena, Italy.

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Author contributions

GI, BE, FE, MM, GM: study conception, design, data interpretation, draft, final approval of submitted version. CI, FC, AC, CVSM, PM, GW, TR: data acquisition. Analysis and interpretation. BS, GG, MC, CE, CA: critical revision of the draft.

Declarations

Conflicts of interest

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