# Herpes Simplex Virus 1 (HSV-1) Reactivation in Critically Ill COVID-19 Patients: A Brief Narrative Review

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## ABSTRACT

Systemic or pulmonary reactivations of herpes simplex virus 1 (HSV-1) have been reported in critically ill patients with COVID-19, posing a dilemma for clinicians in terms of their diagnostic and clinical relevance. Prevalence of HSV-1 reactivation may be as high as > 40% in this population, but with large heterogeneity across studies, likely reflecting the different samples and/or cut-offs for defining reactivation. There is frequently agreement on the clinical significance of HSV-1 reactivation in the presence of severe manifestations clearly attributable to the virus. However, the clinical implications of HSV-1 reactivations in the absence of manifest signs and symptoms remain controversial. Our review aims at providing immunological background and at reviewing clinical findings on HSV-1 reactivations in critically ill patients with COVID-19.

**Keywords:** COVID-19; Herpes simplex; HSV; ICU; Pneumonia; Reactivation; SARS-CoV-2

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# INTRODUCTION

Development of pneumonia by SARS-CoV-2, the etiological agent of coronavirus disease 2019 (COVID-19), may result in severe hypoxemic respiratory failure, requiring orotracheal intubation and invasive mechanical ventilation in the intensive care unit (ICU) [1–4].

In critically ill patients with severe COVID-19 pneumonia, an excessive systemic inflammatory response and a temporary immunosuppression with absolute lymphopenia have been described [5–7]. The use of anti-inflammatory and/or immunosuppressive agents such as systemic steroids and interleukin-6 (IL-6) receptor antagonists, which have been proven beneficial for the treatment of severe COVID-19 pneumonia, may further enhance such a temporary immunosuppression/dysregulation, possibly impairing the normal host response to other infectious agents [8–13].

Against this backdrop, systemic or pulmonary reactivations of herpes simplex virus 1 (HSV-1) have been reported in patients with COVID-19, frequently posing a dilemma for clinicians in terms of their diagnostic and clinical relevance [14–18]. Although HSV-1 reactivation has been already and largely described in critically ill patients without COVID-19, favored by the immunosuppression linked to critical illness (that certainly also contribute to the risk of HSV-1 reactivation in critically ill patients with COVID-19) [19–26], the peculiar impact of SARS-CoV-2 infection and its treatment imply that additional aspects may be involved in influencing HSV-1 reactivation and its clinical significance in this specific population.

In this brief narrative review, we discuss the current evidence on the specific immunological background and clinical implications of HSV-1 reactivation in critically ill patients with COVID-19 pneumonia.

# METHODS

In March 2022 we performed a PubMed search, subsequently extended up to May 2022, using different combinations of the following key words: HSV*; herpes*; COVID-19*; SARS-CoV-2. The retrieved full texts were reviewed and assessed for inclusion in the present narrative review, based on their relevance to the topic according to the authors' judgment (8 observational studies were included plus a few selected case reports to highlight specific aspects unavailable in larger studies; an inductive approach was used to select references pertaining to the discussion on the immunology of HSV-1 reactivation in COVID-19 patients). In the present review we discuss: (1) immunology of HSV-1 reactivation in critically ill patients with COVID-19; (2) results of clinical studies reporting on HSV-1 reactivation in critically ill patients with COVID-19; (3) clinical implications. This article does not contain any studies with human or animal subjects performed by either of the authors.

## Immunology of HSV-1 Reactivation in Critically Ill Patients with COVID-19

The most important immune system components against viruses are the innate immunity and the adaptive, cell-mediated immunity. Some viral infections may predispose to the reactivation of other viruses from latency through the generation of immune defects involving adaptive, innate or both defense mechanisms. A typical example is cytomegalovirus (CMV) reactivation in patients with human immunodeficiency virus (HIV) infection [27, 28].

During the COVID-19 pandemic, several reports highlighted the occurrence of HSV-1 reactivation in critically ill patients with COVID-19 [14, 16, 29]. The possible role of the impairment of the immune system induced by SARS-CoV-2 in predisposing to HSV-1 reactivation has been investigated. HSV-1 is a double-stranded DNA alpha herpesvirus that instigates a lifelong infection within their hosts, establishing a latent infection and reactivating when the host immune system is weakened. We previously observed that as many as 25% of mechanically ventilated COVID-19 patients may reactivate HSV-1 in their low respiratory tract after 30 days of intensive care [15]. In a similar way, Franceschini observed that up to 30% of patients with severe/critical SARS-CoV-2 pneumonia experienced HSV-1 DNAemia, with 62% of them showing clinically relevant manifestations of HSV-1 infection [14]. Notably, a lower rate of detection/reactivation of HSV-1 in critically ill patients admitted to intensive care unit (ICU) was reported in a large prospective study conducted in the pre-COVID-19 era (16%) [25]. This numerical difference in the prevalence of HSV-1 reactivation between COVID-19 and non-COVID-19 patients admitted to ICU could be in line with a specific role of SARS-CoV-2 in favoring HSV-1 reactivation, although it should be noted that another previous observational experience reported high rates of HSV-1 reactivation also in mechanically ventilated patients without COVID-19; thus, this issue deserves further investigation [20].

Generally, it is well known that a key role of innate immune protection against viruses is played by interferons (IFNs). IFNs are cytokines secreted after a complex pathway that begins from microorganism antigens recognition by pattern recognition receptors (PRR). Cellular antiviral response to HSV is initiated by host cellular proteins called PRR (C-type lectin receptors, NOD-like receptors, RIG-I-like receptors, and Toll-like receptors), which recognize molecular signatures of viral particles, known as pathogen-associated molecular patterns (PAMPs), and orchestrate the subsequent cellular responses [30]. After PAMP recognition, PRR activates downstream signaling cascades, production of type I (IFN-α and IFN-β) and III (IFN-λ) interferons, and secretion of other proinflammatory cytokines by multiple myeloid lineages and plasmacytoid dendritic cells [5]. Then, autocrine IFN-I via IFNα/β receptor (IFNAR) activates the Janus kinase (JAK) signal transducer and activator of transcription (STAT) signaling pathway [31]. On the other hand, IFN-λ binds an IFN-λ receptor 1 (IFNLR1) and a second subunit shared with the IL-10 receptor.

Binding of any of these IFNs to their respective receptors leads to the activation of the transcription factor ISGF3 composed of STAT1, STAT2 and IRF9 and the transcriptional activation of a common set of IFN stimulated genes (ISGs). The proteins encoded by the ISGs mediate the antiviral, immunostimulatory and antiproliferative effect of these cytokines [25]. Proinflammatory responses locally recruit a variety of macrophages, neutrophils, natural killer and dendritic cells to clear the viral infection. In addition to their antiviral action, it should be reminded that IFN-I also play a major role in orchestrating the development of the adaptive immune response to infection [32]. They do this indirectly via upregulation of cytokines, chemokines, and intermediate signaling molecules that affect immune cell activation, growth, and trafficking and via direct effects on dendritic cells, NK cells, and lymphocytes.

There are distinctive features during the innate immune response to SARS-CoV-2 infection. Although severe SARS-CoV-2 infection usually leads to an excessive production of proinflammatory cytokines, the production of type I IFNs may be blunted [33]. In this regard, only

minimal amounts of IFN-I have been detected in the peripheral blood or lungs of patients with severe COVID-19 [34, 35], differently from what is registered during influenza infection (dysregulated IFN response). In addition, suppression of IFN-I signaling through SARS-CoV-2 non-structural protein 1 and 6 is significantly higher than those observed in SARS-CoV and MERS-CoV [36]. It is not clear whether (and how much) the IFN-I signaling suppression by SARS-CoV-2 might be responsible for promoting HSV-1 reactivation [37, 38]. It has been demonstrated that patients with STAT1 and TYK2 deficiencies are susceptible to multiple viruses, including HSV-1 [39], and individuals with mutated STAT1 alleles (homozygous) are prone to lethal HSV-1 infections [37]. Of note, another mechanism that contributes to crippling the IFN response in COVID-19 patients is represented by orf6 hijacking of cellular steps in the IFN production and by the generation of anti-IFN Abs occurring in patients with predominantly severe disease course [40, 41]. The onset of anti-IFN Ab production is subsequent to SARS-CoV-2 infection and may contribute to other mechanisms switching off the IFN response and thus contributing to COVID-19 severity and to reactivation of latent infections [40, 41].

HSV-1 has the potential to inhibit IFN-stimulated genes [42]. This mechanism usually is involved in overt HSV-1 replication and might combine with the existing (SARS-CoV-2 induced) impaired IFN response. It is also possible that the above-mentioned IFN-crippling SARS-CoV-2-unique mechanisms may favor the exit of HSV-1 from latency first, thereby subsequently leading to a combination of SARS-CoV-2 and HSV-1 innate immune suppression when both viruses are fully replicating. Overall, a double impairment in IFN production could thus be possibly experienced by critically ill COVID-19 patients with respiratory HSV-1 reactivation, as observed by Seeßle et al. [18]. They demonstrated that, among mechanically ventilated COVID-19 patients who developed HSV-1 reactivation in the lung, the expression of IFN-stimulated genes (IFI44L, RSAD2, ISIG15, MX1, and IFIT1) was reduced after HSV-1 detection [18].

Another mechanism that could contribute to HSV reactivation in critically ill patients with COVID-19 is related to the impaired T cell response, which manifests as lymphopenia and functional exhaustion of CD4+ and CD8+ T cells [43]. The term "T cell exhaustion" is used mostly in relation to effector T cells with a reduced ability to secrete cytokines and an increased expression of inhibitory receptors [44]. Overall, this phenomenon is likely to participate in the secondary immunosuppression induced by SARS-CoV-2.

Besides T cells, also NK cells may experience a functional impairment during SARS-CoV-2 infection [45, 46]. Li et al. observed that severe COVID-19 cases had a decreased number of cytotoxic CD3-CD56dimCD16+ NK cells [46]. They also registered an increased expression of programmed death-1 and CD244 receptors on NK cells from COVID-19 patients, which may indicate an exhausted state of NK cells in COVID-19 patients [46]. Bozzano et al. observed a direct association of severe disease trajectories of COVID-19 with the proportion of CD34+ DNAM-1$^{bright}$CXCR4+ precursors and an inverse association with the proportion of NKG2D+ and of CD103+ NK cells [45].

Among comorbidities, hypertension and metabolic syndrome are the most commonly associated with severe clinical presentation and/or mortality in critically ill patients with COVID-19. Obesity has also been reported to predispose to severe COVID-19, and a high body mass index (BMI) and/or a "large neck phenotype" (reflecting upper body adiposity) have been associated with increased mortality [47, 48]. Obese patients have a decreased ability to produce IFN-α and IFN-β in response to TLR ligands and show higher basal levels of IL-6 compared to non-obese individuals [49].

Many patients with moderate/severe COVID-19 receive anti-inflammatory agents and/or immunosuppressive agents such as dexamethasone and tocilizumab or other immunomodulators (e.g., anakinra, baricitinib, sarilumab). Tocilizumab is a selective IL-6 receptor antagonist. While having a positive effect on the outcome of selected subgroups of patients with COVID-19, the use of tocilizumab has been associated (or suggested to be associated) with

the development of bacterial and fungal super-infections [9, 12, 50]. In patients with rheumatoid arthritis exposed to tocilizumab, the combined incidence rate of herpes simplex and/or herpes zoster virus reactivation may reach 6.27 per 100 person years [51]. In COVID-19 patients treated with tocilizumab, two cases of fatal acute liver failure due to HSV-1 have been described [52]. Franceschini et al. observed no clear difference in tocilizumab exposure when comparing COVID-19 patients who had reactivated HSV-1 and those who did not, although the limitation of the small sample size should be highlighted [14].

Corticosteroids are able to reduce mortality in severe or critical COVID-19 patients; thus, current World Health Organization guidelines for the management of COVID-19 provide a strong recommendation for the administration of systemic corticosteroids in those patients, with > 80% of hospitalized COVID-19 patients receiving steroids (usually dexamethasone) during their stay [9, 53]. In target cells, steroid-activated receptors diminish inflammation by inhibiting the activity of proinflammatory transcription factors, terminating signaling pathways, or upregulating the expression of anti-inflammatory proteins [54]. Nearly all the subtypes of T lymphocytes are sensitive to the action of glucocorticoids, which results in changes in their survival, differentiation, or function [54]. The administration of dexamethasone in patients with severe COVID-19 also alters IFN active neutrophils and downregulates interferon-stimulated genes [55]. In an observational study, patients with COVID-19 who received steroids had a higher rate of HSV-1 reactivation compared to those who did not (76% vs. 49%, $p = 0.036$) [14]. A simplified summary of the concepts discussed in this section is available in Fig. 1.

## Results of Clinical Studies Reporting on HSV-1 Reactivation in Critically Ill Patients with COVID-19

HSV-1 reactivation in patients with COVID-19 has been evaluated in different clinical studies, all observational (either retrospective or prospective) [14–18, 56–58], with some of them focusing exclusively on critically ill patients [15, 17, 18, 56, 58]. Overall, although varying across studies, the prevalence of HSV-1 reactivation in critically ill patients with COVID-19 (detected by polymerase chain reaction [PCR] on blood and/or respiratory specimens) reached > 40% in three different cohorts [18, 56, 58]. A detailed summary of the studies assessing the prevalence of HSV-1 reactivation in critically ill patients with COVID-19, also including information on the definition/cut-off employed for defining reactivation, is shown in Table 1. Across the different studies, PCR testing for HSV-1 DNA was variously performed on bronchoalveolar lavage fluid (BALF), tracheal aspirates, and/or blood. As for the type of specimen/s tested, there was also heterogeneity in the timing of sampling for HSV-1 DNA detection. In most cases, testing was performed at the time of ICU admission or when patients started IMV and possibly repeated when clinical worsening was observed. In some studies, PCR testing was repeated periodically [14, 16, 17, 56]. Regarding serology, anti-HSV-1 IgG levels in patients with severe and critical COVID-19 have been reported to be 4.6 and 6 times higher than in healthy subjects, respectively [59]. In the same study, anti-HSV-1 IgG levels in patients with critical COVID-19 were two times higher than in patients with mild COVID-19 [59].

Looking into the different studies in more detail, Le Balc'h and colleagues were the first to report on HSV (not specified if only type 1 or also type 2) reactivation in critically ill patients with COVID-19 [56]. Overall, 38 mechanically ventilated patients with COVID-19 with a negative HSV PCR at baseline (exact timing of first test not specified) were followed for reactivation during their ICU stay. Of them, 16 patients presented HSV reactivation, and in 7 cytomegalovirus reactivation was also detected [56]. In this study, HSV reactivation was defined as two consecutive positive PCR tests for HSV on tracheal aspirates, which were performed two times a week. Length of ICU stay was 29 days (interquartile range [IQR] 24–47) and 16 days (IQR 12–24) in patients with and without HSV reactivation, respectively ($p < 0.001$), with

**Table 1** Prevalence of HSV-1 reactivation in critically ill patients with COVID-19

| References | Year | Authors | Total patients | HSV-1 reactivation no. (%) | Definition/cut-off for defining HSV-1 re-activation | Comments |
|---|---|---|---|---|---|---|
| [56] | 2020 | Le Balc'h et al. | 38 | 16 (47)[a] | PCR on tracheal aspirate | In 7 cases CMV co-reactivation |
| [14] | 2020 | Franceschini et al. | 70 | 21 (30) | PCR on blood | Steroid treatment associated with HSV-1 reactivation in multivariable analysis (OR 5.13, with 95% CI from 1.36 to 19.32) |
| [16] | 2021 | Meyer et al. | 153 | 40 (26) | PCR on blood or tracheal aspirate | HSV-1 reactivation associated with increased mortality (HR 2.05, with 95% CI from 1.16 to 3.62) |
| [17] | 2021 | Saade et al. | 100 | 12 (12)[b] | PCR on blood, BALF, or skin swab | Reactivation of herpesvirus (HSV, CMV, and/or EBV) was not associated with mortality in this study |
| [18] | 2021 | Seeßle et al. | 18 | 15 (83) | PCR on tracheal aspirate or BALF | Pulmonary HSV-1 reactivation observed from day 11 after symptoms onset |
| [15] | 2021 | Giacobbe et al. | 41 | 12 (29) | PCR on BALF ($\geq 10^4$ copies/ml) | No independent predictors of HSV-1 reactivation were identified; no association was found between HSV-1 reactivation and mortality in this study |
| [58] | 2022 | Fuest et al. | 134 | 61 (46) | PCR on tracheal aspirate or BALF ($\geq 10^3$ copies/ml) | No association was observed between steroid treatment and HSV-1 reactivation and between HSV-1 reactivation and mortality in this study |

*BALF* Bronchoalveolar lavage fluid, *CI* confidence interval, *CMV* cytomegalovirus, *COVID-19* coronavirus disease 2019, *EBV* Epstein-Barr virus, *HR* hazard ratio, *HSV* herpes simplex virus, *OR* odds ratio, *PCR* polymerase chain reaction
[a]Not specified whether only HSV-1 or also HSV-2
[b]Onco-hematological ICU (10/100 patients were on valacyclovir prophylaxis)

similar crude ICU mortality (11% vs. 10%, $p = 0.99$) [56].

Franceschini et al. prospectively assessed the prevalence of HSV-1 reactivation in 70 patients with COVID-19 [14]. Their study did not focus exclusively on ICU patients but was nonetheless limited to patients with severe/critical COVID-19 pneumonia. The patients were screened with quantitative PCR for HSV-1 DNA on plasma twice a week. Overall, 30% of patients (21/70) presented detectable HSV-1 DNAemia. Clinically relevant manifestations of HSV-1 reactivation were registered in 64% of cases (13/21 patients, for a total of 15 events consisting of pneumonia [$n = 4$], herpes labialis [$n = 5$], gingivostomatitis [$n = 3$], hepatitis [$n = 2$], and

encephalitis [$n = 1$]). Need for invasive mechanical ventilation was 57% (12/21) and 22% (11/49) in HSV-1-positive and -negative patients, respectively ($p = 0.005$), whereas all-cause mortality was 29% (6/21) and 18% (9/49) in HSV-1-positive and -negative patients, respectively ($p = 0.344$). In both unadjusted and adjusted (for invasive mechanical ventilation and use of tocilizumab) logistic regression models, treatment with steroids was associated with HSV-1 reactivation (adjusted odds ratio [OR] 5.13, with 95% confidence interval [CI] from 1.36 to 19.32, $p = 0.016$), whereas the same was not observed for treatment with tocilizumab, although notably the direction of the effect was towards an increased risk and the analysis had low power, thereby precluding solid conclusions (adjusted OR 1.91, with 95% CI from 0.36 to 10.21, $p = 0.452$) [14].

In another prospective study conducted by Meyer and colleagues among 153 critically ill patients with COVID-19, blood for HSV-1 PCR testing was collected at ICU admission and then weekly [16]. In addition, regular lower respiratory tract sampling for HSV-1 PCR testing was performed in all mechanically ventilated patients until endotracheal tube removal or death. In this study, HSV-1 reactivation was defined as at least one positive HSV-1 PCR in blood and/or respiratory samples. HSV-1 reactivation was detected in 26% of patients (40/153), and 60-day mortality was numerically higher in patients with HSV-1 reactivation than in those without reactivation (58% vs. 33%, respectively). In an adjusted Cox regression model, HSV-1 was associated with increased mortality (hazard ratio [HR] 2.05, with 95% CI from 1.16 to 3.62, $p = 0.01$) [16].

In a retrospective study, we also assessed the cumulative risk of HSV-1 reactivation detected on BALF samples in critically ill patients with COVID-19, by means of PCR [15]. HSV-1 reactivation was defined in the presence of HSV-1 DNA $\geq 10^4$ copies/ml on BALF samples in the presence of worsening respiratory function. HSV-1 reactivation on deep respiratory samples was reported in 29% of included patients (12/41). With the limit of the small sample size (and consequently of low power), no independent association was observed between HSV-1

reactivation and mortality in an adjusted Cox regression model including HSV-1 reactivation as a time-dependent covariate (HR 1.07, with 95% CI from 0.24 to 4.86, $p = 0.928$). No association was observed between treatment with steroids and HSV-1 reactivation [15].

Among 134 mechanically ventilated patients with COVID-19, respiratory samples for HSV-1 PCR testing (endotracheal aspirate and BALF samples) were routinely collected twice weekly [58]. HSV-1 reactivation on respiratory samples (defined as at least $10^3$ copies/ml) was detected in 46% of patients (61/134) patients. In an adjusted logistic regression model, no association was observed between treatment with steroids and HSV-1 reactivation (OR 1.55, with 95% CI from 0.62 to 3.94, $p = 0.348$). Crude ICU mortality was 57% and 45% in patients with and without HSV-1 reactivation, respectively ($p = 0.219$) [58].

Regarding antiviral treatment, the proportion of critically ill patients with HSV-1 reactivation detected by PCR who received antiviral treatment with acyclovir ranged from 70 to 92% across the different studies [15, 16, 58]. In the study by Franceschini et al., patients with COVID-19 pneumonia admitted to the ICU or receiving non-invasive ventilation received acyclovir prophylaxis [14].

## Clinical Implications

HSV-1 reactivation in the presence of severe manifestations such as systemic skin manifestations, hepatitis, or encephalitis (all of them have been reported to possibly occur [14, 44, 60, 61]), as well as in presence of worsening of respiratory function and pulmonary lesions [15, 58], may be considered as clinically significant. However, reactivations without a manifest clinical picture are more controversial. The uncertain clinical significance of HSV-1 reactivation in the absence of signs and symptoms of infection may reflect the different samples (i.e., blood, respiratory specimens) and/or cut-offs employed in the different studies for defining HSV-1 reactivation [14–17, 56, 58].

Various approaches ranging from antiviral prophylaxis to antiviral treatment of patients

with clinically manifest reactivations have been reported across different studies [14–17, 56, 58]. This heterogeneity reflects several aspects: (1) the still unclear impact on relevant clinical outcomes of both HSV-1 reactivation and its antiviral therapy; (2) the long-debated uncertain impact on mortality of HSV-1 reactivation in critically ill patients without COVID-19, with, on the one hand, a recent randomized controlled trial (RCT) suggesting a lack of impact on mortality (in a way that does not support either prophylaxis or a pre-emptive treatment approach) and, on the other hand, a recent meta-analysis conversely suggesting a potential beneficial effect (with the limitations of high risk of bias and small samples, as also recognized by the authors) [62, 63]; (3) it is possible that, in some cases, detection of HSV-1 DNA on deep respiratory samples may reflect inhalation after oropharyngeal reactivation, without significant pulmonary damage [64]; (4) histopathological confirmation that would prove pulmonary damage by HSV-1 in critically ill patients with COVID-19 (in whom many other causes may be responsible for the worsening of respiratory function and lung lesions,

including SARS-CoV-2 itself) is very rarely available [65].

Despite all these considerations, the lack of standardization in the approach to the diagnosis and management of HSV-1 reactivation in critically ill patients with COVID-19 is certainly hampering comparability and generalization of research findings, limiting our understanding of the best approach to the diagnosis and management of HSV-1 reactivation in patients with COVID-19. Since the immunological background is different between critically ill patients with and without COVID-19, evidence from other critically ill populations may be not extrapolated directly to critically ill patients with COVID-19. Consequently, RCT specifically targeting critically ill patients with COVID-19 should be conducted to reach high-certainty evidence and a standardized approach to HSV-1 reactivation in this peculiar population. Finally, it should also be noted that, despite the presence of adjusted analyses in some studies, any possible independent prognostic implication of HSV-1 reactivation was difficult to extrapolate from the available evidence, owing to the likely large residual or unexplored confounding effect
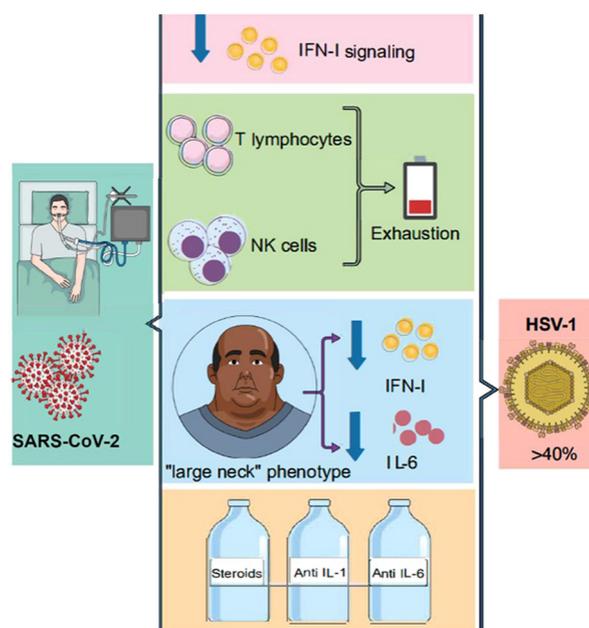


**Fig. 1** Simplified, potential immunological background of HSV-1 reactivation in critically ill patients with COVID-19. *HSV-1* herpes simplex virus 1, *IFN-I* type 1 interferon, *IL-1* interleukin 1, *IL-6* interleukin 6, *NK* natural killer, *SARS-CoV-2* severe acute respiratory syndrome coronavirus 2
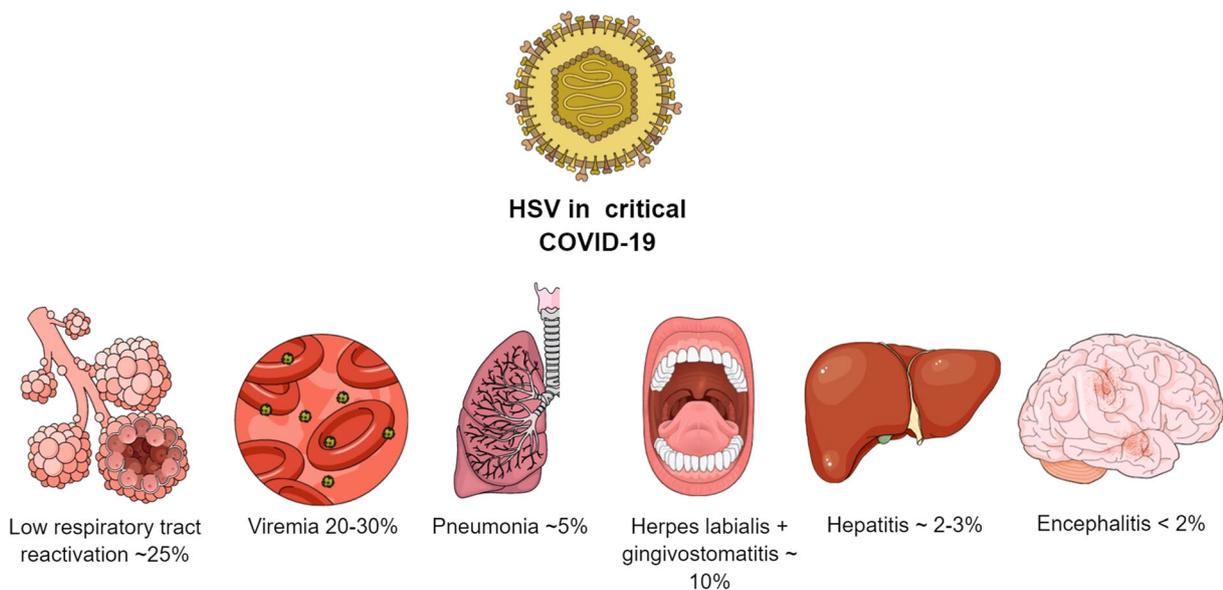
**Fig. 2** Frequency of HSV-1 reactivation in critically ill patients with COVID-19 according to current literature. *COVID-19* coronavirus disease 2019, *HSV* herpes simplex virus

of other concomitant infectious and non-infectious acute diseases.

## CONCLUSIONS

The prevalence of systemic or pulmonary reactivations of HSV-1 is high with a large heterogeneity across studies, likely reflecting the different definitions, samples, and/or cut-offs employed for defining reactivation (an attempt to provide rates of reactivation in different body sites is shown in Fig. 2). Different therapeutic approaches have been proposed from prophylaxis to selected antiviral treatment of patients with clinically manifest reactivations. Future research is needed to better clarify the role of HSV-1 reactivation in critically ill COVID-19 patients from a clinical standpoint.

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***Compliance with Ethics Guidelines.*** This article does not contain any studies with human or animal subjects performed by any of the authors.

***Data Availability.*** Data sharing is not applicable to this article as no datasets were generated or analysed in the current study.

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