Original Research Article

Aspects of human herpes simplex infection or reactivation in COVID-19 patients

ABSTRACT

Background and Aim: Herpes simplex viruses (HSV) occur worldwide and have a high prevalence. In the context of COVID -19 there are several potential triggers for HSV reactivation, such as functional depletion or imbalance of the immune system, use of immunosuppressive drugs to control cytokine response, and physical or psychological stress in consequence of the disease. The aim of this research is to review, by analysing the current scientific literature, the context of the HSV reactivation or infection in the context of the COVID-19 pandemic.
Methods: A systematic review of scientific manuscripts was performed using the PubMed, SciELO, and Google Scholar databases. The evaluated manuscripts were published between 2019 and January 2023. Systematic studies of groups of patients with COVID-19 that evaluated the incidence of HSV reactivations and infections, as well as case reports of HSV reactivation in patients with SARS-CoV-2 infection, were analyzed.
Results: Analysis of systematic studies among patients with COVID-19 revealed incidence rates of HSV reactivation detected by PCR technique, which can range from 12% to 83%. The incidence of clinical manifestations was heterogeneous, and the occurence of atypical clinical forms was considered high. HSV reactivations without clinical symptoms were observed in all studies in patients hospitalized with COVID -19. Determining the severity of infection and distinguishing between benign reactivation and true HSV infection concomitant with COVID-19 is a diagnostic challenge. Currently available scientific investigations are controversial regarding the impact on the prognosis of patients with human herpesvirus reactivation and the possible association between HSV infection and mortality rates. The broad spectrum of atypical forms, as well as difficulties in accurately diagnosing real HSV infection, may lead to underestimating the true impact of concurrent reactivation in COVID-19 patients. Patients receiving invasive mechanical ventilation and corticosteroid therapy are the groups at highest risk for HSV reactivation. Further investigations are needed to clarify the interaction between these two viruses in the context of SARS-CoV-2 disease and treatment.

Keywords: Herpes simplex viruses, COVID-19, Reactivation, Co-infection

1. INTRODUCTION

Herpes simplex viruses (HSV), also known as human Alpha herpesvirus, were the first human herpesviruses to be discovered and are among the most extensively researched viruses by the scientific community [1]. These viruses have a double-stranded DNA genome, an icosahedral capsid, and a bilipidic envelope. HSV have high genomic expressiveness and can encode a large number of viral proteins [2,3]. Although herpesviruses, in general, is capable to infect a wide range of animals [2], humans are the only natural reservoir for HSV. Herpes simplex viruses are classified into two types: HSV-1 and HSV-2. HSV-1 is usually associated with orofacial herpes, while HSV-2 is traditionally linked to genital infections.
The herpes simplex virus type 1 (HSV-1) has a worldwide incidence and high prevalence. The most recent estimates indicate that about 3.7 billion people under 50 years old are carriers of HSV-1, which corresponds to two-thirds of the world population in this age group. It is estimated that 491 million people aged 15-49 years are carriers of HSV-2 [4,5].

However, there has been an increase in the number of infections caused by HSV-1 in the genital clinical presentation, with an estimated 122 million to 192 million individuals aged 15-49 years with this type of infection, mainly in the Americas, Europe, and the Western Pacific [4,5]. HSV-1 has been implicated as the cause of most genital infections, accounting for over 50% of new infections among specific groups such as female university students, heterosexual women, and women with other sexually transmitted infections [6,7,8,9,10,11]. Ayoub et al. [12] note that the epidemiological patterns of genital herpes are transitioning towards a higher prevalence of HSV-1 in the genital clinical form.

HSV-1 is primarily transmitted by direct contact of the infected mucosa or skin with the mucosa or fluids from the active lesion of the host, mainly through the labial mucosa. HSV-2 is usually transmitted through sexual intercourse by contact with the genital mucosae. The transmission of genital herpes occurs particularly during the asymptomatic period of the disease [7,13], which can be attributed to the painful sensitivity during the symptomatic period that discourages sexual activity. Both HSV-1 and HSV-2 infect and replicate in mucoepithelial cells, with incubation periods ranging from 7 to 10 days for HSV-1 and 2 to 12 days for HSV-2 [2].

The initial infection starts at the site of infection or in its vicinity. Viral replication causes cell death through the breaking of the cell wall, resulting in exudate at the lesion site and a subsequent inflammatory response. Necrosis occurs, characterized by eosinophilia and an increase in polymorphonuclear neutrophils. During cell lysis, the released fluid containing a large amount of virus is set between the dermal and epidermal layers and forms vesicles. Skin lesions typically present as small vesicles grouped together on an erythematous base. The rupturing of these vesicles is painful and can result in superficial grey erosions or ulcerations that may or may not form crusts. After the initial active infection, the virus spreads to local sensory neurons and travels through the nerve cords to the sensory ganglia. Upon penetrating the ganglion neurons, it integrates its genome into the extrachromosomal chromatin in the nucleus of the nerve cell. Infected neurons may contain tens or hundreds of copies of the viral genome [2,3,5].

Primary HSV-1 infections usually occur in the first years of life. In addition to the typical oral clinical form, HSV-1 can also cause vesicular lesions on the genital mucosa, fingers, skin abrasions, eyelids, and ocular conjunctiva. The most concerning clinical form of HSV-1 infection occurs when the virus enters the central nervous system and causes herpetic encephalitis. Although rare, this condition has a high mortality rate [2,3,5]. Most herpesvirus infections are benign, but among immunocompromised individuals, they can present as severe or atypical, with clinical symptoms such as esophagitis, colitis, pneumonia, encephalitis, and disseminated herpetic disease [14].

The infection presents itself in two forms: the lytic form, known as the active phase of the disease, characterized by infection and subsequent destruction of epithelial cells and fibroblasts, and the latent form, found in neurons. The occasional reactivation of latent infection triggers viral replication in neurons and reinfection of mucosal epithelial cells, leading to new episodes of the lytic form and increased disease transmission. This reactivation can be caused by various factors, including damage to the tissue innervated by neurons hosting latent viruses, physical or emotional stress, fever, exposure to ultraviolet rays, cold, heat, hormonal dysregulation, inhalation of nanoparticles or fibers, coinfection by helminths, and microbial coinfections [15]. Corticosteroid use is known to trigger the clinical manifestation of HSV in infected patients [16,17,18].

Some viral infections can interfere with the body's defense mechanisms, such as cytomegalovirus [19] and HIV [3,5]. Severe SARS-CoV-2 infections cause dysregulation of the immune system through an exacerbated and acute reaction, with a cytokine cascade and massive mobilization of the cellular immune system. The resulting damage to the defense mechanism increases the risk of opportunistic infections [20,21] and reactivation of latent infections [22,23], including those caused by Herpesviridae [24,25,26]. The context of COVID-19 presents several factors that can be considered as potentially triggering HSV reactivation. The pathophysiology of severe SARS-CoV-2 infection induces a decompensation and functional exhaustion of the immune system [27]. Control of the cytokine cascade in an attempt to contain the damage caused by this imbalance is performed with immunosuppressive drugs. Patients may suffer physical or psychological stress as a result of the disease or the emotional conditions associated with the change in the rhythm of life as a consequence of the pandemic. The aim of this research is to review, by analysing the current scientific literature, the context of the HSV reactivation or infection in the context of the COVID -19 pandemic.

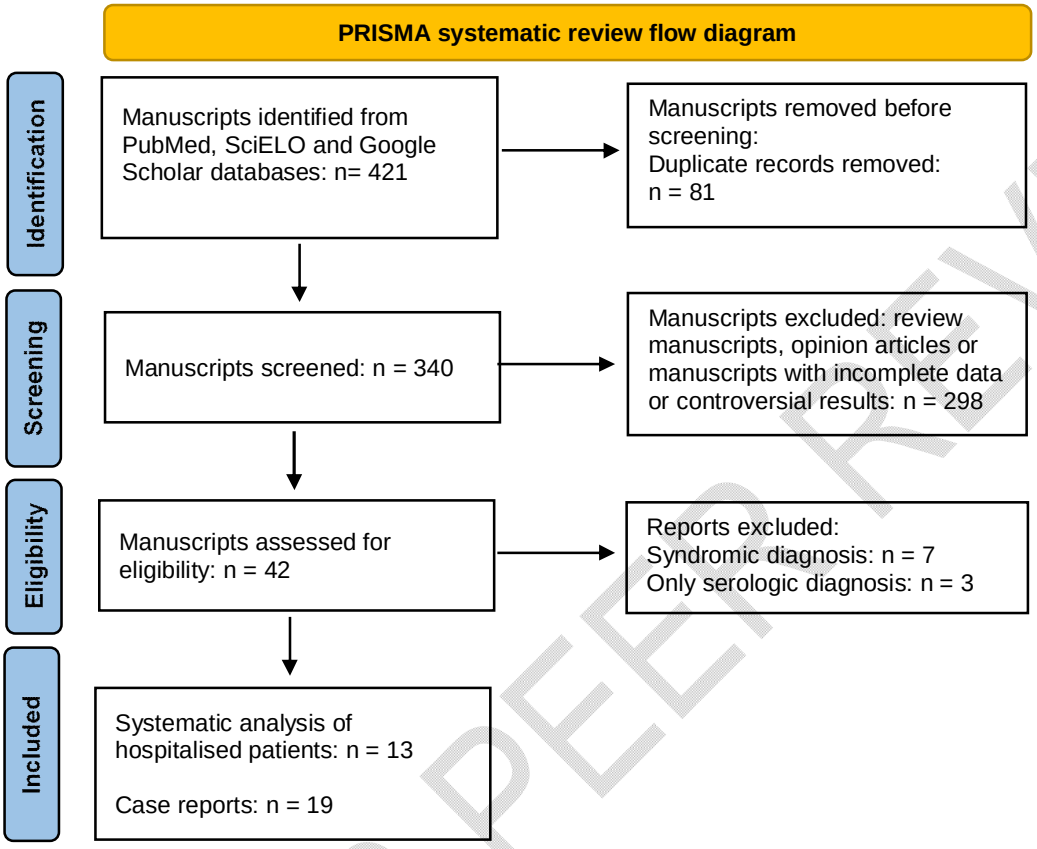
2. METHODS

A systematic review was conducted according to the methodological guidelines proposed by de Moher et al. [28], updated by Page et al. [29], using the PRISMA model. The objective of the review was to examine the relationship between SARS-CoV-2 infection and potential coinfection or reactivation of herpes simplex virus (HSV). The sources for the review included the databases PubMed, SciELO, and Google Scholar, and the search was performed using the following descriptors: "HSV", "herpes simplex", "herpes", "shingles", "reactivation", "COVID-19", and "SARS-CoV-2". The manuscripts reviewed were published in English, Portuguese, and Spanish and had a publication date between December 2019 and January 2023.

Studies that evaluated the incidence of HSV reactivations in individuals with severe COVID-19 and case reports of HSV reactivation in patients with SARS-CoV-2 infection were selected for review. After reading the full text of each article and

case report, relevant information was selected and evaluated. The most important aspects were recorded and summarized for analysis. Review articles, opinion articles, and articles with incomplete data or doubtful diagnostic interpretations were excluded. Cases in which the diagnosis of HSV reactivation was made only by serology criteria or clinical features were discarded. A flow chart was provided to illustrate the rationale for selecting the reference material for the review (Figure 1).

Fig. 1. Flowchart of the screening process of publications according to the PRISMA model.



**Source: the authors*

3. RESULTS AND DISCUSSION

The scientific literature on HSV reactivationos infection as a consequence of COVID-19 or the treatment of SARS-CoV-2 infection is quite diverse in terms of its methods and approach. Most of the studies are circumstantial or episodic and do not allow for the estimation of prevalence.

Using HSV serology in COVID-19 cases should not be considered a defining factor in determining the severity of herpetic disease in patients with severe SARS-CoV-2 infection, especially in those with long-term COVID-19. The immune system dysregulation and immunosuppressive treatment may skew the results of anti-HSV-1 immunoglobulin testing. As demonstrated by Klein et al. [30], IgG reactivity to HSV antigens is lower than expected standards in long-term COVID-19 patients. Furthermore, in patients with less immune impairment, there is evidence that immunoglobulins produced against SARS-CoV-2 cross-react with anti-HSV IgM serology [31], leading to false-positive results and incorrect clinical suspicion of herpes simplex reactivation or real infection.

Clinical suspicion of atypical manifestations or systemic HSV infection in patients with severe COVID-19 should be confirmed through PCR examination, particularly of organic material obtained from the suspected affected organ, to avoid the risk of laboratory misinterpretation that may occur during temporary immunodeficiency in COVID-19. For this reason, scientific references where the diagnosis of HSV reactivation was based exclusively on serological tests were not considered in this review. The most significant results of the articles depicting systematic studies of groups of patients with COVID-19 who presented HSV reactivation are summarized in Table 1.

Table 1. Summary of relevant clinical aspects of articles with groups of patients hospitalized with COVID-19 who presented HSV reactivation.

Reference	Patients with HSV reactivations (% of reactivations/ COVID-19 patients)	Detection	Clinical presentations	Associated with higher mortality rate
Seeßle et al. [32]	15(83%)	CA - tracheal aspirate or bronchoalveolar fluid	-	Not informed
Sánchez-Belmonte et al. [33]	47 (56,6%)	PCR - bronchoalveolar fluid	Pneumonia - 11 (68.8%)	Yes
Luyt et al. [34]	73(50,3%)	PCR-bronchoalveolar fluid	Pneumonia 36 (25%)	No
Le Balc'h et al. [35]	16 (47%)	CRA - tracheal aspirate	-	No
Fuest et al. [36]	61 (46%)	CRP - bronchoalveolar fluid or tracheal aspirate	-	No
Franceschini et al. [37]	21 (30%)	PCR - blood	Pneumonia - 4 (19%) Orolabial - 5 (23.8%) Gingivostomatitis - 3 (14.3%) Hepatitis - 2 (9.5%) Encephalitis - 1 (4.8%)	No
Giacobbe et al. [38]	12 (29%)	PCR - bronchoalveolar fluid	-	No
Reizine et al. [39]	33 (27%)	PCR - blood	-	No
Meyer et al. [40]	40 (26,1%)	PCR - bronchoalveolar fluid PCR - blood	-	Yes
Simmonet et al. [41]	7 (22%)	PCR - blood		No
Chiesa et al. [42]	18 (21,7%)	PCR - skin and mucosa suabe	Typical orolabial and	No
Carneiro et al. [43]	10 (18,9%)	PCR - nasal swab	Neurological symptoms - 4 (40%)	Not informed
Saade et al. [44]	12 (12%)	PCR - blood 10), tracheal aspirate or bronchoalveolar fluid (1)	Cutaneous manifestations - 10 (83.3%)	No

**Source: the authors*

The analysis of systematic studies in patients with COVID-19 revealed varying incidence rates of HSV reactivation detected by PCR, which can range from 12% [44] to 83% [32]. There was a heterogeneity in the clinical manifestations observed, and the incidence of atypical forms can be considered high. Studies showed high incidence rates of HSV reactivations with atypical manifestations, such as pneumonia in 68.8% [33], neurological symptoms in 40% [43], and cutaneous manifestations in 83.3% [44]. The variability in the prevalence of clinical manifestations in some studies may be due to different HSV strains with potential cell tropisms, differences in COVID-19 treatment protocols, and the impact of stressors or immunosuppressive factors of the treatments in each hospital, or a lack of diagnosis due to non-recognition of atypical clinical forms of HSV manifestation. Further research is needed to clarify the interaction between SARS-CoV-2, COVID-19 treatments, and HSV reactivation dynamics in this context. There is a discrepancy in the studies regarding the impact of HSV reactivation on mortality rates; some studies suggest a significant increase in deaths due to HSV reactivation [33, 40], while others report no association between reactivation and mortality rates [34,35,36,37,38,39,41,42,44].

Besides investigations of HSV reactivation in groups of patients hospitalized for COVID-19, case reports of reactivation provide insight into the interaction between these two viruses. A summary of the case reports found in the current scientific literature is described in Table 2.

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Table 2. Summary of relevant clinical aspects of case reports of patients with COVID-19 who had HSV reactivation.

Reference	Number of patients	Detection method	Clinical presentation
Ehsanipur et al. [45]	1	PCR - cerebrospinal fluid	Cerebellitis (HSV2)
Dimitrova et al. [46]	1	PCR - cerebrospinal fluid	Encephalitis
Gupta et al. [47]	8	PCR - cerebrospinal fluid	Encephalitis
Knepley and Paschall [48]	1	PCR - cerebrospinal fluid	Encephalitis
Coletti et al. [49]	1	PCR - cerebrospinal fluid	Encephalitis (HSV-2)
Alfishawy et al. [50]	3	PCR - bronchoalveolar fluid	Pneumonia
Hassan et al. [51]	1	PCR - blood	Pneumonia
Xu et al. [52]	1	PCR - bronchoalveolar fluid	Ulcerative lesions in the bronchi
Busani et al. [53]	2	PCR - blood and cerebrospinal fluid	Hepatitis
Hernández et al. [54]	1	PCR - nasopharyngeal swab	Keratitis and conjunctivitis
González et al. [55]	1	PCR	Acute retinal necrosis (HSV-2)
Guimarães et al. [56]	1	PCR- suabe skin	Cutaneous manifestation
Brandão et al. [57]	2	PCR - oral mucosa	Stomatitis
Franceschi et al. [58]	1	Histopathology	Gingivitis with recession
Kämmerer et al. [59]	1	PCR - oral mucosa swab	Gingivostomatitis
Yeom et al. [60]	3	Histopathology	Glossitis
Kalbhenn et al. [61]	1	PCR - orolabial swab	Orolabial
Sell et al. [62]	1	PCR - oral mucosa swab	Orolabial
Maldonado et al. [63]	1	PCR - blood and nasopharyngeal swabs	No clinical signs

Source: the authors

Results obtained from compiling case reports cannot be compared to studies with comprehensive methodologies because they have different investigation dynamics. Comparing the results with those of broader research carries the possibility of bias or perception distortion, as case reports tend to be described based on rarity, peculiarities, circumstances, or specificities of medical conduct [64,65,66]. Notwithstanding, this kind of investigation can reflect changes in patterns in specific situations, generate hypotheses in comparison with previous consolidated knowledge, and indicate trends before systematic studies that require large amounts of data [64]. In the context of HSV reactivation in COVID-19, case reports also point to the heterogeneity of clinical manifestations, similar to wider inpatient studies. There are many reports of typical forms of HSV reactivation, such as stomatitis and orolabial manifestations. There is also a notable number of reports of clinical manifestations involving the Central Nervous System and pneumonia, which are considered rare in immunocompetent patients but often associated with immunosuppression.

One of the main factors triggering HSV reactivation in COVID-19 is the decreased immune response that fails to control latent infections. CD8 T lymphocytes play an important role in containing HSV in sensory ganglia and persist in these sites, preventing virus dissemination [67]. The recruitment of these cells during the acute phase of COVID-19 may favor reactivation of the lytic phase of herpetic disease or result in atypical clinical manifestations, particularly when combined with immunosuppressive therapies aimed at controlling the exaggerated response to severe SARS-CoV-2 infections. Corticosteroid drugs are known to trigger the lytic phase of HSV [25,68,69]. Besides the reactivation caused by immunosuppression, the use of the antiviral Remdesivir also has the potential to reactivate latent herpesvirus infections [25].

One of the life support procedures for severe SARS-CoV-2 infections in patients is the use of invasive mechanical ventilation. However, this procedure is associated with an increased risk of secondary infections [70,71,72,73]. Invasive mechanical ventilation has also been linked to cases of HSV-1 pneumonia with unfavorable outcomes [74,75]. Seeßle et al. [32] reported a high rate of HSV-1 reactivation in COVID-19 patients undergoing invasive mechanical ventilation, which occurred during a time of increased immune system deregulation and decreased expression of Interferon production genes. Sánchez-Belmonte et al. [33] believe that this reactivation is multifactorial, involving the acute viral disease, drug-induced immunosuppression, and the use of mechanical ventilation. HSV pneumonia typically affects immunodeficient or immunosuppressed patients, but even immunocompetent critically ill patients undergoing mechanical ventilation are at risk [76,77]. The symptoms of herpetic pneumonia, such as fever, myalgia, shortness of breath, cough, chest pain, nausea, vomiting, diarrhea, and abdominal pain [78], often overlap with severe COVID-19 cases, making a clinical diagnosis difficult. Jellinger et al. [78] explain that the low specificity of laboratory and radiological tests, as well as the inability to differentiate between true infection and host status from isolation of HSV in respiratory secretions, presents a diagnostic dilemma. CT imaging and conventional chest radiography in HSV pneumonia resemble the findings in COVID-19, with opacities, multifocal distribution, and consolidations [79,80]. The cytokine cascade in severe COVID-19 and the infection of lung epithelial cells both result in cell lysis and tissue necrosis, making it difficult to determine the extent to

which each virus is contributing to tissue destruction. There is limited research on the impact of HSV reactivation on the prognosis of COVID-19 patients, and criteria for the definition of pneumonia vary among references [32]. Sánchez-Belmonte et al. [33] used qualitative PCR and histopathological examination to differentiate between HSV pneumonia concurrent with COVID-19 and HSV reactivation in the respiratory tract. The results showed higher mortality rates in patients with HSV reactivation (57.4% vs 33.5%) and even higher mortality rates in patients with concurrent SARS-CoV-2 and HSV pneumonia (69.2% vs 30.8%). Meyer et al. [40] also found a higher mortality rate associated with HSV-1 reactivation in COVID-19 patients undergoing mechanical ventilation after 60 days of hospitalization. These results suggest that the impact of simultaneous pneumonia from both viruses may be significantly underestimated.

Neurological complications caused by herpes simplex virus (HSV) in COVID-19 have been observed both in inpatient studies and case reports. Carneiro et al. [43] reported a 40% incidence of neurological symptoms among patients with HSV reactivation. Four case reports of encephalitis [46,47,48,49] and one case of cerebellitis [45] have been found in the current literature review. The image patterns, sites of injury, signs and symptoms in neurological disorders seen in severe SARS-CoV-2 infection are highly heterogeneous [81], but HSV encephalitis presents well-known features, including an acute, necrotizing form that is almost always focal and often asymmetrical, located in the orbitofrontal and temporal lobes, with involvement of the cingulate and insular cortex [82, 83, 84]. These features indicate that the differential diagnosis should be based on the combination of PCR and MRI results to differentiate from other encephalopathies that may occur in COVID-19 [47,49,85].

Monje and Iwasaki [86] highlight that several pathophysiological mechanisms of COVID-19 may cause alterations in the nervous system, such as triggering autoimmune mechanisms that affect glia and neurons, neuroinvasive SARS-CoV-2 infection, a microvascular and thrombotic disease that disrupts the blood-brain barrier mechanism, and cerebral metabolic disturbances due to hypoxia and reactivation of latent herpesviruses causing encephalopathies. HSV encephalitis is considered rare in immunocompetent individuals and is usually associated with immunodepression or immunosuppression conditions [87,88,89]. Future population studies are needed to evaluate the neurological manifestations of all severities of COVID-19 [81], including HSV-caused encephalopathies in coinfection, particularly in long-standing COVID-19 and in patients undergoing extended periods of immunosuppression and treatment-related stress during hospitalization. Persistent stressors can increase the risk of HSV reactivation and potentiate the possibility of central nervous system infection [87,88,90,91].

HSV-1 is highly prevalent among humans, and typical herpes simplex reactivation secondary to COVID-19 may be underestimated, particularly those considered benign. In a study conducted by Shanshal and Ahmed [92], 35% of patients with mild COVID-19 who responded to a questionnaire reported one or more cases of reactivation during SARS-CoV-2 infection, and 42.86% of these considered the clinical presentation to be more severe than in previous episodes. A large number of case reports of reactivation with orolabial eruptions [57,58,59,60,61,62] support the findings of Shanshal and Ahmed (2021). Benign orolabial manifestations due to reactivation are recurrent in HSV hosts exposed to trigger factors. Orolabial herpes during COVID-19 may be highly underestimated, as patients who have previously experienced the benign lytic form of the disease recognize and usually treat the lesions without medical follow-up.

HSV reactivations without clinical symptoms were observed in all studies evaluating patients hospitalized for COVID-19. High rates of herpesvirus reactivation in patients with acute respiratory distress syndrome have been known prior to the COVID-19 pandemic, especially among those admitted to intensive care units and undergoing mechanical ventilation [34,48,40,68]. The incidence of herpesvirus reactivation ranges between 20% and 54% [40]. To determine whether the reactivation is insignificant with a low viral load, a marker of immunosuppression, or the result of a true viral infection, an integrated evaluation combining clinical examination and quantitative PCR is necessary [93]. Even minor herpesvirus reactivations should be monitored as they may develop into a true infection, such as HSV bronchopneumonia, even in immunocompetent patients [94]. The clinical significance of HSV reactivation without obvious clinical symptoms in patients with COVID-19 is still dissonant among health researchers [38].

In the reviewed literature, various therapeutic approaches have been proposed, ranging from prophylactic use of antivirals to initiation of treatment based on the viral load as determined by quantitative PCR tests. Early diagnosis and antiviral therapy with Acyclovir may be crucial in preventing the progression of HSV reactivation to a full-blown infection, potentially improving the prognosis of these patients. However, more studies are needed to determine the efficacy of this drug therapy in severe SARS-CoV-2 infections [32,33,38].

4. CONCLUSION

An analysis of systemic studies in hospitalized patient groups suggests that HSV reactivation rates among individuals with COVID-19 are high, with prevalence rates ranging from 12% to 83%. The differences in results may be due to the methods and samples examined, as well as factors related to COVID-19 treatment protocols and the criteria assigned to HSV reactivation. Determining the severity of the infection and differentiating between benign reactivation or a concurrent actual infection with COVID-19 is a diagnostic challenge, particularly in cases of herpetic pneumonitis. The available scientific investigations are controversial regarding the impact on the prognosis of patients with human herpesvirus reactivation and the possible association between HSV infection and mortality rates.

In a more comprehensive evaluation, case reports indicate a multitude of typical and atypical clinical manifestations of HSV reactivation. The broad spectrum of atypical forms and difficulties in diagnosing actual HSV infection may contribute to underestimating the true impact of concurrent reactivation in COVID-19, especially in severe cases where the focus of treatment is on supporting the life of the Severe Acute Respiratory Syndrome patient. Patients undergoing invasive mechanical ventilation and corticosteroid therapy are at the highest risk of HSV reactivation.

Presently, the diagnosis of HSV reactivationor real HSV infection in COVID-19 patients represents a clinical challenge, as the manifestation of HSV reactivation can be atypical, masked by the Severe Acute Respiratory Syndrome of other COVID-19 symptoms Further investigations are needed to clarify the interaction between these two viruses in the context of SARS-CoV-2 disease and treatment. This includes establishing clear criteria to define real HSV infection during COVID-19, conducting studies in larger patient populations, and researching the usefulness of antiviral therapy to control and prevent HSV during acute SARS-CoV-2 infection.

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