Received: 10 July 2021 | Accepted: 12 October 2021

DOI: 10.1002/jmv.27392

SHORT COMMUNICATION

JOURNAL OF MEDICAL VIROLOGY WILEY

Presence and clinical impact of human herpesvirus-6 infection in patients with moderate to critical coronavirus disease-19

Katia Lino[1,4] | Lilian S. Alves[1,5] | Jessica V. Raposo[6] | Thalia Medeiros[1,5] | Cintia F. Souza[1,4] | Andrea A. da Silva[1,3,5] | Vanessa S. de Paula[6] | Jorge R. Almeida[1,2,4]

[1]Multiuser Laboratory for Research Support in Nephrology and Medical Sciences, Faculty of Medicine, Federal Fluminense University, Niterói, Rio de Janeiro, Brazil

[2]Department of Clinical Medicine, Faculty of Medicine, Federal Fluminense University, Niterói, Rio de Janeiro, Brazil

[3]Department of Pathology, Faculty of Medicine, Federal Fluminense University, Niterói, Rio de Janeiro, Brazil

[4]Postgraduation Program in Medical Sciences, Faculty of Medicine, Federal Fluminense University, Niterói, Rio de Janeiro, Brazil

[5]Postgraduation Program in Pathology, Faculty of Medicine, Federal Fluminense University, Niterói, Rio de Janeiro, Brazil

[6]Laboratory of Molecular Virology, Oswaldo Cruz Institute, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil

Correspondence

Jorge R. Almeida, Laboratório Multiusuário de Apoio à Pesquisa em Nefrologia e Ciências Médicas, Universidade Federal Fluminense, Rua Marques do Paraná, 303, Niterói, Rio de Janeiro, Brazil.
Email: jorgereis@id.uff.br

Funding information

Ministério da Ciência, Tecnologia e Inovação; Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; Conselho Nacional de Desenvolvimento Científico e Tecnológico

Abstract

Human herpesvirus-6 (HHV-6) may cause serious diseases in immunocompromised individuals. SARS-CoV-2/HHV-6 coinfection has been emphasized in previous works, mostly case reports, small series, or epidemiological studies, but few are known about its real clinical outcomes. Here we present a real-world pilot study aiming to understand the frequency and the clinical impact of HHV-6 coinfection in moderate to critically ill patients hospitalized due to COVID-19. SARS-CoV-2 and HHV-6 were evaluated in nasopharyngeal samples at the hospital admission of suspected COVID-19 patients. From 173 consecutive cases, 60 were SARS-CoV-2 positive and 13/60 (21.7%) were HHV-6 positive after identified as the HHV-6B species by a Sanger sequencing. The SARS-CoV-2+/HHV-6+ group was younger but not significant for cardiovascular diseases, diabetes, obesity, and cancer, but significant among therapeutic immunosuppressed patients (as systemic lupus erythematosus and kidney transplant patients). In the medical records, only sparse data on cutaneous or neurological manifestations were found. Biochemical and hematological data showed only a trend towards hyperferritinemic status and lymphopenia. In conclusion, despite the impressive high frequency of HHV-6 coinfection in SARS-CoV-2 positive cases, it did not impact general mortality. We suggest larger future prospective studies to better elucidate the influence of HHV-6 reactivation in cases of COVID-19, designed to specific assessment of clinical outcomes and viral reactivation mechanisms.

KEYWORDS

COVID-19, herpesvirus-6, HHV-6

1 | INTRODUCTION

Human herpesvirus may be the cause of serious diseases particularly in immunocompromised individuals, as autoimmune diseases, cancer, and transplant patients.[1,2] Human herpesvirus 6 (HHV-6), a widespread betaherpesvirus, is implicated in a benign disease of infancy, exanthema subitum, well known to cause febrile seizures, whereas further virus reactivations specially in immunosuppression states can induce severe encephalitis cases, neurocognitive dysfunction, bone marrow suppression, rash, and possibly thrombotic

Katia Lino and Lilian Santos Alves contributed equally to this study.

microangiopathy.[3] HHV-6 DNA can be detected in saliva and in the nasal mucosa,[4] and in general, viral reactivation has been reported as asymptomatic, but in cases of advanced age and/or state of immunosuppression, it may be associated with cases of encephalitis, cutaneous manifestations (pityriasis rosea) and Kawasaki disease; the latter mainly in children.[5] Recently, HHV-6 reactivation in patients with COVID-19 has been associated with some clinical presentations, including pityriasis rosea and Kawasaki disease.[6]

HHV-6 was discovered in 1986 and initially named B-lymphotropic virus human, as it is mainly found infecting and replicating in lymphocytes of the cell lineage. As with all herpesviruses, HHV-6 infection can be asymptomatic and pass unnoticed, but the virus can remain latent until a deficiency host immune system favors its reactivation. After primary infection, HHV-6 is capable of establishing lifelong persistence by the involvement of different stages of the viral life cycle, and it is also capable of reactivation, meaning the active production of detectable mature virions in some body tissues/compartments.[7]

HHV-6 are classified into two closely related groups that have been termed variants A (HHV-6A) and B (HHV-6B) and now originated as distinct species of herpesviruses. HHV-6B is the 13 major causative agents of sudden exanthema, yet with few studies, a disease has not been defined as associated with HHV-6A.[8] Primary infection with HHV-6B is extremely common and usually occurs in early childhood. The most common symptom is a high fever, and although the course is usually benign, some may develop encephalitis.[9,10] For unknown reasons, the frequency of neurological complications varies by geography, being much higher in Japan than in the United States.[10] The epidemiology of HHV-6A is poorly charged. When compared to HHV-6B, a primary infection must occur later in life in Europe, America, and Asia; in sub-Saharan Africa, contrasting data on the prevalence of HHV-6A infection in infants have been reported.[11–13]

Viral coinfections in COVID-19 patients are an emergent issue.[14] SARS-CoV-2 virus, through viral replication mechanisms and immune-inflammatory disturbance, could play a role, triggering HHV-6 reactivation.[15] Moreover, COVID-19 patients also frequently present lymphopenia, which may favor this mechanism.[16] So, this study aims to evaluate the frequency of HHV-6 infections and its clinical impact, including mortality, in a series of hospitalized patients with moderate to critically ill COVID-19 disease.

2 | MATERIALS AND METHODS

We present a retrospective study where hospitalized patients with signs and symptoms of moderate to severe COVID-19 disease were enrolled at Antonio Pedro University Hospital (a central hospital in the Metropolitan Region II of Rio de Janeiro State, based in Niteroi/Brazil, reference for high complexity cases including cancer, autoimmune diseases, heart surgeries, transplants and also for moderate to severe COVID-19 cases). The SARS-CoV-2 presence at hospital admission was evaluated in nasopharyngeal samples in a series of consecutive cases of suspected COVID-19 patients in the period of April to July 2020. We studied HHV-6 presence concomitantly in the same nasopharyngeal samples. Clinical data of the patients were retrieved from the medical records. The study was approved by the Brazilian National Research Ethics Committee (CAAE: 30623520.5.0000.5243).

Nasopharyngeal samples were collected and brought to the laboratory immediately, and RNA was extracted using commercial kit (QIAGEN) according to the manufacturer's instructions to understand if there was HHV-6 infection or reactivation. SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) was performed using the 2019-nCOV RUO Kit (Integrated DNA Technologies, Inc—IDT) and GoTaq® Probe 1-Step RT-qPCR (Promega Corporation). Controls included the IDT 2019-nCoV_N_Positive Control, and Hs_RPP30 Positive Control plasmids. The assay was performed in three separate reactions per specimen for each target (N1, N2, and the human internal control gene RNase P [RP]). For viral load determination, a quantitative RT-PCR (RT-qPCR) was performed using the Bio GeneCOVID-19 PCR Kit (Bioclin/Quibasa), following the manufacturer's instructions. Amplification was performed using the 7500 System (Applied Biosystems, ThermoFisher Scientific) for both RT-qPCR protocols.

The qPCR reaction for HHV-6 was performed using a primer and probe sequences for the U56 region of HHV-6.[17] To investigate the active infection, the HHV-6 detection was performed in the same samples used to detect SARS CoV-2, for this reason, the RNA extracted was used in this study. A saliva sample tested to intermediate replicative was used as positive control.[4] The reaction was performed with the AgPath-ID™ One-Step RT-PCR (Life Technologies) consisting of 20 µl of mix with 1 µl of 25× PCR enzyme (Mix Life Technologies), 2.5 µl of each oligonucleotide (1 µM), Probe 2.0, 0 µl (0.4 µM) and 12.5 µl of 1× PCR buffer (Life Technologies). Quantification of viral load was performed based on the synthetic standard curve. The equipment used was the 7500 Real-Time PCR System (Life Technologies) and the method used was the hydrolysis probe, Taqman system.[4] Moreover, a Sanger sequencing of the HHV-6 positive samples was performed to differentiate the viral species (HHV-6A/B). Thus, we performed the PCR of these samples using primer sequences previously described,[18] with the sequences obtained by sequencing aligned by the Bioedit software.

For analysis, patients were divided into two groups: coinfection (SARS-CoV-2(+)/HHV-6(+)) and without coinfection (SARS-CoV-2(+)/HHV-6(−)) groups. We compared variables such preexisting conditions and clinical outcomes (such as cancer, cardiovascular disease, a composite of diabetes and obesity, requirement of intensive care [a composite for mechanical ventilation requirements, dialysis, and hemodynamic sepsis], use of therapeutic immunosuppression [a composite for autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, and kidney transplantation] and overall mortality during hospitalization); and also cycle threshold values for SARS-CoV-2 N1 and N2 genetic targets and inflammatory biomarkers such as ferritin and C-reactive protein, leukopenia (≤4000 cells/µl) and lymphopenia (≤1000 cells/µl). Data

were expressed as mean ± standard deviation (SD) or *n* (%). Differences between groups were assessed using the χ^2 and Mann–Whitney tests, according to variables characteristics, continuous or categorical. For analyses, we used a statistical package (SPSS) and were considered significant when $p < 0.05$.

3 | RESULTS

The SARS-CoV-2 presence in nasopharyngeal samples was evaluated at the moment of hospital admission in 173 consecutive cases of suspected COVID-19 patients. From these, 60 patients were positive for SARS-CoV-2, from which 13/60 (21.7%) of nasopharyngeal samples were also HHV-6 positive. HHV-6 viral load had a mean ± SD of $2.81 \times 10^5 \pm 9.08 \times 10^5$, respectively. Symptoms at the moment of hospital admission were in general fever, cough throat pain, sneezing, loss of taste, and eventually diarrhea and abdominal pain. Overall, prostration and prominent dyspnea, with O_2 saturation < 95% and a ground glass pattern on thoracic computed tomography (CT) (>50%) were the most frequently observed, constituting the typical presentation of moderate to severe hospitalized cases. The mean time between the onset of COVID-19 symptoms and molecular testing was 8.8 ± 5.7 days.

Among the SARS-CoV-2+/HHV-6+ patients, the mean age was 52.3 ± 22.9 years, and 8/13 (61.5%) were male, and they had comorbidities such as cancer (*n* = 4; 30.8%), cardiovascular disease (*n* = 8; 61.5%), diabetes (*n* = 8; 61.5%), therapeutic immunosuppression status (*n* = 6; 38.5%). We also observed clinical outcomes as the need for mechanical ventilation, acute kidney injury, and sepsis (*n* = 9 each, 69.2%). Four (30.7%) patients died. Table 1 shows clinical and laboratory characteristics of patients with and without HHV-6 associated co-infections. The blood samples for those diagnoses tests were obtained not exceeding the fifth day of hospitalization. In spite of such a high prevalence of HHV-6 DNA found (21.7%), there was only scarce data about cutaneous or neurological manifestations in the medical records, including the emergence and intensive care units.

Furthermore, in a more detailed analysis of Table 1, considering the group of patients with coinfection for comparison, we did not find statistical differences between the groups for any of the studied variables, except for the use of therapeutic immunosuppression ($p = 0.01$). The coinfection group tended to be younger and also to have higher levels of ferritin and leukopenia, but these were not statistically significant. It is noteworthy that we found no differences between viral load values for SARS-CoV-2 and also no impact on the percentage of the requirement for intensive care or even overall impact on hospital mortality. Patients using therapeutic immunosuppression were mainly composed of patients with systemic lupus erythematosus and kidney transplant patients who, due to their small number, it was not possible to make inferences about the types of medications (before admission, the majority was using low doses of oral corticosteroids, mycophenolate mofetil, and tacrolimus). By using Sanger sequencing to differentiate viral species (HHV-6A/B), we note that all 13 HHV-6 positive samples were identified as HHV-6B species.

TABLE 1 Some clinical and laboratory characteristics of hospitalized COVID-19 patients according to HHV-6 positivity

Parameters	All (*n* = 60)	Without HHV-6 coinfection (*n* = 47)	HHV-6 coinfection (*n* = 13)	*p* value
Age, years (mean ± SD)	60.1 ± 18.7	62.3 ± 16.6	52.3 ± 22.9	0.08
Male gender, *n* (%)	37 (61.6)	28 (59.6)	8 (61.5)	0.52
Cancer, *n* (%)	38 (48.7)	17 (36.1)	4 (30.8)	0.71
CVD, *n* (%)	41 (68.3)	33 (70.2)	8 (61.5)	0.55
Diabetes and obesity, *n* (%)	30 (50.0)	22 (46.8)	8 (61.5)	0.34
Therapeutic immunosuppression status, *n* (%)	12 (20.0)	6 (12.8)	6 (46.2)	0.01
Requirement of intensive care, *n* (%)	47 (78.3)	34 (72.3)	9 (69.3)	0.82
Mortality, *n* (%) of deaths	28 (46.7)	24 (51.0)	4 (30.7)	0.19
SARS-CoV-2 viral load (mean ± SD)	2.79E + 04 ± 8.20E + 04	1.64E + 04 ± 2.71E + 04	5.23E + 04 ± 1.31E + 05	0.34
HHV-6 viral load (mean ± SD)			1.30E + 04 ± 1.04E + 06	–
C-reactive protein (mean ± SD)	17.6 ± 13.3	15.8 ± 13.6	18.3 ± 12.3	0.49
Ferritin (mean ± SD)	2134 ± 2299	1666 ± 1763	2882 ± 2985	0.34
Albumin (mean ± SD)	2.9 ± 0.6	2.9 ± 0.7	2.8 ± 0.3	0.75
Leukopenia (<4000/mm^3), *n* (%)	9 (15.0)	6 (12.8)	3 (23.0)	0.35
Lymphopenia (<1000/mm^3), *n* (%)	36 (60.0)	27 (12.8)	9 (69.2)	0.44

Note: Data are presented as mean ± SD or *n* (%), and *p* values were calculated by Mann–Whitney or χ^2 test, respectively.
Abbreviation: CVD, cardiovascular disease.

4 | DISCUSSION

As a pilot study, we investigated the active infection of HHV-6 using nasopharyngeal samples from patients infected with SARS-CoV-2 with moderate to critically ill hospitalized, we found an impressive frequency of 21.7% of HHV-6. A recent study performed in blood samples found 22% of HHV-6 infection among COVID-19 patients in an intensive care unit.[19] All 13 positive cases of HHV-6 were identified as HHV-6B species.

In addition, our aim was also to assess the role of some clinical risk comorbidities and in-hospital outcomes, including mortality, and we were able to demonstrate a significant relationship only with prior therapeutic immunosuppression (as we can see in SLE and kidney transplant patients, for example). Besides, trying to create some relation with cutaneous or neurological manifestations, we realized that this information was very poorly described in medical records and we discuss this.

A very important issue is that herpesvirus reactivation has been reported to be very common in critically ill patients even before the COVID-19 pandemic,[19–21] as well as in cancer, autoimmune diseases, and organ transplantation.[1,22] Guidelines exist in this setting to actively monitor and address them, including therapeutic options, from vaccines to antiviral drugs, ranging from cytomegalovirus (CMV), Epstein–Barr virus (EBV), varicella-zoster virus, and the herpesviridae family, in general. About the presence of HHV-6 in these cases, some clinical outcomes, severity, and prognostic follow-up have already been suggested, but much still needs to be known and how to measure its consequences. In this study, a high incidence rate was found (21.7%), RNA was extracted from nasopharyngeal swabs, and performed RT-PCR. Detection of RNA in the specimen may indicate active HHV-6 infection/reactivation. In a study previously carried out by our group, it showed that salivary gland is an important site of active and persistent infection by roseoloviruses and high viral loads were correlated with mRNA detection levels, suggestive of active replication of HHV-6.[4]

SARS-CoV-2 infection affects T lymphocytes, particularly CD4 T cells, CD8 T cells 4, and natural killer cells, resulting in functional exhaustion and decreases in numbers.[23] So, the resulting immunosuppressive state could encourage reactivation of latent viral infection, resulting in sudden worsening of symptoms in the course of recovery.[22] That is an important point to future studies to help better understand some mechanisms involved and the clinical differences between patients who have or not a reactivation, or a new infection, from these respiratory coinfections.[24]

SARS-CoV-2 has been associated with the development of several skin manifestations, at all ages, and some occurring during active disease or after the course of infection.[25] Adult patients exhibiting cutaneous manifestations of COVID-19 can show different degrees of disease severity. Some cases are self-limited and benign, probably due to the exacerbated immune response to the virus itself; while other cases such as vasculopathies or thrombotic lesions may harbor life-threatening extracutaneous systemic involvement.[25,26] We should also always value neurological signs and symptoms since both SARS-CoV-2 and HHV-6 might affect the neural tissues as well as the immune system and its neurologic long-term consequences, including the development of neuropsychiatric disorders.[27]

On the other hand, skin lesions, for example, pityriasis rosea due to HHV-6B reactivation, in moderate to critically ill patients might not be properly valued and could not even be properly described in medical reports. Perhaps skin lesions could help to indicate coinfection with SARS-CoV-2 and some viruses of the herpes family.

In addition, aware that in immunosuppressed severely ill patients, sometimes sedated and intubated, HHV-6 can trigger encephalitis, we should always have in mind its presumptive diagnosis.[28] This approach is often hidden by these common situations in critical units. As well, in some centers, there could be some difficulty in performing a lumbar puncture and even taking patients to computed tomography (CT) or magnetic resonance imaging (MRI) room, for example. That is an important reason for documenting the presence of coinfection with HHV-6/SARS-CoV-2, which may determine changes in the therapeutic approach of the patient and an improvement in prognosis since usually ganciclovir and foscarnet isolated or in combination are indicated to treat HHV-6 encephalitis.[29]

About COVID-19 patients and intensive care outcomes, a recent study using DNAemia positivity for EBV, CMV, and HHV-6 was associated only with longer ICU length-of-stay,[19] while other study using tracheal aspirates in a longitudinal way observed the same.[20] Regarding risk factors, we found a significant relationship in patients using therapeutic immunosuppression, as already mentioned. We have not found an impact of the HHV-6 infection in terms of the need for intensive care or even on overall mortality. We believe that we should be attentive and careful with these findings, as we have found only a few cases reported in the literature, so far no large systematic studies evaluating the binomial HHV-6 infection (by reactivation) and disease (new) in COVID-19. We must also be aware of our study population, who consisted of a small number of hospitalized COVID-19 patients with comorbidities, formed by high complex clinical cases in view of the particular profile of a central university hospital in Brazil, and due to the high severity of Brazilian patients by the first wave phase of COVID-19 pandemic.

In conclusion, despite the impressive high frequency of HHV-6 coinfection in SARS-CoV-2 positive cases, it did not impact general mortality, maybe due to the fact that all HHV-6-positive patients are species B and also pathogenic differences between HHV-6A/B. We suggest larger future prospective studies to better elucidate the influence of HHV-6 reactivation in cases of COVID-19, designed to specific assessment of clinical outcomes and viral reactivation mechanisms.

ACKNOWLEDGMENTS

This study was supported by CAPES (#001), and Brazilian National Research Council/CNPq (#27968*6 FINEP/RTR/PRPq/RedevCOVID-19). This data funded by Ministério da Ciência, Tecnologia e Inovação; Conselho Nacional de Desenvolvimento Científico e Tecnológico; Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; Ministério da Ciência, Tecnologia e Inovação.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

All authors have contributed substantially to this manuscript. Katia Lino, Lilian S. Alves, Andrea A. da Silva, and Jorge R. Almeida conceived and designed the research project; Katia Lino, Lilian S. Alves, and Thalia Medeiros acquired clinical data; Katia Lino, Lilian S. Alves, Jessica V. Raposo, Thalia Medeiros, and Cintia F. Souza conducted experiments; Jessica V. Raposo and Vanessa S. de Paula contributed with new reagents and analytical tools; Katia Lino, Lilian S. Alves, Jorge R. Almeida, and Vanessa S. de Paula analyzed and interpreted the data; Katia Lino, Lilian S. Alves, Vanessa S. de Paula, and Jorge R. Almeida wrote the manuscript; Jorge R. Almeida and Vanessa S. de Paula edited the final revision of the manuscript. All authors read and approved the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Vanessa S. de Paula https://orcid.org/0000-0002-6314-754X
Jorge R. Almeida http://orcid.org/0000-0001-6155-7978

REFERENCES

1. Zanella MC, Cordey S, Kaiser L. Beyond cytomegalovirus and Epstein-Barr virus: a review of viruses composing the blood virome of solid organ transplant and hematopoietic stem cell transplant recipients. *Clin Microbiol Rev*. 2020;33(4).
2. Sehrawat S, Kumar D, Rouse BT. Herpesviruses: harmonious pathogens bute. relevant cofactors in other diseases? *Front Cell Infect Microbiol*. 2018;8:177.
3. Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of human herpesvirus 6 infections. *Clin Microbiol Rev*. 2015;28(2):313-335.
4. Raposo JV, Sarmento D, Pinto R, et al. Longitudinal study on oral shedding of human betaherpesviruses 6 and 7 in renal transplant recipients reveals active replication. *J Oral Microbiol*. 2020;12(1):1785801.
5. Kawano Y, Kawada JI, Nagai N, Ito Y. Reactivation of human herpesviruses 6 and 7 in Kawasaki disease. *Mod Rheumatol*. 2019;29(4):651-655.
6. Dursun R, Temiz SA. The clinics of HHV-6 infection in COVID-19 pandemic: pityriasis rosea and Kawasaki disease. *Dermatol Ther*. 2020;33(4):e13730.
7. Pantry SN, Medveczky PG. Latency, integration, and reactivation of human herpesvirus-6. *Viruses*. 2017;9(7):194.
8. Yamanishi K, Okuno T, Shiraki K, et al. Identification of human herpesvirus-6 as a causal agent for exanthem subitum. *Lancet*. 1988;1(8594):1065-1067.
9. Hill JA, Zerr DM. Roseoloviruses in transplant recipients: clinical consequences and prospects for treatment and prevention trials. *Curr Opin Virol*. 2014;9:53-60.
10. Tesini BL, Epstein LG, Caserta MT. Clinical impact of primary infection with roseoloviruses. *Curr Opin Virol*. 2014;9:91-96.
11. Kasolo FC, Mpabalwani E, Gompels UA. Infection with AIDS-related herpesviruses in human immunodeficiency virus-negative infants and endemic childhood Kaposi's sarcoma in Africa. *J Gen Virol*. 1997;78(Pt 4):847-855.
12. Bates M, Monze M, Bima H, et al. Predominant human herpesvirus 6 variant A infant infections in an HIV-1 endemic region of Sub-Saharan Africa. *J Med Virol*. 2009;81(5):779-789.
13. Tembo J, Kabwe M, Chilukutu L, et al. Prevalence and risk factors for betaherpesvirus DNAemia in children >3 weeks and <2 years of age admitted to a large referral hospital in sub-Saharan Africa. *Clin Infect Dis*. 2015;60(3):423-431.
14. Aghbash PS, Eslami N, Shirvaliloo M, Baghi HB. Viral coinfections in COVID-19. *J Med Virol*. 2021;93:5310-5322.
15. Jumah M, Rahman F, Figgie M, et al. COVID-19, HHV6 and MOG antibody: a perfect storm. *J Neuroimmunol*. 2021;353:577521.
16. Drago F, Ciccarese G, Rebora A, Parodi A. Human herpesvirus-6, −7, and Epstein-Barr virus reactivation in pityriasis rosea during COVID-19. *J Med Virol*. 2020;93:1850-1851.
17. Raposo JV, Alves A, Dos Santos da Silva A, et al. Multiplex qPCR facilitates identification of betaherpesviruses in patients with acute liver failure of unknown etiology. *BMC Infect Dis*. 2019;19(1):773.
18. Tanaka T, Kogawa K, Sasa H, Nonoyama S, Furuya K, Sato K. Rapid and simultaneous detection of 6 types of human herpes virus (herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, human herpes virus 6A/B, and human herpes virus 7) by multiplex PCR assay. *Biomed Res*. 2009;30(5):279-285.
19. Simonnet A, Engelmann I, Moreau AS, et al. High incidence of Epstein-Barr virus, cytomegalovirus, and human-herpes virus-6 reactivations in critically ill patients with COVID-19. *Infect Dis Now*. 2021;51(3):296-299.
20. Le Balc'h P, Pinceaux K, Pronier C, Seguin P, Tadié JM, Reizine F. Herpes simplex virus and cytomegalovirus reactivations among severe COVID-19 patients. *Crit Care*. 2020;24(1):530.
21. Ong DSY, Bonten M, Spitoni C, et al. Epidemiology of multiple herpes viremia in previously immunocompetent patients with septic shock. *Clin Infect Dis*. 2017;64(9):1204-1210.
22. Xu R, Zhou Y, Cai L, et al. Co-reactivation of the human herpesvirus alpha subfamily (herpes simplex virus-1 and varicella zoster virus) in a critically ill patient with COVID-19. *Br J Dermatol*. 2020;183(6):1145-1147.
23. Zheng M, Gao Y, Wang G, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol*. 2020;17(5):533-535.
24. Massey BW, Jayathilake K, Meltzer HY. Respiratory microbial co-infection with SARS-CoV-2. *Front Microbiol*. 2020;11:2079.
25. Garduno-Soto M, Choreno-Parra JA, Cazarin-Barrientos J. Dermatological aspects of SARS-CoV-2 infection: mechanisms and manifestations. *Arch Dermatol Res*. 2020;313:611-622.
26. Mawhirt SL, Frankel D, Diaz AM. Cutaneous manifestations in adult patients with COVID-19 and dermatologic conditions related to the COVID-19 pandemic in health care workers. *Curr Allergy Asthma Rep*. 2020;20(12):75.
27. Reza-Zaldívar EE, Hernández-Sapiéns MA, Minjarez B, et al. Infection mechanism of SARS-COV-2 and its implication on the nervous system. *Front Immunol*. 2020;11:621735.
28. Wang Y, Wang D, Tao X. Human herpesvirus 6B encephalitis in a liver transplant recipient: a case report and review of the literature. *Transpl Infect Dis*. 2021;23(1):e13403.
29. Costa BKD, Sato DK. Viral encephalitis: a practical review on diagnostic approach and treatment. *J Pediatr (Rio J)*. 2020;96(Suppl 1):12-19.

How to cite this article: Lino K, Alves LS, Raposo JV, et al. Presence and clinical impact of human herpesvirus-6 infection in patients with moderate to critical coronavirus disease-19. *J Med Virol*. 2021;1-5. doi:10.1002/jmv.27392