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Risk factors for *Herpes simplex* virus (HSV) and *Cytomegalovirus* (CMV) infections in critically-ill COVID-19 patients

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ABSTRACT

Background: To assess the prevalence of *Herpes simplex* and *Cytomegalovirus* infection in respiratory samples of critically-ill COVID-19 patients, its role in outcome and mortality and the influence of dexamethasone treatment in the early stage of SARS-CoV-2 infection.

Methods: All mechanically ventilated COVID-19 patients treated on ICU between March 2020 and January 2021 were included. Respiratory specimens were tested for *Herpes simplex* virus (HSV) type 1, 2 and *Cytomegalovirus* (CMV) by quantitative real-time PCR. Clinical parameters were compared in the cohorts with and without HSV-1-infection.

Results: 134 patients with a median age of 72.5 years (73.0% male, n=98) were included. HSV-1 reactivation occurred in 61 patients (45.5%), after median 9 (7-13) days of mechanical ventilation. The main factor for reactivation was length of stay on ICU (24 days *vs* 13 days, p<0.001) and duration of mechanical ventilation (417 *vs* 214 hours, p<0.001). Treatment with dexamethasone and a history of immunosuppression did not associate with HSV-infection in the univariate analysis (39 *vs* 41, p=0.462 and 27.9% *vs* 23.3%, p=0.561, respectively). Both ICU and hospital mortality were not significantly different in the cohorts with and without HSV-infection (57.4% *vs* 45.2%, p=0.219).

Conclusions: Our study shows a high prevalence of HSV-infection in critically-ill COVID-19 patients which was unexpectedly higher than the prevalence of CMV-infections and unrelated to dexamethasone treatment. The main risk factors for HSV and CMV in the studied cohorts were the length of ICU stay and duration of mechanical ventilation. Therefore, we recommend routine monitoring of critically ill COVID-19 patients for these viral co-infections and consider treatment in those patients.

Key words: COVID-19; critical care; mortality; acute respiratory distress syndrome; herpes simplex infection; viral co-infections.

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Availability of data and materials: The data presented in this study are available on request from the corresponding author. The data are not publicly available.

Introduction

Nearly, 5-10% of the patients infected with the new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), require intensive care treatment due to acute respiratory distress syndrome, which potentially leads to complications such as sepsis due to co-infections/secondary infections, and multi-organ failure [1]. Need for invasive mechanical ventilation (IMV) is associated with high mortality rates, ranging from 16% up to 78% [2]. While numerous drug regimens are being investigated in early clinical trial phases to treat COVID-19, only the use of dexamethasone has been included in worldwide recommendations for severe (mechanical ventilated) COVID-19 treatment in patients with need for oxygen so far, as it resulted in lower 28-day mortality in patients requiring invasive mechanical ventilation [3-5]. Glucocorticoids have been used for decades as potent anti-inflammatory and immunosuppressive agents to treat several conditions. However, a dose and duration dependent increased risk for serious infectious complications has been demonstrated by several observational studies [6]. Generally, respiratory viral infections such as SARS-CoV-2 depict a risk factor for bacterial or fungal co-infections that are mostly secondary infections, even without dexamethasone therapy, which increase disease severity and mortality as reported for COVID-19 patients [7,8]. Apart from complications caused by bacterial and fungal infections, data on viral opportunistic infections among patients with COVID-19 are sparse particularly in the combination with dexamethasone therapy [9,10]. It has been shown that *Herpesviridae* reactivation is common even in non-immunocompromised patients with detection rates up to 35% in mechanically ventilated patients [11,12]. It is still a matter of debate, whether these viral infections are of pathogenetic relevance or represent harmless diagnostic findings and whether antiviral treatment is beneficial [13,14].

The present study aimed to investigate the prevalence of *Herpes simplex* and *Cytomegalyvirus* replication in respiratory samples of critically-ill COVID-19 patients, its role in outcome and mortality as well as the impact of dexamethasone treatment in the early stage of SARS-CoV-2 infection.

Methods

We performed an observational single-center cohort study and included all 134 critically-ill patients with confirmed SARS-CoV-2 infection admitted to an intensive care unit (ICU) between March 2020 and January 2021. Patients were treated on two different ICUs in a university hospital with 1,200 beds, one affiliated to the department of internal medicine and one to the department of anesthesiology.

The Ethics Committee of the Technical University of Munich approved this observational study and waived the need to obtain consent for the retrospective compilation, analysis, and publication of the anonymized clinical data (270/21S).

Medical records including clinical charts and nursing records were reviewed. Data collection included patient characteristics, comorbidities, clinical parameters, laboratory findings, information on inpatient management, ICU interventions, and length of ICU and hospital stay.

Laboratory SARS-CoV-2 diagnostic was based on real-time polymerase chain reaction (RT-PCR) and/or serological testing [15]. Patients with positive RT-PCR or positive IgM/IgG serology results were defined as definite COVID-19 cases and included in the study. Based on the local ICU workflow for mechanically ventilated COVID-19 patients, respiratory samples were routinely collected twice a week from critically-ill patients for microbiological and virological diagnostics. Virus replication of *Cytomegalovirus* (CMV) and *Herpes Simplex* virus (HSV) were measured by quantitative RT-PCR of endotracheal aspirates (ETA) and bronchoalveolar lavage (BAL) fluid. A panel for other respiratory viruses including influenza, RSV and metapneumovirus was performed once at ICU admission. In case of a positive HSV and/or CMV replication with a viral load of $>10^5$ copies/ml, an additional virus PCR for HSV and/or CMV from EDTA blood-samples were performed. Treatment was typically initiated in cases of viral loads $>10^5$ copies/ml in ETA/BAL, however, decision to start treatment was left to the attending physician depending on the clinical condition of each patient. In case of treatment, acyclovir was started with 10 mg/kg bodyweight or adapted to the renal function, dialysis or other contra-indications. Treatment was completed when testing on subsequent respiratory samples returned negative and/or in a clinically improved patient. Follow up examinations and if needed treatment were carried out even after extubation on an individual approach (*e.g.,* in immunosuppressed patients).

Statistics

Continuous data are described by median (interquartile range from quartile 25% to quartile 75%), and categorical data by absolute and relative frequencies. Data were analyzed using a chi-square or Mann-Whitney U test for categorical and continuous variables, respectively. Multivariate analyses were performed using logistic regression models. For survival over time log rank tests were used and presented using Kaplan Meier Curves. In addition, cumulative incidence functions were used for competing risk analysis. For multivariate classification of HSV-infection, classification trees (CART-analysis) were obtained. A two-sided p of less than 0.05 was considered statistically significant. Due to the exploratory nature of the study, uncorrected p are reported. Statistical analyses were performed using R v. 4.0.5. The complete anonymized set of individual patient data is available from the authors upon request.

Results

134 patients with a median age of 72.5 (73% male, n=98) fulfilled the study inclusion criteria. Baseline characteristics are summarized in Table 1. In 61 patients (45.5%), at least 10^3 copies/ml of *Herpes simplex* virus type 1 (HSV-1) copies/ml were detected in ETA or BAL samples (HSV-infection cohort). HSV-2 or CMV was not detected in the entire cohort. There was an association of viral load with length of hospital stay. HSV-infection was diagnosed at a median of 9 days (IQR 7-13) upon intubation.

The length of stay on the ICU (24 days *vs* 13 days, p<0.001) and duration of mechanical ventilation (417 hours *vs* 214 hours, p<0.001) was significantly longer in patients with HSV infection. Baseline procalcitonin (0.5 *vs* 0.3 ng/dl, p=0.005), C-reactive protein (18.2 *vs* 12.6 mg/dl, p=0.001) and leukocytes (10.0 *vs* 8.4 G/l, p= 0.031) at ICU admission were significantly higher in the HSV-infection cohort (Table 2).

Univariate analysis showed, that dexamethasone treatment and history of immunosuppression were not associated with the risk of HSV-infection (39 *vs* 41, p=0.462 and 27.9% *vs* 23.3%, p=0.561). Above that, hypertension was one significant influencing factor in the univariate analysis (32 *vs* 24, p=0.035). No difference in ICU and hospital mortality could be detected between the HSV-infected and HSV non-infected cohort (57.4% *vs* 45.2%, p=0.219) (Table 2

and Figure 1). Multivariate analysis revealed the length of ICU stay as the main influencing factor for HSV-infection [OR 1.05 (1.02-1.06)] (Table 3). Diabetes mellitus was also statistically significant in the multivariate analysis, as were leukocytes on admission [OR 3.38 (1.17-1.06) and OR 1.11 (1.02-1.23), respectively]. Immunosuppression and treatment with dexamethasone had no statistically significant effect on the rate of HSV-infections [OR 1.17 (0.42-3.33) and OR 1.55 (0.62-3.94)].

Table 1. Characteristics of COVID-19 patients with mechanical ventilation.

n	134
Age (median [IQR])	72.5 [60 to 78]
Sex = male (%)	98 (73.1)
BMI (median [IQR])	26.3 [23.5 to 30.7]
SOFA (median [IQR])	6 [4 to 11]
Missing (%)	4 (2.9)
LOS ICU (median [IQR])	16 [11 to 31]
LOS hospital (median [IQR])	27 [15 to 43]
Duration of mechanical ventilation (in hours) (median [IQR])	308 [150 to 548]
Missing (%)	2 (1.4)
ICU mortality (yes, %)	68 (50.7)
History of immunosuppression (yes, %)	34 (25.4)
Missing (%)	1 (0.7)
Therapy with dexamethasone (yes, %)	80 (59.7)
Inflammation parameters at ICU admission	
Baseline procalcitonin (median [IQR])	0.3 [0.2 to 1.0]
Baseline CRP (median [IQR])	13.9 [7.5 to 21.9]
Baseline IL-6 (median [IQR])	110.5 [52.2 to 233.3]
Baseline leukocytes (median [IQR])	9.1 [6.2 to 12.0]
Timeline COVID-19 infection	
March till July 2020%)	48 (35.8)
September 2020 till January 2021 (%)	86 (64.2)
Comorbidities	
Malignancy (%)	27 (20.1)
Diabetes mellitus (%)	39 (29.1)
COPD (%)	9 (6.7)
Hypertension (%)	56 (41.7)

BMI, body mass index; SOFA, sequential organ failure assessment; LOS, length of stay; ICU, intensive care unit; CRP, C-reactive protein in mg/dl; IL-6, interleukin 6 in ng/ml; CMV, *Cytomegalovirus* (was considered positive above 1250 Geq/ml); COPD, chronic obstructive pulmonary disease.

Table 2. Univariate analysis of patients with detection of HSV-infection in bronchoalveolar lavage. Results above 500 Geq/ml were considered positive.

	Yes (n=61)	No (n=73)	p
Age (median [IQR])	73 [61 to 78]	72 [57 to 79]	0.590
Sex = male (%)	47 (77.0)	51 (69.9)	0.460
BMI (median [IQR])	27.2 [24.5 to 31.3]	25.8 [23.1 to 29.6]	0.151
SOFA (median [IQR])	7 [4 to 10]	6 [3 to 11]	0.655
LOS ICU (median [IQR])	24 [16 to 43]	13 [6 to 20]	<0.001
Duration of mechanical ventilation (in hours) (median [IQR])	417.0 [267.0 to 767.0]	214.0 [85.0 to 407.0]	<0.001
LOS hospital (median [IQR])	37 [23 to 47]	19 [12 to 33]	<0.001
ICU mortality (yes, %)	35 (57.4)	33 (45.2)	0.219
History of immunosuppression (yes, %)	17 (27.9)	17 (23.3)	0.561
Therapy with dexamethasone (yes, %)	39 (63.9)	41 (56.2)	0.462
Inflammation parameters at ICU admission			
Baseline procalcitonin (median [IQR])	0.50 [0.20 to 1.88]	0.30 [0.20 to 0.62]	0.005
Baseline CRP (median [IQR])	18.15 [10.28 to 24.23]	12.60 [4.70 to 17.90]	0.001
Baseline IL-6 (median [IQR])	109.0 [56.0 to 246.0]	119.0 [47.90 to 202.0]	0.984
Baseline leukocytes (median [IQR])	10.04 [7.12 to 13.70]	8.38 [6.02 to 10.74]	0.031
Admission during September 2020 and January 2021of Covid-19 (%)	41 (67.2)	45 (61.6)	0.625

BMI, body mass index; SOFA, sequential organ failure assessment; LOS, length of stay; ICU, intensive care unit; CRP, C-reactive protein in mg/dl; IL-6, interleukin 6 in ng/ml; CMV, *Cytomegalovirus* (was considered positive above 1250 Geq/ml); COPD, chronic obstructive pulmonary disease.

Subanalyses of patients with high viral load (>10^6 copies /ml) compared to patients with low viral load (<10^5 copies/ml) and without HSV-infection did not show any differences of survival or ICU stay (Figure 2). Characteristics of detection of HSV-infections and treatment are presented in Table 4.

Discussion

In our cohort of critically-ill, mechanically ventilated COVID-19 patients, HSV-infection was prevalent in 46% which is a similar rate compared to a smaller cohort of French COVID-19 patients (42%) and higher comparing a previous study performed in non-COVID-19 critically-ill patients (up to 35%) [10,11]. This higher rate may be explained by the fact that COVID-19 patients are in some way immunocompromised. Studies have shown that infection with SARS-CoV-2 can lead to an impairment in the immune function by damaging lymphocytes, especially B cells, T cells, and NK cells [16]. This decrease in immune function, with the lymphopenia in particular, likely contributes to increased susceptibility to co- and secondary infections [17]. As shown in our study, elevated baseline inflammation parameters such as procalcitonin, C-reactive protein or leukocytes were associated with a significantly higher risk for HSV-infection. Although these laboratory values are not specific for viral infections, they can be considered as a warning sign for potentially infection complications during a prolonged ICU stay. Additionally, we cannot exclude that the frequent examinations of respiratory specimen in this study led to higher detection rates of HSV-infections than in other studies. Length of mechanical ventilation and ICU stay have been described as main risk factors for HSV-infection in previous studies which could be confirmed by our results.

Interestingly, previous immunosuppression and treatment with dexamethasone did not increase the detection of HSV-infection in mechanically ventilated patients. In the RECOVERY trial a regimen of 6 mg dexamethasone for 10 days was evaluated and consequently recommended by international guidelines One possible explanation might be, that either duration or dosage is too low to reach statistical significance in this cohort. As proposed by other studies, the overall severity of the disease (as indicated by the SOFA and APACHE II Scores) was associated with increased morbidity and poorer outcome in patients with viral infections and

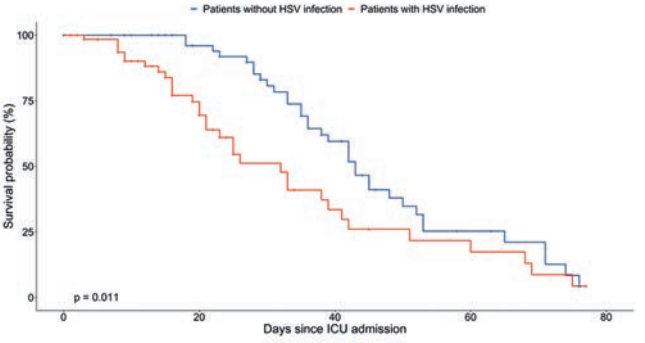

Figure 1. Kaplan Meier Curves for patients with and without HSV infection. The figure shows survival curves plotted based on the days since ICU admission. Red curves indicate patients without detection of HSV infection during ICU stay. Blue curves designate patients with positive HSV replication in bronchoalveolar samples.

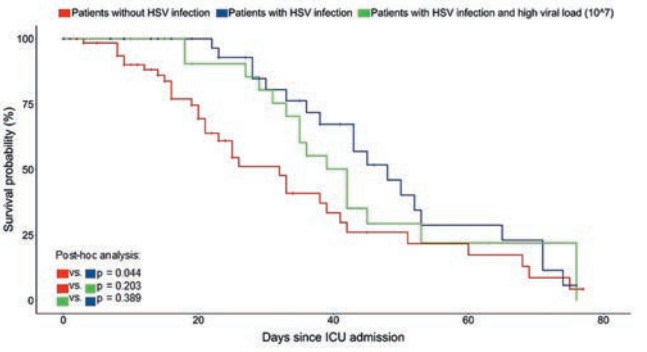

Figure 2. Kaplan Meier Curves for patients without and with HSV-infection stratified by viral load. The figure shows survival curves plotted based on the days since ICU admission. Red curves indicate patients without HSV detection during ICU stay. Blue curves designate patients with positive HSV replication in ETA/BAL samples. Additionally, green curves indicate patients with a high viral load (defined as >10^6 copies /ml). Survival is reduced in the group of patients without HSV-infection (p=0.03). There is no difference between high and low viral load.

Table 3. Multivariate analysis of patients with detection of HSV-infection in bronchoalveolar lavage in a multivariate analysis. Results above 500 Geq/ml were considered positive.

Predictors	Odds ratios	CI (95%)	p
0.01	0.00–0.29	0.014	
Age 1.01	0.98–1.05	0.398	
Sex (ref= male)	1.05	0.71–5.66	0.203
BMI 1.06	0.98–1.15	0.150	
SOFA	0.90	0.80–1.01	0.093
LOS ICU	1.05	1.02–1.08	0.001
History of immunosuppression (ref= yes)	1.17	0.42–3.33	0.764
Therapy with dexamethasone (ref= yes)	1.55	0.62–3.94	0.348
Inflammation parameters at ICU admission			
Baseline PCT	1.02	0.94–1.08	0.653
Baseline CRP	1.01	0.99–1.03	0.329
Baseline leukocytes	1.11	1.02–1.22	0.021
Observations	110		

CI, confidence interval; BMI, body mass index; SOFA, sequential organ failure assessment; LOS, length of stay; ICU, intensive care unit; PCT, serum procalcitonin; CRP, C-reactive protein in mg/dl; IL-6, interleukin 6 in ng/ml.

Table 4. Characteristics of detected HSV-infections and treatment. Results above 500 Geq/ml were considered positive.

Treatment with acyclovir (yes, %)	53 (86.9)
Duration of treatment (in days) (median [IQR])	12 [8 to 16]
Treatment with additional anti-infective therapy n = no (%)	10 (17.9)
Ongoing SarsCoV infection = no (%)	29 (49.2)
Number of dosages per day (%)	
1	8 (13.1)
2	2 (3.3)
3	42 (68.9)
Single dosage in mg (%)	
375	3 (5.9)
750	47 (92.2)
1250	1 (2.2)
Total dosage per day (median [IQR])	2250 [2250 to 2250]
Dosage per bodyweight in kg (median [IQR])	9.4 [7.7 to 10.0]
HSV peak in Geq/ml (median [IQR])	2150000 [183775 to 28250000]
Number of BAL samples (median [IQR])	5 [3 to 8]
LOS ICU until first positive sample	9.00 [7 to 13]

LOS, length of stay; ICU, intensive care unit; IQ, interquartile range; HSV, Herpes simplex virus; BAL, bronchoalveolar lavage.

compromised immune system in contrast to single influencing factors such as dexamethasone therapy [11,18]. This observation applies in particular to infections with CMV, leading to increased mortality [12]. In our cohort, CMV was not detected and we could not find a statistically significant difference in ICU and hospital mortality in COVID-19 patients with or without HSV-infection. This reflects, in our opinion, the importance of the length of ICU stay and duration of mechanical ventilation as influencing factors. If the patients survive the first days of shock and multiorgan failure, secondary infections can occur. To our knowledge, data on CMV infection in severely affected COVID-19 patients apart from case reports are sparse. One study revealed a low CMV incidence of approximately 10%, which was linked to corticosteroid treatment. As only half of the cohort in our study received dexamethasone, the sample size might be too small to detect the presence of CMV [19].

Brenner *et al*. found the morbidity and mortality to be increased in non-COVID-19 patients with a high viral load of HSV (>10^8 copies/ml) [20]. This finding could not be confirmed in a subanalysis of our cohort showing that survival and length of ICU stay were similar independent of the viral load. Of note, we chose >10^6 as cut-off for high viral load, as the number of patients with a >10^8 copies/ml was limited. Although the Kaplan-Meier Curves suggest a trend towards lower mortality in the group with HSV-infection, this cannot be interpreted as a survival advantage. In our opinion, this rather supports that the length of ICU stay and mechanical ventilation are the main influencing factors. We note that detection of HSV-infection might have been missed in patients with a particular severe course of the disease leading to death within the first week after admission to the ICU as the first positive samples occur on average 8 to 9 days. To date, there are no randomized controlled trials investigating the effect of antiviral treatment in critical-ill patients with HSV-infection and an appropriate cut-off value. In a retrospective study performed by Schuierer *et al*., a cut-off of 10^5 copies /ml was chosen to distinguish between high and low viral load. As a result, the treatment with acyclovir in the group with high viral load led to a significantly longer time to death in the ICU, reduced hazard ratio for ICU death, and improved circulatory and pulmonary oxygenation function in patients with ventilator-associated pneumoniae [19]. In all of these studies, the day of material sampling was not consistent and foremost based on clinical symptoms. This may have an effect on the detection of HSV and consequently the group assignment to high and low viral load, as the length of mechanical ventilation may influence the concentration in the respiratory sample [19]. De Vos *et al*. described an exponential increase to reach very high HSV peaks (10^6-10^{10}copies/ml) after a median of 7 days of intubation [21] in a study performed in non-COVID-19 patients from 2009. It remains unclear, why the reactivation of HSV occurs in the first place. As it is known, there is a high prevalence of HSV-1 carriers in the population in contrast to infections with HSV-2, which is typically causative for genital herpes. Luyt *et al*. demonstrated an association of HSV bronchopneumonitis with oral-labial lesions and macroscopic bronchial lesions visible during bronchoscopy. The authors hypothesize that mucosal damage due to intubation and mechanical ventilation may trigger HSV reactivation [21]. As we did not routinely perform bronchoscopy in our study and oral-labial lesions or further symptoms of HSV were not assessed, we cannot confirm this hypothesis.

Lastly, nearly 80% of the patients in our study were treated with additional anti-infective agents due to bacterial and fungal co-infections (Table 4). Frequent use of antimicrobials despite low numbers of confirmed bacterial and fungal co-infections have been reported in a recent study from our group [22]. However, high rates of pulmonary enterobacterial and *Aspergillus* spp. infections have been described in severely affected patients [22]. Whether, this affects the rate of HSV-infections and the clinical course, can only be speculated. As the rate of confirmed co-infections was rather low, especially with respect to blood stream infections (4.2%), it can be postulated, that the infection with HSV had a major influence on the clinical situation of the patient.

This study has some limitations: due to the monocentric observational character, therapy with anti-virals (such as acyclovir) was not covered in this analysis, so that efficacy of antiviral treatments for these patients still remains unclear. However, the viral load adequately decreased over time and correlated with survival/length of ICU stay (Figure 2).

As described in other studies, acyclovir treatment was associated with significant longer time of ICU stay in patients with HSV-infection which means potentially time to recovery of organ dysfunction. As there is no difference in mortality in both groups, also the question, whether these viral infections are of pathogenetic relevance or represent harmless diagnostic findings cannot be answered in a satisfactory manner.

Conclusions

To our knowledge, this is the first study investigating HSV-1 infection including COVID-19 patients receiving corticosteroid therapy. Our study suggests a high prevalence of HSV-infections in critically-ill COVID-19 patients. This justifies the recommendation to regularly monitor the prevalence of viral-coinfections and consider treatment in critically-ill patients on the ICU ideally with a standardized workflow. Surprisingly, detection of HSV was much more common than detection of CMV, which is reported to be associated with poorer outcome. The recommended treatment with corticosteroids for severe forms of COVID-19 does not seem to affect the prevalence of HSV-infection. Whether, HSV infections have an impact on organ function and survival or just reflect the severity of disease and the usefulness of treatment still remains unclear and should be targeted in further investigations.

Abbreviations

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2;
IMV: invasive mechanical ventilation;
CMV: Cytomegalovirus;
HSV: Herpes simplex virus;
ETA: Endotracheal aspirates;
BAL: bronchoalveolar lavage.

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