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Impact and Occurrence of Herpesvirus and Aspergillosis Superinfection in Patients with Severe COVID-19 Pneumonia

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Abstract: Background: Pulmonary superinfections with Herpesviridae and *Aspergillus* spp. are common in severe coronavirus disease 2019 (COVID-19) pneumonia but their epidemiology and impact remain poorly understood. Methods: We conducted a retrospective observational study of 61 mechanically ventilated COVID-19 patients at Deventer Hospital's ICU (2020–2021) who underwent bronchoalveolar lavage (BL) due to clinical deterioration. We analyzed blood and respiratory samples, treatment, and clinical outcomes. Results: Among 61 mechanically ventilated COVID-19 patients who underwent BL, 34 (55.7%) had superinfections, with 18 having COVID-19-associated pulmonary aspergillosis (CAPA), 7 having herpes simplex virus (HSV) infection, and 9 having both. Patients with HSV had later diagnoses (median 14 vs. 8 days, $p = 0.014$), longer mechanical ventilation (median 47 vs. 18.5 days, $p = 0.015$), and longer ICU stays (median 74 vs. 24 days, $p = 0.021$) compared to CAPA patients. At baseline, laboratory parameters and treatment (dexamethasone or tocilizumab) showed no significant association with superinfections. Mortality did not differ significantly among groups. Conclusion: In mechanically ventilated COVID-19 patients undergoing bronchoalveolar lavage, HSV reactivation occurred later in the course of illness and was associated with longer mechanical ventilation and ICU stays compared to CAPA. Baseline parameters did not predict superinfections.

Keywords: herpes simplex virus; COVID-19 superinfection; CAPA

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus), has had a profound global impact, resulting in significant loss of lives. Severe COVID-19, characterized by systemic manifestations, is primarily driven by an excessive inflammatory response mediated by the release of proinflammatory cytokines and chemokines. As of June 2020, the standard of care for modulating the cytokine storm in critically ill COVID-19 patients, particularly those admitted to the intensive care unit (ICU), has included the use of immunomodulatory agents such as corticosteroids and, since February 2021, also interleukin-6 (IL-6) inhibitors [1,2].

One concerning aspect of COVID-19 is the propensity of patients to develop secondary infections, which have been associated with increased mortality, especially in severe cases. The delayed treatment of these superinfections can further exacerbate the mortality rate [3].

A prior study revealed a higher incidence of Herpesviridae reactivations in patients with COVID-19 acute respiratory distress syndrome (ARDS) than previously reported in critically ill patients. Additionally, patients experiencing Herpesviridae reactivation endured more prolonged mechanical ventilation [4]. Furthermore, earlier investigations demonstrated that *Aspergillus* can cause coinfections in severe COVID-19 patients, with a reported incidence ranging from 19.6% to 33.3%, referred to as COVID-19-associated

pulmonary aspergillosis (CAPA), and these cases were associated with a high overall mortality rate of up to 64.7% [5].

The reduction in lymphocytes and compromised host immune function due to COVID-19 may contribute to the susceptibility to coinfections [6]. Concerns have been raised regarding the potential increased risk of superinfections with herpesviruses and *Aspergillus* in COVID-19 patients treated with immunosuppressive agents, such as corticosteroids and IL-6 inhibitors. However, the available data on this matter are currently inconclusive. Notably, the RECOVERY trial demonstrated that the use of dexamethasone reduced 28-day mortality in patients requiring invasive mechanical ventilation or oxygen for COVID-19, with no reported increase in superinfection rates [2]. Furthermore, low-dose steroid treatment in a population without COVID-19 has shown little or no increased risk of infection [7]. Nonetheless, certain observational studies have indicated dose-dependent increases in infection risk, including opportunistic infections [7]. One study of severe COVID-19 patients found no increased risk of superinfection associated with tocilizumab or dexamethasone treatment [8].

The primary objective of this study was to investigate the incidence of Herpesviridae reactivations and CAPA superinfection in mechanically ventilated ICU patients who underwent bronchial lavage (BL) due to clinical deterioration. Additionally, we aimed to identify risk factors associated with clinical outcomes in these patients.

2. Materials and Methods

2.1. Study Design and Population

We retrospectively collected data from electronic records of mechanically ventilated COVID-19 patients admitted to the ICU of Deventer Hospital who underwent bronchial lavage. This study included patients admitted between March 2020 and December 2021, all of whom had a confirmed COVID-19 infection through polymerase chain reaction (PCR) testing. It is noteworthy that, within this timeframe, our dataset predominantly pertains to the B1.1.7 and B1.617.2 variants of the virus [9]. In this study, all participants underwent a regimen of Selective Decontamination of the Digestive Tract (SDD), a prophylactic strategy aimed at reducing the incidence of nosocomial infections by eradicating potential pathogenic bacteria from the oropharynx and gastrointestinal tract. The SDD protocol employed in our study involved the application of non-absorbable antibiotics, along with a short course of intravenous antibiotics, as recommended in the existing literature on SDD practices in intensive care settings [10,11]. This approach was uniformly applied to all patients to minimize the risk of bacterial superinfections. Bronchial lavage was performed when there was relevant clinical respiratory deterioration accompanied by newly emerged chest radiological infiltrates. The decision to perform bronchial lavage was made by a multidisciplinary treatment team, consisting of an intensivist, a microbiologist, and a pulmonologist. BL was always preceded by a CT scan of the chest, with or without intravenous contrast.

2.2. Clinical Parameters

We collected data on the ratio of PO_2 over FiO_2 (P/F ratio in kPa), C-reactive protein (CRP), Lactate Dehydrogenase (LDH), white blood cell count, lymphocyte count, prone positioning on the day of BL, and the treatment administered, including antiviral, antifungal, and immunosuppressant drugs. Additionally, we recorded outcome parameters, including the length of ICU stay, need for renal replacement therapy, duration of mechanical ventilation, and mortality.

2.3. Bronchial Lavage and Testing of Samples

All BL specimens were analyzed for herpes simplex virus (HSV) and Cytomegalovirus (CMV) using polymerase chain reaction (PCR) assays and screened for fungal pathogens through comprehensive fungal cultures and galactomannan antigen testing (using Virclia Elisa®, Vircell, Granada, Spain) to detect Aspergillus. In instances where patients underwent repeated BL procedures, the initial BL specimen that yielded a positive result for

galactomannan, a positive fungal culture for *Aspergillus* species, or a positive PCR result for HSV or CMV was prioritized for analysis.

Pulmonary viral reactivation was characterized by the detection of low PCR cycle threshold (Ct) values (<30) in BL fluid, in conjunction with corroborative PCR positivity in blood specimens, indicative of systemic viral dissemination.

The diagnosis of CAPA was contingent upon the demonstration of pulmonary infection through positive galactomannan antigen testing, the isolation of *Aspergillus* spp. in culture, or the histopathological identification of *Aspergillus*, coupled with the detection of *Aspergillus* DNA via PCR in samples obtained through sterile techniques from pulmonary sites exhibiting infectious pathology [12].

2.4. Statistical Analysis

Statistical analyses were performed using SPSS software, version 24. Continuous variables were described as medians and interquartile ranges (IQR), while categorical variables were summarized as counts and percentages. Comparisons between groups were conducted using the Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. The relationships between baseline or laboratory parameters and herpes reactivation or CAPA were examined using logistic regression analysis. A p-value of less than 0.05 was considered statistically significant. All statistical tests were two-sided and designed to determine the strength of the association between clinical parameters and outcomes among our study cohorts.

2.5. Hospital Hygiene and Infection Prevention Measures

The initial identification of a cluster of infections with *Aspergillus* spp. in the ICU prompted an investigation by the hospital infection prevention team. The adherence to hygiene measures for hospital equipment was investigated, as well as an investigation into ICU room ventilation and air quality.

3. Results

3.1. Baseline Parameters

Among the 160 mechanically ventilated COVID-19 patients admitted to our ICU, 61 underwent bronchial lavage due to clinical and respiratory deterioration. The median age of these patients was 67 (with an interquartile range [IQR] of 63–72) and 45 (73%) of them were male. The median body mass index was 27.9 (IQR 25.6–33.4). Upon admission to the ICU, 52 (85.2%) of the patients received dexamethasone at a dose of 6 mg for 10 days, and 29 (57%) received a single dose of 600 mg tocilizumab.

3.2. Superinfections

As shown in Figure 1, among the 61 patients who underwent bronchial lavage, 18 had CAPA, 7 had herpesvirus reactivation (5 HSV and 2 CMV), 9 had both herpesvirus reactivation (8 HSV and 1 CMV) and CAPA, and 27 had neither viral reactivation nor fungal superinfection. In the total population of ICU-admitted COVID-19 patients (n = 160), the CAPA and herpesvirus reactivation incidences were, respectively, 27 (17%) and 16 (10%).

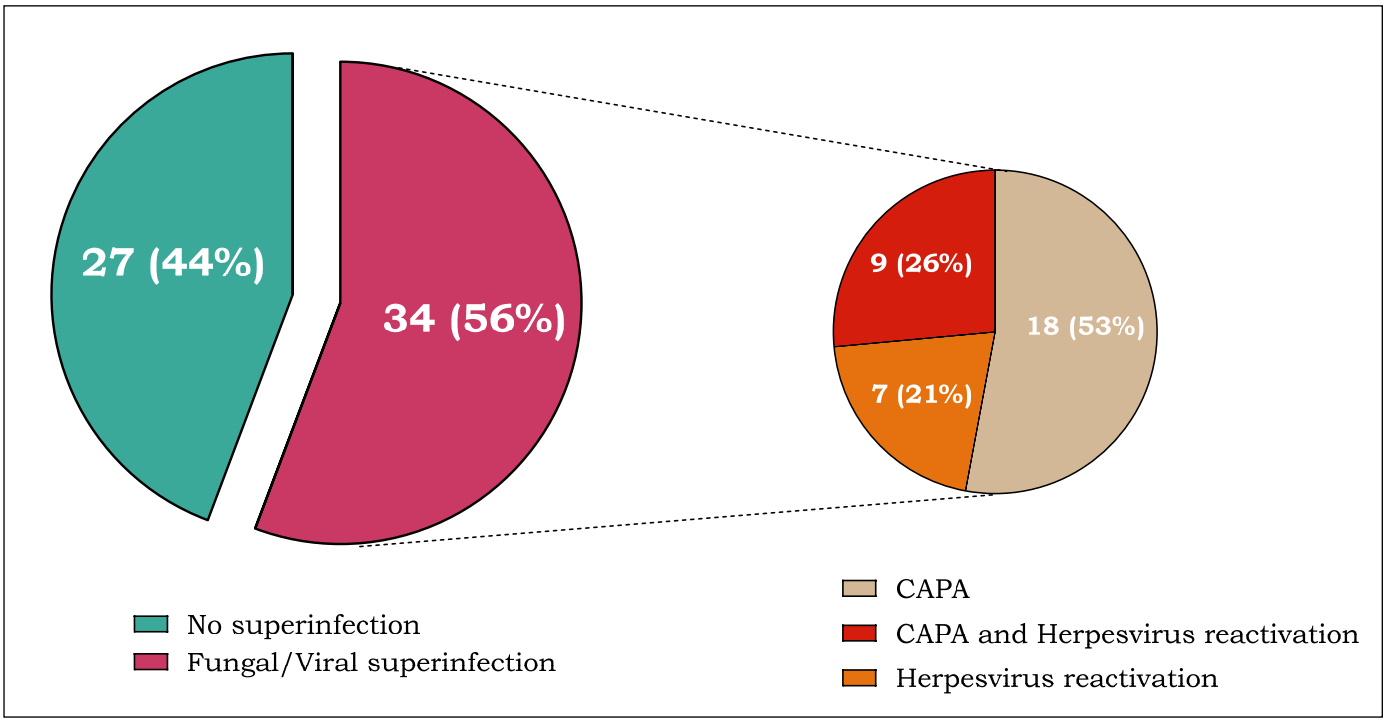

Figure 1. Pie Chart Showing Distribution of Superinfections Among Mechanically Ventilated COVID-19 Patients, Who Underwent Bronchoalveolar Lavage Due To Clinical Deterioration (n = 61). The data are presented as counts and percentages of the total and respective subgroups. Abbreviations: CAPA COVID-19 Associated Pulmonary Aspergillosis.

3.3. Antimicrobial and Anti-Inflammatory Treatment

Patients with CAPA received antifungal treatment, primarily with voriconazole or caspofungin, and in cases of proven azole resistance, liposomal amphotericin B. Patients with a positive herpes virus PCR on BL and PCR tests on whole blood were treated with appropriate antiviral agents. Patients with HSV reactivation received acyclovir, while those with CMV reactivation were treated with ganciclovir.

If the CT scan showed signs of organizing pneumonia or fibrinous organizing pneumonia, prolonged treatment with intravenous corticosteroids (in a typical dose of 1 mg/kg/day), regardless of the 10 days of dexamethasone given early during the ICU admission, was considered by the team members [13]. In the decision to treat with corticosteroids, clinical factors were weighed, such as the risk of promoting CAPA or other opportunistic infections and the nature and distribution of the radiological chest abnormalities. The therapy was continued for several weeks, until a response was noted, and was tapered thereafter. No patients with an active CAPA were treated with corticosteroids, while 25.9% of patients with negative results on both the *Aspergillus* and HSV tests were treated with corticosteroids.

3.4. Outcome

Table 1 shows the comparative analysis between patients exclusively manifesting herpesvirus reactivation and those exclusively presenting with CAPA; the following distinctions were observed. Herpesvirus reactivation exhibited a delayed diagnosis in the course of mechanical ventilation, with a median onset of 14 days compared to 8 days for CAPA (p = 0.014). Furthermore, patients experiencing herpesvirus reactivation displayed significantly prolonged durations of mechanical ventilation (median 47 vs. 18.5 days, p = 0.015) and extended stays in the ICU (median 74 vs. 24 days, p = 0.021).

Table 1. Comparative analysis between patient groups. Data are presented as medians (IQR: interquartile range) and counts (%).

	Total (n = 61)	CAPA (n = 18)	Herpesvirus Reactivation (n = 7)	CAPA and Herpesvirus Reactivation (n = 9)	No CAPA/Herpesvirus Reactivation (n = 27)	p-Value * All Groups	p-Value ± CAPA vs. HSV
Baseline parameters							
Sex (man)	45 (73,8)	15 (83.3)	4 (57.1)	5 (55.6)	21(77.8)	0.306	0.298
Age, years	67 (63–72)	66 (61.5)	65 (64–72)	66 (57–74)	69 (64–72)	0.900	1.000
Dexamethasone	52 (85.2)	16 (88.9)	6 (85.7)	9 (100)	21 (77.8)	0.400	1.000
Tocilizumab	29 (57)	7 (38.9)	5 (71.4)	5 (55.2)	12 (44.4)	0.479	0.202
BMI	27.9(25.6–33.4)	29.3 (25.8–33.6)	25.3 (25–29.4)	29.9 (24.3–34.9)	27.7 (25.0–32.0)	0.754	0.326
Laboratory findings							
White blood cell count, /nL	13.3(8.7–20.4)	13.6 (8.8–20.7)	17.3 (7.1–23.5)	12.2 (10.3–21.3)	12.1 (7.4–20.4)	0.887	0.836
CRP, mL/L	68 (17.5–217.5)	55.5 (21.0–155)	70 (41–244)	83 (3–183)	133 (13–237)	0.725	0.534
P/F-ratio, kPa	19.9 (14.3–22.6)	19.6 (14–23.5)	14.7 (13.9–21.2)	16.6 (13.7–21.1)	20.4 (15.2–23.0)	0.456	0.495
Lymphocytes, /nL	1.0 (0.7–1.5)	0.9 (0.6–1.3)	1.4 (0.7–2.1)	0.8 (0.3–1.4)	1.2 (0.7–1.6)	0.552	0.220
Treatment							
Antifungal,	27 (26.2)	18 (100)	0 (0)	9 (100)	0 (0)	0.000	0.000
Antiviral	16 (15.5)	0 (0)	7 (100)	9 (100)	0 (0)	0.000	0.000
Corticosteroids	11 (10.7)	0 (0)	2 (28.6)	2 (22.2)	7 (25.9)	0.125	0.070
Outcome parameters							
Death in ICU	29 (47.5)	10 (55.6)	1 (14.3)	5 (55.6)	13 (48.1)	0.283	0.090
Renal replacement therapy	18 (29)	4 (22.2)	2 (28.6)	4 (44.4)	8 (29.6)	0.699	1.000
Prone position ventilation	24(39)	7 (38.9)	2 (28.6)	2 (22.2)	13 (48.1)	0.508	1.000
Duration of ventilation, days	24 (14.5–44)	18.5 (13–38.5)	47(31–59)	25 (9.5–45.5)	24 (14–40)	0.099	0.015
Duration of ICU stay, days	28 (17–49.5)	24 (15.5–53.0)	74 (34–88)	29.9 (24.3–34.9)	24 (14–40)	0.010	0.021
Ventilator days to BL, days	9 (5–13.5)	8 (2–12.3)	14 (11–30)	10 (6.5–13.5)	9 (4–15)		0.014
Duration of ventilation after BL, days	15 (6–28)	11 (4.8–28.5)	34 (16–36)	17 (6–23)	15 (7–24)	0.296	0.084
Ventilator-free days at day 60 after BL, days	35.5(26–45.8) [1]	39.5 (23.3–52.8) [2]	26 (23.5–34.3) [3]	37 (22.5–44) [4]	39 (30.8–49.8) [5]	0.322	0.282

* p values comparing the groups are tested using the (continuous variables) or chi-square (categorical variables). ± p values comparing the groups CAPA, and viral infection are tested using the Mann–Whitney U (continuous variables) or Fisher's exact test (categorical variables); [1] (n = 32), [2] (n = 8), [3] (n = 6), [4] (n = 4), [5] (n = 14). Abbreviations: BMI, body mass index; ICU, intensive care unit; CAPA, COVID-19-Associated Pulmonary Aspergillosis; BL, bronchial lavage.

Subsequent examination revealed a significant discrepancy in ICU length of stay among various cohorts: CAPA patients displayed a median duration of 24 days (interquartile range, IQR: 15.5–53.0), while those with viral reactivation had a median ICU stay of 74 days (IQR: 34–88). Patients with combined superinfection exhibited an intermediate ICU stay of 29.9 days (IQR: 24.3–34.9), while those without superinfection had a median ICU stay of 24 days (IQR: 14–40) (p = 0.010).

As shown in Table 2, neither pretreatment with dexamethasone or tocilizumab nor any of the other baseline or laboratory parameters demonstrated a significant association with either herpesvirus reactivation or CAPA in logistic regression analysis. Despite the significant differences in ICU length of stay and the clinical impact of superinfections, there were no discernible disparities in mortality rates between the studied groups.

Table 2. Multiple Logistic Regression Analysis for Predicting CAPA and Herpesvirus Reactivation in Mechanically Ventilated COVID-19 Patients (n = 61).

Variable	Coefficient (B)	SE	Wald	p-Value	Odds Ratio [95% CI]
CAPA					
Sex	−0.222	0.643	0.119	0.730	0.801 [0.227, 2.825]
Age	−0.026	0.044	0.365	0.546	0.974 [0.894, 1.061]
Dexamethasone	−1.247	1.044	1.426	0.232	0.287 [0.037, 2.225]
Tocilizumab	0.854	0.644	1.763	0.184	2.350 [0.666, 8.296]
BMI	0.028	0.065	0.189	0.664	1.029 [0.906, 1.169]
White blood cell count	0.021	0.040	0.267	0.605	1.021 [0.944, 1.104]
CRP	−0.004	0.003	1.460	0.227	0.996 [0.990, 1.002]
PF-ratio	0.000	0.052	0.000	0.992	1.000 [0.903, 1.106]
Lymphocytes	0.026	0.056	0.212	0.645	1.026 [0.919, 1.146]
Constant	0.518	4.162	0.015	0.901	1.678 [-, -]
Herpesvirus reactivation					
Sex	1.258	0.696	3.263	0.071	3.517 [0.899, 13.769]
Age	0.002	0.051	0.001	0.973	1.002 [0.906, 1.108]
BMI	−0.042	0.073	0.330	0.565	0.959 [0.831, 1.106]
Dexamethasone	−0.492	1.312	0.140	0.708	0.612 [0.047, 8.004]
Tocilizumab	−0.630	0.735	0.734	0.392	0.533 [0.126, 2.250]
White blood cell count	0.017	0.043	0.167	0.682	1.018 [0.936, 1.106]
CRP	0.000	0.003	0.015	0.904	1.000 [0.993, 1.006]
PF-ratio	−0.083	0.069	1.449	0.229	0.920 [0.803, 1.054]
Lymphocytes	−0.049	0.100	0.233	0.629	0.953 [0.782, 1.160]
Constant	1.430	4.735	0.091	0.763	4.178 [-, -]

Abbreviations: SE, standard error; CI, confidence interval; BMI, body mass index; CAPA, COVID-19-Associated Pulmonary Aspergillosis.

The inquiry conducted by the hospital's infection prevention team regarding the cluster of *Aspergillus* spp. infections elucidated that the observed escalation in infections could not be attributed to either equipment sanitation practices or the quality of the air and ventilation systems.

4. Discussion

This retrospective study investigated the incidence and clinical associations of CAPA and Herpesvirus superinfections in patients with severe COVID-19 pneumonia admitted to the ICU department. The incidences of CAPA and Herpesvirus reactivation in this population were 17% and 10%, respectively. In patients with respiratory deterioration, the incidences increased to 44% and 15%, respectively. A total of 15 (56%) of the 27 CAPA patients and 6 (38%) of the 15 patients with Herpesvirus reactivation died.

Our findings of a cluster of CAPA cases within our ICU, initially perceived as a rare complication, aligned with the evolving understanding of CAPA as a significant concern among critically ill patients. This observation is consistent with reports from other centers, suggesting that CAPA might emerge in various settings without identifiable nosocomial sources. For instance, Koehler et al. (2020) documented an increased incidence of CAPA in severe COVID-19 cases, emphasizing the need for heightened surveillance and diagnostic vigilance in ICUs treating COVID-19 patients [14].

The incidence of Herpesvirus reactivation in our cohort further contributes to the expanding body of evidence linking severe COVID-19 to viral reactivations, which may exacerbate patient outcomes. Luyt et al. (2020) reported a significant association between Herpesvirus reactivation and prolonged ICU stays among COVID-19 patients, highlighting the intricate interplay between viral infections and COVID-19 severity [15].

The absence of new bacterial superinfections post-bronchoscopy (BL) in our study could be attributed to multiple factors. The implementation of Selective Digestive Decontamination (SDD) might have played a crucial role in minimizing bacterial superinfections, as supported by Roquilly et al. (2021), who demonstrated the efficacy of SDD in reducing ICU-acquired infections among critically ill patients [16]. Additionally, the early identification of bacterial pathogens via sputum culture before BL could have contributed to timely targeted interventions, thereby preventing subsequent bacterial superinfections.

Interestingly, 44% of our patients with respiratory deterioration showed no evidence of superinfection, underscoring the complexity of COVID-19 pathophysiology and the potential involvement of non-infectious mechanisms such as immune dysregulation or thromboembolic events. This is consistent with findings from Grasselli et al. (2020), who noted that a substantial proportion of COVID-19 patients in ICUs experienced deterioration without clear infectious etiologies, suggesting multifactorial contributors to disease progression [17].

The application of high doses of corticosteroids in patients with non-resolving ARDS, as reflected in our cohort, brings to light the contentious nature of this intervention. The study by Lopinto et al. (2021) elucidates an increased mortality risk associated with high-dose corticosteroid therapy in ARDS, emphasizing the critical need for judicious steroid use and further research to delineate its role in COVID-19 management [18,19].

Despite the notable incidences of CAPA and Herpesvirus reactivation, our analysis did not reveal a direct correlation with adverse clinical outcomes. This observation is in line with the study by Prattes et al. (2021), which found that CAPA, while prevalent, did not independently affect mortality in COVID-19 patients, suggesting that the impact of fungal superinfections on outcomes may be modulated by other factors [20].

In our cohort, the incidence of CAPA was remarkably high at 44%, which may prompt considerations for anti-mold prophylaxis in similar ICU settings. However, it is crucial to note that not all cases of severe COVID-19 may warrant such measures. According to the study by Young et al. (2024), prophylactic strategies should not be universally applied to all COVID-19 patients [21]. The research suggests that the decision to use anti-mold prophylaxis should be carefully considered, particularly because COVID-19 itself does not automatically indicate the need for these preventive interventions. This calls for a more nuanced approach, where the benefits of prophylaxis are weighed against potential risks such as drug resistance and interaction. Our findings suggest the importance of targeted prophylaxis. Further studies are needed that will indicate the best candidates for mold prophylaxis among patients.

Our study's retrospective nature and the relatively small sample size may limit the generalizability of our findings. Furthermore, the observational design precludes causal inferences, warranting the cautious interpretation of the associations observed.

5. Conclusions

In conclusion, our results suggest that viral reactivation and fungal superinfection are common in critically ill COVID-19 patients. The timely identification and treatment of these superinfections may reduce the increased mortality that has previously been associated with these superinfections. The reactivation of HSV occurred later in the course of the disease and was associated with a longer duration of mechanical ventilation and longer ICU admission.

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Informed Consent Statement: Patient consent was waived due to the retrospective nature of the study.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

Conflicts of Interest: The authors declare no conflicts of interest.

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