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Review

Severe *Candida* infections in critically ill patients with COVID-19

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ABSTRACT

The frequency of co-infections with bacterial or fungal pathogens has constantly increased among critically ill patients with coronavirus disease 2019 (COVID-19) during the pandemic. Candidemia was the most frequently reported invasive fungal co-infection. The onset of candidemia in COVID-19 patients was often delayed compared to non-COVID-19 patients. Additionally, *Candida* invasive infections in COVID-19 patients were more often linked to invasive procedures (e.g., invasive mechanical ventilation or renal replacement therapy) during the intensive care stay and the severity of illness rather than more "classic" risk factors present in patients without COVID-19 (e.g., underlying diseases and prior hospitalization). Moreover, apart from the increased incidence of candidemia during the pandemic, a worrying rise in fluconazole-resistant strains was reported, including a rise in the multidrug-resistant *Candida auris*. Regarding outcomes, the development of invasive *Candida* co-infection had a negative impact, increasing morbidity and mortality compared to non-co-infected COVID-19 patients. In this narrative review, we present and critically discuss information on the diagnosis and management of invasive fungal infections caused by *Candida* spp. in critically ill COVID-19 patients.

Introduction

Candida species are the most common fungal pathogens and a major morbidity and mortality concern in hospitals. These yeasts are ubiquitous in the gut as a part of the gut mycobiome and hospital flora. They may cause either localized, i.e., oral or vaginal, or invasive disease.[1] Impaired skin barrier, breakdown in gastrointestinal mucous membranes, and surgical interventions predispose to *Candida* species overgrowth. *Candida* spp. originate either from the patient's gut or are exogenously acquired through the hands of the healthcare staff or hospital environment.[2] Beyond intestinal overgrowth, some *Candida* spp. primarily infect patients through the skin. Notably, a troublesome member of the genus is *Candida auris*, which drew considerable attention during the last decade.[3] It became a resilient nosocomial pathogen, able to withstand elevated temperatures (>40°C) and saline-rich environments and tolerate disinfectants and antifungals. It can survive on inanimate surfaces for weeks and colonize the patients' skin and nares for months, enabling the horizontal spread of the pathogen to other patients, and causing outbreaks.[4] This species was first identified in 2009 and globally expanded to evolve into five geographical clades with genetic differences that might impact susceptibility to antifungal agents.[4] An intriguing issue about *Candida auris* (*C. auris*) is its misidentification as another less resistant *Candida* spp., a fact that might result in inappropriate antifungal treatment and therapeutic failure, as almost all strains of *C. auris* are resistant to at least one antifungal class, and more than 90% are fluconazole-resistant.[5]

Invasive candidiasis is infection by *Candida* species in a normally sterile site (deep-seated infection) or bloodstream infection (candidemia). Deep-seated infections and candidemia may occur concurrently or independently; meanwhile, they can be difficult to diagnose.[6] *Candida* colonization, particularly

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when extensive, usually precedes infection and is diagnosed in about one-half of intensive care unit (ICU) patients if actively pursued.[7,8] A recent meta-analysis has found that in patients with sepsis, the odds ratio to develop invasive candidiasis was 3.32 (95% confidence interval [CI]: 1.68–6.58) when colonized compared to the non-colonized status.[7] *Candida* colonization had a very high negative predictive value of 96.9% (95% CI: 92.0–98.9%) for predicting invasive infection; however, the corresponding positive value was very low (9.1%; 95% CI: 5.5–14.6%).[7]

COVID-19 patients, when examined with shotgun metagenomic sequencing, often present with altered fecal mycobiome enriched with members of the genus *Candida*, such as *Candida albicans* and *C. auris*. This gut dysbiosis may persist for up to 12 days following discharge.[9] In severe COVID-19 infection, gut mycobiota diversity can be decreased for months. However, the relative abundance of *Candida* spp. can persist despite mycobiota recovery, while many patients' mycobiome is dominated by *C. albicans*.[10] The overuse of broad-spectrum antibiotics, which was reported during the COVID-19 pandemic, might predispose to breakthrough infections due to multidrug-resistant bacteria and fungi that reside in the patient's flora or are present in the ward and ICU environment.[11] *Candida* co-infection can be either primarily or secondarily acquired, i.e., presented together with or following the onset of COVID-19 disease (superinfection). Fungal co-infections can be severe and may worsen patients' outcomes regarding morbidity and mortality.[12-14]

In the current narrative review, we present and critically discuss up-to-date information on the diagnosis and management of invasive fungal infections caused by *Candida* spp. in critically ill COVID-19 patients, focusing on candidemia.

Incidence and Prevalence

Candida spp., after Gram-negative and Gram-positive bacteria, is the most common nosocomial isolate from the blood of patients already infected with COVID-19.[15] Notably, a multicenter study by Bauer et al.[16] found that the hospital-onset candidemia rate during the pandemic was significantly increased by about 50% compared to the pre-pandemic rate (0.13 *vs.* 0.08/1000 admissions). These findings were corroborated by the study of Routsi et al.[17], which reported a 10.3% incidence of candidemia that was 2.5–3 times higher than the pre-COVID-19 period. During the first wave of COVID-19, the multicenter MYCOVID study reported a candidemia prevalence of 6%. *Candida* bloodstream infection was the second most frequent fungal infection following COVID-19-associated pulmonary aspergillosis in mechanically ventilated COVID-19 patients.[18] However, overall, the epidemiology of COVID-19-associated candidiasis (CAC), regarding both superficial and invasive diseases, differed between studies having a range of 0.7%–23.5%.[19]

Among the members of the genus, *C. albicans* led the isolates in COVID-19 and invasive *Candida* co-infection in several reports.[20,21] On the other hand, regarding non-*C. albicans* isolates, Coşkun and Durmaz[22] found that *Candida parapsilosis* was the leading cause of candidemia cases, *Candida tropicalis* was the second, and *C. albicans* was the third among opportunistic fungal bloodstream infections. Notably, the incidence of *C. parapsilosis* increased during the pandemic.[23] Moreover, *C. auris* and *C. tropicalis* predominated in a quite recent Indian study.[24]

Regarding *C. auris*, a surveillance program conducted in a US hospital from late 2019 to early 2022 reported that one-fifth of the cases (18%) of *C. auris* colonization or infection had a history of COVID-19.[25] During the COVID-19 pandemic, the rate of *C. auris* fungemia was 1.7%, according to an Indian case series, while a Pakistani series presented an incidence rate of 1.6 cases per 1000 COVID-19 admissions.[26,27]

Risk Factors and Pathogenesis

According to clinical prediction scores for prophylaxis of candidiasis in the ICU, several risk factors are considered significant, including mechanical ventilation, central venous catheter placement, use of broad-spectrum antimicrobial treatment, recent major surgery, pancreatitis, and parenteral nutrition.[28] Regarding the COVID-19 population, immunosuppressants, such as corticosteroids and anti-interleukin (IL)-6 agents, predispose to fungal overgrowth and their translocation from the gastrointestinal tract to the bloodstream.[21] During the first wave of COVID-19, Seagle et al.[29], using surveillance data from the United States Centers for Disease Control and Prevention's Emerging Infections Program, performed a case-level analysis aiming to compare the characteristics of candidemia between patients with and without positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during a 30-day period before candidemia. Of 251 included patients with candidemia, one-quarter (25.5%) had COVID-19; the comparison was conducted with a pre-pandemic cohort of 472 cases of candidemia.[29] Patients with candidemia and COVID-19 compared to those without COVID-19 were older, more frequently of Black and Hispanic or Latino race, and more likely to require ICU-level care before and continuous renal replacement therapy (RRT) and invasive mechanical ventilation (IMV) during the 30-day period before candidemia.[29] Common candidemia risk factors, such as prior hospital admission and specific underlying conditions (e.g., chronic liver disease and solid organ malignancies), were not frequent in COVID-19 patients, but candidemia rather resulted from healthcare exposure associated with the management of severe COVID-19 (i.e., IMV, RRT, and administration of corticosteroids and tocilizumab).[29] Similarly, Macauley and Epelbaum[30] found that extended ICU stay, higher sequential organ failure assessment (SOFA) score, and longer central venous catheter duration in COVID-19 patients predisposed to secondary candidemia in non-oncological ICU patients. Alessandri et al.[31], in a single-center study, examined 138 patients with IMV and at least 10 days of ICU stay to delineate the candidemia incidence. A third of patients, who were younger with lower simplified acute physiology score (SAPS) II score, received extracorporeal membrane oxygenation (ECMO) therapy and presented with candidemia more frequently (adjusted subdistribution hazard ratio [95% CI]: 3.91 [1.73–8.86]) Another risk factor was an increased *Candida* score (3.04 [2.09–4.42]) while using vasopressor support was negatively associated with a candidemia event (0.15 [0.05–0.43]).[31]

Regarding *C. auris*, inanimate surfaces and medical objects, such as laryngoscopes and thermometers, become contaminated with *C. auris* viable yeast cells that continuously shed from the skin of colonized or infected patients, mediating transmission

of the fungus and colonization of other patients.[32-34] In situations of over-occupation and compromised infection prevention measures, such as the COVID-19 pandemic, *C. auris* thrives and quickly spreads.[34] In terms of risk factors, COVID-19 and *C. auris* in critically ill patients have several risk factors in common, such as chronic renal disease and diabetes mellitus, which facilitate *C. auris* to harbor itself alongside the virus.[34] In a US study of COVID-19 patients with *C. auris*, the median hospital stay until *C. auris* isolation was 28 days (interquartile range [IQR]: 0–123), and most patients (80%) were critically ill with a need for ICU admission and mechanical ventilation or vasopressor use.[35] Another study from Asia, which compared *C. auris* to non-*C. auris* candidemia in COVID-19 patients found higher prior antifungal exposure (100% *vs*. 27%, respectively).[27]

The results of a systematic review of *C. auris* infection cases in COVID-19 patients (with or without candidemia) showed that two-thirds had an ICU stay, central venous catheter placement, and broad-spectrum antibiotic administration, while the major underlying diseases were diabetes mellitus, hypertension, and obesity.[36] In critically ill COVID-19 patients, prior *C. auris* colonization, particularly multisite colonization, was the only risk factor independently associated with subsequent candidemia; the cumulative risk of *C. auris* fungemia was more than 25% at 60 days following colonization detection.[37]

In terms of pathogenesis, *Candida* invasion inhibits innate immune defense through epigenetic regulation of immune cell functions.[38] Neutrophils and monocytes represent an important host defense mechanism against *Candida* spp. During SARS-CoV-2 infection, a solitary decrease in lymphocytes does not seem to influence the pathogenesis of *Candida* opportunistic infection.[19] Moreover, an *ex vivo* experimental study revealed a decrease in monocyte CD80 upregulation and a lower release of IL-6, tumor necrosis factor (TNF), IL-1a, and IL-1b as COVID-19 patients' blood was stimulated with *C. albicans*.[39] Another implicated immune defect is immune exhaustion following viral sepsis-associated cytokine storm. The number of natural killer (NK) and $CD8^+$ T cells decreases and leads to a protracted immune response that cannot eliminate fungal pathogens.[40] Hoenigl et al.[41] claimed that other patient-associated clinical risk factors play a significant role in *Candida* spp. Co-infection. *C. auris* can secrete extracellular lytic enzymes, such as proteinases, which are more thermotolerant at 42°C compared to those of *C. albicans*.[42] Other relevant lytic molecules include lipases, phospholipases, and hemolysins. Moreover, *C. auris* can evade innate immunity by promoting the failure of neutrophil extracellular trap formation. Finally, it may escape the host immune system by biofilm production.[5]

Diagnosis

Population-based surveillance data analysis indicated that COVID-19-related candidemia occurred later than in patients without COVID-19; i.e., the median time from hospital admission to the initial positive culture for *Candida* was 14 days (IQR: 7–18) compared to 4 days (IQR: 0–14) for patients with and without COVID-19, respectively.[29] In 78% of COVID-19 cases (*vs.* 38%), the diagnostic specimen was collected in the ICU setting, and the median time from the SARS-CoV-2 positive test and the first *Candida* culture was 15 days (IQR: 8–21).[29] Similar results were reported by Kayaaslan et al.[21], showing median times of 13 days *vs.* 27 days between patients with and without COVID-19, respectively. On the other hand, Bishburg et al.[43], in a single-center study, found an even longer time for candidemia in COVID-19 patients: 26-day median time.

The diagnosis of invasive candidiasis usually relies on positive blood cultures or other cultures collected under sterile conditions and is considered the gold standard, although it is not sensitive. Specifically, cultures might be negative in about half of invasive candidiasis cases.[6] The basic culture media for clinical *Candida* species is usually Sabouraud dextrose agar or broth supplemented with chloramphenicol and blood agar. Another medium that can be selective is CHROMagar, which can distinguish the most common *Candida* species. Concerning *C. auris*, salt/dulcitol enrichment broth that contains 10% NaCl allows the growth of the pathogen and inhibits the growth of other *Candida* species.[44] There are other diagnostic tools, including antigens mannan and beta-D-1,3-glucan (BDG) detection, anti-mannan antibodies, *C. albicans* germ-tube antibody (CAGTA), and polymerase chain reaction (PCR)-based assays, which are adjunct to cultures.[45] Although blood culture is the gold standard for diagnosing invasive candidiasis, there are two disadvantages. First, blood cultures have a long turnaround time (it often takes 2–3 days [from 1 to 7 or more] for a culture to become positive and 2–3 more days for species identification and antifungal susceptibility test). Second, blood cultures may fail to detect fungi, especially in low-concentration candidemia (≤1 CFU/mL) or deep-tissue Candida infections without concurrent candidemia. Thus, the diagnostic tools chosen can play a decisive role in the early diagnosis of the infection. However, there is much uncertainty about their usefulness in clinical practice.[6] Biomarker BDG is a cell wall component not only of Candida but also of many other pathogenic fungi (except Mucorales, Cryptococcus, and Blastomyces species); therefore, it cannot distinguish Candida from other fungi (panfungal marker). Its added value lies in its extremely high negative predictive value and high sensitivity for invasive candidiasis; hence, it may help rule out invasive candidiasis in ICU patients.[46] The combined use of mannan and anti-mannan may be preferred over mannan or anti-mannan alone for diagnosing invasive candidiasis.[47] Used separately or in combination with each other, these non-culture-based microbiological techniques contribute to earlier antifungal treatment initiation.[48] PCR-based tests (DNA detection and miniaturized-magnetic resonance-based technology) are widely used for the direct identification of *Candida* species in blood. Nonetheless, these methods lack standardization due to heterogeneity in study designs.[48,49] Furthermore, matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) technology is gaining popularity due to the low turnaround time of less than 5 min to identify a species from an isolated colony. Moreover, there are multiple applications of MALDI-TOF in positive blood cultures with direct identification of yeast without further subculturing.[50] The latest European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines suggest the inclusion of non-culture-based assays as a part of the diagnostic strategy for invasive candidiasis to facilitate the reduction of the use of currently available antifungal agents.[51] Thus, it is worth combining culture and non-culture-based assays to speed up the diagnostic process and more accurately predict invasive candidiasis. Furthermore, it should be emphasized that clinicians should always consider the pre-test probability of invasive can-

didiasis along with test performance to optimize the usefulness of diagnostic tests.[49] Finally, it is recommended to investigate the susceptibility profile of Candida species from non-sterile cultures to guide empirical antifungal therapy.[1]

Regarding *C. auris*, the major diagnostic issue is correct identification, as some biochemical methods could not identify or misidentify it. It is frequently misidentified as *Candida haemulonii* or, less commonly, other *Candida* or *Rhodotorula* spp.[3] Selective chromogenic media may help detect *C. auris* (CHROMagar™ Candida Plus). Additionally, PCR-based assays and MALDI-TOF mass spectrometry may be valuable for correct fungal pathogen identification.[4,52]

Treatment

At present, there is no evidence for a different management of invasive candidiasis in the critically ill COVID-19 population.[1,53] Early untargeted (empirical or pre-emptive) antifungal treatment should be considered for clinically deteriorated septic non-neutropenic patients with COVID-19 despite the weak evidence for a significant reduction in mortality.[54] The first-line treatment consists of intravenous administration of fluconazole (unless there is suspicion for *C. auris*, treatment for which is detailed below*)* or an echinocandin.[1] Echinocandins are fungicidal and cover a broad spectrum of *Candida* species. Additionally, this class presents limited interaction potential with other drugs.[2] The knowledge of *Candida* spp. Local epidemiology concerning resistance to antifungal agents remains crucial for the selection of empirical antifungal treatment. Before azole treatment, colonization with azole-resistant *Candida* strains, or increased incidence of fluconazole-resistant strains based on local surveillance data are the reasons not to administer fluconazole.[1] Intolerance or resistance to echinocandins may be considered in patients treated with this new class of antifungal agents in the past. When any of these parameters exist, a step-up approach with lipid formulation amphotericin B is recommended. Empirical treatment should stop following the failure of clinical response or when microbiological diagnostic methods fail to reveal *Candida* spp.[1] Meanwhile, the high risk of CVC-associated fungal invasion often necessitates their immediate removal.[19] In neutropenic patients, contrary to critically ill individuals, *Candida* invades circulation through the gastrointestinal tract. Otherwise, treatment recommendations remain the same.[1]

Echinocandins are also recommended for targeted treatment of invasive candidiasis. De-escalation from echinocandins (or liposomal amphotericin B) to fluconazole is feasible after 5–7 days of treatment, control of the septic event, and sterilization of blood cultures when the *Candida* isolate is susceptible to fluconazole.[1]

During the COVID-19 pandemic, an increase in the frequency of fluconazole resistance was reported.[17,23,55] In a Spanish candidemia study, the incidence rate of fluconazole-resistant *C. parapsilosis* (FRCP) significantly increased from 0.09 in the pre-pandemic compared to 0.39 per 10,000 patient days during the pandemic period.[23] The FRCP incidence in COVID-19 patients was 1.34 *vs*. 0.16 in the non-COVID group (P <0.001).[23] FRCP candidemia was most frequently associated with surgical ICU admission, previous *Candida* spp. colonization, RRT, total parenteral nutrition (TPN), and arterial catheter use.[23] Notably, in another Spanish study, *C. parapsilosis* resistance to fluconazole and voriconazole increased from 27% and <2% to approximately 60% for both drugs since 2020, i.e., the start of the pandemic.[55] The expansion of various clones around the country was responsible for resistance selection.[55] In line with the above-stated, fluconazole resistance also increased in a Greek center during the pandemic compared to the pre-pandemic periods.[17] The fluconazole-resistance phenotype over the pandemic period occurred in 48.4% of candidemia cases; notably, 54.8% of *C. parapsilosis* isolates were fluconazole-resistant.[17]

On the other hand, *C. auris* treatment can be challenging, as it may present resistance to several (or even all) major antifungal classes, i.e., polyenes, azoles, and echinocandins. Resistance to fluconazole is virtually universal, while amphotericin B is inactive against the fungus in up to 30% of cases.[56] Meanwhile, most *C. auris* strains remain susceptible to the echinocandin class, which is recommended as a first-line treatment.[57] In the case of treatment failure with either clinical or fungal persistence for over 5 days, liposomal amphotericin B can be given. Finally, targeted treatment should follow the available recommendations.[1]

Prevention and Prophylaxis

Candida bloodstream infections are hospital-associated infections amenable to infection control measures. The pandemic took healthcare structures by storm and disrupted proper infection prevention education on central venous catheter insertion and handling. Proper process monitoring and re-education may decrease candidemia incidence to pre-pandemic rates.[58] Properly handling personal protective equipment is considered mandatory.[59] The Centers for Disease Control and Prevention recommends implementing contact precautions, indistinguishable from those dealing with multi-drug-resistant bacteria, to decrease transmission of the pathogen.[60] Management of multidrug-resistant organisms using isolation techniques and strict surveillance was proven crucial for decreasing COVID-19 co-infections. Thorough daily disinfection of surfaces around the patient bed and items in common use with other patients is advised.[60] Additionally, a *C. auris* carrier should, preferably, be isolated; otherwise, all those carriers should be cohorted in a separate ward. The detection of medical objects as the vehicle of *C. auris* transmission and the prompt and meticulous implementation of the above-mentioned measures controlled an outbreak in a German hospital.[32] The pathogen is thermotolerant (up to 42°C), as well as salt tolerant, and can persist for months in the inanimate hospital environment and medical objects. However, it can remain viable for 14 days on a plastic surface. It can form aggregates *ex vivo* that make the fungus physically stronger. Finally, *C. auris* is resilient to some disinfectants, such as quaternary ammonium compounds. The above-presented issues denote the ability of the fungus to persist *ex vivo*, complicating its eradication.[42]

Although colonized critically ill, medical or surgical, patients are at high risk for candidemia or invasive candidiasis, prophylaxis with antifungals is not generally recommended. This is also applicable to COVID-19 patients.[61] Cortegiani et al.[61], in a Cochrane meta-analysis of 22 randomized controlled studies, examined the effect of untargeted antifungal treatment on patients' outcomes. The intervention failed to reduce all-cause

mortality (moderate evidence), although it might have reduced the incidence of colonization and invasive infection in critically ill patients (weak evidence).[61] *Candida* prophylaxis with fluconazole or echinocandins might be considered in targeted patient groups, e.g., patients with recent abdominal surgery and recurrent gastrointestinal perforations or anastomotic leaks.

Finally, Buil et al.[62] studied the incidence of candidemia for a 30-month period after the start of the pandemic in a Dutch university ICU that uses selective digestive decontamination (SDD) as part of their routine practice (to prevent Gram-negative bacteremia and ventilator-associated pneumonia in the Dutch low-resistance setting) and compared their results with a Belgian university ICU that does not use SDD. The incidence was 0% (95% CI: 0–0.97%) and 1.4% (95% CI: 0.19–2.7%, P=0.02), respectively.[62] These findings suggest that SDD might be effective in decolonizing yeast from ICU patients with COVID-19, but further research is needed to generalize the findings.

Outcomes

The outcomes can be grave as most patients develop invasive *Candida* co-infections after a prolonged hospital stay and need invasive devices for monitoring and treatment. In a single-center case–control study of COVID-19 patients, candidemia was associated with quadruple ICU stay (40 days *vs.* 10 days in non-candidemia individuals).[43] Overall, in-hospital candidemia mortality can be as high as 62.5% in COVID-19 *vs*. 32.1% in non-COVID-19 patients.[29] This finding was confirmed by a more recent, large study that showed a respective candidemia mortality of 59.6% *vs*. 30.8% (P <0.001).[16] In the ICU setting, the mortality can be even higher, up to 92.5%.[21] Most patients (73%) with predominantly *C. auris*-related candidemia had an ICU stay lasting over 20 days. The reported mortality can be as high as 64%.[24] In a recent prospective study, *C. auris* colonization and co-infection were independently associated with mortality of hospitalized patients with COVID-19 (odds ratio: 2.36 [95% CI: 1.58–3.52] and 4.64 [95% CI: 3.12–6.91]).[63]

Conclusions

The incidence of *Candida* invasive infections increased during the pandemic. Candidemia was the most frequently reported invasive fungal co-infection in patients with COVID-19, with delayed onset and differences in the risk factors compared to non-COVID-19 patients. Immunological changes caused by SARS-Cov-2 and patient-related risk factors have been implicated in the pathogenesis of *Candida* co-infection. Early empirical or pre-emptive antifungal treatment should be considered for clinically deteriorated septic patients with COVID-19. However, the rise in fluconazole-resistant strains during the pandemic, including a rise in the multidrug-resistant *C. auris,* has made the choice of appropriate empirical or pre-emptive antifungal treatment a more challenging task. Antifungal prophylaxis in patients colonized with *Candida spp* is not generally recommended and might be considered only in targeted patient-groups. A combination of culture- and non-culture-based diagnostic tools, along with the pre-test probability, might contribute to both earlier and more accurate diagnosis of invasive *Candida* infections and, at the same time, to the avoidance of antifungal overuse. Finally, the development of invasive *Candida* co-infection has a negative impact on outcomes, increasing morbidity and mortality compared to non-co-infected COVID-19 patients.

Author Contributions

Despoina Koulenti: Conceptualization, Visualization, Writing – original draft, Writing – review & editing, Supervision. Marios Karvouniaris: Writing – original draft, Writing – review & editing. Elisabeth Paramythiotou: Writing – original draft. Nikolaos Koliakos: Writing – original draft. Nikolaos Markou: Writing – original draft. Paschalis Paranos: Writing – original draft. Joseph Meletiadis: Writing – review & editing, Supervision. Stijn Blot: Writing – review & editing, Supervision.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Not applicable.

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