Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

COVID-19 associated invasive candidiasis

To the Editor,

We have read with special interest the excellent review by Louise Lansbury and colleagues[1], 'Co-infections in people with COVID-19: a systematic review and meta-analysis'. In this review, four fungal pathogens were reported from three studies[2–4], namely *Candida albicans, Candida glabrata, Aspergillus flavus* and *Aspergillus fumigatus*. In addition, Hughes et al.[5] retrospectively analysed hospitalised patients with confirmed COVID-19 infection ($n = 836$) across two acute NHS hospitals. Among the confirmed COVID-19 infection, *C. albicans* infections were attributed to central line source. Chen and colleagues[6] reported both bacterial and fungal co-infections. Recently, Verweij et al.,[6] reported that *Aspergillus* species as co-pathogens are commonly identified in COVID-19 patients and are an important cause of mortality. Fungal co-infections and their impact on COVID-19 patients are still understudied. In this regards, we retrospectively analysed nosocomial mortality related to bloodstream infection and their risk factors associated with Covid-19 patients in the intensive care unit (ICU) at a single center in Oman. Five candidemia cases were reported from adult patients. The demographic and clinical description of patients is summarized in Table 1. All five patients were admitted to the ICU, had a central venous catheter (CVC) in place at the onset of candidemia, and received broad-spectrum antibiotic therapy.

Patient 1, A 76 years old male, was admitted with COVID pneumonia. Three days later, he had worsening respiratory parameters requiring mechanical ventilation (MV) and ICU admission. Laboratory investigations revealed leukocytosis (12,000/mm^3) with neutrophilia (10,000/mm^3) and lymphocytopenia (500/mm^3). Results showed elevated inflammatory markers (CRP of 199 mg/l, D-dimer of 80, ferritin of 1240 μg/l, LDH of 565 IU/l and Ca of 1.94 mmol/l). His 14 days of ICU admission were complicated by cytokine storm, upper gastrointestinal bleeding and multi-organ failure requiring continuous hemodialysis. He had persistent fever requiring multiple courses of broad-spectrum antimicrobials. His-respiratory and metabolic parameters deteriorated significantly with increasing vasopressors requirement. His-last blood culture grew *C. albicans* from central line. Patient died.

Patient 2, A 68 years old male with hypertension, admitted with severe COVID pneumonia requiring MV and ICU admission. Laboratory investigations showed leukocytosis (13,700/mm^3) with neutrophilia (12,400/mm^3) and lymphocytopenia (600/mm^3). His-inflammatory markers were as following (CRP of 226 mg/l, D-dimer of 6.1, ferritin of 739 μg/l, LDH of 639 IU/l, ALT of 71 IU/l with estimated GFR of 53. He had worsening renal functions and respiratory parameters with new persistent fever. His-blood culture grew *C. albicans.* He was started on caspofungin with line removal. Patient died.

Patient 3, A 38 years old male admitted with COVID pneumonia requiring MV and ICU admission. Initial blood investigations showed WBC of (8500/ mm^3, ANC of (7100/ mm^3), lymphocyte count of (900/ mm^3), CRP of 207 mg/l, D-dimer of 4.5, ferritin of 2270 μg/l, LDH of 1260 IU/l, ALT of 52 IU/l, AST of 101 IU/l, Ca of 1.89 mmol/l and creatinine of 103 μmol/l with an estimated GFR of 74. His-prolonged hospital stay was complicated by cytokine storm. He was persistently febrile and grew *C. galabrata* from blood culture. Micafungin was initiated and later shifted into caspofungin. One week later, he developed a high fever with increasing vasopressors requirement with a positive *C. galabrata* from peripheral site. Amphotericin B was added but his condition deteriorated and died.

Patient 4, A 64 years old man with hypertension, dyslipidemia and stroke admitted with COVID pneumonia. Five days later, he had worsening respiratory parameters requiring MV and ICU admission. His-laboratory reports showed a WBC of 5800/ mm^3), ANC of (4900/ mm^3) and lymphocyte count of 600/ mm^3), CRP of 12 mg/l, D-dimer of 46, ferritin of 700 μg/l, LDH of 580 IU/l, and Ca of 2.07 mmol/l. His-blood culture grew *C. albicans* and *C. tropicalis* from a peripheral site. Caspofungin was started and voriconazole was added based on sensitivity results.

Patient 5, A 49 years old man with obesity and hypertension admitted with COVID pneumonia. Three days later he had worsening respiratory parameters requiring MV and ICU admission. His-blood investigations showed a WBC of 8900/ mm^3), ANC of (6900/ mm^3) and his lymphocyte count was (1300/ mm^3), CRP of 132 mg/l, D-dimer of 0.4, ferritin of 730 μg/l, LDH of 510 IU/l, ALT of 58 IU/l, AST of 51 IU/l, Ca of 2.06 mmol/l. He received an empirical course of antibiotics in view of his persistent fever, after which he showed a good clinical improvement. However, his inflammatory markers started rising again and a repeat peripheral blood culture grew *C. albicans* and was given caspofungin.

Despite progress in public health and hospital care, infections continue to develop in hospitalised patients with COVID-19. COVID-19 patients in ICU, are at high risk of developing nosocomial infections associated with MV and respiratory manifestation.[7] Medical procedures and invasive techniques are considered as potential routes of bacterial and fungal infections which are common complications of viral pneumonia.[8] Invasive candidiasis is rare but associated with considerable mortality in critically ill patients.[9] The main risk factors for our invasive candidemia patients are; prolong hospital stays, CVC, surgical procedure and the use of broad-spectrum antibiotics (Table 1). All our 5 patients were diagnosed as invasive candidiasis by the positive blood culture. Three *Candida* species were identified; *C. albicans, C. galabrata* and *C. tropicalis* using Maldi-tof and susceptibility results shown in Table 2. All patients underwent CVC removal. Persistent candidemia occurred in one patient despite CVC removal and appropriate antifungal therapy. Four patients received antifungal therapy; two

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Table 1
Clinical characteristics of 5 patients with covid-19 associated candidemia.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	76y	68y	38 y	64y	49
Sex	M	M	M	M	M
Underlying conditions	Pneumonia	Pneumonia/ hypertension	Pneumonia/hypertension, dyslipidemia/old stroke	Pneumonia/ hypertension	Pneumonia
Real Time PCR for COVID-19	Positive	Positive	Positive	Positive	Positive
Peripheral blood culture	–	Positive	Positive	Positive	Positive
CV line blood culture	Positive	Positive	–	Positive	–
Positive culture from other sites	TS	–	CV tip	ETT	–
Presence of central venous catheter at onset of candidemia	Yes	Yes	Yes	Yes	Yes
Broad spectrum antibiotic prior to candidemia	Yes	Yes	Yes	Yes	Yes
Mechanical ventilation (MV)	Yes	Yes	Yes	Yes	Yes
ICU admission prior to candidemia	Yes	Yes	Yes	Yes	Yes
Cytokine storm	Yes	No	Yes	No	No
Colonization with *Candida* species prior to candidemia	No	No	No	No	No
Treatment with antifungals	No	Yes	Yes	Yes	Yes
Outcome	Died	Died	Died	Alive	Alive

Table 2
Maldi-tof Identification and antifungal sensitivity results for *Candida* isolates.

Identification (Maldi-tof)	Patient 1 *C. albicans*	Patient 2 *C. albicans*	Patient 3 *C. galabrata*	Patient 4 *C. albicans C. tropicalis*	Patient 5 *C. albicans*
Antifungal Susceptibility Testing by Viteck 8					
Flucanazole	ND	S	ND	S	S
Amp B	ND	S	ND	S	S
Caspofungin	ND	S	ND	S	S
Voriconazole	ND	S	ND	S	S
Micanafungin	ND	S	ND	S	S
Flucytocin	ND	S	ND	S	S

received caspofungin alone, two received combination of (caspofungin + amphotericin B) and (voriconazole + caspofungin) and one patient did not receive any antifungals. Despite antifungal therapy, 3 out of 5 patients died. Our observations suggest increased risk for critically ill COVID-19 patients to develop co-infection with *Candida*, which is likely to increase mortality rates. Considering the high mortality, the need for early recognition of candidemia and appropriate antifungal therapy are basic requirements to improve the outcome of COVID-19 patients in ICU. With this report, we aim to call attention of clinicians to recognize the nosocomial infections associated with COVID-19 patients.

Declaration of Competing Interest

The authors declare no conflict of interest

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