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ORIGINAL ARTICLE

Fungal Coinfections in COVID-19-Positive Patients at a Tertiary Care Hospital in Saudi Arabia

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ABSTRACT

Background: *Most coronavirus disease 2019 (COVID-19) patients present with mild or moderate severity of the disease. However, disease comorbidities may require mechanical ventilation and intensive care (IC), which predispose COVID-19 patients to secondary opportunistic fungal infections.* ***Objective:*** *An observational retrospective cohort study was conducted to investigate the relationship between fungal coinfections and morbidity and mortality rates in patients with severe COVID-19 admitted to a tertiary hospital in Makkah, Saudi Arabia.* ***Methodology:*** *This work was conducted on 1,220 patients with COVID-19 admitted to a Saudi Tertiary Care Hospital in Makkah city from June 1, 2020, to May 30, 2021, to evaluate the existence of fungal infections. COVID-19 cases were confirmed by real-time reverse transcription-polymerase chain reaction (RT-PCR). Statistical analysis was performed via SPSS version 22.0 (IBM, USA).* ***Results:*** *Of the 1,220 included samples, fungal coinfections were detected in 57 (4.7%) patients. Candida albicans was the major isolated strain in 39 (68.4%) patients, and the primary source of infection was sputum (40 patients: 70.2%). Most samples were isolated from the ICU (41 patients; 71.9%); bacteria coinfection was detected in 12 (21%) severely ill patients.* ***Conclusion:*** *Mindfulness of the plausibility of fungal coinfection is important to control infection and ultimately reduces the risk and the delay in diagnostic and treatment process. It will also guide the diagnostic tools in identifying high-risk patients and quickly determine the most appropriate interventions for reducing the possibility of infection besides morbidity and mortality rates.*

INTRODUCTION

The world health organization (WHO) stated that nearly all people infected with the coronavirus disease 2019 (COVID-19) virus would experience mild to moderate respiratory illness and recover without treatments. Older people with underlying medical problems including chronic respiratory disease, cardiovascular disease, diabetes and cancer are most potential to promote sever illnesses[1]. COVID-19 coinfection with other microorganisms, such as viruses, bacteria, and fungi, is critical. It increases the difficulties correlated to the diagnosis, treatment, and sequel of COVID-19 and intensify the disease symptoms and increase the morbidity and mortality rates [2].

The commensal microbiota ecosystem can modulate and be modulated by infected viruses, easing either stimulatory or suppressive effects[3]. During hospitalization, patients with COVID-19 have additional risk factors for invasive pulmonary aspergillosis (IPA) associated with intubation and corticosteroid therapy[4].

The emergence of the COVID-19 pandemic brought new challenges for healthcare workers worldwide. Among COVID-19 patients requiring hospitalization, many develop severe acute respiratory distress syndrome, are admitted to an ICU and are exposed to various agents related to candidemia[5]. Coinfections nearly repress the patient's immune system, increase antibacterial therapy intolerance, and limit the outcome of the infection[6].

In most individuals, COVID-19 infection is mild; however, coinfection can increase the susceptibility of patients to severe disease by affecting the body's immunity[7]. Besides the diffuse alveolar damage with severe inflammatory exudation, COVID-19 patients are always immunosuppressed, decreasing CD4 and CD8 cells[8]. COVID-19 infection can destroy lymphocytes,

mainly B cells, T cells, and NK cells, which leads to immune frailty during the disease period[9]. The decrease in lymphocytes and host immune functions may be the main reasons for co-infection[10].

Due to the higher co-infection rate in severely infected patients, the mortality rate is higher in severe cases compared with the non-severe group[11]. Widely seriously ill patients are most potential to take medications through invasive catheters, leading to raise sensitivity to secondary infections. Critically ill COVID-19 patients have higher pro-inflammatory (IL-1, IL-2, IL-6, TNF-α) and anti-inflammatory (IL-4, IL-10) cytokine levels, the lower cluster of differentiation (CD) interferon-gamma expression, and fewer CD cells. This difficult clinical condition expand the risk of severe fungal infections, such as invasive pulmonary aspergillosis, invasive candidiasis, or *Pneumocystis jirovecii* pneumonia[12].

Nearly all COVID-19 patients who have mild or moderate disease; however, others with comorbidities may need mechanical ventilation and intensive care, which influence them to be secondary and opportunistic infections[13]. Critically ill patients, especially those admitted to the ICU who required mechanical ventilation or those who had extended hospitalizations up to 50 days), were more probable to evolve fungal coinfections[14].

It is serious to notice that COVID-19 severely ill patients can develop fungal infections during the middle and later stages of the disease[15]. Thus, the current study investigated the correlation between fungal coinfections and morbidity and mortality in patients with severe COVID-19 admitted to a tertiary hospital in Makkah, Saudi Arabia.

METHODOLOGY

We conducted an observational retrospective cohort study on 1,220 patients with COVID-19 admitted to a Saudi Tertiary Care Hospital in Makkah city from June 1, 2020, to May 30, 2021, to assess the presence of fungal infection. Following the WHO guidance, the diagnosis of SARS-CoV-2 i.e., the COVID-19 virus) cases was confirmed by Real time reverse transcription-polymerase chain reaction RT-PCR) assays of nasopharyngeal swabs. All the patients admitted to the hospital during the study period who met the clinical diagnostic criteria and had confirmed RT-PCR were included. The patients were admitted to the medical, surgical, or ICU departments.

Collection of Data:

Data were collected and reviewed by one of the health information system researchers of the hospital. The data included demographic information i.e., age, sex, comorbidities, laboratory results of inflammatory markers and microbiological tests, management procedures, and outcomes).

Procedures:

The inflammatory markers were assayed using the Dimension® EXL™ fully automated system (SIEMENS Healthcare Diagnostics, USA). Complete blood pictures were analyzed via the SYSMEX XN-1000 cell counter (SYSMEX America, USA). Fungal infections were tested using standard microbiologic procedures. The number of days from COVID-19 diagnosis to the date of fungal infection diagnosis and the whole length of stay (LOS) were calculated.

Statistical analysis:

A descriptive analysis of the data was performed, including demographics, clinical data, and laboratory results. The quantitative, continuous data were described as medians (interquartile range (IQR)), while categorical data were presented as frequencies (percentage). Statistical 1 analysis were done via SPSS version 22.0 (IBM, USA).

RESULTS

The study included 1,220 samples. Fungal coinfections were detected in 57 (4.7%) patients aged 29–104 years (median 61; IQR 51–73 years), of which 30 (52.6%) were males. The median (IQR) duration from COVID-19 diagnosis to fungal infection diagnosis was 7 (4–12) days. While the median (IQR) ICU LOS was 13 (7–21) days. The primary demographic data 6 are shown in Table (1).

Table 1: Basic Demographic, Clinical, and Laboratory Performance.

Age (Median, 25th/75th percentile)	**61 (51-73)**
Sex (Male (%))	**30 (53%)**
Comorbidities N (%)	**N (%)**
HPN	**39 (68%)**
DM **(Diabetic foot)**	**39 (68%)** **3 (5%)**
Chronic kidney disease **(On Dialysis)**	**12 (21%)** **8 (14%)**
Cardiovascular disease	**16 (28%)**
Cerebrovascular disease	**7 (12%)**
Neurological disability	**7 (12%)**
Lung fibrosis	**2 (4%)**
Atrial fibrillation	**2 (4%)**
SCD	**2 (4%)**
Other comorbidities Hypothyroidism, Hepatitis C viral infection, Liver disease, Bronchial asthma, COPD, Pulmonary HPN, Interstitial lung disease, Bed-ridden with sores	**1 for each (2%)**
No comorbidity	**9 (16%)**
Inflammatory markers (Median, 25th / 75th percentile)	
Leukocytes	**13.14 (8.93/20.70)**
Neutrophils	**8.9 (6.81/15.72)**
Lymphocytes	**1.3 (0.65/1.60)**
NLR	**5.84 (2.34/12.54)**
CRP mg/L	**140 (86.9/251)**
Ferritin ng/ml	**984.32 (420.81/1873.22)**
Procalcitonin ng/ml	**0.83 (0.28/2.30)**
LDH U/L	**1040.65 (548/1976.34)**
D-dimer mg/L	**6.31 (3.78/15.61)**
Critical durations (Median days, 25th/75th percentile)	
ICU LOS	**13 (7-21)**
Days from Covid to fungal infection	**7 (4-12)**

HPN: Hypertension, DM: Diabetes mellites, SCD: Sickle Cell Disease, COPD: Chronic obstructive pulmonary disease, NLR: Neutrophil/Lymphocyte ratio, CRP: C-reactive protein, LDH: Lactate dehydrogenase, LOS: Length of Stay. The mean age of discharged patients (60.84) was significantly lower than that of those who died (55.6; <0.0001). *Candida albicans* was the significant isolated strain (39 patients: 68.4%), whereas the primary source of infection was sputum (40 patients: 70.2%). Aspergillus was isolated from 2 (3.5%) sputum samples. *Candida tropicalis* was the major candida non-albicans (12 patients: 21.1%) species. The sources of isolated fungal strains are shown in Table (2).

Table 2: Sources of Isolated Fungal Strains

	Sputum	Urine	Blood	Total
C. albicans	**26**	**9**	**4**	**39**
C. tropicalis	**12**	**0**	**0**	**12**
Aspergillus	**2**	**0**	**0**	**2**
C. famata	**0**	**0**	**1**	**1**
C. glabrata	**0**	**0**	**1**	**1**
C. auris	**0**	**0**	**1**	**1**
C. parasilosis	**0**	**0**	**1**	**1**
Total (%)	**40 (70)**	**9 (16)**	**8 (14)**	**57 (100)**

The majority of samples were isolated from the ICU (41 patients: 71.9%). The departmental isolated fungal strains are displayed in Table 3. The primary strain isolated from the ICU was *C. albicans* (25 patients: 60.98%), followed by *C. tropicalis*. Only one strain of *Candida auris* was isolated from the blood sample of one ICU patient. The isolated strains from the ICU are showen in Table (3).

Table 3: Departments of Isolated Fungal Strains

	ICU			Medical	Surgical	Total
	Sputum	Blood	Urine			
C. albicans	21	4	٠	13	1	39
C. tropicalis	12	٠	٠	0	0	12
Aspergillus	1	٠	٠	1	0	2
C. famata	٠	1	٠	0	0	1
C. glabrata	٠		٠	0	0	1
C. auris	٠	1	٠	0	0	1
C. parasilosis	٠	1	٠	0	1	1
Total (%)	34 (60)	7 (12)	0 (0)	14 (25)	2 (3)	57(100)

Bacterial coinfection was detected in 12 (21%) severely ill patients; Klebsiella strains were the most common. The number of patients with bacterial coinfection who died (9) was significantly higher than those discharged (3), indicating that bacterial coinfection increased mortality risk. In contrast, 27 (37.4%) COVID-19 patients improved and were discharged Table (4).

Table 4: Main Management Procedures and Outcome

Drugs administered	N (%)	Duration (Median days, 25th/75th percentile)
Corticosteroids	48 (84)	6 (4-9)
Antibiotics	57 (100)	7 (4-11)
Antifungal	12 (21)	
Immunomodulatory drugs	3 (5)	
Risk factors	**N (%)**	**Duration (Median days, 25th/75th percentile)**
Mechanical ventilation	27 (48)	5 (2.5-9)
Central line	30 (53)	4 (2-10)
Previous hospitalization	25 (44)	6 (4-20)
Bacterial infection 12 (21)		
***Klebseilla pneumoniae* 7, *Acinetobacter spp*. 3, *E-coli* 2**		

Outcome N (%)		Improved N (%)	Dead N (%)
Mechanical ventilation	27 (48)	9 (16)	18 (32)
Diabetes mellitus	37 (65)	16 (28)	21 (37)
Central Line	30 (53)	12 (21)	18 (32)
Cardio -vascular disease	16 (28)	6 (11)	10 (18)
ICU admission	42 (74)	20 (35)	22 (39)
Bacterial coinfection	12 (21)	3 (5)	9 (16)

The central management procedures and outcomes of the study patients are presented in table 4. Forty-eight patients (84%) received corticosteroid therapy for a median (IQR) duration of 6 (4–9) days. Twenty-seven patients (47.5%) required mechanical ventilation for a median (IQR) duration of 5 (2.5–9) days. Eighteen (31.8%) patients died. Detailed management is highlighted in Table(5).

Table 5: Detailed Management Mentioned in Table 2

	Type	Dose	No. of Patients (%)
Corticosteroids			
	Dexamethasone	**6 mg OD**	**33 (58)**
	Hydrocortisone	**50 mg QID**	**8 (14)**
		100mg OD	**2 (4)**
	Methylprednisolone	**60 mg BID**	**5 (1)**
		40 mg OD	**2 (4)**
	Prednisolone	**40 mg OD**	**2 (4)**
	Fludrocortisone	**0.2 mg OD**	**1 (2)**
Antibiotics			**N. %**
	Linezolid		**30 (53)**
	Cefepime		**22 (39)**
	Tazocin		**20 (35)**
	Ceftriaxone		**15 (26)**
	Levofloxacin		**15 (26)**
	Meropenem		**12 (21)**
	Vancomycin		**11 (19)**
	Azithromycin		**6 (11)**
	Tigecycline		**6 (11)**
	Others: Colistin 4, Clindamycin 3, Ceftazidime, Gentamycin, Imipenem, Metronidazole 2 each		
Antifungal			**N. %**
	Anidulafungin		**3 (5)**
	Caspofungin		**2 (4)**
	Mixed antifungal (Amphotericin B, Miconazole, Fluconazole)		**5 (1)**
	Local miconazole for 14 days		**1 (2)**
Immunomodulatory drugs			**N. %**
	Tocilizumab		**2 (4)**
	Interferon Beta		**1 (2)**

OD: Once daily, BID: Twice daily, QID: Four times daily

The average of hospital days was significantly longer (P=0.043) among patients who died (17.57 days) compared with those who were cured (13.68 days). The number of patients who died (18; 31.8%) following invasive mechanical ventilation was significantly higher than those discharged (9; 15.7%), emphasizing that this procedure increased mortality risks. Diabetes mellitus (37 patients: 64.9%) and cardiovascular diseases (16 patients: 28%) were also considered high mortality risks (Table 4).

DISCUSSION

COVID-19 infection can destroy lymphocytes, mainly B cells, T cells, and NK cells, which leads to immune deficiency during the disease period [16].

The decreased lymphocytes and host immune function may be the main reason for co-infection[9]. Alternatively, critically ill COVID-19 patients have higher cytokine levels, lower CD4 interferon-gamma expression, and fewer CD4 and CD8 cells. This difficult clinical situation increases the risk of severe fungal co-infection [17]. In our analysis, the rate of fungal co-infection was 4.7%; this relatively lower rate might be due to early detection of infection and administration of antifungal agents.

Our results are consistent with many authors in China: Zhang et al.[18] obtained a fungal co-infection rate of 3.2%, Chen et al.[21] had five (5/99; 5%) cases of fungal infection, and Yang et al.[14] had Three (3/52; 5.8%) patients with fungal co-infection. Other studies reported higher rates of fungal co-infection ranging from 10% to 29%.

In Zhang's et al.[18] study, the fungal Coinfection was 10.9%. Another study from Italy found that 11% of COVID-19 infection cases reported co-infections with other bacteria and fungi [19]. Contrastingly, Pemán et al.[12] reported the fungal co-infection rate at 29.5 %. Regarding the patients aged 75, 4 % of infected patients were over 50 years old, it is consistent with previous Chinese and Brazilian studies on COVID-19, showing that 65% of patients over 50 were more likely to develop severe COVID-19 [11,20].

We detected a high prevalence of Candida species: *C. albicans* (68.4%) and *C. tropicalis* (21%). Additionally, Salehi et al.[16] found that *C. albicans* was

the most common pathogen, which accounted for 70.7%.

In contrast, Chen et al.[21] showed that among the 99 cases of COVID-19 pneumonia in Wuhan, fungal infections included *C. albicans* and *C. glabrata*. The higher risk of death from infections by non-albicans Candida species (56%) in contrast to *C. albicans* (44%) may be related to the lower sensitivity of some species to antifungal medication. Bacterial co-infections were detected in 12 (21%) severely ill patients in the ICU; 9 out of them died.

The most prevalent bacterial strains were *Klebsiella pneumoniae* and *Acinetobacter baumannii*, reported in a retrospective, single-center study conducted by Chen et al.[21] among COVID-19 pneumonia patients in Wuhan. The mortality rate is more significant in severe versus non-severe cases due to the higher co-infection rate in severe patients (10). Notably, It is worth mentioning that patients with severe COVID-19 undergo many interventions that favor opportunistic infections (i.e., parenteral nutrition, broad-spectrum antibiotic treatment, mechanical ventilation, corticosteroids, and central venous catheter placement) [22].

The mortality rate showed that 52% of the total patients were admitted to the ICU, and 67% mechanically-ventilated patients died. This corroborates a Brazilian study in which 59% and 80% of ICU and mechanically-ventilated patients died, respectively [11].

Diabetes (64.9%) and cardiovascular disease (28%) were the chief comorbidities found in our study; additionally, hospitalization duration was considered a risk factor. Lansbury et al.[13] found that severe COVID-19 and organ damage in diabetes and cardiovascular patients can lead to sever organ failure and resulting mortality. However, Silva et al.[23] stated that fungal co-infections increased the risk of mortality in patients suffering from cardiovascular disease and/or diabetes; those with hospitalizations also had an increased odd of dying (OR = 13.45; R2=0.31).

CONCLUSION

Our data elucidate that severely ill COVID-19 patients with fungal and/or bacterial co-infections require more extended hospitalization and also higher relative mortality risks than those without co-infections. Furthermore, co-infections can increase the risk of mortality in other patients with multiple comorbidities. Thus, we emphasize that the early diagnosis of fungal and bacterial infections will help to recognize high-risk patients and decide the best interventions necessary to avoid mortality.

This manuscript has not been previously published and is not under consideration in the same or substantially similar form in any other reviewed media. I have contributed sufficiently to the project to be included as author. To the best of my knowledge, no conflict of interest, financial or others exist. All authors have participated in the concept and design, analysis, and interpretation of data, drafting and revising of the manuscript, and that they have approved the manuscript as submitted.

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